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Image 2000

USER: RITCHWOOD, JASMINE M (jmr)

FOLDER: K024367 - 222 pages (FOI:04005047)

COMPANY: SINCLAIR PHARMACEUTICALS, LTD. (SINCPHAR)

PRODUCT: DRESSING, WOUND AND BURN, HYDROGEL W/DRUG AND/OR BIOLOGIC (MGQ)

SUMMARY: Product: SINCLAIR WOUND AND SKIN EMULSION

DATE REQUESTED: Thu Jun 07 24:00:00 2007

DATE PRINTED: Tue Jul 31 13:55:44 2007

Note: Releasable Version

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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K024367

Attachment 6

510(k) Summary

JUL 28 2003

December 30, 2002

1. **Submission Applicant & Correspondent:**

Name: Sinclair Pharmaceuticals, Ltd.
Address: Borough Road
Godalming
Surrey
GU7 2AB
United Kingdom

Phone No.: 1-972-939-2442
Contact Person: Michael Killeen

2. **Name of Device:** **SINCLAIR WOUND AND SKIN EMULSION ™**
Trade/Proprietary/Model Name: **SINCLAIR WOUND AND SKIN EMULSION ™**
Common or Usual Name: Dressing, Wound & Burn, Hydrogel w/Drug or Biologic
Classification Names: Dressing, Wound & Burn, Hydrogel w/Drug or Biologic

3. **Devices to Which New Device is Substantially Equivalent:**
   - Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240, from Medix Pharmaceuticals Americas Inc. and
   - Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing.

4. **Device Description:**
Sinclair Wound and Skin Emulsion is a non sterile viscous emulsion / gel formulation, which is presented for both Prescription (requires physician diagnosis of disease state) and over-the-counter (OTC) use.

5. **Intended Use of the Device:**
The prescription product requires a physician to diagnose the disease state, while the OTC product is indicated for general symptoms such as burning and itching in minor skin irritations and minor burns. This formulation, when applied to the burn, injured tissue or skin, forms a protective barrier that helps to keep the wound moist.

6. **Summary of Technological Characteristics of the Device Compared to the Predicate Devices:**
All products referenced are non sterile emulsion/gel types that are applied topically to relieve the symptoms of various dermatoses.

7. **Tests and Conclusions:**
Functional and performance testing has been conducted to assess the safety and effectiveness of **SINCLAIR WOUND AND SKIN EMULSION ™** and all results are satisfactory.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 28 2003

Mr. Michael Killeen
Executive Director
Sinclair Pharmaceuticals, Ltd.
Borough Road
Godalming, Surrey
United Kingdom GU7 2AB

Re: K024367
Trade/Device Name: Sinclair Wound and Skin Emulsion™
Regulation Name: Hydrogel wound dressing and burn dressing
Regulatory Class: Unclassified
Product Code: MGQ
Dated: April 25, 2003
Received: May 6, 2003

Dear Mr. Killeen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97) you may obtain. Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,

Miriam C. Provost

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-714; Released by CDRH on 02-01-2016.

K024367

Attachment 3 - Indications for Use Statement	
510(k) Number NA	
Device Name	**SINCLAIR WOUND AND SKIN EMULSION** ™
Indications for Use	FOR TOPICAL DERMATOLOGICAL USE ONLY **Description Rx Product:** Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process. **Directions For Use (Rx and OTC):** Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice. **Description OTC Product:** Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn.

PLEASE DO NOT WRITE BELOW THIS LINE- CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

Miriam C. Provost
(Division Sign-Off)
Division of General, Restorative and Neurological Devices

510(k) Number K024367

Prescription Use _____ OR Over-The Counter Use _____
(per 21 CFR 801.109)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 28 2003

Mr. Michael Killeen
Executive Director
Sinclair Pharmaceuticals, Ltd.
Borough Road
Godalming, Surrey
United Kingdom GU7 2AB

Re: K024367
Trade/Device Name: Sinclair Wound and Skin Emulsion™
Regulation Name: Hydrogel wound dressing and burn dressing
Regulatory Class: Unclassified
Product Code: MGQ
Dated: April 25, 2003
Received: May 6, 2003

Dear Mr. Killeen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Sincerely yours,

Miriam C. Provost

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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K024367

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510(k) Number NA	
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Indications for Use	FOR TOPICAL DERMATOLOGICAL USE ONLY **Description Rx Product:** Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process. **Directions For Use (Rx and OTC):** Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice. **Description OTC Product:** Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn.

PLEASE DO NOT WRITE BELOW THIS LINE- CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

Miriam C. Provost
(Division Sign-Off)
Division of General, Restorative and Neurological Devices

510(k) Number K024367

Prescription Use _____ OR Over-The Counter Use _____
(per 21 CFR 801.109)

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Michael Killeen
Executive Director
Sinclair Pharmaceuticals Limited
Borough Road
Godalming
Surrey GU7 2AB
United Kingdom

MAR 2 8 2003

Re: K024367
Trade Name: Sinclair Wound and Skin Emulsion™
Dated: December 30, 2002
Received: December 31, 2002

Dear Mr. Killeen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a legally marketed predicate device based solely on the information you provided. To complete the review of your submission, we require the following information:

1. The indication for use statement includes treatments that are not identified in predicate wound dressing indications for use, e.g., various types of dermatoses, including atopic dermatitis and allergic contact dermatitis. In addition, the indication for use statement describes the device mechanism of action. Please revise the indications for use statement to be consistent with predicate wound dressings or provide information that supports the intended use on various types of dermatoses, atopic dermatitis and allergic contact dermatitis. In addition, please remove the mechanism of action statement.

2. The indications for use state that the product will manage and relieve the burning, itching, and pain experienced with various types of dermatoses. Please provide information obtained from clinical evaluation of the product's ability to relieve pain associated with the indications for use for your device.

3. The device is provided non-sterile. Radiation dermatitis may result in the skin barrier being breached and the labeling indicates that the device may be used on broken skin. Please conduct testing of the product in accordance with the Anti-Microbial Preservatives-Effectiveness <51> microbiological test identified in the USP.

4. Butyrospermum parkii is identified as Sheanut oil under 21 CFR 184.1702. FDA believes that individuals who have nut sensitivities could have an allergic response to the wound dressing. Please include a Warning on the product label informing people that the product contains nut oil or provide information to demonstrate that Sheanut oil does not elicit allergy responses.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

5. Please provide toxicity information for the following wound dressing ingredients: (b)(4) [redacted] (arachidyl glucoside, behenyl alcohol, arachidyl alcohol), bisabolol, proctone olamine, vitis vinifera, and telmesteine. In lieu of toxicity information, identification of predicate wound dressings containing these ingredients could address our concerns.

6. The wound dressing formulation contains ingredients that were not identified in predicate wound dressings, or in the same ingredient combinations for predicate wound dressings. Please provide biocompatibility test evaluations for cytotoxicity, irritation and sensitization assessments or information from human clinical experience to address these concerns.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (Act). You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations.

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete.

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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If you have any questions concerning the contents of the letter, please contact Peter L. Hudson, Ph.D., at (301) 594-3090. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or at (301) 443-6597, or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Celia M. Witten, Ph.D., M.D. for
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

Mr. Michael Killeen
Executive Director
Sinclair Pharmaceuticals Limited
Borough Road
Godalming
Surrey GU7 2AB
United Kingdom

Re: K024367
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Dated: December 30, 2002
Received: December 31, 2002

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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6. The wound dressing formulation contains ingredients that were not identified in predicate wound dressings, or in the same ingredient combinations for predicate wound dressings. Please provide biocompatibility test evaluations for cytotoxicity, irritation and sensitization assessments or information from human clinical experience to address these concerns.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (Act). You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations.

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete.

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

If you have any questions concerning the contents of the letter, please contact Peter L. Hudson, Ph.D., at (301) 594-3090. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or at (301) 443-6597, or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-410	Hudson	5/23/03						
HFZ-410	Ogden for SPR	3/27/03						

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

cc: HFZ-401 DMC
HFZ-404 510(k) Staff
HFZ-410 Division
D.O.
f/t:PLawtonHudson:dlw:03-27-03

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

December 31, 2002

SINCLAIR PHARMACEUTICALS, LTD.
BOROUGH RD.
GODALMING, SURREY,
UNITED KINGDOM GU7 2AB
ATTN: MICHAEL KILLEEN

510(k) Number: K024367
Received: 31-DEC-2002
Product: SINCLAIR WOUND AND SKIN EMULSION

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

As a reminder, we would like to mention that FDA requires all 510(k) submitters to provide an indications for use statement on a separate page. If you have not included this indications for use statement in addition to your 510(k) summary (807.92), or a 510(k) statement (807.93), and your Truthful and Accurate statement, please do so as soon as possible. If the above mentioned requirements have been submitted, please do not submit them again. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the DMC will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMICA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMICA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016 K024367

SINCLAIR

December 30th, 2002

Document Mail Center (HFZ-401)
Food and Drug Administration (FDA)
Center for Devices and Radiological Health (CDRH)
Office of Device Evaluation
9200 Corporate Blvd.
Rockville, MD 20850
USA

FDA/CDRH/OCE/PMO
2002 DEC 31 A 10:

RE: 510(k) Submission for *Sinclair Pharmaceuticals Ltd.*
Sinclair Wound and Skin Emulsion™

Dear 510(k) review staff,
In accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 807.87, Sinclair Pharmaceuticals, Ltd. is submitting, in duplicate, a Premarket Notification 510(k) for *Sinclair Wound and Skin Emulsion™*.

Confidentiality
We regard our intent to market this product as confidential. The existence of this 510(k) has not been revealed to anyone other than our employees. Therefore we request that the Agency not disclose this intent until the 510(k) clearance is granted.

All items marked "Confidential" may be trade secret, confidential commercial or financial information as defined in 21 CFR 20.61. We request that the Agency not make public disclosure of this information without prior consultation with Sinclair Pharmaceuticals Ltd. as provided by 21 CFR 20.45.

We would appreciate your earliest attention to this 510(k) and we trust that the information provided will enable the Agency to reach a substantial equivalence determination.

Should you have any questions, please contact me via phone at 1 972-939-2442, fax at 1-972-236-2282, or e-mail at mkilleen@sinclairpharma.com
Dswift " " "

Yours sincerely,

Michael Killeen
Executive Director

Enclosure: 510(k) Submission for Sinclair Wound and Skin Emulsion™

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

SK10 194 SU UNCLASS

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510(k) Pre-market Notification

Sinclair Wound and Skin Emulsion™

Michael Killeen
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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I. CDRH Submission Cover Sheet

CDRH SUBMISSION COVER SHEET	
Date of submission: December 20, 2002	FDA Document Number:

Section A :Type of Submission

PMA	PMA Supplement	PDP	510(k)	Meeting
☐ Original Submission ☐ Modules Submission ☐ Amendment ☐ Report ☐ Report Amendment	☐ Regular ☐ Special ☐ Panel Track ☐ 30-day Supplement ☐ 135-day Supplement ☐ Real time Review ☐ Amendment to PMA Supplement	☐ Presubmission summary ☐ Original PDP ☐ Notice of Intent to start clinical trials ☐ Intention to submit Notice of Completion ☐ Notice of Completion ☐ Amendment to PDP ☐ Report	☑ Original Submission ☑ Traditional ☐ Abbreviated ☐ Special ☐ Additional information ☐ Traditional ☐ Abbreviated ☐ Special	☐ Pre-IDE ☐ Pre-PMA ☐ Pre-PDP ☐ 180-day meeting ☐ Other (specify)
IDE	**Humanitarian Device Exemption**	**Class II Exemption**	**Evaluation of Automatic Class III Designation**	**Other Submission**
☐ Original Submission ☐ Amendment ☐ Supplement	☐ Original Submission ☐ Amendment ☐ Supplement ☐ Report	☐ Original Submission ☐ Additional info	☐ Original Submission ☐ Additional info	Describe Submission

Section B Applicant or Sponsor

Company Name: Sinclair Pharmaceuticals Ltd		Establish registration Number:
Division name (if applicable): Not applicable		Phone number: +44 1483 428 611
Street Address: Borough Road		Fax number: +44 1483 860 927
City: Godalming	~~State~~: Surrey	Country: UK
Contact Name: Michael Killeen		
Contact Title: Executive Director		Contact e-mail address: mkilleen@sinclairpharma.com

Section C: Submission correspondent (if different from above)

Company Name:		Establish registration Number:
Division name (if applicable): Not applicable		Phone number:
Street Address:		Fax number:
City:	State:	Country:
Contact Name:		
Contact Title:		Contact e-mail address:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Section D1: Reason for Submission - PMA, PDP, or HDE		
☐ New Device: ☐ Withdrawal ☐ Additional or expanded indications ☐ Licensing agreement	☐ Change in design, component, or specifications: ☐ software ☐ Color Additive ☐ Material ☐ Specifications ☐ Other (specify below)	☐ Location Change: ☐ Manufacturer ☐ Sterilizer ☐ Packager ☐ Distributor
☐ Process Change: ☐ Manufacturing ☐ Sterilization ☐ Packaging ☐ Other (specify below)	☐ Labeling change: ☐ Indications ☐ Instructions ☐ Performance characteristics ☐ Shelf life ☐ Trade Name ☐ Other (specify below)	Report Submissions: ☐ Annual or periodic ☐ Post-approval study ☐ Adverse reaction ☐ Device defect ☐ Amendment
☐ Response to FDA correspondence: ☐ Request for applicant hold ☐ Request for removal of applicant hold ☐ Request for extension ☐ Request to remove or add manufacturing site		☐ Change in ownership ☐ Change in correspondent
☐ Other reason (specify):		
Section D2: Reason for submission-IDE		
☐ New device ☐ Addition of Institution ☐ Expand/Extend Study ☐ IRB Certification ☐ Request hearing ☐ Request waiver ☐ Termination of Study ☐ Withdrawal of Application ☐ Unanticipated Adverse Event ☐ Notification of Emergency Use ☐ Compassionate Use Request ☐ Treatment IDE ☐ Continually availability request ☐ Other reason (specify):	☐ Change in: ☐ Correspondent ☐ Design ☐ Informed Consent ☐ Manufacturer ☐ Manufacturing Process ☐ Protocol - Feasibility ☐ Protocol - Other ☐ Sponsor ☐ Report Submission ☐ Current Investigator ☐ Annual Progress ☐ Site waiver limit reached ☐ Final	☐ Response to FDA letter concerning: ☐ Conditional Approval ☐ Deemed Approval ☐ Deficient final report ☐ Deficient progress report ☐ Deficient investigator report ☐ Disapproval ☐ Request extension of time to respond to FDA ☐ Request meeting
Section D3: Reason for Submission - 510(k)		
☑ New device ☐ Addition or expanded indications ☐ other reason (specify):	☐ Change in technology ☐ Change in design	☐ Change in materials ☐ Change in manufacturing process

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Section E: Additional Information on 510(k) Submissions				
Product codes of devices to which substantial equivalence is claimed:				Summary of, or statement concerning, safety and effectiveness data:
1 MGQ	2	3	4	☑ 510(k) summary attached
5	6	7	8	☐ 510(k) statement

Information on devices to which substantial equivalence is claimed:

510(k) Number	Trade or proprietary or model name	Manufacturer
1. K964240	1. Biafene Wound Dressing Emulsion RE	1. Medix Pharmaceuticals Americas Inc.
2. K961758	2. Carrasyn® Wound Dressing	2. Carrington Laboratories Inc

Section F: Product Information Applicable to all Applications	
Common or usual or classification name: Dressing, wound & burn, hydrogel w/drug or biologic	
Trade or proprietary or model name	Model Number
1 Sinclair Wound and Skin Emulsion	NA
2	

FDA document numbers of all prior related submissions (regardless of outcome): none

1	2	3	4	5	6
7	8	9	10	11	12

Data included in submission: ☐ Laboratory testing ☐ Animal trials ☐ Human trials

Section G: Product Classification - Applicable to all Applications		
Product Code: MGQ Dressing, wound & burn, hydrogel w/drug or biologic	C.F.R. section 878.4022	Device Class: ☐ Class I ☐ Class II ☐ Class III ☑ Unclassified

Classification panel: Hydrogel wound and burn dressing

Indications (Prescription product):

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion has a mechanical action which helps to relieve pain, by adhering to the injured tissue and protecting it from further irritation. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Indications (OTC product):

Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Note: Submission of this information does not affect the need to submit a 2891 or 2891a Device Establishment Registration form		FDA Document Number:	
Section H: Manufacturing / Packaging / Sterilization Sites			
☑ Original ☐ Add ☐Delete	FDA Establishment Registration Number:	☐ Manufacturer ☐ Contract sterilizer ☑ Contract Manufacturer ☐ Repackager / relabeler	
Company / Institution name: Biokosmes SRL		Establishment Registration Number: NA	
Division name (if applicable) NA		Phone Number: 011 39 0341 36 81 21	
Street Address: Via Ugo Bassi 1		Fax Number: 011 39 0341 36 81 52	
City: Lecco	State:	Country: Italy	Zip Code: 22053
Contact Name: Dr. Gianluca Braguti			
Contact title: Technical Director		Contact e-mail address:	
☐ Original ☐ Add ☐Delete	FDA Establishment Registration Number: Awaiting issue from FDA, Form filed 07/02	☐ Manufacturer ☐ Contract sterilizer ☐ Contract Manufacturer ☐ Repackager / relabeler	
Company / Institution name:		Establishment Registration Number:	
Division name (if applicable) NA		Phone Number:	
Street Address:		Fax Number:	
City:	State:	Country:	Zip Code:
Contact Name:			
Contact title:		Contact e-mail address:	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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II. Device Name	The device trade names and common/classifications names are:	
	Device Trade Name	**Common/Classification Name**
	Sinclair Wound and Skin Emulsion	Dressing, wound & burn, hydrogel w/drug or biologic
III. Address and Registration #	The address and registration number of the manufacturer and sterilization sites for the devices are:	
	Manufacturer	**Sterilization Site**
	Sinclair Pharmaceuticals, Ltd Borough Road Godalming Surrey GU7 2AB UK FDA registration number: Awaiting issue from FDA Form filed 01/02	NA
IV. Device Class	MGQ Unclassified, as are the predicate devices.	

V. Predicate Device Information	**Trade Name**	**510(k) Number**	**SE Date**
MGQ 79	Medix Pharmaceuticals Americas Inc. Biafene Wound Dressing Emulsion (RE) Radiodermatitis Emulsion	K964240	Jan. 22, 1997
	Carrington Laboratories RadiaGel Wound Dressing	K961758	July 11, 1996

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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VI. Labeling and Intended Use	A draft product container/ box label (which contains Instructions for Use) for the Rx product can be found in Attachment 1A and draft label for the product/ box for the OTC product can be found in Attachment 1B. Predicate device labeling and product information can be found in Attachment 2A (Biafene), Attachment 2B (Carrasyn®) and Attachment 2C (RadiaCare).
	Prescription labeling: Under the supervision of a healthcare professional, **Sinclair Wound and Skin Emulsion** is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion has a mechanical action which helps to relieve burning, itching and pain by adhering to the injured tissue and protecting it from further irritation. Sinclair Wound and Skin Emulsion may also be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin, by maintaining a moist wound & skin environment, which is beneficial to the healing process. **Sinclair Wound and Skin Emulsion** has similar indications when compared to the predicate Medix Pharmaceuticals Americas Inc. Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240 and Carrington Laboratories Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing. **Sinclair Wound and Skin Emulsion** is also intended for the Over-The-Counter (OTC) market with indications for less acute symptoms, which are not disease specific. OTC labeling: Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn. **The Indications for Use statement** is included in Attachment 3.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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VII. Device Description and Comparison	**Sinclair Wound and Skin Emulsion** is a viscous emulsion / gel formulation, which is presented for both Prescription (requires physician diagnosis of disease state) and over-the-counter (OTC) use. The prescription product requires a physician diagnosis to recognize the disease state, while the OTC product is indicated for general symptoms such as burning and itching in minor skin irritations and minor burns. This formulation, when applied to the burn, injured tissue or skin, forms a protective barrier that helps to keep the wound moist. As with the predicate devices (Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240 and Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing, **Sinclair Wound and Skin Emulsion** has a mechanical function as a barrier and is indicated for symptom management by adhering to the injured tissue and skin margins, soothing tissue insult of various etiologies. **Sinclair Wound and Skin Emulsion** viscous emulsion/gel, is comprised of Purified Water, Ethylhexyl palmitate, Pentylene glycol, Butyrospermum parkii, Capryloyl glycine, Glyceryl stearate, Peg-100 stearate, Arachidyl glucoside, Behenyl alcohol, Arachidyl alcohol, Bisabolol, Tocopheryl acetate, Glycyrrhetinic acid, Carbomer, Ethylhexylglycerin, Piroctone olamina, Sodium hydroxide, Allantoin, Dmdm hydantoin, Vitis vinifera, Disodium EDTA, Ascorbyl tetraisopalmitate, Sodium hyaluronate, Propyl gallate, Telmesteine and Butylene glycol. A formulations comparison chart may be found as Attachment 4.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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VIII. Substantial Equivalence

SINCLAIR WOUND AND SKIN EMULSION™ is substantially equivalent to the following two devices:

1. Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240, from Medix Pharmaceuticals Americas Inc. and
2. Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing

Biafene RE is an emulsion formulation reduces the frequency and severity of radiation induced skin reactions when used prophylactically and heals reactions once they occur.

Carrasyn® and RadiaCare Gel are Hydrogel Wound Dressings formulated for the management of radiation-induced dermatitis. They can be used pre-radiation therapy to condition the skin as well as for management of skin reactions post-radiation therapy.

Product Name	Sinclair Wound and Skin Emulsion	Medix Biafene RE	Carrington RadiaGel
Method of Use	For topical application	For topical application	For topical application
# of applications per day	As needed	3 times a day	2-3 times a day
Claim	Management of radiation dermatitis and other dermatoses	Reduce frequency and severity of radiation dermatitis	Management of radiation dermatitis, diabetic ulcers, pressure ulcers, stasis ulcers
Area of Use	Topical wound and skin care	Topical wound and skin care	Topical wound and skin care
Disease State	Dermatitis	Dermatitis	Dermatitis
Type of Product	Topical emulsion	Topical emulsion	Topical gel
Presentation	Non Sterile	Non Sterile	Non Sterile

In summary, the **SINCLAIR WOUND AND SKIN EMULSION**™ described in this submission is, in our opinion, substantially equivalent to the predicate devices Medix Pharmaceuticals Americas Inc., Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240 and Carrington Laboratories Carrasyn® Hydrogel Wound Dressing 510(k) K961758 also marketed as RadiaCare Gel Wound Dressing.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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IX. 510(k) Summary	The **SINCLAIR WOUND AND SKIN EMULSION** ™ 510(k) Summary may be found as Attachment 6.
X. Truthful & Accurate Statement	The **SINCLAIR WOUND AND SKIN EMULSION** ™ Truthful & Accurate Statement may be found as Attachment 7.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 1A
Sinclair Wound and Skin Emulsion ™ - Draft Product Container / Box Labeling

Front Label Rx - Draft

Sinclair
Wound and Skin Emulsion

Topical Dermatological Relief

Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion has a mechanical function as a barrier and helps to relieve burning, itching and pain by adhering to the injured tissue and protecting it from further irritation. Sinclair Wound and Skin Emulsion may also be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin, by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Rx

Federal law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice.

Back Label Rx - Draft

Sinclair
Wound and Skin Emulsion

Topical Dermatological Relief

For external use only.

Sinclair Wound and Skin Emulsion viscous emulsion/gel, is comprised of Purified Water, Ethylhexyl palmitate, Pentylene glycol, Butyrospermum parkii, Capryloyl glycine, Glyceryl stearate, Peg-100 stearate, Arachidyl glucoside, Behenyl alcohol, Arachidyl alcohol, Bisabolol, Tocopheryl acetate, Glycyrrhetinic acid, Carbomer, Ethylhexylglycerin, Piroctone olamina, Sodium hydroxide, Allantoin, Dmdm hydantoin, Vitis vinifera, Disodium EDTA, Ascorbyl tetraisopalmitate, Sodium hyaluronate, Propyl gallate, Telmesteine and Butylene glycol.

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Surrey UK, GU7 2AB
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Attachment 1B
Sinclair Wound and Skin Emulsion ™ - Draft Product Container / Box Labeling

Front Label OTC - Draft	Back Label OTC - Draft
Sinclair ***Wound and Skin Emulsion*** Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn. Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice.	**Sinclair** ***Wound and Skin Emulsion*** For external use only. **Sinclair Wound and Skin Emulsion** viscous emulsion/gel, is comprised of Purified Water, Ethylhexyl palmitate, Pentylene glycol, Butyrospermum parkii, Capryloyl glycine, Glyceryl stearate, Peg-100 stearate, Arachidyl glucoside, Behenyl alcohol, Arachidyl alcohol, Bisabolol, Tocopheryl acetate, Glycyrrhetinic acid, Carbomer, Ethylhexylglycerin, Piroctone olamina, Sodium hydroxide, Allantoin, Dmdm hydantoin, Vitis vinifera, Disodium EDTA, Ascorbyl tetraisopalmitate, Sodium hyaluronate, Propyl gallate, Telmesteine and Butylene glycol. Sinclair Pharmaceuticals Limited Godalming Surrey UK, GU7 2AB Tel: +44 1483 428 611

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 2A
Biafene RE (Radiodermatitis Emulsion) Instructions and Considerations

APPLICATION INSTRUCTIONS

BIAFINE®RE reduces the frequency and severity of radiation induced skin reactions when used prophylactically. BIAFINE®RE is effective in managing radiodermatitis once it has occurred.
Do not apply 4 hours prior to radiation sessions. Do not halt applications during your radiation regimen, even for one day.

Prophylaxis:

- Applications should begin immediately following the first session.
- Gently massage a generous amount of BIAFINE®RE into the irradiated area, three times per day, seven days a week.

Management of erythoma and/or dry desquamation:

- Gently massage a generous amount of BIAFINE®RE on and around the affected area, three times per day, seven days a week.

Management of moist/wet desquamation:

- Apply a thick layer (1/4 – 1/2 inch) of BIAFINE®RE on and around the affected area, cover with a moist gauze, secondary dressing, and secure.
- Renew dressing every 24 hours.

Post-Radiation Session:
Sometimes skin reactions (such as skin hardening, flaking, scaling, etc.) appear several weeks or months after the last radiation session. Since BIAFINE®RE works on skin reactions from the surface inward, interrupting or stopping BIAFINE®RE applications too quickly may result in a reaction appearing days or weeks later. Consult a physician regarding recommended therapy duration.

- Gently massage a generous amount of BIAFINE®RE into the irradiated area, three times per day, seven days a week.

CONSIDERATIONS

If the irradiated area is marked with a pen and not tattoos, care should be taken to only apply BIAFINE®RE within the marked area since it may erase pen markings. It will not erase tattoos.

BIAFINE®RE, the number 1 choice for reducing the severity and frequency or radiation reactions, and for healing reactions once they occur.[4] BIAFINE®RE is the ONLY product on the market today to have shown in clinical trials that it is effective in reducing the severity and frequency of radiation reactions if used prophylactically.[5] Other products in use today such as "petrolatum" based products, "Aloe Vera" based gels/hydrogels have been shown to have no effect in either reducing reactions or treating reactions.

---

1 Calabreal, Paul, M.D., et al, 1986. "Medical Oncology". Pp. 280-281
2 Berhow,Robert, M.D., et al, 1992. "The Merck Manual 16th Ed".
3 Love, Susan M, M.D. 1995. "Dr. Susan Love's Breast Book".
4 RTOG 97-13
5 Selected data on file.
6 Int. J. Radiation Oncology. Vol. 36, No. 2 pp. 345-349, 1996.

For further information, please contact:

MEDIX PHARMACEUTICALS AMERICAS, INC.
YOUR PARTNER IN HEALING
12505 Starkey Road, Suite M
Largo, FL 33773
PH: 1-888-BIAFINE (242-3463) or 1-727-507-9844
FAX: 1-727-507-9855
Web Site www.biafine.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 2B
Carrasyn Hydrogel Wound Dressing 510(k) # K961758

*U.S. Patent no. 4,917,890
**U.S. Patent nos. 4,735,935 and 4,957,907

NDC 53303-010-30
CARRINGTON™
Carrasyn®
HYDROGEL*
WOUND DRESSING
LOW EXUDATE
Reorder no. 101030
NET WT. 3 OZ. (85g)

Carrington Laboratories, Inc.
2001 Walnut Hill Lane
P.O. Box 168128
Irving, TX 75016-8128
For further information call:
1-800-358-5205
www.carringtonlabs.com

NDC 53303-010-30
CARRINGTON™
Carrasyn®
HYDROGEL*
WOUND DRESSING
LOW EXUDATE
Reorder no. 101030
NET WT. 3 OZ. (85g)

0 53303 01030 6

WARNING: If condition worsens or does not improve within 10 to 14 days, consult a physician. Keep this and all similar products out of the reach of children. Discontinue use if sensitivity occurs.

302178 Rev.1

A non-oily hydrogel for the management of: Radiation Dermatitis, Diabetic Ulcers, Foot Ulcers, Post Surgical Incisions, First & Second Degree Burns, Pressure Ulcers (I-IV), Stasis Ulcers, Cuts, Abrasions, Skin Conditions associated with Peristomal Care, Sunburn.

INGREDIENTS (alphabetical order): Acemannan** hydrogel from *Aloe vera* L., Carbomer, Citric Acid, Edetate Disodium, Imidurea, L-Glutamic Acid, Methylparaben, Panthenol, Polyvinylpyrrolidone, Potassium Sorbate, Purified Water, Sodium Benzoate, Sodium Chloride, Sodium Metabisulfite, Trolamine.

DIRECTIONS: Flush wound with a suitable wound cleanser, such as CARRAKLENZ™. Apply dressing to cover area, including marginal areas; apply as often as needed. If gauze is used as a wound covering, it should be moistened with a suitable wound cleanser; CARRAKLENZ™ is recommended. The product sometimes turns amber in color, a natural phenomenon having no impact on efficacy. Intended for single patient use only.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

Attachment 2C
Carrington RadiaCare Gel (Carrasyn 510(k) # K961758)

NDC NO. 53303-021-30

CARRINGTON™

RADIACARE™ GEL

HYDROGEL* WOUND DRESSING

A non-oily formulation for the Radiation Patient

Formulated for the management of Radiation Dermatitis

Reorder no. 106042

NET WT. 3 OZ. (85g)

DIRECTIONS: Cleanse the target area with a suitable wound cleanser such as RADIACARE™ KLENZ wound cleanser. Apply a liberal amount of RADIACARE™ GEL to the target area and massage into the skin. If skin is broken, apply approximately 1/4" RADIACARE™ GEL to the affected area 2-3 times daily, and cover with dressing of choice. Treatment should be continued until condition is resolved.

INGREDIENTS (alphabetical order): Allantoin, Aloe vera Gel Extract containing Acemannan** hydrogel, Carbomer, Methylparaben, Panthenol, Propylene Glycol, Purified Water, Quaternium 15, Trolamine.

WARNING: If condition worsens or does not improve within 10 to 14 days, consult a physician. Keep this and all similar products out of the reach of children. Discontinue use if sensitivity occurs.

0 53303 02130 2

Carrington Laboratories, Inc.
2001 Walnut Hill Lane
P.O. Box 168128
Irving, TX 75016-8128

300165 Rev. 0

For technical support or further information call: 1-800-358-5205

*U.S. Patent No. 4, 917, 890
**U.S. Patent Nos. 4,735,935 and 4,957,907

LOT NO. AND EXP. - SEE CRIMP

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

Attachment 3 - Indications for Use Statement

510(k) Number NA	
Device Name	**SINCLAIR WOUND AND SKIN EMULSION** ™
Indications for Use	FOR TOPICAL DERMATOLOGICAL USE ONLY **Description Rx Product:** **Sinclair Wound and Skin Emulsion** is a non-steroidal hydrolipidic cream indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. **Sinclair Wound and Skin Emulsion** helps to relieve burning, itching and pain by adhering to the injured tissue and protecting it from further irritation. **Sinclair Wound and Skin Emulsion** may also be used to relieve the pain of first and second degree burns. **Sinclair Wound and Skin Emulsion** helps to relieve dry waxy skin, by maintaining a moist wound & skin environment, which is beneficial to the healing process. **Directions For Use (Rx and OTC):** Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice. **Description OTC Product:** Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn.

PLEASE DO NOT WRITE BELOW THIS LINE- CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-The Counter Use _____
(per 21 CFR 801.109)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Formulation Comparison Chart

Function	Sinclair	Medix	Carrington
Diluent	Purified water	Demineralized water	Purified Water
Emolient	Ethylhexyl palmitate	Cetyl Palmitate	
Humectant	Pentylene glycol	Propylene Glycol	Propylene Glycol[4)]
Skin conditioning agents	nut oil Butyrospermum parkii	Trolamine	Triethanolamine salicylate (Trolamine)
Emolient	Capryloyl glycine	Monoglycol Stearate	
Surfactant – component (b)(4) Surfactant – component (b)(4)	(b)(4) Glyceryl stearate[1)] Peg-100 stearate[1)]	Stearic Acid	
Surfactant – component of (b)(4) Emulsion stabilizer – component of (b)(4) Emulsion stabilizer – component of (b)(4)	(b)(4) Arachidyl glucoside[2)] Behenyl alcohol[2)] Arachidyl alcohol[2)]	? Parrafin Wax	Sodium Chloride[3)]
Skin conditioning agents	Bisabolol	Squalene	Panthenol
Antioxidant	Tocopheryl acetate		
Skin conditioning agents	Glycyrrhetinic acid	Avacado Oil	Aloe Vera extract with Acemannan™
Emulsion stabilizer	Carbomer		Carbomer
Skin conditioning agents	Ethylhexylglycerin	Liquid Parrafin	
Cosmetic biocide	Piroctone olamina	Sorbic Acid	Quaternium 15[4)]
pH adjuster	Sodium hydroxide	Triethanolamine	
Skin conditioning agents	Allantoin		Allantoin[4)]
Preservative	DMDM hydantoin	Methylparaben	Methylparaben
Skin conditioning agents	Vitis vinifera		
Chelating agent	Disodium EDTA		Disodium EDTA[3)]
Antioxidant	Ascorbyl tetraisopalmitate		
Skin conditioning agents	Sodium hyaluronate		
Antioxidant	Propyl gallate		
Antioxidant	Telmesteine		
Humectant	Butylene glycol		L-Glutamic Acid[3)]
Preservative		Propylparaben	Imidurea[3)]
Preservative			Potassium Sorbate[3)]
Preservative			Sodium Benzoate[3)]
Preservative			Sodium Metabisulfite[3)]
Emulsion stabilizer			Polyvinylpyrrolidone[3)]
Fragrance (Biafene RE only)		Fragrance (herb)	

1) (b)(4) 2) (b)(4) 3) Carrasyn ingredient 4) RadiaCare ingredient

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 5

CONFIDENTIAL

Gras List Identification

Ingredient	% of Total	Function	CFR Reference	Legally marketed product
Purified water	(b)(4) [redacted]	diluent	--	--
Ethylhexyl palmitate		emolient	NA	INCI registered cosmetic ingredient
Pentylene glycol		solvent	NA	INCI registered cosmetic ingredient
Butyrospermum parkii		skin conditioning agents	184.1702	GRAS INCI registered cosmetic ingredient
Capryloyl glycine		emolient	NA	INCI registered cosmetic ingredient
(b)(4) [redacted] Glyceryl stearate[1)] Peg-100 stearate[1)]		surfactant – component of (b)(4) [redacted] surfactant – component of	NA	INCI registered cosmetic ingredient INCI registered cosmetic ingredient
(b)(4) [redacted] Arachidyl glucoside[2)] Behenyl alcohol[2)] Arachidyl alcohol[2)]		Surfactant, component o (b)(4) [redacted] Stabilizer, component of Stabilizer, component of	NA	INCI registered cosmetic ingredient INCI registered cosmetic ingredient INCI registered cosmetic ingredient
Bisabolol		skin conditioning agents	NA	INCI registered cosmetic ingredient
Tocopheryl acetate		antioxidant	NA	INCI registered cosmetic ingredient
Glycyrrhetinic acid		skin conditioning agents	NA	Gelclair 510(k) K013056
Carbomer		emulsion stabilizer	701.3	RadiaGel Wound Dressing 510(k) K961758, Carrington Labs GRAS
Ethylhexylglycerin		skin conditioning agents	α Tocop Acet 182.8892	GRAS INCI registered cosmetic ingredient
Piroctone olamine		cosmetic biocide	NA	INCI registered cosmetic ingredient
Sodium hydroxide		pH adjuster	582.1763	GRAS INCI registered cosmetic ingredient
Allantoin		skin conditioning agents	NA	RadiaGel Wound Dressing 510(k) K961758, Carrington Labs
DMDM hydantoin		preservative	NA	INCI registered cosmetic ingredient
Vitis vinifera		skin conditioning agents	NA	INCI registered cosmetic ingredient
Disodium EDTA		chelating agent	NA	INCI registered cosmetic ingredient
Ascorbyl tetraisopalmitate		antioxidant	NA	INCI registered cosmetic ingredient
Sodium hyaluronate		skin conditioning agents	145.135	Gelclair 510(k) K013056 GRAS
Propyl gallate		antioxidant	582.3660	GRAS INCI registered cosmetic ingredient
Telmesteine		antioxidant	NA	European Oral mucolytic
Butylene glycol	[redacted]	solvent	NA	INCI registered cosmetic ingredient

(b)(4) [redacted] Note that percentages may not equal 100% due to rounding.
Cosmetic chemical reviews made with FDA Cosmetic Labeling Guidelines and INCI registration data.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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510(k) Summary

December 30, 2002

1. **Submission Applicant & Correspondent:**

Name: Sinclair Pharmaceuticals, Ltd.
Address: Borough Road
Godalming
Surrey
GU7 2AB
United Kingdom

Phone No.: 1-972-939-2442
Contact Person: Michael Killeen

2. **Name of Device:** **SINCLAIR WOUND AND SKIN EMULSION ™**
Trade/Proprietary/Model Name: **SINCLAIR WOUND AND SKIN EMULSION ™**
Common or Usual Name: Dressing, Wound & Burn, Hydrogel w/Drug or Biologic
Classification Names: Dressing, Wound & Burn, Hydrogel w/Drug or Biologic

3. **Devices to Which New Device is Substantially Equivalent:**
   - Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240, from Medix Pharmaceuticals Americas Inc. and
   - Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing.

4. **Device Description:**
Sinclair Wound and Skin Emulsion is a non sterile viscous emulsion / gel formulation, which is presented for both Prescription (requires physician diagnosis of disease state) and over-the-counter (OTC) use.

5. **Intended Use of the Device:**
The prescription product requires a physician to diagnose the disease state, while the OTC product is indicated for general symptoms such as burning and itching in minor skin irritations and minor burns. This formulation, when applied to the burn, injured tissue or skin, forms a protective barrier that helps to keep the wound moist.

6. **Summary of Technological Characteristics of the Device Compared to the Predicate Devices:**
All products referenced are non sterile emulsion/gel types that are applied topically to relieve the symptoms of various dermatoses.

7. **Tests and Conclusions:**
Functional and performance testing has been conducted to assess the safety and effectiveness of **SINCLAIR WOUND AND SKIN EMULSION ™** and all results are satisfactory.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 7

Truthful and Accurate Statement

The following statement is provided as required by 21 CFR 807.87 (j):

I certify that, in my capacity as an Executive Director of Sinclair Pharmaceuticals, I believe to the best of my knowledge, that all data and information submitted in this pre-market notification are truthful and accurate and that no material facts for a review of the substantial equivalence of this device have been knowingly omitted from this submission.

Date: December 20, 2002

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Memorandum

July 2, 2003

From: Reviewer(s) - Name(s) [signature] DXK

Subject: 510(k) Number K024367/S1

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☒ Is substantially equivalent to marketed devices. K1-5E
- ☐ NOT substantially equivalent to marketed devices.
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Section 522 Postmarket Surveillance?	☐ YES	☒ NO
Is this device subject to the Tracking Regulation?	☐ YES	☒ NO
Was clinical data necessary to support the review of this 510(k)?	☒ YES	☐ NO
Is this a prescription device?	☒ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☒ NO
Special 510(k)?	☐ YES	☒ NO
Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	☐ YES	☒ NO

Truthful and Accurate Statement ☐ Requested ☒ Enclosed

☒ A 510(k) summary OR ☐ A 510(k) statement

☐ The required certification and summary for class III devices

☒ The indication for use form

Combination Product Category (Please see algorithm on H drive 510k/Boilers) 4

Animal Tissue Source ☐ YES ☒ NO Material of Biological Origin ☒ YES ☐ NO
Grape seed extract

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

☐ No Confidentiality ☐ Confidentiality for 90 days ☐ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: 21CFR MGG Hydroxyl varnish and burn dressing

Additional Product Code(s) with panel (optional): MGJ

Review: [signature] PRSB 7/18/03
(Branch Chief) (Branch Code) (Date)

Final Review: Miriam C. Provost 7/25/03
for (Division Director) (Date)

Revised:4/2/03

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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REVISED: 3/14/95

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K 024367

Reviewer: [illegible]

Division/Branch: DGRND / PRSB

Device Name: SINCLAIR WOUND AND SKIN EMULSION

Product To Which Compared (510(K) Number If Known): K964240

	YES	NO	
1. Is Product A Device	✓		If NO = Stop
2. Is Device Subject To 510(k)?	✓		If NO = Stop
3. Same Indication Statement?	✓		If YES = Go To 5
4. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NE
5. Same Technological Characteristics?		✓	If YES = Go To 7
6. Could The New Characteristics Affect Safety Or Effectiveness?		✓	If YES = Go To 8
7. Descriptive Characteristics Precise Enough?	✓	✓	If NO = Go To 10 If YES = Stop SE
8. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NE
9. Accepted Scientific Methods Exist?			If NO = Stop NE
10. Performance Data Available?	✓		If NO = Request Data
11. Data Demonstrate Equivalence?	✓		Final Decision:

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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1. Intended Use:

2. Device Description: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device over-the-counter or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. Explain why not a device:

2. Explain why not subject to 510(k):

3. How does the new indication differ from the predicate device's indication:

4. Explain why there is or is not a new effect or safety or effectiveness issue:

5. Describe the new technological characteristics: Device & ingredients not found in predicates

6. Explain how new characteristics could or could not affect safety or effectiveness: New ingredients are GRAS and have been evaluated

7. Explain how descriptive characteristics are not precise enough: new ingredient - telmisartan

8. Explain new types of safety or effectiveness questions raised or why the questions are not new:

9. Explain why existing scientific methods can not be used:

10. Explain what performance data is needed:

11. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

ATTACH ADDITIONAL SUPPORTING INFORMATION

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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510(K) MEMORANDUM

TO: **K024367/S001**

FROM: Peter L. Hudson, Ph.D., Biologist
ODE/DGRND/Plastic and Reconstructive Surgery Devices Branch

DATE: 6/30/03

SUBJ: Sinclair Wound and Skin Emulsion
Sinclair Pharmaceuticals, Ltd.
Mr. Michael Killeen
972-939-2442
972-236-2282 (fax)

Recommendation: Substantially equivalent to the predicate wound dressings, Biafene Wound Dressing Emulsion (K964240) and RadiaGel Wound Dressing (K961758):

Procode: MGQ
Class: Unclassified
Regulation Number: 878.4022
Regulation Name: Hydrogel wound and burn dressing with drug/biologic/animal tissue

REVIEW:

Does the product contain drugs or biologicals? Yes, tocopheryl acetate – vitamin E. The label lists the component and indicates its purpose.

1. **Indication and/or Intended Use Statement**

Subject Device

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion has a mechanical action which helps to relieve pain, by adhering to the injured tissue and protecting it from further irritation. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Predicate Device(s)

Medix Pharmaceuticals Americas Inc., Biafene Wound Dressing Emulsion (RE) Radiodermatitis Emulsion (K964240)

Biafene is intended to be used as a wound dressing for the following indications:

- Superficial wounds
- Minor abrasions

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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- Leg ulcers
- Donor sites
- 1st and 2nd degree burns, including sunburns
- radiation dermatitis

*For dermal ulcers, including full thickness wounds and pressure sores, consult a physician

Carrington Laboratories, RadiaGel Wound Dressing (K961758)
Radiagel is indicated for:

- Radiation dermatitis
- Diabetic ulcers foot ulcers post surgical incisions
- 1st and 2nd degree burns
- Pressure ulcers I-IV
- Stasis ulcers
- Cuts
- Abrasions
- Skin conditions associated with peristomal care
- Sunburn

Discussion of equivalency
I called the company's representative and asked them to revise the indications for use to be consistent with predicate IFUs and to remove language regarding the method of action from the IFU.

The sponsor's revised indication for use is:

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis, and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relive the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

As reviewed below, the sponsor's response is sufficient to demonstrate the equivalence of the revised indications for use (see response below to deficiency 1).

2. **Technological Characteristics (Design, Materials, Sizes, etc.)**
Subject Device
The gel formulation contains: purified water, ethylhexyl palmitate, pentylene glycol, butyrospermum parkii, capryloyl glycine, glyceryl stearate, PEG-100 stearate, (b)(4) [redacted] (b)(4) [redacted] arachidyl glucoside, behenyl alcohol, arachidyl alcohol), bisabolol, tocopheryl acetate, glycyrrhetinic acid, carbomer, ethylhexylglycerin, piroctone olamina, sodium hydroxide, allantoin, DMDM hydantoin, vitis vinifera, disodium EDTA, ascorbyl tetrisopalmitate, sodium hyaluronate, propyl gallate, telmesteine and butylene glycol

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Predicate Device(s)
Medix Pharmaceuticals Americas Inc., Biafene Wound Dressing Emulsion (RE)
Radiodermatitis Emulsion (K964240)
Contains demineralized water, cetyl palmitate, propylene glycol, trolamine, monoglycol stearate, stearic acid, paraffin wax, squalene, avocado oil, liquid paraffin, sorbic acid triethanolamine, methylparaben, propylparaben, fragrance

Carrington Laboratories, RadiaGel Wound Dressing (K961758)
Contains purified water, propylene glycol, triethanolamine salicylate (trolamine), sodium chloride, panthenol, aloe extract with acemannan, carbomer, quaternium 15, allantoin, methylparaben, disodium EDTA, L-glutamic acid, imidurea, potassium sorbate, sodium benzoate, sodium metabisulfite, polyvinylpyrrolidone

Discussion of equivalency
All of the ingredients listed in the subject device are either found in predicate wound dressings or were identified as GRAS or as registered cosmetic ingredients. The one exception is telmesteine which is identified as a European Oral Mucolytic. The following ingredients are novel or raise concern:

1. butyrospermum parkii (b)(4) – listed in 21 CFR 184.1702 and identified as Sheanut oil, derived from the Shea tree Butyrospermum parkii. It is composed of triglycerides containing an oleic acid moiety at the 2-position and saturated fatty acids, usually stearic or palmitic acids, at the 1- and 3- positions. It is listed as GRAS.
2. (b)(4) (arachidyl glucoside, behenyl alcohol, arachidyl alcohol) – these reagents are listed as a surfactant, stabilizer and stabilizer, respectively. Cosmetic ingredient listing.
3. bisabolol - Cosmetic ingredient listing.
4. tocopheryl acetate (b)(4) – 21 CFR 182.8892, GRAS
5. glycyrrhetinic acid – used in predicate, Gelclair (K013056)
6. piroctone olamina - Cosmetic ingredient listing.
7. vitis vinifera - Cosmetic ingredient listing.
8. ascorbyl tetraisopalmitate - Cosmetic ingredient listing.
9. propyl gallate – listed in 21 CFR 582.3660 and identified as GRAS/used as an antioxidant
10. telmesteine – European Oral Mucolytic

See responses to deficiencies #5 and #6 below.

3. Comparative Performance Data (in vitro, animal and/or clinical)

Safety Data

Subject Device

No biocompatibility evaluations were provided. I contacted Mr. Killeen to request this information since the subject device identifies a number of ingredients that were not identified in predicate products. Mr. Killeen stated that sensitization and irritation evaluations have been conducted and that the information will be submitted.

See deficiency #6 and response below.

ID

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Predicate Device(s)
Cytotoxicity, irritation and sensitization evaluations in animals and/or human subjects were conducted.

Effectiveness Data
Subject Device
No effectiveness information was submitted. Mr. Killeen stated that the product had been evaluated in clinical settings and that the information was being prepared for publication. He stated that he would provide the information in the near future – see review of deficiency 1 below.

Predicate Device(s)
Both products were cleared based upon human clinical experience.

Discussion of Equivalency
Additional biocompatibility and effectiveness information will be provided by the sponsor to demonstrate product equivalency – see review of deficiency 6 below.

5. **Sterilization**

The product is meant to be used on intact, unbroken skin, i.e., skin showing evidence of dermatitis or allergic response, and skin with 1st and 2nd degree burn injury. Dermatitis is defined as inflammation of the skin evidenced by itching, redness, and various skin lesions. Second degree burn is defined as burn in which damage extends through the epidermis and into the dermis but not of sufficient extent to interfere with regeneration of epidermis.

The Biafene wound dressing is provided non-sterile and was cleared for indications that included broken skin because the formulation contains preservatives and the device had passed the preservative test as specified in the USP Preservatives test. The Carrasyn wound dressing product is supplied sterile.

See deficiency #3 and sponsor's response below.

6. **Labeling**

(OTC and Prescription)
Carton/Pouch Labels (page 13 and 14)
The revised label contains a notice regarding the nut oil and identifies the purpose for vitamin E as antioxidant.

7. **Claims**

Relief of burning, itching and pain and the relief of dry, waxy skin. Information to support these claims is to be provided – see review of deficiency 1 and 2 below.

8. **Has sponsor provided all administrative requirements?**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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- Truthful and Accurate Statement (Page 22)
- 510(k) Summary or Statement (Page 21)
- Indication for Use Page (Page18)

9. Summary

The sponsor has evaluated their product in 2 clinical studies. A number of skin-based irritation sensitization preclinical studies have also been conducted. In these evaluations the product has either demonstrated a potentially positive clinical benefit or has not demonstrated dermal irritancy or sensitization. A number of the ingredients of the product have been cleared via predicate wound dressing applications in the past. Additional information provided indicates that the novel ingredients are non-toxic. Clinically, the various indications for use are treated in the same manner, regardless of etiology. The sponsor has, in my opinion, provided sufficient information in order to reach a determination of substantial equivalence.

Deficiencies

The following deficiencies were sent via letter to the sponsor (dated March 27, 2003). The sponsor's responses are provided and reviewed following each deficiency.

1. The indication for use statement includes treatments that are not identified in the predicate wound dressing indications for use provided, e.g., various types of dermatoses, including atopic dermatitis and allergic contact dermatitis. In addition, the indication for use statement describes a possible mechanism of action. Please revise the indications for use statement to be consistent with predicate wound dressings or provide information that supports the intended use on various types of dermatoses, atopic dermatitis and allergic contact dermatitis. In addition, please remove the mechanism of action statement.

The sponsor has replied that "in treating dermatoses such as atopic dermatitis, allergic contact dermatitis and radiation dermatitis, physicians are faced with conditions that manifest themselves with symptoms in common. Where possible the physician treats the underlying cause but symptom relief is a mainstay of management." The sponsor listed symptoms of various dermatoses, including radiation, atopic and allergic contact dermatoses: pruritus, erythema, inflammation, desquamation, edema, localized pain, scaling skin, cracked stratum corneum, oozing, and lichenification. I discussed the issue with Dr. Dora Vega. Specifically I asked Dr. Vega if she agreed with the sponsor's contention that the various dermatoses present with the same symptomology. Dr. Vega stated that the dermatoses identified do share the symptoms in common and therefore can be judged to be, without regard to etiology, similar. Inflammation is the major encompassing symptom to be treated. I asked her if she felt the indications for use were sufficiently equivalent to be listed in common. She stated that she did. The two predicate products both were cleared for the treatment of radiation-induced dermatitis and therefore form a basis, due to symptom commonalities, for the addition of atopic and allergic contact dermatoses to be also listed as treatable indications for use. In addition the sponsor has evaluated their product clinically for the treatment of atopic dermatitis and allergic contact dermatitis. Supportive information regarding the indications for use includes:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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- Double blind, randomized, vehicle controlled study of atopic dermatitis patients
- A currently open clinical trial enrolling allergic dermatitis pediatric patients

Caputo and Veraldi – atopic dermatitis patients
As part of the clinical protocol, pain relief and relief from itching was documented via CRFs. Thirty adult patients were followed in 5 office visits over a 36 day time period (15 patients per control or treatment group). Patients with mild to moderate atopic dermatitis were treated with either the subject device or an emollient vehicle only. Patients had experienced atopic dermatitis for a mean of 13 years (median 8 years) and their current episode had lasted between 3 and 6 months. The treatments were applied *ad hoc* for 3 weeks, with assessments at weekly visits and a final assessment after a 2 week period. The symptom improvement provided by the control or treatment product was rated by participating patients at each visit. The primary outcome measure was a modified EASI (Eczema Area and Severity Index) score. The secondary outcome was an assessment of the severity of the dermatitis by Rajke and Langeland's criteria. An improvement in the Modified EASI score, and the severity of the dermatitis was associated with treatment with the subject device. The assessment of pain reduction and outcomes were equivalent to predicate wound dressing evaluations. RCH 7/22/03

In addition, results indicated that 93% of the treated patients rated their treatment as "quite good" (53%) or "slightly helped" (40%), whereas 53% of the control patients rated their treatment as "quite good" (13%) or "slightly helped" (40%).

Open clinical trial enrolling contact dermatitis pediatric patients, Innocenti
In this open clinical study conducted by Innocenti et al, 25 pediatric patients with allergic contact dermatitis were enrolled. The cream was applied on the affected areas twice a day for two weeks after which the lesions were stated to be "greatly improved and some had disappeared". The investigator stated that no localized or systemic undesirable side effects were observed during or after the treatment.

I believe the clinical information and the sponsor's clinical rationale regarding commonalities of symptoms (and the treatment of those symptoms) adequately justifies the inclusion of atopic and contact allergic dermatoses as part of the product's indications for use. In addition, Dr. Vega concurs that the symptomologies of these dermatoses are common and are treated similarly. No additional information is necessary. The sponsor has adequately addressed the deficiency.

2. The indications for use state that the product will manage and relieve the burning, itching, and pain experienced with various types of dermatoses. Please provide information obtained from clinical evaluation of the product's ability to relieve pain associated with the indications for use for your device.

The sponsor refers to the double blind, IRB controlled atopic dermatitis study noted above as proof for the ability of the device to relieve pain and itching. No additional information is necessary. The sponsor has adequately addressed the deficiency.

3. The device is provided non-sterile. Radiation dermatitis may result in the skin barrier

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being breached and the labeling indicates that the device may be used on broken skin. Please conduct testing of the product in accordance with the Anti-Microbial Preservatives-Effectiveness <51> microbiological test identified in the USP.

The sponsor conducted preservative effectiveness testing in accordance with the British Pharmacopeia. In the test 4 micro-organisms are inoculated into the formulation and recovery of the organisms is attempted at time points after inoculation. The organisms evaluated were:

- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Aspergillus niger*
- *Candida albicans*

No organisms were recovered at 24 hours post-innoculation. The formulation met the requirements of the test. There is predicate evidence for legally marketed wound dressings, provided as non-sterile, intended for use on broken skin. The subject device has passed the requirements of the preservative effectiveness evaluation as set forth by the British Pharmacopeia which is similar to the USP antimicrobial preservative effectiveness test. The sponsor has adequately addressed the deficiency. No additional information is required.

4. Butyrospermum parkii is identified as Sheanut oil under 21 CFR 184.1702. FDA believes that individuals who have nut sensitivities could have an allergic response to the wound dressing. Please include a Warning on the product label informing people that the product contains nut oil or provide information to demonstrate that Sheanut oil does not elicit allergy responses.

The sponsor has agreed to amend their label to contain the following:

- Caution: Sinclair Wound and Skin Emulsion™ contains a nut oil, and patients with a known allergy to nuts or nut oils should consult their physician before using this topical application.

The sponsor has adequately addressed the deficiency. No additional information is required.

5. Please provide toxicity information for the following wound dressing ingredients: (b)(4) [redacted] (arachidyl glucoside, behenyl alcohol, arachidyl alcohol), bisabolol, piroctone olamine, vitis vinifera, and telmesteine. In lieu of toxicity information, identification of predicate wound dressings containing these ingredients could address our concerns.

(b)(4) [redacted] (arachidyl glucoside, behenyl alcohol, arachidyl alcohol): To address the potential toxicity associated with the (b)(4) [redacted] ingredient, the sponsor provided the test report, *Evaluation of the Irritating and Sensitizing Potentials of an Ingredient Used in Cosmetics, by Repeated Epicutaneous 48 Hour Applications Under Occlusive Patch*. The test article was

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tested at 3 concentrations after 4 successive applications up to 72 hours by the occlusive epicutaneous route to the skin of 10 human subjects. The study results indicated that the highest concentration tested (5%) did not elicit a primary or cumulative irritation reaction, nor any cutaneous sensitization reaction. A second study of the Montanov reagent in 21 female subjects supported the belief that the material is well-tolerated.

Bisabolol: LD_{50} rat (>5000 mg/Kg) – acute skin irritation, used extensively in the cosmetic industry

Piroctone olamine: The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers lists piroctone olamine as non-sensitizing, non-teratogenic, and the systemic toxicity has been measured in a 90 day oral test NOEL in rats: 100 mg/kg/day. Human evaluation of 1% and 0.5% concentrations indicated that the formulation was well tolerated.

Vitis vinifera: Grape seed extract. A primary skin irritation report indicated that leucocianidine was not an irritant.

Telmesteine: LD_{50} oral rat/mouse (>4000 mg/Kg).

6. The wound dressing formulation contains ingredients that were not identified in predicate wound dressings, or in the same ingredient combinations for predicate wound dressings. Please provide biocompatibility test evaluations for cytotoxicity, irritation and sensitization assessments or information from human clinical experience to address these concerns.

The sponsor notes that clinical evaluation of the product has not observed any device-related adverse events (adult atopic dermatitis patients and pediatric contact allergy dermatitis patients). In addition the sponsor has provided the results from the following tests:

- ISO Closed Patch Sensitization Study (guinea pig): non-sensitizer
- ISO Skin Irritation Study (rabbits): slight irritant
- Clinical report on patch and photo-patch tests (humans, N = 22): slight to mild irritant potential

The sponsor has adequately addressed the deficiency. No additional information is required.

6/30/03

Name Date

Plastic and Reconstructive Surgery Devices Branch

7/21

A number of wound dressings include relief of pain in their indications for use. The study to assess pain relief is typical for study that has been conducted historically - few patients + subjective assessment. S. Kroder

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SCREENING CHECKLIST
FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS

510(k) Number: K02 4367

The cover letter clearly identifies the type of 510(k) submission as (Check the appropriate box):

☐ Special 510(k) - Do Sections 1 and 2

☐ Abbreviated 510(k) - Do Sections 1, 3 and 4

☒ Traditional 510(k) or no identification provided - Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present or Adequate	Missing or Inadequate
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510)] Manual.	✓	
Table of Contents.	✓	
Truthful and Accurate Statement.	✓	
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	✓	
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).	✓	
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510)] Manual.	✓	
Statement of Indications for Use that is on a separate page in the premarket submission.	✓	
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510)] Manual.	✓	
510(k) Summary or 510(k) Statement.	✓	
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	✓	
Identification of legally marketed predicate device. *	✓	
Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).]	N.A.	
Class III Certification and Summary. **	N.A.	
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]	N.A.	
510(k) Kit Certification ***	N.A.	

* - May not be applicable for Special 510(k)s.
** - Required for Class III devices, only.
*** - See pages 3-12 and 3-13 in the Premarket Notification [510)] Manual and the Convenience Kits Interim Regulatory Guidance.

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Section 2: Required Elements for a SPECIAL 510(k) submission:

	Present	Inadequate or Missing
Name and 510(k) number of the submitter's own, unmodified predicate device.		
A description of the modified device and a comparison to the sponsor's predicate device.		
A statement that the intended use(s) and indications of the modified device, as described in its labeling are the same as the intended uses and indications for the submitter's unmodified predicate device.		
Reviewer's confirmation that the modification has not altered the fundamental scientific technology of the submitter's predicate device.		
A Design Control Activities Summary that includes the following elements (a-c):		
a. Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.		
b. Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.		
c. A Declaration of Conformity with design controls that includes the following statements:		
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.		
A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.		

Section 3: Required Elements for an ABBREVIATED 510(k)* submission:

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)		
For a submission, which relies on a recognized standard, a declaration of conformity [For a listing of the required elements of a declaration of conformity, SEE **Required Elements for a Declaration of Conformity to a Recognized Standard,** which		

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is posted with the 510(k) boilers on the H drive.] For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has not been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device and any additional information requested by the reviewer in order to determine substantial equivalence.		
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.		

* - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:		✓
b) Sterilization and expiration dating information:	N.A.	
i) sterilization process		
ii) validation method of sterilization process		
iii) SAL		
iv) packaging		
v) specify pyrogen free		
vi) ETO residues		
vii) radiation dose		
viii) Traditional Method or Non-Traditional Method		
c) Software Documentation:	N.A.	

Items with checks in the "Present or Adequate" column do not require e additional information from the sponsor. Items with checks in the " Missing or Inadequate" column must be submitted before substantive review of the document.

Passed Screening ___ Yes ✓ No

Reviewer: [signature]

Concurrence by Review Branch: [signature] for SPR

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Date:

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Internal Administrative Form

	YES	NO
1. Did the firm request expedited review?		✓
2. Did we grant expedited review?	N/A	
3. Have you verified that the Document is labeled Class III for GMP purposes?	N.A.	
4. If, not, has POS been notified?	N.A.	
5. Is the product a device?	✓	
6. Is the device exempt from 510(k) by regulation or policy?		✓
7. Is the device subject to review by CDRH?	✓	
8. Are you aware that this device has been the subject of a previous NSE decision?		✓
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?	N.A.	
10. Are you aware of the submitter being the subject of an integrity investigation?		✓
11. If, yes, consult the ODE Integrity Officer.	N.A.	
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.	N.A.	

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Attachment 3 - Indications for Use Statement

510(k) Number NA	
Device Name	**SINCLAIR WOUND AND SKIN EMULSION** ™
Indications for Use	FOR TOPICAL DERMATOLOGICAL USE ONLY **Description Rx Product:** Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process. **Directions For Use (Rx and OTC):** Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice. **Description OTC Product:** Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn.

PLEASE DO NOT WRITE BELOW THIS LINE- CONTINUE ON ANOTHER PAGE IF NEEDED

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-The Counter Use _____
(per 21 CFR 801.109)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Section E: Additional Information on 510(k) Submissions				
Product codes of devices to which substantial equivalence is claimed:				Summary of, or statement concerning, safety and effectiveness data:
1 MGQ	2	3	4	☑ 510(k) summary attached
5	6	7	8	☐ 510(k) statement

Information on devices to which substantial equivalence is claimed:

510(k) Number	Trade or proprietary or model name	Manufacturer
1. K964240	1. Biafene Wound Dressing Emulsion RE	1. Medix Pharmaceuticals Americas Inc.
2. K961758	2. Carrasyn® Wound Dressing	2. Carrington Laboratories Inc

Section F: Product Information Applicable to all Applications

Common or usual or classification name:
Dressing, wound & burn, hydrogel w/drug or biologic

Trade or proprietary or model name	Model Number
1 Sinclair Wound and Skin Emulsion	NA
2	

FDA document numbers of all prior related submissions (regardless of outcome): none

1	2	3	4	5	6
7	8	9	10	11	12

Data included in submission: ☐ Laboratory testing ☐ Animal trials ☐ Human trials

Section G: Product Classification - Applicable to all Applications

Product Code:	C.F.R. section	Device Class:
MGQ Dressing, wound & burn, hydrogel w/drug or biologic	878.4022	☐ Class I ☐ Class II ☐ Class III ☑ Unclassified

Classification panel: Hydrogel wound and burn dressing

Indications (Prescription product):

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Indications (OTC product):

Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn.

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VI. Labeling and Intended Use	A draft product container/ box label (which contains Instructions for Use) for the Rx product can be found in Attachment 1A and draft label for the product/ box for the OTC product can be found in Attachment 1B. Predicate device labeling and product information can be found in Attachment 2A (Biafene), Attachment 2B (Carrasyn®) and Attachment 2C (RadiaCare).
	Prescription labeling: Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process. **Sinclair Wound and Skin Emulsion** has similar indications when compared to the predicate Medix Pharmaceuticals Americas Inc. Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240 and Carrington Laboratories Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing. **Sinclair Wound and Skin Emulsion** is also intended for the Over-The-Counter (OTC) market with indications for less acute symptoms, which are not disease specific. OTC labeling: Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn. **The Indications for Use statement** is included in Attachment 3.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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VII. Device Description and Comparison	**Sinclair Wound and Skin Emulsion** is a viscous emulsion / gel formulation, which is presented for both Prescription (requires physician diagnosis of disease state) and over-the-counter (OTC) use. The prescription product requires a physician diagnosis to recognize the disease state, while the OTC product is indicated for general symptoms such as burning and itching in minor skin irritations and minor burns. This formulation, when applied to the burn, injured tissue or skin, forms a protective barrier that helps to keep the wound moist. As with the predicate devices (Biafene Wound Dressing Emulsion (Radiodermatitis Emulsion) in 510(k) K964240 and Carrasyn® Hydrogel Wound Dressing 510(k) K961758, which is also marketed under the name RadiaCare Gel Hydrogel Wound Dressing, **Sinclair Wound and Skin Emulsion** has a mechanical function as a barrier and is indicated for symptom management by adhering to the injured tissue and skin margins, soothing tissue insult of various etiologies. **Sinclair Wound and Skin Emulsion** viscous emulsion/gel, is comprised of Purified Water, Ethylhexyl palmitate, Pentylene glycol, Butyrospermum parkii, Capryloyl glycine, Glyceryl stearate, Peg-100 stearate, Arachidyl glucoside, Behenyl alcohol, Arachidyl alcohol, Bisabolol, Tocopheryl acetate (anti-oxidant), Glycyrrhetinic acid, Carbomer, Ethylhexylglycerin, Piroctone olamina, Sodium hydroxide, Allantoin, Dmdm hydantoin, Vitis vinifera, Disodium EDTA, Ascorbyl tetraisopalmitate, Sodium hyaluronate, Propyl gallate, Telmesteine and Butylene glycol. A formulations comparison chart may be found as Attachment 4.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 1A

Sinclair Wound and Skin Emulsion ™ - Draft Product Container / Box Labeling

Front Label Rx - Draft

Sinclair
Wound and Skin Emulsion

Topical Dermatological Relief

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Rx

Federal law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice.

Back Label Rx - Draft

Sinclair
Wound and Skin Emulsion

Topical Dermatological Relief

For external use only.

Sinclair Wound and Skin Emulsion viscous emulsion/gel, is comprised of Purified Water, Ethylhexyl palmitate, Pentylene glycol, Butyrospermum parkii, Capryloyl glycine, Glyceryl stearate, Peg-100 stearate, Arachidyl glucoside, Behenyl alcohol, Arachidyl alcohol, Bisabolol, Tocopheryl acetate (anti-oxidant), Glycyrrhetinic acid, Carbomer, Ethylhexylglycerin, Piroctone olamina, Sodium hydroxide, Allantoin, Dmdm hydantoin, Vitis vinifera, Disodium EDTA, Ascorbyl tetraisopalmitate, Sodium hyaluronate, Propyl gallate, Telmesteine and Butylene glycol.

Caution: Sinclair Wound and Skin Emulsion™ contains a nut oil, and patients with a known allergy to nuts or nut oils should consult their physician before using this topical preparation.

Sinclair Pharmaceuticals Limited
Godalming
Surrey UK, GU7 2AB
Tel: +44 1483 428 611

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Attachment 1B
Sinclair Wound and Skin Emulsion ™ - Draft Product Container / Box Labeling

Front Label OTC - Draft	Back Label OTC - Draft
Sinclair ***Wound and Skin Emulsion*** Sinclair Wound and Skin Emulsion helps to nourish skin and relieve the burning and itching associated with many common types of skin irritation. Sinclair Wound and Skin Emulsion may also be used to soothe minor burns, including sunburn. Apply **Sinclair Wound and Skin Emulsion** to the affected skin areas 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover **Sinclair Wound and Skin Emulsion** with a dressing of choice.	**Sinclair** ***Wound and Skin Emulsion*** For external use only. **Sinclair Wound and Skin Emulsion** viscous emulsion/gel, is comprised of Purified Water, Ethylhexyl palmitate, Pentylene glycol, Butyrospermum parkii, Capryloyl glycine, Glyceryl stearate, Peg-100 stearate, Arachidyl glucoside, Behenyl alcohol, Arachidyl alcohol, Bisabolol, Tocopheryl acetate (anti-oxidant), Glycyrrhetinic acid, Carbomer, Ethylhexylglycerin, Piroctone olamina, Sodium hydroxide, Allantoin, Dmdm hydantoin, Vitis vinifera, Disodium EDTA, Ascorbyl tetraisopalmitate, Sodium hyaluronate, Propyl gallate, Telmesteine and Butylene glycol. Caution: Sinclair Wound and Skin Emulsion™ contains a nut oil, and patients with a known allergy to nuts or nut oils should consult their physician before using this topical preparation. Sinclair Pharmaceuticals Limited Godalming Surrey UK, GU7 2AB Tel: +44 1483 428 611

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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SINCLAIR

June 6, 2003

Peter Hudson, Ph.D.
Office of Device Evaluation
Center for Devices and
Radiological Health
Office 300-J
9200 Corporate Dr
Rockville, MD 20850

Re: K024367
Trade Name: Sinclair Wound and Skin Emulsion™

Dear Dr. Hudson:
In regard to our e-mails and telephone conversations, I am enclosing 2 copies of the following documents:

- A draft copy of the randomized, double blind clinical trial conducted by Drs. Ruggero Caputo and Stefano Veraldi on patients with atopic dermatitis
- An abstract from the Innocenti open study conducted on patients with irritant contact dermatitis. Please note that a clinical trial specific to Irritant Contact Dermatitis has been scheduled with Dr. Howard Maibach but the start date has been delayed while the IRB works through the recently enacted HIPAA requirements.
- Study data on (b)(4) [redacted] as reported in Section B of our response to Dr. Witten in the April 25th letter. The documents that you requested are cited as, Experts Report 70168RD and Experts Report 704 65RD.

Please contact me at your need with any additional questions that may arise.

Sincerely,

Michael Killeen
Executive Director

Sinclair Pharmaceuticals Limited Borough Road, Godalming, Surrey, UK, GU7 2AB
US Office, Carrollton, TX +1-972-939-2442 www.sinclairpharma.com mkilleen@sinclairpharma.com
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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TITLE:
A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of Sinclair Wound and Skin Emulsion™ in the symptom management of mild to moderate atopic dermatitis

AUTHORS:
Dr. Ruggero Caputo
Dr. Stefano Veraldi

ADDRESS:
Istituto Dermatologico Europeo
University of Milan, Italy
Via della Pace 9
20122, Milano

COMMENTS:
This clinical study was compiled using Sinclair Wound and Skin Emulsion™ product as submitted in 510(k) # K024367. *Atopiclair*™ is the working name for Sinclair Wound and Skin Emulsion™ in this study.

This is a working draft has not been accepted for publication. Changes in formatting and textual presentation may be made at the time of publication.

This document should be regarded as Confidential information.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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SUMMARY

BACKGROUND Atopic dermatitis (AD) is a chronic skin disorder characterised by, pruritis, erythema, inflammation, dryness/xerosis and infectious colonisation of the lesions all of which seriously detract from the patient's quality of life. AD typically presents during early childhood and may continue, or even begin, in adulthood. Patients seek relief from the pain and itching of AD and for healing of the underlying lesions. *Atopiclair* is a hydrolipidic wound dressing, which has been developed for the relief and management of itching, pain and burning experienced with atopic dermatitis and allergic contact dermatitis. *Atopiclair* acts by adhering to the injured tissue, protecting it from further irritation and helping to relieve symptoms, and also by maintaining a moist wound and skin environment, which is beneficial to the healing process.

OBJECTIVES The present study set out to examine the effectiveness of *Atopiclair* in the management of the various clinical signs and symptoms of AD.

RESULTS A 5-week study in patients with mild to moderate atopic dermatitis showed that *Atopiclair* offered significant benefits over control (emollient vehicle only), when applied *ad hoc* for 3 weeks, with assessments at weekly visits and a final assessment after a 2 week follow-up period. *Atopiclair* improved the clinical signs of atopic dermatitis (affected area and EASI score) compared to control. The symptom improvement given by *Atopiclair* (view of itch and view of *Atopiclair*) was also rated by participating patients as statistically significantly better than control.

CONCLUSIONS Based on the results of this study, *Atopiclair* offers a safe and effective alternative for the relief and management of itching, pain and burning experienced with atopic dermatitis and allergic contact dermatitis.

KEYWORDS: atopic dermatitis, eczema, chronic skin disease, emollient, wound dressing, skin healing

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Introduction

Atopic dermatitis (AD) is a recurring, pruritic and inflammatory disease of the skin, which significantly reduces patients' quality of life. (Hanifin Ling et al 2001). Typical clinical presentations of AD include various types of lesions (erythema, oedema and vesicles) in the acute/subacute phase, and crusts, scaling, dryness/xerosis and lichenification in the chronic phase. Rashes on the skin are often very itchy and can be widespread or limited to a few areas (Wellington & Jarvis). The disease is caused or influenced by a number of factors including exposure to environmental factors, genetic susceptibility, and immunologic abnormalities (Eichenfield Lucky 2002). Indeed, AD is often the first clinical manifestation of allergic disease and often precedes allergic respiratory disease. These three diseases comprise an 'atopic triad' with several common features, including alterations in immune cell response and inflammatory regulators (Leung et al).

AD generally manifests during early childhood when it is known as infantile eczema. The worldwide incidence in children has been estimated at 10-15% (Wellington & Jarvis) and 7-21% (Eichenfield Lucky 2002). It is estimated that about 80% of children with AD will also go on to develop asthma or allergic rhinitis. (Eichenfield et al 2003) AD has a particularly negative effect on the lives of children, and also on the families of children with the disease. Childhood AD disrupts the formation and maintenance of important interpersonal relationships, resulting in the limited interactions of the child with others and often reduced academic achievement and social development. Families of children with AD suffer the stress of providing care for a child with a chronic disease; the associated problems of cost, hospital visits, sleep interruption, for example, are considerable. (Wellington Jarvis)

The most obvious signs and symptoms of AD often improve by early adulthood, yet the disease does persist in adults, with similar pathopsychological consequences, and often in a form which is more difficult to diagnose. (Wellington Jarvis) AD can cause frustration to both the patient and the physician.

Guidelines for the management of atopic dermatitis have been developed in the US (Leung et al) and the UK (BJD). A wide-ranging approach is generally recommended that includes skin hydration, emollients, topical corticosteroids, and the removal or treatment of exacerbating factors, e.g. allergens, irritants, emotional stressors and infectious agents (Leung et al). Therapy of mild to moderate AD typically starts with liberal use of emollients, which should be continued even if the disease improves or another treatment is being used (Wellington Lucky). Topical corticosteroids provide a broad immunosuppressive and anti-inflammatory effect (Eichenfield Lucky 2002) and, in combination with emollients are the mainstay of therapy. (Leung et al). However, prolonged corticosteroid therapy is to be avoided because of side effects (skin atrophy, hypopigmentation, secondary infection and acne (Paller Eichenfield 2001). Corticosteroids should be used with caution in children, because of potential suppression of the hypothalamic-adrenal axis and body growth (Eichenfield Lucky 2002).

Other treatments include oral antihistamines, which have anxiolytic effects and may relieve pruritis and itch in some patients (Wellington Jarvis). Skin infections (especially S. *aureus*) should be treated early with short doses of staphylococcal antibiotics (Leung et al). Recommended therapy in more severe cases includes

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systemic antihistamines, corticosteroids, immunomodulating drugs (e.g. cycloporin) or phototherapy (UVA, UVB and PUVA) (Kang Lucky). The newer immunumodulators, tacrolimus (Eichenfield) (Hanifin Ling) and pimecrolimus (Kang Lucky), may be applied topically to reduce local inflammation. In practice, patients tend to try many treatments before finding one suitable for their needs.

Atopiclair is a hydrolipidic wound dressing developed for the relief and management of itching, pain and burning experienced with atopic dermatitis and allergic contact dermatitis. *Atopiclair* acts by adhering to the injured tissue etc, helping to keep dry skin moist.

A barrier and moisturising cream such as that formed by *Atopiclair* could potentially assist in the management of the symptoms of AD. The barrier could also potentially improve symptoms by relieving the intense desire to itch or scratch.

The study set out to examine the effectiveness of *Atopiclair* in the management of the various clinical signs and symptoms of AD.

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Methods and Materials

Participants

Participants were considered eligible for the study if they met the following inclusion criteria: caucasian skin without recent suntan, >18 years, diagnosed with mild to moderate dermatitis (Hanifin & Rajka) and with atopic dermatitis graded between 3.0 and 7.5 (Rajka & Langeland), and with <20% cutaneous surface involvement. Patients were required to give written informed consent. Female sexually active patients were required to test negative in a pregnancy test and agree to use active birth control for the duration of the study and for two weeks afterwards.

Patients receiving systemic medications (antihistamines, corticosteroids, NSAIDs, or other topical and systemic investigational drugs) were maintained on the medications at a constant dose throughout the study. Patients receiving topical medications (antihistamines, corticosteroids, NSAIDs) were taken off the medications in a wash-out period of 7 days before the start of the study period. The wash-out periods for patients on phototherapy (UVA, UVB, PUVA) or tranquilisers were 4 weeks and 5 days respectively.

The following patients were excluded from the study: patients with a cutaneous or systemic viral (including HIV or AIDS), mycotic or bacterial disease requiring a topical or systemic therapy, patients with a systemic disease (including a neoplastic disease or history of a neoplastic disease), patients with insulin-dependent diabtetes mellitus uncontrolled by diet, pregnant or breast-feeding patients, patients with another skin condition other than atopic dermatitis, patients with a history of allergy to the ingredients of *Atopiclair*, patients previously treated with *Atopiclair* or had participated in previous Sinclair-sponsored studies, patients with a history of substance or alcohol abuse or any other psychological condition that may have adversely affected their cooperation with the study, patients with friends or relatives working at the study centre.

Patients attended a dermatology clinic for the purposes of the study and data were collected at this location. 30 patients whose AD had been classified as mild to moderate dermatitis according to Hanifin and Rajka's criteria, and with a score of 3.0-7.5 according to Rajka and Langeland's criteria, were recruited to the study. The sample size was considered large enough to gain an initial impression of the difference between the control and intervention groups. The study was supported by a grant from Sinclair Pharmaceuticals, Borough Road, Godalming, Surrey, GU7 2AB, UK, manufacturers of *Atopiclair*.

Interventions

Patients were examined at visit 1 (baseline) and a demographics questionnaire (age gender, ethnicity, history of exposure to irritants or other actors that may contribute to atopic dermatitis) was completed. Patients were then randomised by the investigating team to receive *Atopiclair* or control according to their order of entry into the study. *Atopiclair* and control were presented in identical, blindly labelled containers. Each container was labelled with the patient's study number. The tubes containing *Atopiclair* or control were labelled blindly with directions for use, i.e. for the contents of the tube to be used on either the left or right hand side of the body. The control

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ointment tube contained an emollient cream that was used as the vehicle for *Atopiclair*. Patients, observers and all trial personnel were blinded to the study code.

Patients applied the study substance for the first time following visit 1, and three times each day thereafter for 21 days. Patients were examined again at 8 days (visit 2), 15 days (visit 3) and 22 days (visit 4) after visit 1. Response to therapy was recorded at each visit. At visit 4 patients stopped using the cream and they were then re-examined two weeks later at visit 5.

Objective

The objective of the study was to assess the effect of *Atopiclair* on the signs and symptoms of AD.

Outcomes

The primary outcome measure was a modified EASI (Eczema Area and Severity Index) score. The Modified EASI Score (for patients ≥7 years old at baseline) equalled (EASI Score + Itch score) multiplied by (Affected area score head/neck x 0.1) plus (Affected area score Upper limbs x 0.2) plus (Affected area score Trunk x 0.3) plus (Affected area score Lower Limbs x 0.4).

Several secondary outcomes (clinical signs and symptoms) were measured. The clinical signs were: severity of atopic dermatitis (graded according to the criteria set out by Rajka & Langeland, percentage of body area affected, and the EASI score (Hanifin Thurston et al 2001). The clinical symptoms were: the patient's view of itch (Itch score measured on a visual analogue scale), quality of life (hours of sleep), the patient's view on how much the cream helped the pain and itch, and whether the patient would choose to use the cream again.

Adverse events observed by the clinicians or reported by patients were assessed by the study investigators. No laboratory or instrumental tests were performed.

Statistical methods

Efficacy measures in the treatment groups were compared using the Wilcoxon rank sum test on changes from baseline (visit 1) for visits 2 to 4, and from visit 4 (when treatment was stopped) for visit 5 (follow up visit two weeks later). Patients' views of treatments in the two groups were compared using the Cochran-Armitage test for trend in a 2 x k contingency table with ordered categories.

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Results

Participant flow

Thirty patients were randomised between the two study groups from an initial assessment group of 39. (**Figure 1**).

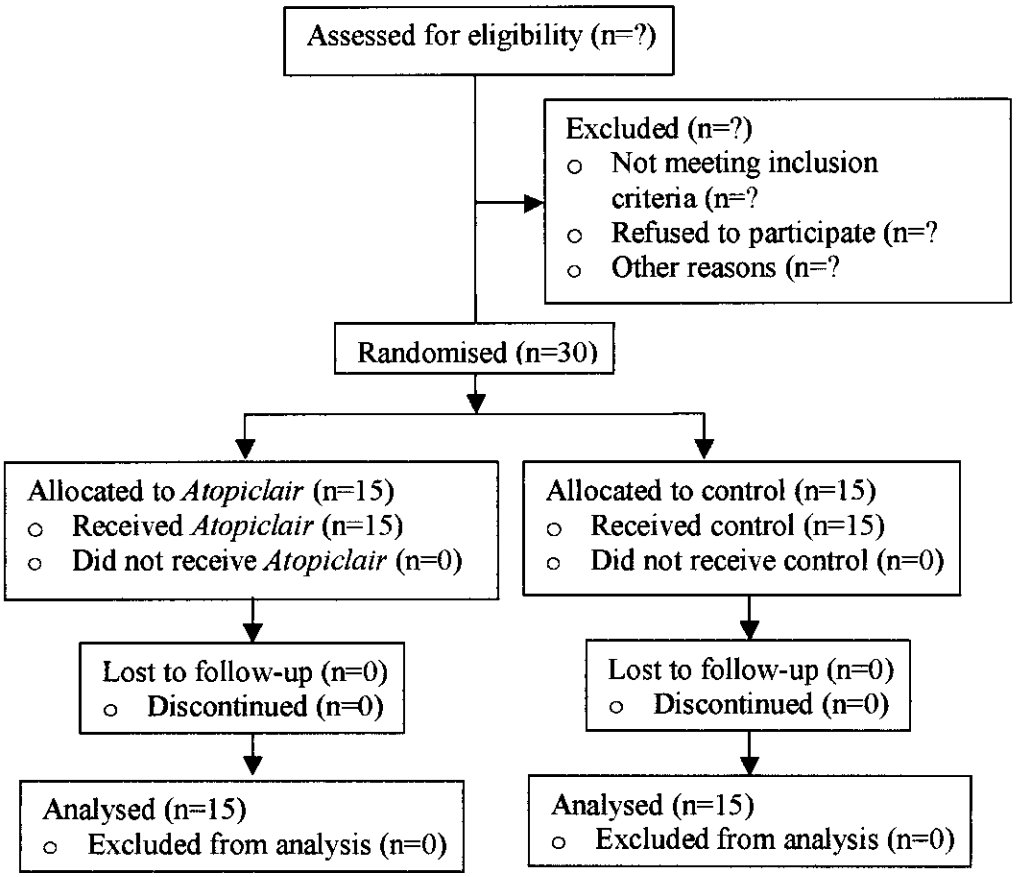

Figure 1 Flow of participants through each stage of the study

Recruitment
The enrolment period was from November 11-18, 2002. The last patient completed the study on February 21st, 2003.

Baseline data
16 men and 14 women were recruited into the study (**Table 1**), and all patients completed the study. Overall median age was 24 and mean age was 27. Patients had experienced atopic dermatitis for mean 13 years (median 8 years) and their current episode had lasted between 3 and 6 months in all patients. The two groups were comparable in terms of age, sex, duration of condition, duration of current episode and initial severity.

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TABLE 1 Baseline data: Patient Characteristics on Entry to the Study

		Group			
		Control		*Atopiclair*	
		N	%	N	%
Number of patients		15	(100%)	15	(100%)
Gender					
F		5	(33%)	9	(60%)
M		10	(67%)	6	(40%)
Skin colour					
Caucasian		15	(100%)	15	(100%)
Rajka & Langeland criteria					
Score 3		10	(67%)	8	(53%)
Score 4		2	(13%)	4	(27%)
Score 5		1	(7%)	1	(7%)
Score 6		1	(7%)	1	(7%)
Score 7		1	(7%)	1	(7%)
Location patch					
Not recorded		10	(67%)	10	(67%)
Face		1	(7%)	2	(13%)
Face, hands		-	-	1	(7%)
Hands		1	(7%)	1	(7%)
Lower limbs		3	(20%)	1	(7%)
Age (years)	Median		24		21
	Range		18-83		13-43
How many years has patient had AD	Median		8		11
	Range		2-35		3-38
Duration of current episode (days)	Median		120		150
	Range		90-180		90-180

Numbers analysed

The clinical outcomes of both patient groups (*Atopiclair* n=15, control n-=15) were analysed on an intention-to-treat basis. Further ancillary analysis was not performed.

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Outcomes

A general trend of improvement in all clinical outcomes, except for sleep, was noted from baseline through visits 2, 3 and 4. The results in terms of improvement between visits 1 and 4 are shown in **Table 2**. Statistically significant differences were observed from visit 3 (affected area, patient's view of itch) or visit 4 (EASI). The improvement in the primary outcome (modified EASI) with *Atopiclair* was almost twice the improvement recorded with the control cream, but the difference was not statistically significant.

Table 2: Improvement in clinical outcomes between visit 1 and visit 4 (22 days)

Outcome	**Improvement *Atopiclair* group (mean ± SD, n=15)**	**Improvement control group (mean ± SD, n=15)**	**P (Wilcoxon Rank Sum Test)**
Primary outcome			
Modified EASI	4.5 ± 4.9	2.3 ± 3.1	p=0.16
Secondary outcomes			
Grading of severity of atopic dermatitis (by Rajke and Langeland's criteria)	0.5 ± 0.7	0.2 ± 0.6	p=0.08
Affected area	4.0 ± 3.0	0.5 ± 1.5	p<0.001
EASI	4.0 ± 3.9	0.7 ± 2.6	p=0.003
Patient view of itch	1.3 ± 0.5	0.5 ± 0.6	p=0.001
Quality of sleep	0.0 ± 0.0	-0.1 ± 0.4	p=0.15

Efficacy: patient opinion
Five of fifteen (33%) patients stated that they would use *Atopiclair* again, compared to 1/15 (7%) patients who were using the vehicle cream. Conversely, 1/15 (7%) stated that they would not use *Atopiclair* again compared to 5/15 (33%) patients using the vehicle cream. Nine of fifteen (60%) patients in each group stated that they 'may use the cream again'. The greater patient acceptability of *Atopiclair* was statistically significant compared to control (p=0.042 by the Cochran-Armitage test).

Patients were also asked for their view of how good they thought the cream was at relieving the pain and itch of their atopic dermatitis. In the *Atopiclair* group, 8/15 (53%) patients stated "quite good", 6/15 (40%) patients stated "slightly helped" and 1/15 (7%) patients stated "did not help". The comparative scores for the same parameters in the control group were 2/15 (13%), 6/15 (40%) and 7/15 (47%). Patients' preference for the effects of *Atopiclair* on pain and itch was statistically significant compared to the control group (p=0.008 by the Cochran-Armitage test).

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Follow-up visits
A decline in the improvement of all clinical outcomes (except sleep which did not improve) was recorded between visit 4 (end of treatment) and visit 5 (follow-up, two weeks later). This effect was greater in the *Atopiclair* group than in the control group, and this difference reached significance in the affected area, EASI and 'patient's view of Itch' measurements (**Table 3**).

Table 3: Decline in clinical improvement during follow up (between visit 4 and visit 5 (14 days)

Outcome	**Improvement *Atopiclair* group (mean ± SD, n=15)**	**Improvement control group (mean ± SD, n=15)**	**P (Wilcoxon Rank Sum Test)**
Primary outcome			
Modified EASI	-2.0 ± 4.0	-0.7 ± 1.8	p=0.14
Secondary outcomes			
Grading of severity of atopic dermatitis (by Rajke and Langeland's criteria)	-0.3 ± 0.7	-0.1 ± 0.3	p=0.19
Affected area	-2.3 ± 2.9	-0.3 ± 1.3	p<0.009
EASI	-1.5 ± 3.0	-0.7 ± 1.8	p=0.024
Patient view of itch	-1.1 ± 0.4	-0.3 ± 0.5	p=0.001
Quality of sleep	0.0 ± 1.1	0.1 ± 0.4	p=0.15

Adverse events
No observed or reported adverse events were recorded in either patient group.

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Discussion

Atopiclair demonstrated significant clinical benefits over the control group, in both the clinical signs and clinical symptoms. Improvements were recorded in affected area, EASI and the patient's view of itch. The control group itself, as an emollient, would normally be expected to show some beneficial effect, and therefore *Atopiclair* demonstrated improvement over a standard treatment. The benefit became apparent progressively between 15 and 22 days of using the study substance. This statistical difference in the outcome measurements was reflected by the patient's desire to use *Atopiclair* in the future.

The greater decline in improvement after treatment in the *Atopiclair* group reflects the fact that improvements between visit 1 and visit 4 had been greater in the *Atopiclair* group. It is worth noting that the deterioration in clinical outcomes did not exceed the improvements seen between visits 1 and 4.

The primary endpoint, the modified EASI score, was improved almost two-fold in the *Atopiclair* group but the difference against the vehicle cream did not reach statistical significance. The modified EASI score is the sum of two secondary outcome variables, the EASI score and the Itch score, both of which were improved by a statistically significant degree. The objective of the study was to determine if there was any symptom relief provided by *Atopiclair*, and in this regard the study was a success.

It is hypothesised that *Atopiclair* forms a protective layer over the lining of the skin. The lack of observed or reported adverse events in either group indicates that *Atopiclair* and the emollient alone are well-tolerated. Protection of the skin from additional irritation helps to relieve symptoms, and maintains a moist wound and skin environment which has been shown by previous researchers to be beneficial to the healing process.

Patients' actual use of the study creams may be a source of imprecision in the study. The quantity and frequency of application of emollients required to achieve maximal effect is often underestimated (BJD). The BHD guidelines recommend that emollients be applied every 4 hours or at least 3-4 times per day (BJD). The recommended prescription for use in generalised eczema in an adult is 600g per week. Furthermore, emollients are ideally applied when the skin is moist and therefore hydrated. One standard regime comprises bathing the skin in lukewarm water for at least 20 minutes to hydrate the skin, followed by application of the emollient within 3 minutes of ceasing bathing to maintain hydration. (Wellington Jarvis).

In this preliminary study, patients were only instructed to apply the study creams as often as possible. Their views of the study substance were recorded, but their compliance with the use of the creams, and how and when the creams were applied, were not.

There are many corticosteroid creams on the market available to sooth the itch and reduce the inflammation associated with atopic dermatitis. Indeed, effective care of the skin can control the disease in many patients (Wellington Jarvis). Based on the results of this study, *Atopiclair* can provide an effective option to the conventional therapy for managing the clinical signs and symptoms of mild to moderate atopic dermatitis.

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ACKNOWLEDGEMENTS

The authors thank David Thompson for performing the statistical analysis and Mark Carew for preparing the manuscript for publication.

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Abstracts

EFFICACY OF A NON-STEROIDAL CREAM, ATOPICLAIR, IN PATIENTS AFFECTED WITH CONTACT DERMATITIS

Atopiclair is a co-adjuvant therapeutic option in several inflammatory skin diseases (atopic dermatitis, nappy rash, post-peeling rash, sunburn, etc.).
We applied Atopiclair on patients affected with contact dermatitis (CD) in order to ascertain the efficacy of the cream on this skin disease.
The cream was applied on the affected areas twice a day for two weeks after which the lesions had greatly improved and some had disappeared.
No localised or systemic undesirable side effects were observed during or after the treatment.
Atopiclair contains dipotassium glycyrrizinate and vitis vinifera in acqueos phase and ascorbyl tetraisopalmitate in lipid phase which have a powerful anti-radical, anti-oxidant and soothing action.

Dr. Marcello Innocenti – *University of Milan*

OPEN CLINICAL TRIAL USING A NON-STEROIDAL CREAM, ATOPICLAIR, IN PATIENTS AFFECTED WITH ATOPIC DERMATITIS

Atopic dermatitis (AD) is a very common inflammatory disease affecting mainly children.
It is a chronic dermatitis with acute phases at irregular intervals.
The role of both humoural and cellular immunity system is important.
We observed that Atopiclair is an excellent therapeutic co-adjuvant in mild to moderate AD during exacerbated phases both on its own and together with steroids so as reduce the quantity of steroids employed.
We treated ten patients affected with AD.
The cream was applied on the affected areas twice a day; we noted the rapid on-set of action on itching and the other signs of inflammation (erythema and vesicles) and the substantial improvement of the patches within about 30 days of treatment.
The safety and ease of handling of Atopiclair make this product a valid alternative therapeutic option.

Dr. Marcello Innocenti – *University of Milan*

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SPONSOR : (b)(4) [redacted]

TEST ARTICLE :
(b)(4) [redacted]

TOLERANCE STUDY

SUMMARY

CLINICAL STUDY FOR THE APPRECIATION OF THE CUTANEOUS LOCAL TOLERANCE, WITH EVALUATION OF COMEDOGENICITY OF A TEST ARTICLE, APPLIED UNDER NORMAL CONDITIONS OF USE, TWICE A DAY FOR 4 WEEKS, IN 21 FEMALE VOLUNTEERS, HEALTHY ADULTS, HAVING AN OILY OR A MIXED WITH AN OILY TENDENCY SKIN FACE, WITH AN ACNEIC TENDENCY : "IN-USE TEST"

VOLUNTEERS

29 female volunteers were recruited and selected after a general medical examination taking into account the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the study protocol : 22 came to I.E.C. on the day of start of treatment.

All the panelists were then finally included by the Investigator on the basis of a clinical examination specific to the study, performed just before its start, after signature more particularly of the compensation modes form and of the informed consent statement. One of them have abandonned during the study (not linked to the test article applications).

Analysis of the results was thus made from a selection of 21 female volunteers, healthy adults, from 20 to 44 years old.

Among these 21 panelists, all had an acneic tendency skin face, 9 an oily skin and 12 a mixed with an oily tendency skin. 8 of them (38%) had a "sensitive" skin face.

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PROTOCOL

The test article was applied daily, twice a day (in the morning and in the evening) for 4 consecutive weeks, to the skin of the face and of the neck, in 21 female volunteers, healthy adults, having an oily or a mixed with an oily tendency skin face, with an acneic tendency. These applications were performed by the volunteer himself, at home and under the normal conditions of use of a skin face care cosmetic.

The local tolerance was appreciated, after the 4 week applications period, from cutaneous clinical examinations allowing observation of the functionnal and physical signs linked to use of the test article.

Comedogenicity was evaluated by a statistical comparison (non parametrical Wilcoxon test with two linked samples - "two-tailed", significativity : $p < 0.05$ -) of the number of retentional and inflammatory elements obtained at the start and at the end of the study.

The values obtained allowed interpretation of the results according to the type of the test article and to the effects searched by the Study Monitor.

RESULTS AND CONCLUSION

Analysis of the results obtained revealed on the whole :

- **As regards irritation or discomfort**, a very good tolerance of the test article in 19 out of the 21 panelists who participated in the whole study.
The 2 other volunteers, with a « sensitive » skin face, showed discomfort reactions, revealed by a sensation of cutaneous dryness, of weak to moderate intensity, on the cheeks, for about 5 to 15 minutes after each application, as well as moderate tugging, for one of them having antecedents of reactions linked to a cosmetic.
These liminal and isolated phenomenon are without any particular significance.

- **As regards comedogenicity**, the significant absence of comedogenicity. No significant statistically increase of the number of retentional and inflammatory elements evaluated to the face skin, was noted between the beginning and the end of the study.

As a conclusion, the applications of the test article (b)(4) [redacted] formulated at (b) (ref. (b)(4) [redacted] performed twice a day for 4 consecutive weeks, under the normal conditions of use to the skin of the face and of the neck, in 21 female volunteers, healthy adults, having an oily or a mixed with an oily tendency skin face, with an acneic tendency, proved, on the whole, to be WELL TOLERATED and NON COMEDOGENIC.

The allegations of type « tolerance tested under dermatological control » and « non comedogenic » can thus be justified.

Lyon,
25 November 1997

J.P. GUILLOT
Senior Pharmacologist - Toxicologist
I.E.C. Manager

Dr. G. RIGOT-MULLER, M.D.
Post graduate in Dermatology
Investigator
Study Director

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QUALITY CONTROL

This study was conducted in conformity with the standard operating procedures of the Clinical Research Center, the general procedures of I.E.C., the signed protocol and the general principles of the Good Clinical Practices published by I.C.H. (Guideline of 1st March 1996).

The control of the clinical studies which are not included in the application field of the Law Huriet is carried out periodically. It is designed to ensure that all critical phases (test article applications and examinations or measurements) of a particular study type are controled, at least once per month, for the studies performed during this time period. Dates of these controls and study type concerned are given below.

The results of these controls were reported to the Investigator and to the General Management.

Types of study	Dates of controls	Dates of reports to the Investigator	Dates of reports to the General Management
. Identical study :	30 September 1997	2nd October 1997	10 October 1997
. Miscellaneous :	TUOR :		
	23 September 1997	24 September 1997	3rd October 1997
	PEU :		
	7 October 1997	10 October 1997	17 October 1997
	EPS :		
	8 October 1997	9 October 1997	16 October 1997
	ARPC :		
	28 October 1997	29 October 1997	7 November 1997

This report has been controled by I.E.C. Quality Control Unit and is an accurate account of the procedures followed, and accurately records the original raw laboratory data generated in this study.

	Dates of control	Dates of reports to the Investigator	Dates of reports to the General Management
Report (vs. raw data) :	25 November 1997	25 November 1997	25 November 1997

Signature :

N Guillot

Nicole GUILLOT
Head of Quality Control Unit

Date : 25 November 1997

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INSTITUT D'EXPERTISE CLINIQUE

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PROMOTEUR : (b)(4) [redacted]

PRODUIT ETUDIE :
(b)(4) [redacted]

ETUDE DE TOLERANCE

RESUME

APPRECIATION DE LA TOLERANCE LOCALE CUTANEE,
AVEC EVALUATION DE LA COMEDOGENESE D'UN PRODUIT,
APPLIQUE DANS DES CONDITIONS NORMALES D'UTILISATION,
2 FOIS PAR JOUR PENDANT 4 SEMAINES,
CHEZ 21 VOLONTAIRES DE SEXE FEMININ,
ADULTES SAINS, A LA PEAU DU VISAGE GRASSE OU MIXTE A
TENDANCE GRASSE, ET A TENDANCE ACNEIQUE :
"TEST D'USAGE"

VOLONTAIRES

29 volontaires, de sexe féminin, ont été recrutés et sélectionnés après un examen médical général tenant compte des critères d'inclusion et de non inclusion, ainsi que des concepts d'interdiction et de restriction définis dans le protocole de l'étude : 22 se sont présentés à l'I.E.C. le jour du début de l'essai.

Tous les panélistes ont ensuite été définitivement admis par le médecin Investigateur sur la base d'un examen clinique spécifique à l'étude, réalisé juste avant le début de l'essai, après avoir signé notamment la fiche de modalités d'indemnité et le formulaire de consentement libre, éclairé et exprès. L'un d'entre eux a abandonné au cours de l'essai (abandon non lié à l'application du produit).

L'analyse des résultats a donc porté sur un panel de 21 volontaires de sexe féminin, adultes sains, âgés de 20 à 44 ans.

Parmi ces 21 volontaires, tous avaient une peau du visage à tendance acnéique, 9 avaient une peau de nature grasse et 12 une peau mixte à tendance grasse. 8 d'entre eux (38%) présentaient une peau du visage "sensible".

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PROTOCOLE

Le produit étudié a été appliqué quotidiennement, deux fois par jour (le matin et le soir), pendant 4 semaines consécutives, sur la peau du visage et du cou, par 21 volontaires, de sexe féminin, adultes sains, à la peau du visage de nature grasse ou mixte à tendance grasse, et à tendance acnéïque. Ces applications ont été effectuées, par le volontaire lui-même, à son domicile et dans les conditions normales d'utilisation d'un produit cosmétique pour le soin du visage.

La tolérance locale a été appréciée, après les 4 semaines d'applications, à partir d'examens cliniques cutanés permettant d'observer les signes fonctionnels et physiques liés à l'utilisation du produit.

La comédogénèse a été évaluée par comparaison statistique (test non paramétrique de Wilcoxon à deux échantillons liés - "two-tailed", significativité : $p < 0,05$ -) du nombre des éléments rétentionnels et inflammatoires obtenu au début et à la fin de l'étude.

Les valeurs obtenues ont permis d'interpréter les résultats en fonction du type de produit étudié et des effets recherchés par le Moniteur de l'Etude.

RESULTATS ET CONCLUSION

L'analyse des résultats obtenus a révélé dans l'ensemble :

- **Sur le plan de l'irritation ou de l'inconfort**, une très bonne tolérance du produit étudié chez 19 des 21 panélistes qui ont participé à la totalité de l'étude.
  Les 2 autres volontaires, à la peau du visage "sensible", ont présenté des réactions d'inconfort, se traduisant par une sensation de sécheresse cutanée, d'intensité faible à modérée, sur les joues, pendant environ 5 à 15 minutes après chaque application, ainsi que, pour l'un d'entre eux ayant eu des antécédents de réactions liés à l'utilisation d'un produit cosmétique, par des tiraillements de la peau d'intensité modérée.
  Ces phénomènes, isolés et liminaux, restent sans signification particulière.

- **Sur le plan de la comédogénèse**, l'absence significative de comédogénicité. Aucune augmentation statistiquement significative du nombre des éléments rétentionnels et inflammatoires,évalué sur la peau du visage, n'a été constatée entre le début et la fin de l'étude.

En conclusion, les applications du produit (b)(4) [redacted] **effectuées deux fois par jour pendant 4 semaines consécutives, dans les conditions normales d'utilisation sur la peau du visage et du cou, par 21 volontaires de sexe féminin, adultes sains, à la peau du visage grasse et ou mixte à tendance grasse, et à tendance acnéique, se sont avérées, dans l'ensemble, BIEN TOLEREES et NON COMEDOGENES.**

Les allégations de type "tolérance testée sous contrôle Dermatologique" et "non comédogène" peuvent donc être justifiées.

Fait à Lyon,
le 25 novembre 1997

J.P. GUILLOT
Expert Pharmacologue - Toxicologue
Directeur de l'I.E.C.

Dr. G. RIGOT-MULLER
Dermatologue
Investigateur
Directeur de l'Etude

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CONTROLE QUALITE

Cette étude a été réalisée en conformité avec les procédures standard du Centre de Recherches Cliniques, les procédures de fonctionnement générales de l'I.E.C., le protocole signé et les principes généraux des Bonnes Pratiques Cliniques publiées par l'I.C.H. (Guideline du 1er mars 1996).

Le contrôle des études cliniques, ne rentrant pas dans le champ d'application de la loi Huriet, est réalisé périodiquement. Il est destiné à assurer que toutes les phases importantes (applications du produit et examens ou mesures) d'un essai donné sont contrôlées, au moins une fois par mois, pour les études réalisées pendant cette période. Les dates de ces contrôles et le type d'essais concernés sont indiquées ci-dessous.

Les résultats de ces contrôles ont fait l'objet d'un rapport soumis à l'Investigateur et à la Direction Générale.

Types d'étude	Dates des contrôles	Dates des compte-rendus à l'Investigateur	Dates des compte-rendus à la Direction
. Essai identique :	30 septembre 1997	2 octobre 1997	10 octobre 1997
. Divers :	TUOR :		
	23 septembre 1997	24 septembre 1997	3 octobre 1997
	PEU :		
	7 octobre 1997	10 octobre 1997	17 octobre 1997
	EPS :		
	8 octobre 1997	9 octobre 1997	16 octobre 1997
	ARPC :		
	28 octobre 1997	29 octobre 1997	7 novembre 1997

Ce rapport a été contrôlé par le Service du Contrôle Qualité de l'I.E.C. et est un compte-rendu fidèle des procédures suivies, ainsi qu'un enregistrement exact des données originales générées dans cette étude.

	Date du contrôle	Date des compte-rendus à l'Investigateur	Date des compte-rendus à la Direction
Rapport (vs. données brutes) :	25 novembre 1997	25 novembre 1997	25 novembre 1997

Signature :

Nicole GUILLOT
Responsable du Contrôle Qualité

Date : 25 novembre 1997

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CONFIDENTIAL

REPORT : TOLERANCE STUDY

SPONSOR : (b)(4) [redacted]

CLINICAL STUDY : EVALUATION OF THE IRRITATING AND SENSITIZING POTENTIALS OF AN INGREDIENT USED IN COSMETICS, BY REPEATED EPICUTANEOUS 48 HOURS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 50 (OR 49, OR 48) HEALTHY ADULT VOLUNTEERS (Marzulli and Maibach's method)

TEST ARTICLE : (b)(4) [redacted]

REPORT : N (b)(4) [redacted] of 16 July 1997

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49 page document

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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INSTITUT D'EXPERTISE CLINIQUE

REPORT

CLINICAL STUDY FOR THE EVALUATION OF THE IRRITATING AND SENSITIZING POTENTIALS OF AN INGREDIENT USED IN COSMETICS, BY REPEATED EPICUTANEOUS 48 HOURS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 50 (OR 49, OR 48) HEALTHY ADULT VOLUNTEERS (Marzulli and Maibach's method)

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- Clinical Investigator Coordinator: (Study Director) : Dr. P. JAY, M.D.
  Post graduate in Dermatology
- Clinical Investigator : Dr. L. COLIN, M.D., post graduate in Dermatology - Venereology and in Applied Immuno-Allergology
- Assistant Study Director : M. LHERITIER, D.E.R.B.H., graduated es-Sciences - Senior Pharmacologist - Toxicologist

Test article : (b)(4) [redacted]

Study request : protocol n° (b)(4) [redacted] of 21 March 1997

Report : n° 70168RD3, of 16 July 1997

Study timetable :

- Start of the study : April 1997
- End of observations : June 1997
- End of the study (signature of the final report by the Investigator) : 16 July 1997

This document has to no contractual value : any copy, even incomplete, must be submitted to a written authorization from I.E.C.

(b)(4) [redacted] rocessed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

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AUTHENTICATION

The study subject of the present report was conducted under my responsibility, in compliance with the experimental protocol, the procedures of the Clinical Research Facility and the regulations of the Good Clinical Practices.

All observations and numerical data obtained during this study are reported in the present document. After reading, I certify that these data are an accurate reflexion of the results obtained.

Dr. Pierre JAY, M.D.
Investigator
and
Study Director

I read this report and I agree with its content.

Jean-Pierre GUILLOT
I.E.C. Manager

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SPONSOR (b)(4) [redacted]

TEST ARTICLE (b)(4) [redacted]

TOLERANCE STUDY

SUMMARY

CLINICAL STUDY FOR THE EVALUATION OF THE IRRITATING AND SENSITIZING POTENTIALS, BY EPICUTANEOUS REPEATED 48 HOURS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 50 (OR 49, OR 48) HEALTHY ADULT VOLUNTEERS
(Marzulli and Maibach's method)

VOLUNTEERS

PRELIMINARY STUDY

The preliminary study was performed in a panel of 10 healthy adult volunteers, males and females, composed of 9 women and 1 man from 21 to 63 years old.

MAIN STUDY

67 volunteers, males and females, were recruited and selected after a general medical examination taking into account the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the study protocol : 52 came to I.E.C. on the day of start of treatment.

50 panelists were then finally included by the Investigator on the basis of a clinical examination specific to the study, performed just before its start, after signature more particularly of the compensation modes form and of the informed consent statement : one of them abandonned during the induction period and another one during the rest period (not linked to the test article applications).

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Analysis of the results was thus made from a selection of :
- 50 volunteers for the evaluation of Primary Cutaneous Irritation,
- 49 panelists for the evaluation of cumulative irritation,
- 48 volunteers for the evaluation of cutaneous sensitization,
composed of 45 (or 44, or 43) women and 5 men, from 19 to 59 years old.

PROTOCOL

Determination of the optimum concentration to be used during the Main Study was carried out during a Preliminary Study.

PRELIMINARY STUDY (irritating potential)

The absence of pathological irritation, as regards primary and cumulative irritations of the test article, was checked from 3 concentrations after 4 successive applications, performed for about 48 or 72 hours, during the week-end, by the occlusive epicutaneous route to the skin of the arm of 10 panelists, males and females, healthy adults (9 women and one man, from 21 to 63 years old). These applications were performed to the same area, at the dose level of 0.02 ml, per volunteer, of the test article diluted just before administration at 1.0 - 2.5 and 5.0% (W/W) in distilled water. The preparation at 1.0%, being under a liquid form, was put onto a disc of filter paper (7 mm in diameter) just before application and kept in contact with the skin by means of an occlusive patch.

MAIN STUDY (irritating and sensitizing potentials)

This study was performed in 50 other volunteers, males and females, healthy adults, with the test article studied at a single concentration, determined according to the results obtained during the Preliminary Study (highest concentration not provoking any primary and cumulative irritation reactions and clinically significant).

The protocol of this study was allocated into 3 distinct periods :

- Induction period : during which the "preparing" or "sensitizing" contacts between epidermis and test article may occur, which may possibly induce the allergical process without showing evidence of any clinical manifestation of hypersensitivity :

. 9 consecutive applications, to the same area, of about 0.02 ml, per volunteer, of the test article diluted at 5.0% (W/W) in distilled water just before administration, by the occlusive epicutaneous route (Finn Chambers on Scanpor) for about 48 or 24 (4th application) hours, or 72 hours for the first 2 week-ends, to the skin of the arm of 50 (or 49) volunteers, males and females, healthy adults. This preparation, being under a liquid form, was put onto a disc of filter paper (7 mm in diameter) just before application and kept in contact with the skin under occlusive patch (Finn Chambers on Scanpor).

- Rest period : or incubation period during which the cells transformations possibly go on, leading to the modification of reactivity :

. 15 days without any application.

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- "Challenge" phase" : corresponding to the contact between the epidermis and the test article applied during the induction period and which aim is to reveal a clinical manifestation of induced immunological hypersensitivity :

. single application of about 0.02 ml, per volunteer, of the test article diluted at (b)(4) [redacted] W/W) in distilled water, just before administration, by the epicutaneous occlusive route for about 48 hours, to the skin of the back. This preparation, being under a liquid form, was put onto a disc of filter paper (7 mm in diameter) just before application and kept in contact with the skin under occlusive patch (Finn Chambers on Scanpor).

CLINICAL EXAMINATIONS, ANALYSIS AND INTERPRETATION OF THE RESULTS

The cutaneous reaction, control of the primary and cumulative irritations, was evaluated by the macroscopic examination of the reactions possibly observed after removal of each patch corresponding to the Preliminary Study and to the induction period of the Main Study.

The cutaneous reaction, control of the sensitization, was evaluated by the macroscopic examination of the reactions possibly noted about 24 and 48 hours after removal of the patches corresponding to the "challenge" application (Main Study).

These examinations were performed, for the 1st (Preliminary Study and induction), 4th (Preliminary Study), 8th (induction) and 10th (challenge) applications, by comparison to the reactions possibly obtained with a patch containing only the vehicle (distilled water), applied in parallel under the same conditions, as "negative" control.

Analysis and interpretation of the results were carried out as a function of the data obtained under the experimental conditions used.

- **As regards cutaneous tolerance (Preliminary and Main Studies)**, this analysis was completed by a calculation of the Mean Irritation Index (M.I.I.) equal to the total of the quotations of the readings (4 for the Preliminary Study and 8 corresponding to induction of the Main Study), divided by the number of volunteers included into this study and the number of readings performed (maximum M.I.I. = 4).

- **As regards evaluation of the sensitizing potential (Main Study)**, a reaction which intensity is equal to 3 (erythema with infiltration, papulae, vesicles) was considered as positive. If a reaction of individual irritation was noted during the 1st application, or after those corresponding to induction, or if an erythema was observed to the control area (right side), the test article was considered as "positive" if the challenge application had provoked a reaction which intensity was clearly higher, and/or if it had a tendency to increase as readings advanced.

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RESULTS AND CONCLUSION

PRELIMINARY STUDY

. Test article at 1.0% in active ingredient : Mean Irritation Index = 0
. Test article at 2.5% in active ingredient : Mean Irritation Index = 0.
. Test article at 5.0% in active ingredient : Mean Irritation Index = 0.

As this test article should be used between about 1.0% and 5.0% in the cosmetic formulations, and taking the indices obtained into account, the concentration of 5.0% (maximum non-irritant concentration under the experimental conditions used) was chosen for the Main Study.

MAIN STUDY

- Percentage of panelists having presented with a hardly visible irritation reaction (score = 1), during induction : $\sum$ of the scores = 1 = 29%

- Percentage of panelists having presented with several hardly visible irritation reactions (score = 1) , but no well visible to severe irritation reaction (score ≥ 2), during induction : $\sum$ of the scores > 1 = 8%

- Percentage of panelists having presented with one or several well visible to severe irritation reactions (score ≥ 2), during induction : $\sum$ of the scores ≥ 2 = 0%

The Mean Irritation Index (M.I.I.), obtained during induction, was equal to 0.06, thus allowing arbitrary classification of the test article applications as "non-irritant".

No pathological irritation, nor sensitization reaction significant of a cutaneous intolerance was noted.

- Percentage of sensitization reactions observed = 0%

No reaction of cutaneous sensitization was noted.

As a conclusion and from the results obtained under the experimental conditions used, the single then repeated cutaneous applications of this test article, diluted at (b)(4) [redacted] under occlusive patch, in the healthy adult volunteer, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization reaction.

Lyon,
16 July 1997

J.P. GUILLOT
Senior Pharmacologist - Toxicologist
I.E.C. Manager

Dr. P. JAY, M.D.
Dermatologist
Investigator
Study Director

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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QUALITY CONTROL

This study was conducted in conformity with the state of mind as regards drugs testing of the Good Clinical Practices published by the F.D.A. (Federal Register, dated 8 August 1978 - Part V - Docket n° 77 N - 0278), the E.E.C. (Directive 91/507) and the "Ministère de la Santé Française" (1987), as well as to the standard operating procedures of the testing facility, the general procedures of I.E.C. and to the signed protocol.

The control of the clinical studies which are not included in the application field of the Law Huriet is carried out as a continuous process designed to ensure that where possible all critical phases of a particular study type are inspected at least once per month. Dates of inspection and study type are given below :

The results of these controls were reported to the Investigator and to the General Management.

Controls	Dates of controls	Dates of reports to the Investigator	Dates of reports to the General Management
Technical phase(s) :	Preliminary : 21 April 1997 12 May 1997 19 June 1997	22 April 1997 13 May 1997 24 June 1997	28 April 1997 19 May 1997 26 June 1997
Report (vs. raw data) :	15 July 1997	15 July 1997	15 July 1997

Signature :

Nicole GUILLOT
Head of Quality Control Department

Date : 16 July 1997

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1. STUDY OBJECTIVE

Evaluation of the cutaneous irritating and sensitizing potentials of a raw material (emulsifying product) used in cosmetics, by repeated applications to the skin under occlusive patch, in 10 + 50 healthy adult volunteers, males and females.

2. PRINCIPLE

PRELIMINARY STUDY (irritating potential : determination of the optimum dose level to be used for the Main Study)

Verification of the absence of pathological irritation, as regards primary and cumulative irritations of the test article (3 concentrations) after 4 successive applications, performed for about 48 or 72 hours, during the week-end. These applications are performed to the same area, at the dose level of 0.02 ml, per volunteer, of the test article, by the epicutaneous occlusive route (Finn Chambers on Scanpor) to the skin of the arm of 10 panelists, males and females, healthy adults.

MAIN STUDY (irritation and sensitizing potentials)

This study is performed in 50 other panelists, males and females, healthy adults, with the test article, at a single concentration, determined according to the results obtained during the Preliminary Study (highest concentration which does not provoke any primary and cumulative irritation reactions clinically significant).

- Induction period : during which the "preparing" or "sensitizing" contacts occur between the epidermis and the test article, which will possibly induce the allergical process without showing evidence of any clinical manifestation of hypersensitivity:

. 9 consecutive applications, to the same area, of 0.02 ml, per volunteer, of the test article, by the occlusive epicutaneous route for about 48 or for the 2 week-ends 72 hours, to the skin of the arm of 50 healthy adult volunteers, males and females.

- Rest period : or incubation period during which the cells transformations possibly go on, leading to a modification of reactivity :

. 15 days without any application.

- "Challenge" phase : corresponding to the contact between the epidermis and the test article applied during the induction period and which aim is to reveal a clinical manifestation of induced immunological hypersensitivity :

. single application of 0.02 ml, par volunteer, of the test article, by the epicutaneous occlusive route for 48 hours, to the skin of the back.

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The cutaneous reaction, control of the primary and cumulative irritations, is evaluated by the macroscopic examination of the reactions possibly observed after removal of each patch corresponding to the Preliminary Study and to the induction period of the Main Study.

The cutaneous reaction, control of the sensitization, is evaluated by the macroscopic examination of the reactions possibly noted about 24 and 48 hours after removal of the patches corresponding to the "challenge" application (Main Study).

These examinations are carried out, for the 1st (Preliminary Study and induction), 4th (Preliminary Study), 8th (induction) and 10th (challenge) applications, by comparison to the reactions possibly obtained with a patch (without test article) or if necessary with a vehicle known as being neutral, non-irritant, non-sensitizing and non-comedogenic, applied in parallel under the same conditions, as "negative" control.

Analysis and interpretation of the results are performed according to the data obtained under the experimental conditions used.

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3. TEST ARTICLE

3.1. Designation : (b)(4) [redacted]

3.2. Identification code number for the study : (b)(4) [redacted]

3.3. Formulation and colour : white waxy scales.

3.4. Analytical controls :

It was under the responsibility of the Study Monitor to determine the identity, the physico-chemical characteristics and any other criteria which could allow identification of the batch of test article.
For this type of study, no analytical dosage was made and neither stability, nor absorption of the test article were evaluated by I.E.C.

3.5. Packaging : plastic container.

3.6. Quantity supplied and date of receipt :

1 x 150 g, received on 11 April 1997.

3.7. Storage : protected from heat (between + 5° C and + 25° C) and light.

A sample of the test article will be kept in our facilities for two months as of the date of despatch of the final report. From this date on, and with no contrary advice of the Study Monitor, the test article will be destroyed.

3.8. Vehicle : distilled water.

3.9. Preparations applied :

- Preliminary Study :
The test article designated as [redacted] (b)(4) [redacted] was diluted at 1.0 - 2.5 and 5.0% (W/W) in the vehicle and in a sufficient quantity for 3 applications.

- Main Study :
The test article designated as [redacted] (b)(4) [redacted] was diluted at (b)(4) (W/W) in the vehicle and in a sufficient quantity for 3 applications.

4. VOLUNTEERS

4.1. Principle of recruitment, selection and inclusion

The procedure for recruitment, selection and inclusion of the volunteers who accepted to collaborate to this study, after informed consent, was elaborated to grant them a clear and precise information, allowing them to appreciate the aim and the consequences of their consent.

This procedure particularly included :
- a preliminary interview during which they were explained in particular the objective and the protocol of the study, the study timetable, the compensation modes, as well as the possible benefits, the constraints linked to the study and the foreseeable risks even in case of stop of the study before its normal end ;
- the signature of an informed consent statement by the volunteer : he could thus make his decision completely free taking the conditions proposed into account ;
- the notification of his take over by the insurances in civil liability subscribed independently by the Sponsor and I.E.C., once the volunteer has been definitively admitted for study by the Investigator.

The volunteers recruited for this study were selected by the M.D. responsible for recruitment and selection on the basis of the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the protocol.

The final inclusion of the volunteers was determined by the M.D. Investigator, Study Director, from a pre-study medical auto-questionnaire and from a clinical medical examination specific to the study, performed just before the start of treatment.

4.2. Inclusion criteria

- Origin : Caucasian.
. Justification for origin : the white colour of Caucasian' skin allows easier evaluation of the cutaneous reactions.

- Age : adults from 18 to 70 years old (the year range 65-70 should not represent more than 10% of the total number of volunteers).

- Sex : male and female.

- Weight : included within the limits of the scale proposed by the Metropolitan Insurance Company.

- Health condition : it corresponded to the selection criteria defined in the procedures of I.E.C., in order to eliminate, as much as possible, the volunteers incuring risks or presenting with redhibitory affections for the clinical studies performed by I.E.C. These criteria were evaluated on the basis of questionnaires and clinical examinations listed in the protocol.

- Volunteers able to justify of a fixed abode.

- Comprehension of the French language : Francophone volunteers, able to read the documents they were presented with and to hold to what they were explained.

- Social cover : the volunteers should be affiliated to a social security organization.

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4.3. Non-inclusion criteria

- Volunteers not presenting with the above-mentioned inclusion criteria.

- Volunteers not having respected article L 209-17, law of 20 December 1988 modified, involving :
. prohibition concerning the simultaneous acceptance of several biomedical research projects without direct benefit to the individual,
. the grace period during which a person may not be involved in any other biomedical research projects without direct benefit to the individual.

- Volunteers having participated in a test for the verification of the good cutaneous or peri-ocular local tolerance during the two last weeks and/or to active sensitization type studies during the last four months.

- Volunteers deprived from liberty by a judiciary or administrative decision, seek volunteers in situation of urgence (article L 209-5).

- Under age or full age volunteers protected by law, as well as those admitted in sanitary or social facilities, ever since the research can be performed in another manner (article L 209-6).

- Volunteers having refused to give their agreement by signing the informed consent statement.

- Volunteers having undergone organ excision (kidney, lung, spleen, liver), an organ transplant, a skull concussion with extended loss of consciousness since less than 5 years or with present after-effects.

- Volunteers, either pregnant or breastfeeding mothers, or not using medically acceptable contraceptive methods.

- Volunteers having :
. *the following disorders :* cardiovascular, pulmonar, digestive, neurologic, psychiatric, genital, haematological, endocrine, having a redhibitory aspect for the study concerned ;
. *an immunological deficit ;*
. *a background of drug intolerance* (local or general anaesthetics), and intolerance to cosmetics, to body hygiene or domestic products, to clothes, to products used at work such as colophane, rubber (gloves, glues, adhesive tapes), nickel, aluminium ... ;
. *an allergic background :* asthma, periodic spasmodic rhinitis ;
. *a skin disease,* and in particular : urticaria, oedema, eczema, recurrent herpes, herpes zoster having erupted less than three months before, pityriasis versicolor, common acne with a sudden rise of inflammation or nodular or kystic acne, psoriasis, ichtyosis, lichen planus, chronic lupus erythematosis, cheloïd scars, severe pigmentary disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity, very important perspiration ;
. *a febrile illness :* more than 24 hours of fever within the 8 days prior to the first application of the test article.

- Volunteers having had or being in the course of a long-term treatment, in particular with antihistamine, steroïds, Beta blockers (including collyrium) and of desensitization.

- Volunteers who recently suffered from insolation, or having followed heliotherapy during the month preceeding the study.

- Volunteers smoking more than 10 cigarettes a day and not accepting restriction of their tobacco consumption during the two days prior to the start of the study and throughout the whole study.

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4.4. Prohibition and Restriction

For all the time of the applications (thus excepted during the rest period), the volunteers should not wet the treated area or apply adhesives. They should not use other products on the body (except water and soap or the usual cleaning product) during the study. In case of use of drugs, they should inform the Investigator, who remained responsible for keeping or not the volunteer in the study.

4.5. Number of volunteers

The Preliminary Study was performed in a panel of 10 non-exclusive volunteers, males and females, healthy adults.

The Main Study was carried out in a non-exclusive selection of :
- 50 volunteers for the evaluation of Primary Cutaneous Irritation,
- 49 panelists for the evaluation cumulative irritation,
- 48 volunteers for the evaluation of cutaneous sensitization.

Justification :
- For the Preliminary Study : irritation being a collective phenomon, of inflammatory origin, 9 to 10 volunteers correspond to a minimum acceptable number, to verify the good local epicutaneous tolerance of a test article.
- For the Main Study : sensitization being an individual phenomenon, of immunitary origin, 25 to 50 panelists correspond to a minimum acceptable number, to show evidence of the sensitizing potential of a test article.

4.6. Recording

The volunteers were registered and allocated in the order of their selection, this being made progressively as they arrived.

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5. CLINICAL STUDY (EXPERIMENTAL DESIGN)

5.1. Application

5.1.1. Application areas

Applications of the test article were performed on a surface of about 50 mm2 per test article (8 mm in diameter) on one hand, for the Preliminary Study and induction of the Main Study to the left arm (bending side) and on the other hand, for the challenge phase (Main Study) on the back to the left of the spine, between the hips and shoulders. These areas had previously been submitted to a specific examination, at the occasion of the final inclusion by the Investigator, i.e. just before the start of the study, in order to keep only surfaces free from any macroscopic trace of irritation or of any abnormality which could interfere with interpretation of the results.

5.1.2. Preparation of the application areas

The surfaces defined above during the Preliminary and the Main Studies were previously cleaned with distilled water, then dried with paper in cotton-wool cellulose.

5.1.3. Patch tests

Applications of the test article, during the Preliminary and the Main Studies, were performed under occlusive patches (épitest : Finn Chambers on Scanpor, delivered by Promédica).

The "Finn Chamber" makes an isolation chamber which ensures a good occlusion limited to the application area of the test article : it is composed of an aluminium cupule 8 mm in diameter covering a contact surface of 50 mm2.

Each cupule is individually mounted onto an adhesive tape (Scanpor : Norgesplaster A/S Norway) applied in such a manner as to exert equal pressure on all cupules.

During the Preliminary Study, the test article in a 1.0% (W/W) dilution in distilled water, being under a liquid form, was put, just before application, onto a disc of filter paper (7 mm in diameter) previously inserted into the cupule.

The other preparations of the test article (Preliminary and Main Studies), were directly put into the cupule which was filled at 2/3 of its volume.

5.1.4. Dose levels and concentrations

Preliminary Study :
- About 0.02 ml, per volunteer, of the test article diluted at 1.0 - 2.5 and 5.0% (W/W) in distilled water, just before administration, and measured with a 1 ml Tuberculine, graduated in 1/100° ml and with an adjusted taper, or with an automatic micropipette (Eppendorf Multipipette 4780 E : 10 to 50 µl).

Main Study :
- About 0.02 ml, per volunteer, of the test article diluted at 5.0% (W/W) in distilled water, just before administration, and measured with a 1 ml Tuberculine, graduated in 1/100° ml and with an adjusted taper, or with an automatic micropipette (Eppendorf Multipipette 4780 E : 10 to 50 µl).

- Justification for the dose level : it is the capacity of the cupule indicated by the manufacturer of the "Finn Chambers on Scanpor".

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5.1.5. Route of administration

- Route : local epicutaneous.

- Justification for the route : normale route of use and propitious to the induction of a sensitization.

5.1.6. Methods of application

5.1.6.1. PRELIMINARY STUDY

- **Application area** : left arm (bending side) and always to the same area.

- **Test articles applied** : 3 concentrations of 4 test articles having been studied at the same time and in the same volunteer, the patches previously identified were cautiously applied to the skin, at the rate of one or two series of 2 parallel rows of several isolation chambers.
In parallel to the application of each concentration of the test article, i.e. on the panelist's left arm (bending side), an isolation chamber containing only the vehicle (distilled water), was applied, at Day 1 and Day 8, under the same conditions, to act as "negative" control in order to verify the irritant potential of the test articles after about 48 hours of occlusive applications.

- **Frequency and duration of administration** : 4 applications allocated on 2 weeks as follows :

1st week	:	Day 1 (Monday : 1st application), Day 3 (Wednesday), Day 5 (Friday),
2nd week	:	Day 8 (Monday).

- **Duration of exposure** : about 48 hours (1st, 2nd and 4th applications) or about 72 hours (3rd application).

5.1.6.2. MAIN STUDY

5.1.6.2.1. Induction period

- **Application area** : left arm (bending side) and always to the same area.

- **Test articles applied** : 11 test articles (8 from Seppic + 3, thus coming from 2 different Sponsors) having been studied at the same time on the same volunteer, the patches previously identified were cautiously applied to the skin, at the rate of one or two series of 2 parallel rows of several isolation chambers.
In parallel to the application of the test articles, i.e. on the volunteer's left arm (bending side), an isolation chamber containing only the vehicle (distilled water), was applied, at Day 1 and Day 17, under the same conditions, to act as "negative" control in order to verify the irritant potential of the test articles after about 48 hours of occlusive applications.

- **Frequency and duration of administration** : 9 applications allocated on 3 weeks as follows :

1st week	:	Day 1 (Monday : 1st application), Day 3 (Wednesday), Day 5 (Friday),
2nd week	:	Day 9 (Tuesday), Day 10 (Wednesday), Day 12 (Friday),
3rd week	:	Day 15 (Monday), Day 17 (Wednesday), Day 19 (Friday).

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- **Duration of exposure** : about 24 hours (4th application), 48 hours (1st, 2nd, 5th, 7th and 8th applications) or 72 hours (3rd and 6th applications). For the 1st and the 3rd week-ends, the volunteer was asked to remove himself the patch at home, i.e. on Day 8 and Day 21, about 72 and 48 hours after the 3rd and 9th applications.

5.1.6.2.2. Rest period

The volunteers were not submitted to any application from Day 21 (Sunday) to Day 35 (Sunday) inclusive, i.e. for a 15 day period

5.1.6.2.3. "Challenge" phase

- **Application area** : back.

- **Test article applied** : the test article (left side of the spine), as well as a patch containing only the vehicle (distilled water), applied, under the same conditions, in parallel to the test article, to act as "negative" control (right side of the spine).

- **Frequency and duration of administration** : single application at Day 36 (Monday).

- **Duration of exposure** : about 48 hours.

5.1.7. Security

In the case when the adhesive of the patch had provoked an intolerance leading to the stop of the applications on the concerned area, the bandage was not applied to the same site than that of the previous application, but to a site located near it.

When, during induction and as of the 2nd application, a clear sign of intolerance (well visible erythema or oedema : score ≥ 2) was observed to the application area of a test article when removing the patches, its application was interrupted until the "challenge" phase.

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5.2. Observations and clinical examinations

5.2.1. Reading intervals

- Preliminary study :

The cutaneous examinations were performed about 30 minutes after removal of the patches for the 1st and 4th applications of the test article (i.e. on Day 3 and Day 10) and just after removal of the patches for the 2 other applications.

- Main study :

The cutaneous examinations were performed on one hand, during induction, about 30 minutes after removal of the patches of the 1st and 8th applications of the test article (i.e. at Day 3 and Day 19), and immediately after removal of the patches of the 5 other applications, in order to appreciate its possible irritation potential and on the other hand, about 24 and 48 hours after removal of the patch corresponding to the "challenge" application (i.e. at Day 39 and Day 40) to evaluate its possible sensitizing potential.

Except if severe reactions necessitated it, no cutaneous examination was performed after the last application (Day 19) for which the volunteer had removed the patch himself at home.

Special attention was paid to the reading carried out after the 1st application (Day 3), in order to verify the irritative potential of the test articles applied, under the above-mentioned conditions.

5.2.2. Evaluation of the cutaneous irritation and of the sensitizing potential

The cutaneous readings were always performed under the same conditions, in particular as regards lighting ("day light"lamp : 6500°K).

The cutaneous reactions possibly observed during induction and the "challenge" phase were evaluated, for each volunteer, according to the following numerical scales :

5.2.2.1. For irritation reactions (induction)

No reaction.....0
Hardly visible erythema.....1
Well visible erythema.....2
Erythema with oedema.....3
Severe erythema and/or oedema leading to a bullae detachment with or without erosion.....4

N.B. : any other abnormality (dryness, thickening, shining or worn aspect ...) will also be noted.

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5.2.2.2. For sensitization reactions (challenge)

(scale of the International Contact Dermatitis Research Group : I.C.D.R.G.)

No visible cutaneous reaction.....0 (-)
Very slight and hardly visible erythema.....1 (+?)
Erythema with small infiltration and sometimes
papulae (no vesicles, no bullae).....2 (+)
Erythema with infiltration, papulae, vesicles.....3 (++)
Severe erythema with infiltration, coalescent vesicles leading to bullae.....4 (+++)

N.B. : any other abnormality (epidermal erosion, subjective sensations : pruritus, prickings, burning sensation ...) were also mentioned.

A reaction which intensity was equal to 3 was considered as positive. If an individual irritation reaction was noted during the 1st application or after those corresponding to induction, or if erythema was observed to the control (right side) area, the test article was considered as "positive" if the challenge application provoked a reaction which intensity was clearly higher.

For the examinations performed at Day 3 (Preliminary or Main Studies), Day 10 (Preliminary Study), Day 19 (induction of the Main Study) and Day 39, Day 40 (challenge), the results, which are listed in the report, correspond to those obtained by difference between the area on which the test article was applied and that of the "negative" control.

5.3. Data analysis and interpretation of the results

Analysis and interpretation of the results were performed according to the data obtained under the experimental conditions used.

- **As regards cutaneous tolerance**, this analysis was completed by a calculation of the Mean Irritation Index (M.I.I.), equal to the total of the quotations of the 4 (Preliminary Study) or 8 (Main Study) readings corresponding to induction divided by the number of volunteers included into this study and the number of readings performed :

$$\text{M.I.I.} = \frac{\Sigma \text{ quotations of the 4 or 8 readings (all volunteers)}}{\text{Number of volunteers x 4 or 8 (readings)}}$$

For this index calculation, it was defined that :

. in case of absence of a volunteer to an examination, the quotation of the day of absence is identical to that of the previous day ;
. in case of stop of an application for a too severe reaction, the maximum quotation (4) is attributed on the day following stop of the test article application for the considered area and this, until the end of the tolerance test ;
. in case of stop of the applications for any other reason, the quotations of the volunteer are excluded of the indices calculation.

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The M.I.I. thus obtained allowed arbitrary classification of the test article as follows :

M.I.I.	Classification of the test article
lower than 0.25	non-irritant
0.25 to 1 not included	slightly irritant
1 to 2 not included	mean irritant
2 to 3 not included	very irritant
3 to 4	very severely irritant

- **As regards evaluation of the sensitizing potential**, a reaction of intensity equal to 3 was considered as positive. If a reaction of individual reaction was noted during the 1st application, or after those corresponding to induction, or if an erythema was observed to the control area (right side), the test article was considered as "positive" if the challenge application provokes a reaction which intensity is clearly higher, and/or if it has a tendecy to increase as readings advanced.

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6. REGULATIONS, CONFIDENTIALITY AND LEGAL FORMALITIES

6.1. Regulations

This study, without any direct therapeutical finality for the volunteer, was performed in agreement with the French law n° 88-1138 dated 20 December 1988 modified by laws n° 90-86 of 23 January 1990 and n° 94-360 of 25 July 1994 and Decree n° 90-872 dated 27 September 1990, concerning protection of the persons undergoing biomedical research : the information concerning the volunteers included in this study were sent to the national card-index of persons undergoing biomedical research without direct benefit to the individual and the advice of the "Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale de Lyon A" was requested. It was also performed according to the most recent recommandations of the World Medical Association (Declaration of Helsinki, 1964, amended in Hong-Kong, 1989).
The Investigator, on examination of the documents supplied by the Sponsor, accepted that this study is implemented (see in appendix, the study acceptability form).

6.2. Confidentiality

Any information regarding the healthy condition of the volunteers and the results of the clinical examinations, performed before the start of treatment, for their recruitment, their selection and inclusion, are submitted to the rules of the medical secrecy according to Article 226-13 and following of the French Penal Code and to the Code of medical deontology (Decree dated 18 June 1979, articles 11, 12 and 13) : in no case, this information will be given to the Sponsor with their identity.

To ensure preservation of the volunteers' anonimity, those were identified by a code number using 5 letters, corresponding to the first 3 letters of their surname, then the first 2 letters of their first christian name, and for the study, by a number corresponding to their inclusion order in the test.

At the end of the study, the page called "Volunteer Identification Form", in which are mentionned particularly the name and address of the volunteer, was taken from the laboratory notebook and destroyed.

"The investigators and any person who collaborated to the studies are bent on professionnal secrecy especially as regards the nature of the test articles, the studies, the persons on test and the results obtained" (extract from Article R 5120 of Decree n° 90-872, dated 27 September 1990, law n° 88-1138, dated 28 December 1988, modified, dealing with the protection of the persons undergoing biomedical research : law Huriet).

6.3. Legal formalities

6.3.1. Subscription of insurance by I.E.C. and the Sponsor

I.E.C. and the Sponsor subscribed separately an insurance to guaranty their civil liability vis-a-vis the volunteers :

. I.E.C. : A.G.F., contract n° 77.106.407
. Sponsor : U.A.P., contract n° 6.759.273.

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Extract from law n° 88-1138 modified, dated 20 December 1988, regarding protection of persons undergoing biomedical research (Article L.209-7) :

> "In case of biomedical research with no direct benefit to the individual, the sponsor, even when not at fault, takes responsibility for the compensation of any harmful effects of the research on a person undergoing it and that of his beneficiaries, notwhithstanding the possible action of a third-party or the voluntary withdrawal of the person who initially consented to undergo the research.
>
> In case of biomedical research with direct benefit to the individual, the sponsor takes responsibility for the compensation of any harmful effects of the research on a person undergoing it and that of his beneficiaries, unless he proves that such adverse effects are not attributable to his or any participating party's action, not withstanding the possible action of a third-party or the voluntary withdrawal of the person who initially consented to undergo the research.
>
> The biomedical research needs the former subscription, by its sponsor of insurance covering his and any other participating party's liability as it results from this article, irrespective of the relationship between the sponsor and the participating parties. The provisions of this article are binding on all parties".

6.3.2. Information sent by I.E.C. to the National card-index of the persons undergoing biomedical research without direct benefit to the individual

I.E.C. took the necessary steps to provide information, consult and keep this card-index up-to-date, this one being managed by the revelant Administrative Authorities (Title VI of Decree n° 90-872, dated 27 September 1990 : Article R.2039 and following). They also informed the volunteers of the existence of this card-index and of the data contained.

6.3.3. Information sent by I.E.C. to the "Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon A"

On receipt of the protocol duly signed by the Sponsor, of the information allowing to judge of the possibility of performing the study, of the insurance attestation and of his payment discharge to the Treasury (or of a declaration specifying that he pays the fixed duty of 9,500 francs to the relevant collecting administration), I.E.C. took the necessary steps to ask for the advice of the "Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon A" : they expressed a favourable advice for the realisation of this study (see appendix).

6.3.4. Sponsor's letter of intent to the relevant Administrative Authorities

On receipt of the advice of the "Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon A" and before having this research performed, the Sponsor had to send to the relevant Administrative Authorities a letter of intent written according Article R.2032 and following of Decree n° 90-872, 27 September 1990 and of the Arrêté of 14 February 1991 concerning the intent declaration form.

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6.3.5. Information and informed consent

An information sheet was given to each volunteer, in order to precise to him more particularly :
- the aim of the research, its methodology and its duration ;
- the the constraints linked to the study and the foreseeable risks, including in case of stop of the research before its normal end ;
- the non-inclusion period, the amount of the compensation, the possibility for the volunteer to check the exactitude of the data contained in his medical file and their subsequent destruction ;
- the advice of the "Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon A", mentioned in article L.209-12 of the "Code de la Santé Publique" ;
- its registration in the national card-index as stated in article L.209-17.

This information allowed the volunteer to sign an informed participation consent, with full knowledge of the facts.

6.3.6. Data recording and archiving

All data were immediately transcribed in laboratory notebooks constituted, paginated and fastened before the start of the study.

The original documents, including the final report and all raw data, are kept in the archives of I.E.C. for 15 years, at the following addresses :

. For the 3 to 6 months following despatch of report :
I.E.C., 87 rue de Sèze, 69006 Lyon - France
. For the following years :
Société Générale d'Archives (S.G.A.), 23 Traverse Santi, 13015 Marseille.

Once this period is over, and unless advised of the contrary by the Study Monitor, archives will be destroyed by S.G.A..

7. PROTOCOL COMPLIANCE

- Clinical Investigator was Dr. P. JAY, and not Dr. L. COLIN, as mentioned in the protocol.

- 48 panelists participated in the whole Main Study, insted of the 50 panelists specified in the protocol.

- During the Main Study, Monday 19 May 1997 (Day 8) being a Bank Holiday (Whit Monday), no cutaneous examination nor any application were performed. Volunteers removed their patches themselves, at home (Monday 19 May 1997), the cutaneous reading was made on the following day on Day 9 (Tuesday 20 May) and was followed by an application which duration was of about 24 hours.

- On Day 3 for the Main Study and for panelists n° 11 and 43, the cutaneous examinations were realised 6 and 1 minutes in advance respectively, after removal of the patches, compared to the 30 minutes (± 5 minutes) mentioned in the protocol and the procedures.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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- During the first application (Day 3 of the Main Study) and for panelists n° 38 and 55, the cutaneous examinations were made with 5 minutes of delay, after removal of the patches, compared to the 30 minutes (± 5 minutes) specified in the protocol and the procedures.

- An application of patches containing only the vehicle (distilled water) was performed during the 4th application of the Preliminary Study. Thus, the examinations were made by comparison with the « negative » control.

These deviations are not considered to have affected the quality or the interpretation of the results obtained.

8. BIBLIOGRAPHICAL REFERENCE

Marzulli F.N. and Maibach H.I.
Contact allergy, predictive testing in man.
Contact Dermatitis, 1976, 2,1 - 17

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

9. RESULTS

9.1. Volunteers

The Preliminary Study was performed in a panel of 10 volunteers, healthy adults, males and females, composed of 9 women and 1 man, from 21 to 63 years old (table I).

For the Main Study, 67 panelists, males and females, were recruited and selected for its realisation.

52 came to I.E.C. on the day of start of treatment : 50 were included by the Investigator. One of them (n° 54) abandonned during the induction period and another one (n° 35) during the rest period (not linked to the test article applications).

The study was thus made from a selection of :
- 50 volunteers for the evaluation of Primary Cutaneous Irritation,
- 49 panelists for the evaluation of cumulative irritation,
- 48 volunteers for the evaluation of cutaneous sensitization,

composed of 45 (or 44, or 43) women and 5 men, healthy adults, from 19 to 59 years old (table V).

9.2. Clinical examinations (tables II to VII)

Preliminary Study :
See detailed results listed in tables II to IV.

Main Study :
See detailed results listed in tables VI and VII.

10. DISCUSSION AND CONCLUSION

PRELIMINARY STUDY

As this test article should be used between about 1.0% and 5.0% in the cosmetic formulations, and taking the indices obtained into account, the concentration of (b)(4) [redacted] (maximum non-irritant concentration under the experimental conditions used) was chosen for the Main Study.

MAIN STUDY

No pathological irritation, nor sensitization reaction significant of a cutaneous intolerance was noted.

The Mean Irritation Index (M.I.I.), obtained during induction, was equal to 0.06, thus allowing arbitrary classification of the test article applications, as "non-irritant".

As a conclusion and from the results obtained under the experimental conditions used, the single then repeated cutaneous applications of this test article, diluted a (b)(4) [redacted] under occlusive patch, in the healthy adult volunteer, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization reaction.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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APPENDIX

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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PRELIMINARY STUDY

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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TABLE I

FEMALE VOLUNTEERS' PHYSICAL CHARACTERISTICS

VOLUNTEERS N°	AGE (years old)	HEIGHT (cm)	WEIGHT (kg)
33	24	158	50
34	21	165	51
35	51	167	59
36	36	166	57
37	24	160	47
40	63	161	66
41	21	156	47
43	36	163	56
44	25	172	52
MEAN VALUES	33.4	163.1	53.9

MALE VOLUNTEER'S PHYSICAL CHARACTERISTICS

VOLUNTEER N°	AGE (years old)	HEIGHT (cm)	WEIGHT (kg)
42	22	159	50

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

TABLE II

RESULTS OF OBSERVATIONS AND OF CLINICAL EXAMINATIONS

IRRITATION

STUDY : evaluation of the irritating potential by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE : (b)(4) [redacted] diluted at (b)(4) [redacted] (W/W) in distilled water.

VOLUNTEERS N°	IRRITATION REACTIONS (0 to 4) DAYS				Σ QUOTA-TIONS
	3*	5	8	10*	
33	0	0	0	0	0
34	0	0	0	0	0
35	0	0	0	0	0
36	0	0	0	0	0
37	0	0	0	0	0
40	0	0•	0	0	0
41	0	0	0	0	0
42	0	0	0	0	0
43	0	0	0	0	0
44	0	0	0	0	0

TOTAL = 0
M.I.I. = 0
CONCLUSION = Non-Irritant

* Examinations performed in comparison with a "negative" control (patch containing only the vehicle) and about 30 minutes after removal of the patches.

Other observation :

• : worn skin.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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TABLE III

RESULTS OF OBSERVATIONS AND OF CLINICAL EXAMINATIONS

IRRITATION

STUDY : evaluation of the irritating potential by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE (b)(4) [redacted] diluted at (b)(4) [redacted] W/W) in distilled water.

VOLUNTEERS N°	IRRITATION REACTIONS (0 to 4) DAYS				Σ QUOTA-TIONS
	3*	5	8	10*	
33	0	0	0	0	0
34	0	0	0	0	0
35	0	0	0	0	0
36	0	0	0	0	0
37	0	0	0	0	0
40	0	0	0	0	0
41	0	0	0	0	0
42	0	0	0	0	0
43	0	0	0	0	0
44	0	0	0	0	0

TOTAL = 0
M.I.I. = 0
CONCLUSION = Non-Irritant

* Examinations performed in comparison with a "negative" control (patch containing only the vehicle) and about 30 minutes after removal of the patches.

Other observations : nothing to report.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

TABLE IV

RESULTS OF OBSERVATIONS AND OF CLINICAL EXAMINATIONS

IRRITATION

STUDY : evaluation of the irritating potential by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE (b)(4) [redacted] diluted at (b)(4) [redacted] W/W) in distilled water.

VOLUNTEERS N°	IRRITATION REACTIONS (0 to 4) DAYS				Σ QUOTA-TIONS
	3*	5	8	10*	
33	0	0	0	0	0
34	0	0	0	0	0
35	0	0	0	0	0
36	0	0	0	0	0
37	0	0	0	0	0
40	0	0	0	0	0
41	0	0	0	0	0
42	0	0	0	0	0
43	0	0	0	0	0
44	0	0	0	0	0

TOTAL = 0
M.I.I. = 0
CONCLUSION = Non-Irritant

* Examinations performed in comparison with a "negative" control (patch containing only the vehicle) and about 30 minutes after removal of the patches.

Other observation : nothing to report.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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MAIN STUDY

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

TABLE V

FEMALE VOLUNTEERS' PHYSICAL CHARACTERISTICS

VOLUNTEERS N°	AGE (years old)	HEIGHT (cm)	WEIGHT (kg)
01	48	165	66
02	53	171	57
04	45	160	54
06	49	170	82
07	24	155	50
08	20	161	52
09	43	166	61
10	31	169	62
11	27	154	48
12	49	161	65
16	24	153	52
18	35	155	46
20	37	154	48
21	22	156	56
23	56	155	53
24	26	175	65
26	48	168	60
27	23	158	46
28	30	154	44
30	40	161	64

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TABLE V (continuation)

FEMALE VOLUNTEERS' PHYSICAL CHARACTERISTICS

VOLUNTEERS N°	AGE (years old)	HEIGHT (cm)	WEIGHT (kg)
31	48	161	64
32	41	163	54
34	24	168	53
35	59	163	57
36	21	167	56
37	24	155	50
38	25	171	53
43	26	166	55
44	44	167	66
45	37	145	51
46	27	167	60
47	29	163	54
49	20	165	53
51	25	170	66
52	25	156	47
53	22	160	58
54	24	157	55
55	45	161	56
58	54	165	48
60	30	159	62

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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TABLE V (continuation)

FEMALE VOLUNTEERS' PHYSICAL CHARACTERISTICS

VOLUNTEERS N°	AGE (years old)	HEIGHT (cm)	WEIGHT (kg)
61	19	168	52
63	28	170	55
64	21	157	49
65	22	161	59
66	22	165	53
MEAN VALUES	33.2	162.0	55.9

MALE VOLUNTEERS' PHYSICAL CHARACTERISTICS

VOLUNTEERS N°	AGE (years old)	HEIGHT (cm)	WEIGHT (kg)
15	32	170	55
22	24	183	76
48	23	163	75
57	21	182	85
67	32	171	63
MEAN VALUES	26.4	173.8	70.8

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

TABLE VI

RESULTS OF OBSERVATIONS AND OF CLINICAL EXAMINATIONS

IRRITATION

STUDY : evaluation of the irritating and sensitizing potentials by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE : (b)(4) [redacted] diluted at (b)(4) [redacted] W/W) in distilled water.

VOLUNTEERS N°	IRRITATION REACTIONS (0 to 4) DAYS								Σ QUOTA-TIONS
	3*	5	9	10	12	15	17	19*	
01	0	0	0	0	0	0	0	0•	0
02	0	0	0	0	0	0◊	0	0	0
04	0	0	0	0	0	0	0	0	0
06	0	1	0	0	0	0	0	0	1
07	0	0	0	0	0	0	0	0	0
08	0	0	0	0	0	0	0	0	0
09	0	0	0	0	0	0	0	1	1
10	0	0	0	0	0	0	0	0	0
11	0	0	0••	0	0◊	0	0	0	0
12	0	0	0	0	0	0	0	1	1
15	0	0	0	0	0◊	0	0	0	0
16	0	0	0	1	1	0	0	0	2
18	0	0	0	0	0	1	1	0	2
20	0	1	0•	0	0	0	0	0	1
21	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0◊	0	0
27	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0◊	0◊	0	0	0
30	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	1	1
34	0	0	0	0	0	0	0	0	0

* Examinations performed in comparison with a "negative" control (patch containing only the vehicle) and about 30 minutes after removal of the patches.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Report N° (b)(4) [redacted]

Other observations :

• : worn skin

•• : dryness

◊ : whitish aspect of the skin.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

TABLE VI (continuation)

RESULTS OF OBSERVATIONS AND OF CLINICAL EXAMINATIONS

IRRITATION

STUDY : evaluation of the irritating and sensitizing potentials by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE : (b)(4) [redacted] diluted at (b)(4) (W/W) in distilled water.

VOLUNTEERS N°	IRRITATION REACTIONS (0 to 4) DAYS								Σ QUOTA-TIONS
	3*	5	9	10	12	15	17	19*	
35	0	0	0	0	0	0	0	0	0
36	0	0	1	0	1	0	0	0	2
37	0	0	1	0	0	0	0	0	1
38	0	0	0	0	0	0	0	0	0
43	0	0	0	0	1	0	0	0	1
44	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0
46	0	0	0	0	00	0	0	0	0
47	0	0	0	0	0	0	0	1	1
48	0	0	0	0	0	1	0	0	1
49	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0
52	1	0	1	0	0	0	0	1	3
53	0	1	0	0	0	0	0	0	1
54	0	/	/	/	/	/	/	/	/
55	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0
63	0	0	1	0	0	0	0	0	1
64	0	0	0	0	0	0	1	0	1
65	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	1	1
67	1	0	0	0	0	0	0	0	1

TOTAL = 23
M.I.I. = 0.06
CONCLUSION = Non-Irritant

* Examinations performed in comparison with a "negative" control (patch containing only the vehicle) and about 30 minutes after removal of the patches.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

Other observations :

◊ : whitish aspect of the skin.

/ : abandonned during the study.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

TABLE VII

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS

SENSITIZATION

STUDY : evaluation of the irritating and sensitizing potentials by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE : [redacted] (b)(4) [redacted] diluted at (b)(4) (W/W) in distilled water.

VOLUNTEERS N°	SENSITIZATION REACTIONS (0 to 4)		CONCLUSION + (sensitization) - (lack of sensitization)
	(about) 24 h	(about) 48 h	
01	0	0	-
02	0	0	-
04	0	0	-
06	0	0	-
07	0	0	-
08	0	0	-
09	0	0	-
10	0	0	-
11	0	0	-
12	0	0	-
15	0	0	-
16	0	0	-
18	0	0	-
20	1	0	-
21	0	0	-
22	0	0	-
23	0	0	-
24	0	0	-
26	0	0	-
27	0	0	-
28	0	0	-
30	0	0	-
31	0	0	-
32	0	0	-
34	0	0	-

Other observations : nothing to report.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

TABLE VII (continuation)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS

SENSITIZATION

STUDY : evaluation of the irritating and sensitizing potentials by epicutaneous applications under occlusive patch, in the adult volunteer.

TEST ARTICLE (b)(4) [redacted] diluted a (b)(4) [redacted] W/W) in distilled water.

VOLUNTEERS N°	SENSITIZATION REACTIONS (0 to 4)		CONCLUSION + (sensitization) - (lack of sensitization)
	(about) 24 h	(about) 48 h	
35	/	/	/
36	1	0	-
37	0	0	-
38	0	0	-
43	0	0	-
44	0	0	-
45	0	0	-
46	0	0	-
47	0	0	-
48	0	0	-
49	0	0	-
51	2+	1	-
52	0	0	-
53	0	0	-
54	/	/	/
55	0	0	-
57	0	0	-
58	0	0	-
60	0	0	-
61	0	0	-
63	0	0	-
64	0	0	-
65	0	0	-
66	0	0	-
67	0	0	-

Other observations :

/ : abandonned during the study

+ : pruritus

Vol. n° 51 : score at 72 h. = 0 (no pruritus).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

(b)(4) sed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

STUDY ACCEPTABILITY FORM

DOCUMENTS EXAMINED BY THE CLINICAL INVESTIGATOR COORDINATOR (Study Director)

	NO	YES
- Formula of the ingredient to be studied :		
. Qualitative formulation	[ ]	[X]
. Quantitative formulation	[X]	[ ]
- Normal conditions of use of the test article :	[ ]	[X]
- Requisite :		
. Synthesis of the toxicological results on the raw material	[ ]	[X]
. Engagement attestation on innocuity	[ ]	[X]
- Copy of the specific insurance attestation supplied by Sponsor :	[ ]	[X]
- Payment receipt or attestion, supplied by Sponsor, for the fixed duty of 9,500 francs to the collecting administration of Lyon :	[ ]	[X]
- Study protocol : Evaluation of the irritating and sensitizing potentials by epicutaneous applications, under occlusive patch, in 50 adult volunteers :	[ ]	[X]

CONSULTATIVE COMMITTEE'S ADVICE : FAVOURABLE [X] NOT FAVOURABLE [ ]

CLINICAL INVESTIGATOR COORDINATOR'S CONCLUSION (Study Director) :

Study accepted [X] Study refused [ ]

Reason for refusal (if accepted, please indicate : /) : /

Made in Lyon, on : [0][9] [0][5] [9][7]

Investigator Coordinator's (Study Director) signature

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CONSULTATIVE COMMITTEE'S ADVICE

COMITE CONSULTATIF DE PROTECTION
DES PERSONNES DANS LA RECHERCHE
BIOMEDICALE DE LYON A
Hôpital HOTEL-DIEU
Porte 16
Place de l'Hôpital
69288 LYON CEDEX 02
Tél : 04.78.42.94.48
Fax : 04.78.42.94.69

RECU LE
23. AVR. 1997

- Réf : AN/FL
97039/82A(97)
Réf à rappeler SVP
pour ce dossier
- Copie à Mr. GUILLOT (I.E.C.)

Lyon, le 16 avril 1997

Madame le Docteur COLIN
Dermatologue
INSTITUT D'EXPERTISE CLINIQUE
87, rue de Sèze
69006 LYON

Madame,

Le Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon A, lors de sa séance du 15 Avril 1997, a étudié le protocole que vous lui avez soumis, intitulé :

"Etude clinique pour l'évaluation des pouvoirs irritant et sensibilisant de divers ingrédients utilisés en cosmétique, par applications épicutanées répétées de 48 heures sous patch occlusif, chez 2 x 10 + 50 volontaires adultes sains" - Protocole n° 70168 PT du 21 Mars 1997

dont vous êtes l'investigateur coordonnateur et la Société (b)(4) [redacted] promoteur. Il s'agit d'une étude "sans bénéfice individuel direct".

A l'issue de la délibération, le Comité a émis un *avis favorable* à la réalisation de cette étude.

Il conviendrait toutefois d'homogénéiser le titre de l'étude qui est mentionnné sur le protocole, la fiche d'information et le consentement. Afin qu'il n'y ait pas confusion pour les volontaires qui participeraient à plusieurs protocoles, il serait souhaitable de mentionner le numéro de protocole dans les documents d'information.

Dans le cadre des améliorations qui peuvent être apportées à ces protocoles, l'attestation d'engagement (page 24) devrait préciser en en-tête les coordonnées du promoteur,

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Nous vous prions de croire, Madame, à l'expression de nos salutations les meilleures.

Pour le Comité Lyon A

Le Président - Alain NAGEOTTE,

Membres du Comité Lyon A :

Madame BARRIERE Marie-Louise, Médecin conseil, qualifiée domaine social - Monsieur BRAZIER Jean-Louis, Pharmacien, Pasteur Rockefeller - Madame BRUNAT-MENTIGNY Maud, Chef de service en Pédiatrie, Centre Léon Bérard - Monsieur BUFFARD Gabriel, psychologue - Monsieur CASTELLA Henri, expert-comptable, qualifié domaine social - Madame DECARAT Françoise, Infirmière-Surveillante, Service d'Urologie, Hôpital de l'Antiquaille - Monsieur DELAMATE François, Cardiologue, Hôpital Cardiologique - Madame ELOY Mary, Chirurgien, Directeur de Recherches INSERM et BIOMATECH - Monsieur FIERE Denis, Chef de Service Hématologie, Hôpital Edouard Herriot - Monsieur FROSSARD Joseph, Professeur en Droit - Monsieur LOCHER François, Pharmacien, Pharmacie Centrale des H.C.L. - Monsieur MONESTIER Jean, Pharmacien d'Officine - Monsieur NAGEOTTE Alain, Pharmacien Chef, Hôpital Edouard Herriot - Monsieur PERREAU Jean-Marie, Psychologue - Madame RUBIO Christine, Infirmière, Service Hémodialyse, Clinique du Tonkin - Monsieur SALLE Bernard, Chef de service en pédiatrie, Hôpital Edouard Herriot - Madame SASCO Annie, Médecin épidémiologiste, CIRC - Monsieur SCHEUBEL Franck, Professeur de Biologie - Monsieur VIGNOLES Patrick, Professeur de philosophie.

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service, Food and Drug Administration

Memorandum

From: Reviewer(s) - Name(s) [illegible]

Subject: 510(k) Number K024367

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☒ Requires additional information (other than refuse to accept). AI letter
- ☐ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
  - De Novo Classification Candidate? ☐ YES ☐ NO
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Postmarket Surveillance?	☐ YES	☒ NO
Is this device subject to the Tracking Regulation?	☐ YES	☐ NO
Was clinical data necessary to support the review of this 510(k)?	☒ YES	☐ NO
Is this a prescription device?	☐ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☐ NO
Special 510(k)?	☐ YES	☒ NO
Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	☐ YES	☐ NO

This 510(k) contains:

Truthful and Accurate Statement ☐ Requested ☒ Enclosed
(required for originals received 3-14-95 and after)

☒ A 510(k) summary OR ☐ A 510(k) statement

☐ The required certification and summary for class III devices

☒ The indication for use form (required for originals received 1-1-96 and after)

Animal Tissue Source ☐ YES ☐ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

☐ No Confidentiality ☒ Confidentiality for 90 days ☐ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: Additional Product Code(s) with panel (optional):

Review: Neil R.P. Ogden for SPR (PRSB) 3/27/03
(Branch Chief) (Branch Code) (Date)

Final Review: _____
(Division Director) (Date)

Revised:8/17//99

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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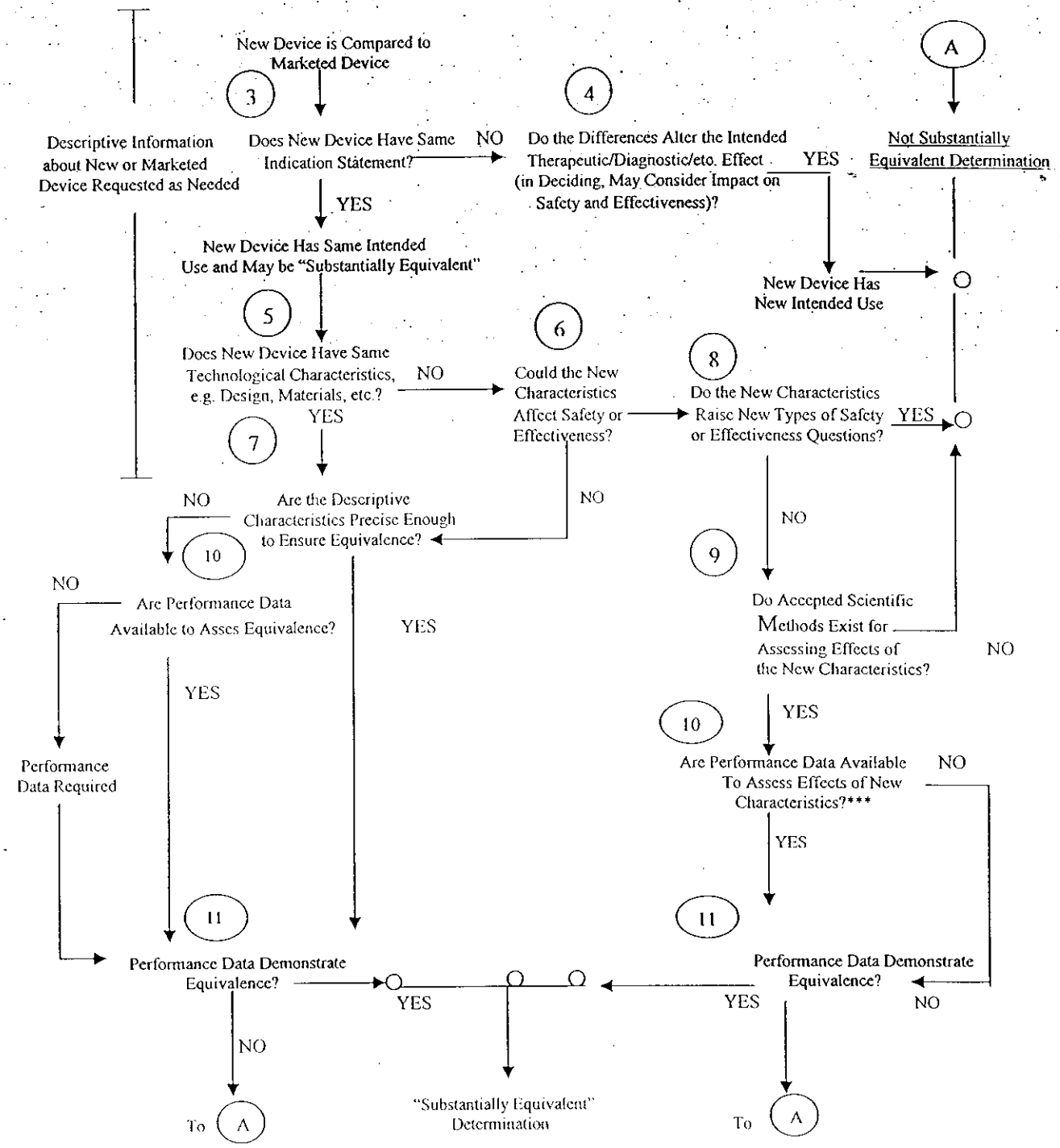
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



❖ 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

❖❖ This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

❖❖❖ Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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510(K) MEMORANDUM

TO: K024367

FROM: ODE/DGRND/Plastic and Reconstructive Surgery Devices Branch

DATE: 3/27/03

SUBJ: Sinclair Wound and Skin Emulsion
Sinclair Pharmaceuticals, Ltd.
Mr. Michael Killeen
972-939-2442
972-236-2282 (fax)

Recommendation:	Additional information is required
Procode:	MGQ
Class:	Unclassified
Regulation Number:	878.4022
Regulation Name:	Hydrogel wound and burn dressing

REVIEW:

Does the product contain drugs or biologicals? Yes, tocopheryl acetate – vitamin E.

1. **Indication and/or Intended Use Statement**
   Subject Device
   Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion has a mechanical action which helps to relieve pain, by adhering to the injured tissue and protecting it from further irritation. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.
   Predicate Device(s)
   Medix Pharmaceuticals Americas Inc., Biafene Wound Dressing Emulsion (RE) Radiodermatitis Emulsion (K964240)
   Biafene is intended to be used as a wound dressing for the following indications:

   - Superficial wounds
   - Minor abrasions
   - Leg ulcers

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- Donor sites
- 1st and 2nd degree burns, including sunburns
- radiation dermatitis

*For dermal ulcers, including full thickness wounds and pressure sores, consult a physician

Carrington Laboratories, RadiaGel Wound Dressing (K961758)
Radiagel is indicated for:

- Radiation dermatitis
- Diabetic ulcers foot ulcers post surgical incisions
- 1st and 2nd degree burns
- Pressure ulcers I-IV
- Stasis ulcers
- Cuts
- Abrasions
- Skin conditions associated with peristomal care
- Sunburn

Discussion of equivalency
I called the company's representative and asked them to revise the indications for use to be consistent with predicate IFUs and to remove language regarding the method of action from the IFU.

2. **Technological Characteristics (Design, Materials, Sizes, etc.)**
Subject Device
The gel formulation contains: purified water, ethylhexyl palmitate, pentylene glycol, butyrospermum parkii, capryloyl glycine, glyceryl stearate, PEG-100 stearate, (b)(4) [redacted] (b)(4) [redacted] arachidyl glucoside, behenyl alcohol, arachidyl alcohol), bisabolol, tocopheryl acetate, glycyrrhetinic acid, carbomer, ehtylhexylglycerin, piroctone olamina, sodium hydroxide, allantoin, Dmdm hydantoin, vitis vinifera, disodium EDTA, ascorbyl tetrisopalmitate, sodium hyaluronate, propyl gallate, telmesteine and butylene glycol

Predicate Device(s)
Medix Pharmaceuticals Americas Inc., Biafene Wound Dressing Emulsion (RE)
Radiodermatitis Emulsion (K964240)
Contains demineralized water, cetyl palmitate, propylene glycol, trolamine, monoglycol stearate, stearic acid, paraffin wax, squalene, avocado oil, liquid paraffin, sorbic acid triethanolamine, methylparaben, propylparaben, fragrance

Carrington Laboratories, RadiaGel Wound Dressing (K961758)
Contains purified water, propylene glycol, triethanolamine salicylate (trolamine), sodium chloride, panthenol, aloe extract with acemannan, carbomer, quaternium 15, allantoin, methylparaben, disodium EDTA, L-glutamic acid, imidurea, potassium sorbate, sodium benzoate, sodium metabisulfite, polyvinylpyrrolidone

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Discussion of equivalency
All of the ingredients listed in the subject device are either found in predicate wound dressings or were identified as GRAS or as registered cosmetic ingredients. The one exception is telmesteine which is identified as a European Oral Mucolytic. The following ingredients are novel or raise concern:

1. butyrospermum parkii (6%) – listed in 21 CFR 184.1702 and identified as Sheanut oil, derived from the Shea tree Butyrospermum parkii. It is composed of triglycerides containing an oleic acid moiety at the 2-position and saturated fatty acids, usually stearic or palmitic acids, at the 1- and 3- positions. GRAS
2. (b)(4) [redacted] (arachidyl glucoside, behenyl alcohol, arachidyl alcohol) – these reagents are listed as a surfactant, stabilizer and stabilizer, respectively. Cosmetic ingredient listing.
3. bisabolol - Cosmetic ingredient listing.
4. tocopheryl acetate (1%) – 21 CFR 182.8892, GRAS
5. glycyrrhetinic acid – used in predicate, Gelclair (K013056)
6. piroctone olamina - Cosmetic ingredient listing.
7. vitis vinifera - Cosmetic ingredient listing.
8. ascorbyl tetraisopalmitate - Cosmetic ingredient listing.
9. propyl gallate – listed in 21 CFR 582.3660 and identified as GRAS/used as an antioxidant
10. telmesteine – European Oral Mucolytic

3. Comparative Performance Data (in vitro, animal and/or clinical)

Safety Data
Subject Device
No biocompatibility evaluations were provided. I contacted Mr. Killeen to request this information since the subject device identifies a number of ingredients that were not identified in predicate products. Mr. Killeen stated that sensitization and irritation evaluations have been conducted and that the information will be submitted.

Predicate Device(s)
Test methods and results

Effectiveness Data
Subject Device
No effectiveness information was submitted. Mr. Killeen stated that the product had been evaluated in clinical settings and that the information was being prepared for publication. He stated that he would provide the information in the near future.

Predicate Device(s)
Both products were cleared based upon human clinical experience.

Discussion of Equivalency
Additional biocompatibility and effectiveness information will be provided by the sponsor to demonstrate product equivalency.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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5. **Sterilization**

   The product is meant to be used on intact, unbroken skin, i.e., skin showing evidence of dermatitis or allergic response, and skin with 1st and 2nd degree burn injury. Dermatitis is defined as inflammation of the skin evidenced by itching, redness, and various skin lesions. Second degree burn is defined as burn in which damage extends through the epidermis and into the dermis but not of sufficient extent to interfere with regeneration of epidermis.

   The Biafene wound dressing is provided non-sterile and was cleared for indications that included broken skin because the formulation contains preservatives and the device had passed the preservative test as specified in the USP Preservatives test. The Carrasyn wound dressing product is supplied sterile.

6. **Labeling**

   (OTC and Prescription)
   Carton/Pouch Labels (page 13 and 14)

7. **Claims**

   Relief of burning, itching and pain and the relief of dry, waxy skin. Information to support these claims is to be provided.

8. **Has sponsor provided all administrative requirements?**
   - Truthful and Accurate Statement (Page 22)
   - 510(k) Summary or Statement (Page 21)
   - Indication for Use Page (Page18)

9. **Summary**

   Additional information is being requested (see questions below).

Deficiencies

1. The indication for use statement includes treatments that are not identified in the predicate wound dressing indications for use provided, e.g., various types of dermatoses, including atopic dermatitis and allergic contact dermatitis. In addition, the indication for use statement describes a possible mechanism of action. Please revise the indications for use statement to be consistent with predicate wound dressings or provide information that supports the intended use on various types of dermatoses, atopic dermatitis and allergic contact dermatitis. In addition, please remove the mechanism of action statement.

2. The indications for use state that the product will manage and relieve the burning, itching, and pain experienced with various types of dermatoses. Please provide information obtained from clinical evaluation of the product's ability to relieve pain associated with the indications for use for your device.

3. The device is provided non-sterile. Radiation dermatitis may result in the skin barrier

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being breached and the labeling indicates that the device may be used on broken skin. Please conduct testing of the product in accordance with the Anti-Microbial Preservatives-Effectiveness <51> microbiological test identified in the USP.

4. Butyrospermum parkii is identified as Sheanut oil under 21 CFR 184.1702. FDA believes that individuals who have nut sensitivities could have an allergic response to the wound dressing. Please include a Warning on the product label informing people that the product contains nut oil or provide information to demonstrate that Sheanut oil does not elicit allergy responses.

5. Please provide toxicity information for the following wound dressing ingredients: Montanov® 202 (arachidyl glucoside, behenyl alcohol, arachidyl alcohol), bisabolol, proctone olamine, vitis vinifera, and telmesteine. In lieu of toxicity information, identification of predicate wound dressings containing these ingredients could address our concerns.

6. The wound dressing formulation contains ingredients that were not identified in predicate wound dressings, or in the same ingredient combinations for predicate wound dressings. Please provide biocompatibility test evaluations for cytotoxicity, irritation and sensitization assessments or information from human clinical experience to address these concerns.

3/27/03

Name Date

Plastic and Reconstructive Surgery Devices Branch

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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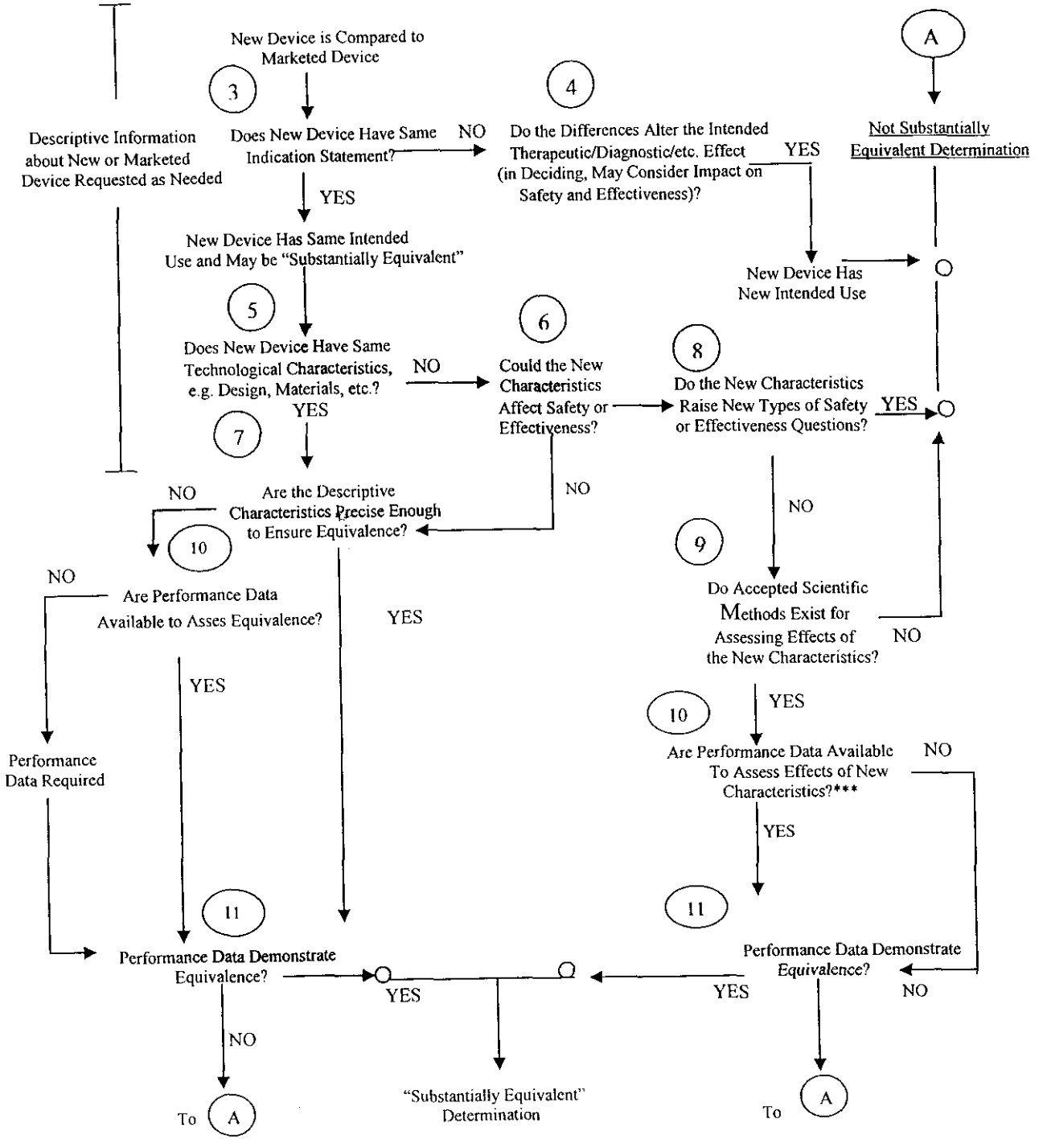

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❖❖❖ Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 06, 2003

SINCLAIR PHARMACEUTICALS, LTD.
BOROUGH RD.
GODALMING, SURREY,
UNITED KINGDOM GU7 2AB
ATTN: MICHAEL KILLEEN

510(k) Number: K024367
Product: SINCLAIR WOUND AND SKIN EMULSION

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

If you have procedural or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and
Radiological Health

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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SINCLAIR

April 25th, 2003

Celia Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Re: K024367
Trade Name: Sinclair Wound and Skin Emulsion™

Dear Dr. Witten:
We received your response letter dated March 27th by mail in our United Kingdom office on April 10th. We appreciate the opportunity to answer your questions before the "clock" starts running again.

In your response you listed 6 specific requests, which I have copied into the body of this reply and will present answers on a question by question basis.

FDA question:

1. The indication for use statement includes treatments that are not identified in predicate wound dressing indications for use e.g., various types of dermatoses, including atopic dermatitis and allergic contact dermatitis. In addition the indication for use statement describes the device mechanism of action. Please revise the indications for use statement to be consistent with predicate wound dressings or provide information that supports the intended use on various types of dermatoses, atopic dermatitis and allergic contact dermatitis. In addition please remove the mechanism of action statement.

Sinclair response:
In treating dermatoses such as atopic dermatitis, allergic contact dermatitis and radiation dermatitis, physicians are faced with conditions that manifest themselves with symptoms in common. Where possible the physician treats the underlying cause but symptom relief is a mainstay of management. Therefore as might be expected and as stated in the attached letter by Professor Howard I. Maibach M.D.[1], the approach to topical treatments for these dermatoses is identical across the disease states.

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[1] Appendix A

Sinclair Pharmaceuticals Limited Borough Road, Godalming, Surrey, UK, GU7 2AB
US Office, Carrollton, TX +1-972-939-2442 www.sinclairpharma.com mkilleen@sinclairpharma.com
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Sinclair Wound and Skin Emulsion™ has been shown in a double blind, randomized, vehicle controlled study[2] of atopic dermatitis patients, to provide statistically significant symptom relief (pain and itch) when compared to the vehicle (emollient base). There were no adverse events reported or observed.

Additional testing was conducted in an open clinical trial[3] with all factors tailored to the allergic contact dermatitis pediatric population (25 patients), where similar relief was noted and again, no adverse events experienced. Our experience with the above mentioned clinical trials supports our claim of symptom relief, due to the commonality of symptoms across the range of dermatoses cited. According to the PDR Dermatology Prescribing Guide (2002 First Edition), "topical corticosteroids are indicated for the relief of pruritic and inflammatory manifestations of corticosteroid responsive dermatoses."[4] A careful review of the 34 topical corticosteroids listed in the Dermatology Prescribing Guide, reveals that each formulation carries the same indications, with no distinction as to the type or the source of the dermatoses.

Once again, after a differential diagnoses two actions are necessary, the first to isolate and remove the causative agent, the second action as a general rule is prescribing a suitable strength topical corticosteroid.

The specific symptoms that we identify in the table on the following pages, are demonstrated (through literature research in dermatology as footnoted) to be the common manifestations of various dermatoses.

---

[2] Caputo, R., M.D. and Veraldi, S., M.D.
[3] Innocenti, M., M.D.
[4] Dermatology Prescribing Guide, PDR 2002, Medical Economics Company Inc, Montvale, NJ

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Symptoms of Various Dermatoses and skin conditions, including Radiation Dermatitis, Atopic Dermatitis and Allergic Contact Dermatitis

Symptom	Radiation Dermatitis[5]	Atopic Dermatitis[6]	Allergic Contact Dermatitis[7]
Pruritus (itching)	√	√	√
Erythema (redness)	√	√	√
Inflammation (warmth)	√	√	√
Desquamation (shedding)	√	√	√
Edema (swelling)	√	√	√
Localized Pain	√	√	√
Scaling skin	√	√	√
Cracked stratum corneum (surface skin)	√	√	√
Oozing (serous)	√	√	√
Lichenification (thickened skin)	√	√	√

We intended that our label claims specifically identify the symptoms that our product is indicated to relieve, providing physicians with a clear and well-defined set of expectations for symptom relief across the range of dermatoses. We believe that physicians have a keen understanding of the fact that symptoms parallel each other with these dermatoses, and are most often treated by the same therapy, regardless of the underlying diagnosis.

As further documentation of the similarity of the symptoms and the likelihood of providing relief, we offer the following:

Atopic Dermatitis (AD)
An overview of the symptoms of atopic dermatitis is provided from the work of Thomas B Fitzpatrick M.D., Chairman Emeritus of the Harvard Medical School Department of Dermatology[8]:

That patients have dry skin and pruritus is the essential element of atopic dermatitis. In the acute phase, poorly defined patches, papules and plaques of erythema present with or without scale. Edema is noted, with widespread involvement; skin appears puffy and edematous. Erosions or fissures may occur with crusting resulting from serous oozing. The presence of excoriation in the acute phase and lichenification in the chronic phase are a result of scratching.

Atopic dermatitis is defined throughout the literature as an intensely pruritic and erythematous inflammatory recurring skin disorder. Many of the additional symptoms (desquamation, pain, cracked skin, oozing or bleeding fissures, skin thickening) that patients experience are a result of scratching to relieve the intense itching.

---

[5] Walter and Miller's Textbook of Radiotherapy 6th Edition, Bomford, C.K., Churchill Livingstone Publisher 2003
[6] Color Atlas and Synopsis of Clinical Dermatology 4th Edition, Fitzpatrick T.B., McGraw Hill Publisher, 2001
[7] Ibid
[8] Pages 30-35, Color Atlas and Synopsis of Clinical Dermatology 4th Edition, Fitzpatrick T.B.

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As noted in the chart on the preceding page, the symptoms of AD, allergic contact dermatitis and radiation dermatitis are similar in their predictability but may vary in timing and intensity.

Allergic Contact Dermatitis (ACD)
While diverging from atopic dermatitis in etiology, ACD presents in the same fashion as AD and radiation dermatitis. Borrowing from Dr. Joseph F. Fowler, Jr[9] speaking before the American Academy of Dermatology, "affected skin may become red, swollen, and blisters often appear, which may break, leaving crusts and scales. Later the skin may darken and become leathery and cracked. The rash is generally confined to the site of contact, although severe cases may extend outside the contact area, especially if the allergen is on your fingers and then transmitted to the face, eyelids or genitals."

"It's important to note that allergic contact dermatitis, such as metal allergy, can be difficult to distinguish from other rashes," stated Dr. Fowler. "However, dermatologists can determine clues about the nature of a rash based on its location on the body and the patient's lifestyle and work habits."

In the acute phase, ACD is characterized by an acute, intensely pruritic, eczematous dermatitis often accompanied by blisters at the site of contact. There are initially well-demarcated areas of erythema with pain experienced in some cases. Blisters often develop and lead to erosion, scaling of skin and crusting after rupture of blisters.

In the subacute phase, Fitzpatrick notes that "plaques of mild erythema showing small dry scales or superficial desquamation" are some of the symptoms exhibited.

Radiation Dermatitis (RD)
According to Bomford and Kunkler in Walter and Miller's Textbook of Radiotherapy, a typical 4 to 5 week course of fractionated radiotherapy yields a predictable series of skin responses, recognized as acute radiation dermatitis.

"No skin changes are observed during the first 2 weeks, apart from a faint erythema. During the third week, the main erythema develops. The skin is warm, red and edematous, itching and local discomfort are reported by the patient. During the fourth and fifth week of irradiation, dry desquamation occurs, sometimes progressing to moist desquamation. The desquamation process often progresses to an inflammatory and serous discharge."[10]

Note that the symptoms listed in the comparative chart on the previous page, have all been identified by Bomford et al[11], as occurring in different stages of acute radiation dermatitis.

At the risk of being repetitive, we believe that the literature supports the statement that, symptomatic manifestations of AD, ACD and RD are generally mirror images of each other and

[9] American Academy of Dermatology's 2003 Annual Meeting in San Francisco, March 24, 2003
[10] Page 298, Walter and Miller's Textbook of Radiotherapy 6th Edition, Bomford, C.K.
[11] Walter and Miller's Textbook of Radiotherapy 6th Edition, Bomford, C.K., Churchill Livingstone Publisher 2003

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are as a matter of course, treated with the same therapy, irrespective of the diagnosis assigned to the specific outbreak.

In accordance with your request, we will amend the Indications for Use and remove the mechanism of action statement.

The new Indications for Use will read:

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Previously submitted Indications for Use: (shown for comparison only)

Under the supervision of a healthcare professional, Sinclair Wound and Skin Emulsion is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Sinclair Wound and Skin Emulsion has a mechanical action which helps to relieve pain, by adhering to the injured tissue and protecting it from further irritation. Sinclair Wound and Skin Emulsion may be used to relieve the pain of first and second degree burns. Sinclair Wound and Skin Emulsion helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

FDA question:

2. The indications for use state that the product will manage the burning, itching and pain experienced with various types of dermatoses. Please provide information obtained from clinical evaluation of the product's ability to relieve pain associated with the indications for use in your product.

Sinclair response:

We have conducted an IRB registered double blind, randomized, vehicle controlled clinical study to validate our claims of symptom (pain and itch) relief. The trial was populated by 30 adult patients followed in 5 office visits over a 36 day period of time.

CLINICAL TRIAL DATA

The data presented here is extracted from a paper undergoing final compilation for submission to be published, so we would request that this data be kept strictly confidential.

As part of the study protocol, the Case Record Forms (CRF) recorded specific patient responses as to whether the products were effective at relieving their pain and itching.

In the Sinclair Wound and Skin Emulsion™ group, the responses combine to show that 93% of patients received pain and itch relief. This was broken down into 53% of patients who stated

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Sinclair Wound and Skin Emulsion™ was "quite good" at relieving pain and itch, while 40% of the patients stated it "slightly helped" to relieve pain and itch.

Patients' preference for the beneficial effects of Sinclair Wound and Skin Emulsion™ on pain and itch was statistically significant when compared to the control group (p=0.008 by the Cochran-Armitage test).

The comparative scores for the same parameters in the control group (vehicle) were 13% responded "quite good" relief and 40% noted that the vehicle "slightly helped."

RESULTS A 5-week study in patients with mild to moderate atopic dermatitis showed that Sinclair Wound and Skin Emulsion™ offered significant benefits over control (emollient vehicle only), when applied *ad hoc* for 3 weeks, with assessments at weekly visits and a final assessment after a 2 week follow-up period. The symptom improvements provided by Sinclair Wound and Skin Emulsion™ and the vehicle, were rated by participating patients at each visit.

PARTICIPANTS
Participants were considered eligible for the study if they met the following inclusion criteria: fair/light skin without recent suntan, >18 years, diagnosed with mild to moderate dermatitis (Hanifin & Rajka) and with atopic dermatitis graded between 3.0 and 7.5 (Rajka & Langeland), and with <20% cutaneous surface involvement. Patients were required to give written informed consent. Female sexually active patients were required to test negative in a pregnancy test and agree to use active birth control for the duration of the study and for two weeks afterwards.

STATISTICAL METHODS
Efficacy measures in the treatment groups were compared using the Wilcoxon rank sum test on changes from baseline (visit 1) for visits 2 to 4, and from visit 4 (when treatment was stopped) for visit 5 (follow up visit two weeks later). Patients' views of treatments in the two groups were compared using the Cochran-Armitage test for trend in a 2 x k contingency table with ordered categories.

BASELINE DATA
16 men and 14 women were recruited into the study, and all patients completed the study. Overall median age was 24 and mean age was 27. Patients had experienced atopic dermatitis for mean 13 years (median 8 years) and their current episode had lasted between 3 and 6 months in all patients. The two groups were comparable in terms of age, sex, duration of condition, duration of current episode and initial severity.

We believe that our detailed approach to data gathering and validation in this study provides verification of our claim of pain relief, especially given the commonality of the symptoms and treatments in the referenced dermatoses.

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FDA question:

3. The device is provided non-sterile. Radiation dermatitis may result in the skin barrier being breached and the labeling indicates that the device may be used on broken skin. Please conduct testing of the product in accordance with the Anti-Microbial Preservative Effectiveness <51> microbiological test identified in the USP.

Sinclair response:
We have in fact conducted preservative effectiveness testing in accordance with the British Pharmacopoeia at an independent laboratory. The results follow on the next 3 pages:

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BODYCOTE MATERIALS TESTING LTD HEALTHCARE LABORATORY,
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Sinclair Pharmaceuticals Ltd

PRESERVATIVE EFFICACY TEST

For

Atopiclair Cream

Checked & approved by D J R Clapperton
Analytical Group Director
22nd April 2003

Sinclair Pharmaceuticals Limited Borough Road, Godalming, Surrey, UK, GU7 2AB
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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1. Introduction

A preservative efficacy test was carried out on Atopiclair Cream to determine the effectiveness of preservation of the formulation. Analysis was carried using the British Pharmacopoeia method. Appendix XVI C : Efficacy of Antimicrobial Preservation

Known amounts of test organisms were introduced to sample and the effectiveness of kill measured over a period of 28 days.

The test calls for four organisms to be used.

2. Results

Lot 30124

Organism Culture Ref Inoculum, cfu/g	*Pseudomonas aeruginosa* *ATCC9027* *2,600,000*		*Staphylococcus aureus* *ATCC6538* *1,200,000*		*Aspergillus niger* *ATCC16404* *410,000*		*Candida albicans* *ATCC10231* *390,000*	
Timepoint	Recovered, cfu/ml	% Recovery	Recovered, cfu/ml	% Recovery	Recovered, cfu/ml	% Recovery	Recovered, cfu/ml	% Recovery
Initial	126,000	5	100,500	8	170	0.04	83,500	21
24 hours	0	0	0	0	0	0	0	0
48 hours	0	0	0	0	5	0.001	0	0
7 days	0	0	0	0	0	0	0	0
14 days	0	0	0	0	0	0	0	0
28 days	-	-	-	-	-	-	-	-
Outcome	Passes test		Passes test		Passes test		Passes test	

Tests terminated at 14 days as in each case total kill was achieved after 7 days and maintained at 14 days. The sample meets the requirements for all organisms.

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3. **Conclusion**

The sample meets the requirements of the test.

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FDA question:

4. Butryospermum parkii is identified as Sheanut oil under 21 CFR 184.1702. FDA believes that individuals who have nut sensitivities could have an allergic response to the wound dressing. Please include a warning on the product label informing people that the product contains nut oil or provide information to demonstrate that Sheanut oil does not elicit allergy responses.

Sinclair response:
Our amended label with warning will read as follows:
Caution: Sinclair Wound and Skin Emulsion™ contains a nut oil, and patients with a known allergy to nuts or nut oils should consult their physician before using this topical preparation.

FDA question:

5. Please provide toxicity information for the following wound dressing ingredients: (b)(4) [redacted] (arachidyl glucoside, behenyl alcohol, arachidyl alcohol), bisabolol, piroctone olamine, vitis vinifera and telmesteine. In lieu of toxicity information, identification of predicate wound dressings containing these ingredients could address our concerns.

Sinclair response:
Toxicity information for the requested materials is attached as Appendix B (b)(4) [redacted] Appendix C (bisabolol), Appendix D (piroctone olamine), Appendix E (vitis vinifera), and Appendix F (telmesteine).

FDA question:

6. The wound dressing formulation contains ingredients that were not identified in predicate would dressings, or in the same ingredient combinations for predicate wound dressings. Please provide biocompatibility test evaluations for cytotoxicity, irritation and sensitization or information from human clinical experience to address these concerns.

Sinclair response:
As mentioned in previous answers, human clinical testing (Veraldi) that measured safety has recorded that no adverse events have been reported or observed. In addition to the double blind study cited above, an Open Pilot Study was conducted by Dr. M Innocenti, in which he treated 25 pediatric patients aged 1 month to 5 years, who were suffering from ACD. Doctor Innocenti also reported that no adverse events were observed during or after treatment.

Attached you will find Appendix G (ISO Closed Patch Sensitization Study), Appendix H (ISO Skin Irritation Study) and Appendix I (Patch and Photo patch tests) which reports on Sinclair Wound and Skin Emulsion™ under the name of Xclair. There is no difference in the formulation, only the name recorded in the test. We believe that these tests provide the required data.

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Regarding cytotoxicity, these assays were developed for typically physical devices that presumably release minimal amounts of chemicals.

For formulations of the type in this application, we believe the preferred assay is the rabbit or the human irritation study, as these have a higher laboratory – clinical correlation to man. We therefore selected the above-mentioned tests as most relevant to human needs.

Thank you for your time and attention to this matter. I am available to address any questions that you may have, please call at 972-939-2442 at your convenience. We at Sinclair Pharmaceuticals hope that your questions have been answered to your satisfaction and we look forward to a timely resolution of this application.

Sincerely,

Michael Killeen
Executive Director

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Celia Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Appendix - A

Re: K024367
Trade Name: Sinclair Wound and Skin Emulsion™

Dear Dr. Witten:
Sinclair Pharmaceuticals has requested that I provide a commentary on the standards of treatment relative to various dermatoses and their relation to symptom relief provided by the product cited above.

I have been a Professor at the University of California, San Francisco, with a clinical focus on dermatopharmacology and allergic contact dermatitis. I have served on editorial boards of more than 30 scientific journals, published over 1,700 papers and serve as a consultant to several firms in professional and or consumer dermatology.

My intention here is to offer my experience in treating various dermatoses, ranging from Radiation Dermatitis (RD) through Atopic (AD) and Allergic Contact Dermatitis (ACD).

These disease states manifest symptoms that are identical to the untrained eye. Pruritus, erythema and inflammation show up as the most common and most severe of the typical signs and symptoms. While the sequence and severity of their appearance may vary from patient to patient, their arrival is certain in all types of dermatitis.

Corticosteroids are the gold standard of treating pruritus and inflammation in dermatitis[1]. This is evidenced for RD in literature (Radiation and Oncology 59 2001, 257-265, *Potent corticosteroid cream significantly reduces acute radiation dermatitis* – Boström, Lindman – attached), as well as in common practice.

Using topical corticosteroids to relieve itch and inflammation in AD and ACD has long been established among physicians and has even extended into the OTC market for consumer treatment of itching and minor rashes.

Given that corticosteroids generally alleviate the symptoms of dermatoses irrespective of etiologies, the Sinclair product should provide similar symptom relief in these dermatoses[2].

I would be pleased to provide additional information on the diseases or symptoms, as you request. Please call on me if I can be of any service.

Sincerely,

H. Maibach M.D. (GSK)

Howard I. Maibach, M.D.

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[1] Topical Corticosteroids, Maibach & Surber, Karger Publishing 1992, ISBN 3-8055-5332-3

[2] A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of Sinclair Wound and Skin Emulsion™ in the management of mild to moderate atopic dermatitis, Authors: S. Veraldi M.D, R. Caputo, M.D. 2003

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ELSEVIER

Radiotherapy and Oncology 59 (2001) 257–265

RADIOTHERAPY & ONCOLOGY

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Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study

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Received 8 December 2000; received in revised form 25 January 2001; accepted 12 February 2001

Abstract

Purpose: Radiation-induced dermatitis is a very common side effect of radiation therapy, and may necessitate interruption of the therapy. There is a substantial lack of evidence-based treatments for this condition. The aim of this study was to investigate the effect of mometasone furoate cream (MMF) on radiation dermatitis in a prospective, double-blind, randomized study.

Material and methods: The study comprised 49 patients with node-negative breast cancer. They were operated on with sector resection and scheduled for postoperative radiotherapy using photons with identical radiation qualities and dosage to the breast parenchyma. The patients were randomized to receive either MMF or emollient cream. The cream was applied on the irradiated skin twice a week from the start of radiotherapy until the 12th fraction (24 Gy) and thereafter once daily until 3 weeks after completion of radiation. Both groups additionally received non-blinded emollient cream daily. The intensity of the acute radiation dermatitis was evaluated on a weekly basis regarding erythema and pigmentation, using a reflectance spectrophotometer together with visual scoring of the skin reactions.

Results: MMF in combination with emollient cream treatment significantly decreased acute radiation dermatitis ($P = 0.0033$) compared with emollient cream alone. There was no significant difference in pigmentation between the two groups.

Conclusions: Adding MMF, a potent topical corticosteroid, to an emollient cream is statistically significantly more effective than emollient cream alone in reducing acute radiation dermatitis. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Corticosteroid; Radiation dermatitis

1. Introduction

Acute radiation dermatitis is a common side effect of radiotherapy in many forms of cancer (e.g. head and neck, breast and low pelvic carcinomas). The intensity of the reaction depends on the radiotherapy fraction schedules, the total dose, the treated skin area, and also individual variations [47]. The initial erythema may be seen within 24 h after the first radiation [44]. A secondary and progressive erythema normally appears after 10–20 Gy, depending on the schedule, and reaches a maximum approximately 1–2 weeks after completion of radiotherapy [48]. A severe acute skin reaction, e.g. moist desquamation, bullae/ulcers and skin necrosis, may necessitate discontinuation of the radiotherapy, which may negatively influence the outcome [16] and impair the patient's quality of life.

The treatment of acute radiation dermatitis varies between different oncology centers in Sweden (unpublished data), Germany [52], and the United Kingdom [2]. A number of non-steroid creams have been investigated in randomized trials [15,29,31–33,38,45]. Only sucralfate cream and hyaluronic acid have shown statistically significant positive effects [31,32].

Acute radiation dermatitis is an inflammatory skin reaction and is commonly treated by topical use of corticosteroids. The anti-inflammatory effects of corticosteroids in general are achieved through vasoconstriction, decreased capillary permeability, and inhibition of leukocyte proliferation and migration [51], but their mechanisms are still not completely understood. The inflammatory processes in acute radiation are controlled partly by proinflammatory cytokines [26]. Interleukin (IL)-6 is supposed to be one of the key mediators of radiation-induced inflammation [9]. Recently Beetz et al. [3] reported an upregulation of IL-6 expression in an irradiated human epithelial cell line, which could be inhibited by corticosteroids.

The value of using topical corticosteroids in practice in

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PII: S0167-8140(01)00327-9

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acute radiation dermatitis has been discussed in the literature, but the opinions still vary [4,5,6,19,21,39].

The primary aim of this study was to determine whether a corticosteroid cream, mometasone furoate (MMF), used as prophylaxis and treatment, could reduce the intensity of the erythema in acute radiation dermatitis. Secondary aims were to study the differences pigmentation and the subjective symptoms of itching, burning and pain. MMF cream is a moderately to potent corticosteroid, and it has been demonstrated to have an equal effect to betamethasone valereate [43]. However, in the United States it is classified according to the Stoughton–Cornvell Scale as a medium potent steroid because of the low risk of atrophy. MMF (Elocon) has three potential advantages over other topical corticosteroids. First, it is a potent corticosteroid with a low risk of overt cutaneous atrophy [8,24,25,28], and secondly, the cream has been claimed to have a prolonged effect lasting for 24 h, and could thus be administered in a once-a-day schedule [8]. Thirdly, it has been confirmed that MMF has a strong inhibitory effect on the IL-6 activity, both on the transcriptional and protein level, during radiotherapy [3]. To select as homogeneous patient material as possible, only breast cancer patients treated with photons to the same target, receiving the same radiation quality and dosage schedule, and without any systemic adjuvant therapy were included.

2. Patients and methods

This randomized, double-blind, controlled study was conducted over a period of 29 months. The study is a part of a larger joint project engaging oncologists, dermatologists and pathologists, in which correlations between radiation dermatitis and UV-sensibility, p53 activation and histological changes are being investigated. The ethics committee at Uppsala University, Sweden approved the study. Schering–Plough AB, Sweden contributed to the study with the blinded tubes and a minor research grant.

2.1. Patients

Fifty women entered the study (Table 1). The inclusion criteria were women undergoing breast-conserving surgery for histopathologically proven primary breast adenocarcinoma without lymph node metastasis. The patients should be scheduled for fractionated radiotherapy of the breast parenchyma with the same accelerator. Exclusion criteria were concomitant systemic anticancer treatment and known cutaneous diseases or severe systemic diseases. Also patients who had recently been in the sun or on a tanning bed were excluded. The patients received oral and written information and an informed consent was required before inclusion in the study.

2.2. Radiotherapy

The patients were treated with tangential 5 MV photon beam radiotherapy to the breast parenchyma from one specific linear accelerator (Philips SL 75-5), as previously described in detail [30]. The patients were positioned supine with elevated arms and flexed elbows, and a Vac Fix bag was used for support and immobilization. The radiation oncologist palpated the breast parenchyma and defined the treatment fields during simulation. The cranial and caudal portals were 2 cm from the parenchyma, and the medial field border was in the centerline of the patient. Wedges were used to optimize the dose distribution and no bolus was allowed. The treatment planning was based on a single transverse central slice and the treatment planning system used was Helax-TMS [22]. Therapy was delivered in 2 Gy fractions, with a dose normalization point at the center of the target [20], 5 days per week to a total dose of 54 Gy. The dose rate was 3 Gy/min at the dose maximum depth of 12 mm. In vivo dosimetry with semiconductor detectors was performed once a week and the fields were verified and compared with the X-rays from the simulation at least one time during the treatment.

2.3. Topical application of mometasone furoate cream or emollient cream

The patients were randomized to receive blinded tubes of either the potent corticosteroid mometasone furoate cream 0.1% (Elocon, Schering–Plough) or an emollient cream (Diprobase, Schering–Plough) used as placebo. The patients were instructed to apply the study cream on the irradiated area twice a week up to 24 Gy and thereafter once daily until 3 weeks had elapsed after completion of the radiotherapy. All patients in the MMF and placebo groups also applied non-blinded emollient cream (Diprobase) over the radiation area once daily, starting on the first day of irradiation and continuing until 3 weeks after completion of radiotherapy.

2.4. Assessment measures

The area to be irradiated was investigated and documented before the start of radiotherapy in conjunction with a postoperative conference and at a special visit to the Dermatology Department. Either of two dermatologists investigated the patients. Punch biopsies from the treated breast were taken before and after the treatment for future studies of any late side effects. The irradiated skin area was evaluated at 24, 34, 44 and 54 Gy, and 3 weeks after completion of radiotherapy. In case of extensive acute radiation dermatitis and/or severe subjective symptoms, the patients could receive further topical treatment, decided by the dermatologist. However, the patient would also be expected to continue with the blinded cream and not be excluded from the study.

For quantitative evaluation of the erythema/pigmentation, a reflectance spectrophotometer (DermaSpectrometer, Cortex; Technology, Hadsund, Denmark), with digital readout was used [12]. The instrument emits green light at 568 and red at 655 nm, corresponding to the absorption peaks of

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Table 1
Characteristics of the patients in the mometasone furoate (MMF) cream and the emollient cream group ($n = 49$)[a]

Characteristics	MMF		Emollient	
Total number of patients	24		25	
Median age (range) (years)	58	(48–72)	60	(47–76)
Menopausal status				
Pre-	4	17%	3	12%
Post-	19	79%	21	84%
Breast				
Right	10	42%	10	40%
Left	14	58%	15	60%
Brassiere cup size				
Size A	0	0%	1	4%
Size B	14	58%	15	60%
Size C	8	33%	6	24%
Size D	2	8%	3	12%
Tumor location				
Medial	5	21%	9	36%
Lateral	17	71%	15	60%
Central	2	8%	1	4%
Mean tumor size (range) (mm)	11.0	(4–25)	11.0	(3–20)
TNM				
T1N0M0	23	96%	25	100%
T2N0M0	1	4%	0	0%
Axillary node dissection				
Yes	18	75%	22	88%
No	6	25%	3	12%
Median number of nodes (range)	10	(3–23)	10	(1–20)
Skin phototype				
Type 1	0	0%	0	0%
Type 2	6	26%	5	20%
Type 3	16	70%	17	68%
Type 4	1	4%	3	12%
Dose				
54 Gy	22	92%	22	88%
56 Gy	2	8%	3	12%
Median days of treatment (range)	39	(36–45)	39	(34–50)
Mean CRE (range)	16.4	(16.2–16.6)	16.4	(16.1–16.8)
Maximum dose, average (range) (%)	108.0	(105.2–112.8)	108.2	(103.9–115.2)

[a] CRE, cumulative radiation effect; skin phototype, a subjective assessed determined sunburning and tanning tendency arbitrarily graded [12]. The two groups were well balanced.

hemoglobin and melanin, respectively. The intensity of the emitted light is detected by a photodetector as a relative and dimensionless average erythema index and melanin index, after compensating for temperature and for ambient light penetrating into the sensor. The measured skin area is circular with a diameter of 11 mm.

The irradiated area as well as the corresponding area on the untreated breast was divided into five regions (medial breast, lateral breast, areola, under the breast, and axilla) (Fig. 1). All five regions in each breast were measured in triplicate. The mean of the three assessments in each of the five regions (Fig. 1) of the untreated breast was subtracted from the corresponding mean value of the triplicate in each of the five regions in the treated breast to compensate for background erythema and pigmentation. The resulting values were designated objective region values (ORV). A so-called 'patient erythema-index mean' (PEM) and 'patient melanin-index mean' (PMM) were calculated as the average of the five ORV for the two respective wavelengths, and represented a patient's average reaction for a given dose. The total patient erythema index (TPE) and the total patient melanin index (TPM) were defined as the mean of all five PEM and PMM in each patient, respectively.

The adverse reaction in the skin was visually described and recorded with reference to erythema, edema, ulceration/bullae, and moist desquamation. The interpretation of the adverse reaction in the skin was graded on a seven-point scale; 0 = no reaction, 1 = just perceptible erythema, 2 = mild erythema, 3 = moderate erythema, 4 = severe erythema, 5 = severe erythema and edema, 6 = moist desquamation or ulceration/bullae. Each of the five regions in the treated breast was evaluated at every visit.

The patients' subjective experiences of itching, burning, and pain in the irradiated area were classified by the patients

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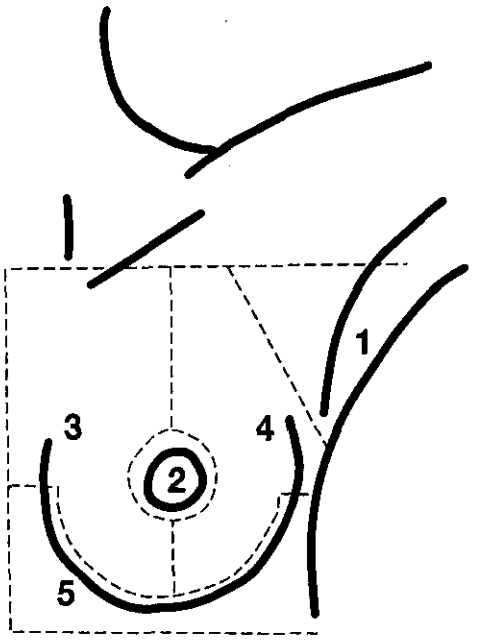

Fig. 1. The irradiation area was divided into five regions: axilla (1), areola (2), medial breast (3), lateral breast (4), and under the breast (5).

using a Visual Analogue Scale (VAS) (10 cm in length; 0 = no symptom, 10 = worst possible symptom). The patients were photographed at every visit for later verification of the dermatitis.

2.5. Statistical methods

Under the assumption of an overall mean difference of 0.5 units and a standard deviation of 0.5 units, 42 patients (21 in each group) were required to achieve a power of 90% to reject a null hypothesis of equality, applying a two-sided test at the 5% significance level (normal approximation). With an estimated fraction of 15% of the patients being not evaluable, a total of 50 patients had to be included in the study.

The patients fulfilling the inclusion and exclusion criteria were randomized into one of two treatment arms (emollient versus MMF), using computer-generated randomization list and the closed envelope system at the first visit to the dermatologist. Neither the oncologist, the dermatologist, the radiotherapy technicians, the nurses nor the patients knew the content of either of the blinded tubes. The code was broken after the last patient had fulfilled her follow-up. An independent statistician performed all the statistical analyses. The intention-to-treat principle and two-tailed tests were used. The Mann–Whitney *U*-test was used for all statistical comparisons in the total objective erythema, maximal scored erythema, the total objective pigmentation and the subjective scored symptoms (itching, burning and pain).

3. Results

Fifty women with diagnosed breast cancer without signs of lymph node metastasis (T1–2 N0 or Nx M0) entered the study. One patient, after being randomized in the study, refused further participation before the start of the MMF treatment and any evaluation, and could not therefore be included in the final analysis. Thus 49 patients were eligible for evaluation.

All patients were healthy, with a WHO performance status of 0 and with no signs of remaining breast cancer. No patient received concomitant adjuvant therapy or any drugs that could have interfered with the effect of the radiation, except for one patient in the emollient group. She was given systemic glucocorticosteroid treatment for 3 weeks after 42 Gy because of acute eruption of erythema nodosum localized to her lower extremities. The two groups were well balanced regarding age, menopausal status, treated breast, primary tumor data, and skin phototype (Table 1). Also, the total delivered radiotherapy doses, length of treatment and estimated maximum skin dose in the central slice, proved to be well balanced. The estimated breast sizes (reported as brassiere sizes) were also comparable.

In five cases (two in the MMF group and three in the emollient group) the duration of treatment was prolonged as a result of treatment interruption because of machine service or holidays, and an extra fraction (2 Gy) was added to a total dose of 56 Gy. In these patients the 54 Gy evaluation was made at 56 Gy. The +3-week evaluation was performed earlier in three patients; in the MMF group one patient was investigated only 7 days after cessation of radiotherapy, and in the emollient group two patients were followed up after 10 and 15 days, respectively, because of holidays. In one patient in each group the +3-week evaluation was not done.

3.1. Evaluation of erythema and pigmentation using reflectance spectrophotometry

The mean PEM was higher in the emollient group than in

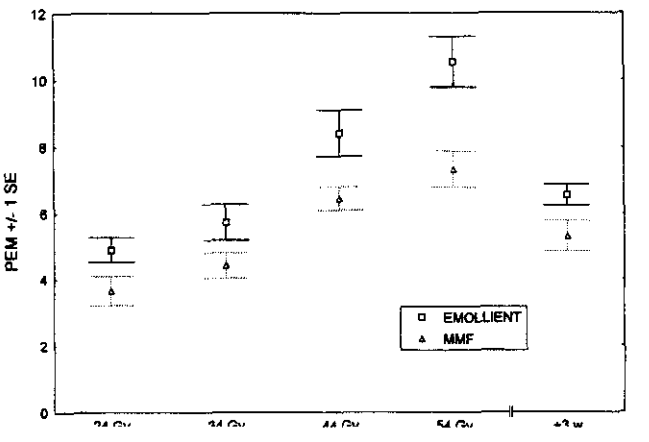

Fig. 2. Means (with SE) of the patient erythema index mean (PEM) in each of the two groups at different dose levels and three weeks after completion the radiotherapy. □ indicates the group treated only with emollient cream and △ indicates the group treated with mometasone furoate cream plus emollient cream.

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Table 2
Data of the total objective skin reactions (total patient erythema index (TPE) and the total patient melanin index (TPM)) and maximum erythema scores (E-score) for each patient in the study ($n = 50$)

Patient no.	Cortisone	TPE	TPM	Maximum E-score	Patient no.	Cortisone	TPE	TPM	Maximum E-score
1	No	7.9	1.9	3	3	Yes	7.0	3.6	3
2	No	9.1	2.9	3	5	Yes	3.9	1.5	2
4	No	11.2	2.1	3	6	Yes	5.5	7.2	6
8	No	8.6	6.2	6	7	Yes	5.3	1.5	2
9	No	6.5	0.2	2	10	Yes	7.9	7.7	2
12	No	4.4	6.3	3	11	Yes	5.8	0.8	2
13	No	8.4	6.4	4	14	Yes	6.5	2.9	3
15	No	4.9	7.2	3	18	Yes	4.3	4.3	6
16	No	11.1	8.0	6	19	Yes	5.9	3.3	4
17	No	8.1	7.1	6	20	Yes	5.0	3.3	3
22	No	7.0	4.0	4	21	Yes	5.6	4.6	4
23	No	7.5	1.2	6	26	Yes	5.4	4.3	2
24	No	6.8	7.8	6	28	Yes	2.9	2.7	2
25	No	5.4	3.1	6	29	Yes	5.1	3.1	2
27	No	4.0	3.3	6	30	Yes	5.4	1.2	3
31	No	10.8	3.3	6	34	Yes	6.0	2.8	3
32	No	6.1	1.1	3	36	Yes	7.2	2.2	6
33	No	7.6	4.8	4	37	Yes	5.9	3.7	3
35	No	10.0	6.2	6	38	Yes	5.8	2.9	3
39	No	4.8	3.9	4	40	Yes	3.5	1.2	6
41	No	4.9	2.9	2	42	Yes	6.3	4.2	3
44	No	7.0	1.3	4	43	Yes	2.3	4.6	2
45	No	6.4	5.8	3	46	Yes	5.9	4.4	3
48	No	5.5	1.0	6	47[a]	Yes	ND	ND	ND
50	No	7.0	5.6	3	49	Yes	6.1	2.5	3
Mean		7.2	4.1	–	Mean		5.4	3.4	–
Median		7.0	3.9	4	Median		5.7	3.2	3
Minimum		4.0	0.2	2	Minimum		2.3	0.8	2
Maximum		11.2	8.0	6	Maximum		7.9	7.7	6

[a] Patient no. 47 in the cortisone-treated group was not eligible for evaluation. ND, not determined.

the MMF group at all studied radiation dose levels (Fig. 2). The TPE was statistically significantly lower ($P = 0.0033$) in the mometasone furoate group than in the group treated only with emollient cream (Table 2).

The emollient group showed an increase in mean PMM during the follow-up period (Fig. 3), but no significant difference ($P = 0.31$) in the median total patient melanin index (TPM) was found between the MMF and the emollient group (Table 2).

3.2. Evaluation of the acute radiation dermatitis and pigmentation by scoring

Before the start of treatment no patients exhibited erythema on the irradiated field except one patient in the emollient group, in whom slight postoperative inflammation was suspected in the lower part of the breast (scored as 2). All other areas in the patients were scored as 0 at baseline. The MMF-treated patients showed a less pronounced maximal skin erythema reaction than patients in the emollient cream group (Tables 2 and 3). The difference was statistically significant ($P = 0.011$).

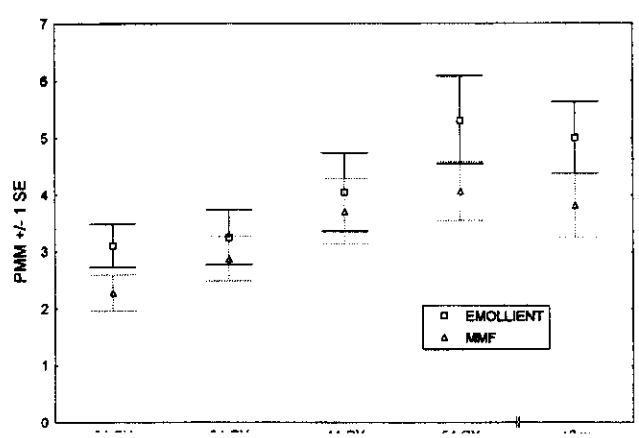

Fig. 3. Means (with SE) of the patient melanin index mean (PMM) in the two groups at different dose levels and three weeks after completion of the radiotherapy. □ indicates the group treated only with emollient cream and △ indicates the group treated with mometasone furoate cream.

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Table 3
The maximal assessed erythema score for the patients in each group, during the study period[a]

	Maximal score					
	1	2	3	4	5	6
Emollient ($n = 25$)	0	2	8	5	0	10
MMF ($n = 24$)	0	8	10	2	0	4

[a] The patients in the emollient group had significantly worse skin reactions than the patients in the MMF group ($P = 0.011$).

3.3. Numbers of failures in the emollient and the mometasone furoate groups

Six patients in the emollient group required further topical treatment because of subjective severe symptoms from the regions with moist desquamation (Table 4). None of the patients had any clinical sign of infection in the skin. The patients continued with their blinded tubes but applied the optional treatment separately on these sore areas. The code was not broken. One patient had a suspected eruption of lupus erythematosus in the irradiated area after 24 Gy and she received betamethasone valerate clioquinol cream after 44 Gy. Three patients in the MMF group needed further treatment because of severe moist desquamation in the axilla (Table 4). However, two of these patients forgot to apply the study cream in the axilla during the treatment period. These two patients started to use MMF (the blinded tube) again in the axilla and then improved.

3.4. Subjective experience of pain, burning and itching

The majority of the patients had no or very mild symptoms during the study. Patients in the group receiving MMF cream experienced less itching and burning than in the group treated with emollient cream only, but the difference did not reach the significance ($P = 0.069$ and $P = 0.087$, respectively) level. No difference in pain was seen ($P = 0.42$)

4. Discussion

Acute radiation dermatitis is associated with epidermal basal cell and endothelial cell damage, and with an inflammatory reaction [1,17]. A severe acute dermatitis is associated with considerable discomfort for the patient who may cause a delay of the radiation and thus reduce the antitumoral effect [17]. In the present study using an objective scoring system, we have demonstrated that MMF, used from the first day of radiotherapy until 3 weeks after its completion, in combination with emollient cream, is statistically significantly superior to emollient cream only, in reducing acute radiation dermatitis. The clinical value of this finding is most obvious to understand when comparing every patient's maximal reaction. This result also showed a clear significant benefit for MMF-treatment. Besides that, the number of patients requiring complementary treatment indicates a substantial benefit of adding MMF to emollient cream. Most patients had only mild subjective symptoms due to the moderate skin doses given to this group. Patients in the MMF group clearly tended to report less itching and burning than patients did in the control group, but in this study this results were not statistically significant.

The potential effectiveness of local or systemic corticosteroids in the treatment of acute radiation dermatitis has been reviewed in the literature [4–6,10,18,19,21,23,34–36,39,40]. In humans, only two previous studies have shown positive effects of use of local corticosteroids in the treatment of acute radiation dermatitis [4,6]. In these studies, steroid cream of similar potency to MMF were used. Other authors did not find any benefit of steroid therapy [14,19,39]. This lack of positive previous results could be due to several factors.

The use of less potent corticosteroids in two of the studies [14,39].

Table 4
Patients in each group needing optional treatment specified at the dose level before failure and the sore region[a]

	CRE (Gy)	Optional local treatment	Sore region
Emollient group	44	MMF	Axilla
	44	Betamethasone valerate	Upper half of the breast
	44[b]	Betamethasone valerate + clioquinol	Whole breast
	50	Fusidic acid	Areola
	54	Triamcinolone acetonide + halquinol	Axilla
	54	Betamethasone valerate + neomycin	Axilla
MMF group	44[c]	MMF	Axilla
	54[c]	MMF	Axilla
	54	Fusidic acid	Axilla

[a] Potent steroids with or without antibiotics were mostly chosen.
[b] The patient with eruption of lupus erythematosus.
[c] The two patients who did not apply the study cream (MMF) in the axilla from the beginning.

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Occurrence of the 'break through phenomenon'. Björnberg and co-workers [15] reported that four out of 23 patients developed severe dermatitis after 3 weeks on radiotherapy despite initial good effects of fluocinolone acetonide ointment. He refers to this as a 'break through phenomenon' [5]. Glees et al. discussed this as a possible explanation for the lack of effect of clobetasone butyrate, a moderately potent corticosteroid compared with hydrocortisone, a mild corticosteroid cream [14]. The mechanisms underlying this phenomenon are unclear. It is tempting to speculate, however, that this phenomenon is due to the development of contact dermatitis in reactions to the use of local steroids [50].

*Variations in the local corticosteroid administration regimes*in the different studies. In some studies which failed to demonstrate positive effects of corticosteroids, the treatment was begun only when the acute radiation dermatitis became manifest [14,39]. Björnberg and co-workers, on the other hand, started treatment at the initiation of radiotherapy [4–6]. The importance of applying topical steroids from the start of the radiotherapy is underlined by the fact that signs of radiation dermatitis may be seen already after the first radiation dose [46].

Heterogeneity of the patient material and radiotherapy schemes may have influenced the results. Previous studies have included patients with different cancer type as well as different radiotherapy doses.

*Patients serving as their own controls.*In the majority of the studies the irradiated area was divided into smaller regions to evaluate the effects of different local treatments [4,5,14]. In only one study was the patients randomized to use one of two different treatments [14]. Our study design was to randomize the patients to receive only one of the two tested creams in order to avoid any undesired extra-regional effects or potential systemic effects. Comparisons of different irradiated regions in the same patient can also be hazardous, in view of differences in skin radiation doses and the regional skin quality.

*Subjective evaluation methods.*In previous steroid studies only subjective scoring methods have been used to evaluate the intensity of the erythema. Visual grading of slight erythema is difficult, as is scoring of a combination of erythema with moderate or marked pigmentation. To avoid these shortcomings, we have evaluated the intensity of the erythema and pigmentation separately with a reflectance spectrophotometer. The use of a reflectance spectrophotometer for quantification of erythema in acute radiodermatitis has been described previously [11,46]. Since this method could give false low values in more severe skin reactions (ulceration, bullae, moist desquamation), a visual evaluation was also performed.

The relatively limited use of potent topical corticosteroids during radiotherapy may be due to the fear of increasing the risk for development of atrophia, telangiectasia in the irradiated area. However, MMF has demonstrated a high degree of efficacy and a potentially low risk of cutaneous atrophy [8,24,25,28,43]. During our relatively short observation period no sign of telangiectasia or macroscopically atrophic skin was observed. A long-term follow-up study with skin biopsies has been initiated to evaluate this potential problem. Another theoretical reason for not using potent topical corticosteroids may be a fear of suppression of the pituitary–adrenal axis. The risk for this event is very low, however, as MMF is used on a relatively small body area (<5%), and the percutaneous absorption of this cream is only 0.4% [7,27,41,49]. In the liver MMF is reduced to three different metabolites with very little intrinsic activity [27]. The risk of secondary skin infection may be one reason that many oncologists hesitate to use steroid cream for radiation dermatitis. In our study no signs of secondary infection in the skin have been recorded.

In the future the control of acute radiation dermatitis could be of increasing importance, as more frequent use of hyperfractionated radiation schedules most likely will increase the incidence. The promising results from randomized trials [21,37,42] will probably lead to an increase in the number of patients irradiated at both the breast and regional lymph nodes. This in turn could increase the use of electrons for minimizing the cardiopulmonary side effects [13] and lead to higher skin doses [13].

In conclusion, this study has demonstrated that a potent local corticosteroid cream, mometasone furoate, is statistically significantly more beneficial than emollient cream only, in the treatment of acute radiation dermatitis. The results from this study support the use of moderately to potent steroid cream from the first day of radiotherapy until 3 weeks after its completion, as prophylaxis against acute radiation dermatitis.

Acknowledgements

This study was mainly supported by grants from the Swedish Cancer Society, Lions Cancer Research foundation, Torsten and Ragnar Söderberg's Foundation. The authors wish to thank Marianne Johansson and the rest of the staff of the Radiotherapy Department in Uppsala for their assistance and enthusiasm.

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Appendix B

MONTANOV® 202

Glucolipid O/W emulsifier of vegetable origin

- For a light and evanescent touch
- For a long-lasting moisturising action
- Perfect dermo-compatibility :
  - non comedogenic
  - non sensitising
- A pure and ecological concept

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I. DEFINITION

(b)(4) [redacted] is **a new emulsifier derived from materials of vegetable origin :**

- glucose extracted from corn
- fatty phase extracted from rape seed oil.

The originality of (b)(4) [redacted] lies in the absence of ethylene oxide. The characteristic oxyethylated group of traditional non ionic emulsifiers is replaced in this case by a natural holoside. A product composed of a hydrophilic glucolipid and a lipophilic fatty chain is thus obtained.

(b)(4) [redacted] [redacted] is distinguished from (b)(4) [redacted] by its greater level of lipophilia. This is due to the specific composition of the fatty chain.

II. PROPERTIES

(b)(4) [redacted] differs from the other products in the (b)(4) [redacted] range by :

→ **the evanescent feel** it gives to creams. This **light texture** is particularly suitable for producing emulsions intended **for greasy skins.**

→ a better ability to produce **fluid o/w emulsions.**

Like the other products in this range, (b)(4) [redacted] gives emulsions a **long-lasting moisturising** action.

Furthermore, (b)(4) [redacted] is an excellent **co-emulsifier** with the esters of fatty acids and ethoxylated fatty acids such as SIMULSOL 165.

1. LONG LASTING MOISTURISING EFFECT

Because of its glucolipid structure, (b)(4) [redacted] *has intrinsic moisturising* properties which enables formulation of active excipients likely to prevent epidermal dehydration. Its use reinforces the action of moisturising active ingredients traditionally used (urea, glycerin, NaPC & hyaluronic acid).

(b)(4) [redacted] moisturising effect was demonstrated in vivo in comparison to a commonly used emulsifier, using the corneometer method.

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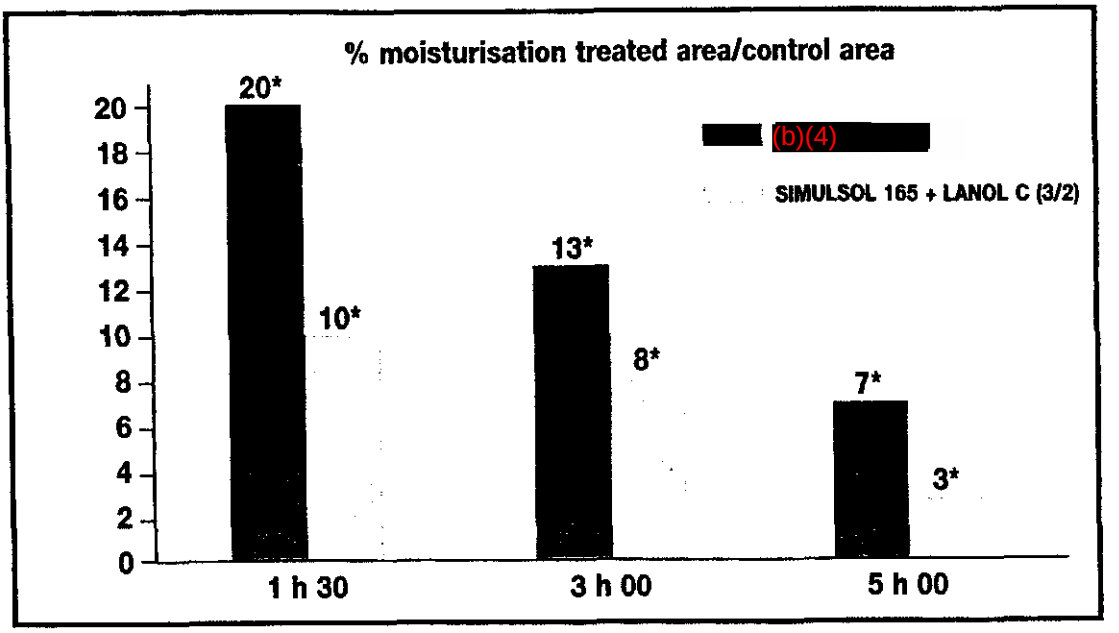

Composition of formulas tested

Emulsifiers	5 %
Cetearyloctanoate	20 %
SEPIGEL 305	1 %
Preservatives	qs
Water	qsp 100 %

Conclusion :

(b)(4) demonstrates **a long-lasting moisturising effect.** Moisturisation lasts to a significant extent - 5 hours after application of the emulsion - unlike traditional emulsifiers (DERMSCAN Expert Report 97-2117).

2. SENSORIAL ANALYSIS

During the sensorial analysis of emulsions based on (b)(4) the adjectives most frequently used by the panellists were :

"lightness" "evanescence" "silkiness"

When compared to emulsions based on (b)(4) they seem to be " richer ".

(b)(4) is the ideal emulsifier for emulsions intended for greasy skins and sun-care and make-up products...

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3. EMULSIFYING PROPERTIES IN RELATION TO THE NATURE OF THE FATTY PHASE

Like the other (b)(4) products, (b)(4) can be used to emulsify a wide range of fatty phases.

	(b)(4)	5 %
	Fatty phase	20 %
	Water	qsp 100 %

	Appearance	Stability	
		R.T.	40°C
mineral oil	cream	> M3	> M3
isododecane	cream	> M3	> M3
cyclomethicone	cream	> M3	> M3
dimethicone	cream	> M3	> M3
squalane	cream	> M3	> M3
sweet almond oil	cream	> M3	> M3
jojoba oil	cream	> M3	> M3
cetearyloctanoate	cream	> M3	> M3
isononylisononanoate	cream	> M3	> M3
benzoate 12-15	cream	> M3	> M3

To obtain perfect stability at 50°C the addition of a stabilising agent is recommended, for example : 0.2% SEPIGEL 305, 0.5% SEPIGEL 501, 0.05% Carbomer, 1% Al Mg Silicate, 0.2% xanthan gum, etc.

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4. (b)(4) [redacted] AS A CO-EMULSIFIER

Self-emulsifying products based on the esters of fatty acids and ethoxylated fatty acids (like SIMULSOL 165) are widely used in the cosmetics industry, but generally have stability problems at 40°C and 50°C.

The combination of (b)(4) [redacted] with SIMULSOL 165 improves the stability very easily as you can see in the table below.

	SIMULSOL 165 5 % Fatty phase 20 % Water qsp 100 %			**SIMULSOL 165** 2 % (b)(4) [redacted] 3 % Fatty phase 20 % Water qsp 100 %		
Nature of the fatty phase	**Stability**			**Stability**		
	RT	**40°C**	**50°C**	**RT**	**40°C**	**50°C**
Mineral oil	NS	NS	NS	> M3	> M3	> M1
Sweet Almond Oil	NS	NS	NS	> M3	> M3	> M1
Dimethicone	NS	NS	NS	> M3	> M3	> M1
Triglycerides	NS	NS	NS	> M3	> M3	> M1

Key : NS = not stable > M3 = stability > 3 month

This kind of combination produces creams with a light and evanescent feel.

5. LOTION FORMULATION

With (b)(4) [redacted] it is possible to produce lotions whose viscosity doesn't change through time, using, for example the following type of formula :

(b)(4) [redacted] [redacted]	3 %
Oil	10 %
Stabilising agent	qs
Preservatives	ps
Water	qsp 100 %

We particularly recommend the following as a stabilising agent :

- SEPIGEL 501 (approx. 0.5 %)
- Xanthan gum (approx. 0.5 %)
- A combination of both

Interesting results are also obtained when using the (b)(4) [redacted] /SIMULSOL A040 pair at 2.7%/0.3% with the same stabilising agent.

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6. CONSISTENCY AGENT

(b)(4) [redacted] has a high melting point. This property is advantageous in any type of formulation where a wax is used, for example : W/O emulsions, mascaras, lipsticks, etc.

In this case (b)(4) [redacted] acts as a consistency agent and improves the product's substantivity.

7. BEHAVIOUR UNDER HYDROLYSIS

Because of its etherised structure (b)(4) [redacted] has an excellent level of chemical stability and an aptitude to emulsify in strong acid or alkaline media without risk of degradation.

(b)(4) [redacted] is compatible with all oxidising or oxidisable active ingredients, acids and bases (e.g. AHAs and vitamins).

(b)(4) [redacted] can be used to produce specific formulas such as depilatory creams, perm products, self tanning products (DHA) or lighteners (Hydroquinone), etc.

III. TOXICOLOGICAL DATA

TESTS ON HEALTHY HUMANS

- CUTANEOUS TOLERANCE

- ***Single application***

When tested using the occlusive patch test at a concentration of (b)(4) [redacted] in paraffin oil on 10 subjects over 48 hours, (b)(4) [redacted] does not provoke any irritation reaction.
Its tolerance is judged to be **very satisfactory** (Experts Report IEC R 61073 D).

- ***Repeated applications***

After repeated applications using 4 occlusive patches over 48 hours on 10 healthy volunteers at a concentration of (b) [redacted] in water (b)(4) [redacted] does not provoke any irritation reaction.
Its tolerance is judged to be **very satisfactory** (Experts IEC Report (b)(4) [redacted]

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- SENSITISATION

(b)(4) [redacted] was tested at a concentration of 5% on 50 healthy volunteers using MARZULLI and MAIBACH's protocol.

Induction period
9 consecutive applications under an occlusive dressing for 48 hours on the same area of a 5% dilution of (b)(4) [redacted] in water.

Rest period
15 days without any application.

"Break out" phase
A single epicutaneous application under an occlusive dressing over approximately 48 hours of a 5% dilution of (b)(4) [redacted] in distilled water.

Results
Each volunteer was examined on the 1st, 4th, 8th and 10th applications. Possible reactions are noted in comparison to the control patch (vehicle = water).

Conclusion
Under these test conditions, (b)(4) [redacted] **did not provoke a primary or cumulative irritation reaction, nor skin sensitisation.** (Experts Report IEC (b)(4) [redacted]

- COMEDOGENESIS :

(b)(4) [redacted] was tested at a concentration of (b)(4) in an emulsion on 20 volunteers.

Protocol
- 20 volunteers with greasy or mixed, acne prone skins who have each undergone an individual clinical examination by a dermatologist (before and after treatment),
- 2 applications per day,
- 4 weeks.

Emulsion tested
(b)(4) [redacted]

Isohexadecane	5 %
SEPIGEL 305	0.2 %
Water	qsp 100 %
Preservative	qs

Results
Analysis of results revealed that under these test conditions (b)(4) [redacted] is "**non comedogenic**" and "**well tolerated, under dermatological control**". (Experts Report IEC (b)(4) [redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118

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ALTERNATIVE TESTS

- HET-CAM

When tested on the chorioallantoic membrane of a hen's egg using the technique developed by LUEPKE and published in the Journal Officiel de la République Française, (b)(4) [redacted] in a 1 % dilution in water is classified as being **non irritant** with a reading of 0. (Internal Report).

- RBCA TEST

➡ ***Hemolysing power***

The assessment of the hemolysing power of (b)(4) [redacted] with red blood cells was carried out using the technique laid down in INVITTOX n°37.

The test consists of determining, after plotting a dose/effect curve, the concentration in product required to provoke a lysis of 50% of the red blood corpuscles. This value is noted as H50.

In the case of (b)(4) [redacted] the reading H 50 > 1000 ppm of (b)(4) [redacted] (b)(4) [redacted] is obtained which falls into the classification of **non hemolysing.**

➡ ***Denaturing power***

The assessment of the denaturing power consists in measuring the degree of denaturation of the oxyhemoglobin. This effect, which is secondary to the hemolysis, indicates the extent of the alteration of intracellular proteins.

Because of its high level of lipophillia, this parameter could not be assessed.

When tested according to the RBCA technique, (b)(4) [redacted] [redacted] has shown a **very good level of tolerance.**

SUMMARY

(b)(4) [redacted] **like the other products in the** (b)(4) [redacted] **range,**

- has an excellent level of tolerance (tested under dermatological control)
- Hypoallergenic,
- Non comedogenic.

(b)(4) [redacted] is the first choice excipient for sensitive skins, for greasy, acne prone skins and for dehydrated skins which are often delicate.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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IV. RECOMMENDATIONS FOR USE

Because of (b)(4) [redacted] high melting point we recommend that you follow the instructions below to produce emulsions based on (b)(4) [redacted]

- Heat the fatty phase within a double jacketed tank at 80-85°C (or in a water bath if you are in a laboratory),

- Produce the emulsion at 80-85°C in tanks equipped with a rotor/stator propeller and a planetary mixer (in the laboratory the use of a SILVERSON mixer is highly recommended)

- Avoid any sudden cooling

N.B. : For formulas based on (b)(4) [redacted], a minimum of 4 parts oil for 1 part (b)(4) [redacted] (b) [redacted] is recommended.

V. REGULATORY DATA

Proposed INCI name : (b)(4) [redacted]

Japan : Proposed INCI name

CAS N° : (b)(4) [redacted]

EINECS N° : (b)(4) [redacted]

VI. ANALYTICAL DATA

Characteristics	Values	Méthods
Appearance	Flakes	Visual
Acid value	1 max	NFT 60-204
Hydroxyl value	210-230	(b)(4) [redacted] 080 A
pH 5 %	5,5 - 7,5	NFT 73-206
Colour (VCS)	3 max	NFT 20-030
Water (1 %)	1 max	(b)(4) [redacted] 006 B
Melting point (°C)	70 - 80	(b)(4) [redacted] 009 A

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VII. APPLICATIONS

Due to its intrinsic properties, (b)(4) [redacted] is the first choice emulsifier for specific emulsions such as :

- Emulsions intended for greasy skins,
- Light body emulsions,
- Cream for sensitive skin,
- Moisturising cream,
- Foundations,
- Sun milk, after sun milk, self tanning products,
- Emulsion lipsticks,
- Mascaras,
- Specific products (depilatory, permanent and colouring products, etc...)

The following formulas illustrate the uses of (b)(4) [redacted]

FOI

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Appendix C

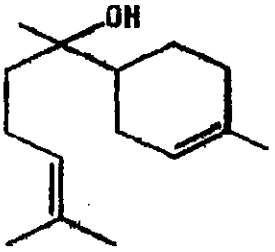
BISABOLOL

CAS No.
515-69-5

EINECS No.
208-205-9

Empirical Formula:
$C_{15}H_{26}O$

Definition: Bisabolol is the terpene that conforms to the formula:



Information Source(s): See note below regarding entries, and links.CIR: [S], JCIC, JCLS, JSQI, MI-12(1281)

Chemical Class(es): Alcohols

Function(s): Skin-Conditioning Agent - Miscellaneous

Reported Product Categories: Skin Care Preparations, Misc.; Moisturizing Preparations; Aftershave Lotions; Body and Hand Preparations (Excluding Shaving Preparations); Cleansing Products (Cold Creams, Cleansing Lotions, Liquids and Pads); Face and Neck Preparations (Excluding Shaving Preparations); Paste Masks (Mud Packs); Night Skin Care Preparations; Bath Soaps and Detergents; Bath Preparations, Misc.; Eye Makeup Preparations, Misc.; Shaving Cream (Aerosol, Brushless and Lather); Skin Fresheners; Deodorants (Underarm); Foundations; Personal Cleanliness Products, Misc.; Suntan Gels, Creams, and Liquids; Fragrance Preparations, Misc.; Lipsticks; Baby Lotions, Oils, Powders and Creams; Eye Makeup Removers

Technical/Other Name(s):
3-Cyclohexene-1-Methanol, α,4-Dimethyl-α-(4-Methyl-3-Pentenyl)-
α,4-Dimethyl-α-(4-Methyl-3-Pentenyl)-3-Cyclohexene-1-Methanol
1-Methyl-4-(1-hydroxy-1,5,5-trimethyl-4-pentenyl) Cyclohex-1-ene

Trade Name(s):
AEC Alpha Bisabolol (A & E Connock)
Alpha-Bisabolol (BASF)
Dragosantol 2/012681 (Dragoco)

Trade Name Mixture(s):
Antidandruff Agent Special(1) (Croda GmbH)
Anti-Irritant Liposomes(2) (Collaborative Labs)
Catezomes B(3) (Collaborative Labs)
Chamomile CL 2/033026(4) (Dragoco)
Extrapone Chamomile P 2/033023(5) (Dragoco)
Extrapone Chamomile Special 2/033021(6) (Dragoco)
Extrapone Mixture 2/788950(7) (Dragoco)
Fruitapone Cranberry B 2/036600(8) (Dragoco)
Fruitapone Grapefruit B 2/036150(9) (Dragoco)
Fruitapone Guarana B 2/036200(10) (Dragoco)
Fruitapone Kiwi B 2/036250(11) (Dragoco)
Fruitapone Lime B 2/036300(12) (Dragoco)
Fruitapone Mango B 2/036350(13) (Dragoco)
Fruitapone Orange B 2/036400(14) (Dragoco)
Fruitapone Papaya B 2/036450(15) (Dragoco)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Fruitapone Passionfruit B 2/036500(16) (Dragoco)
Fruitapone Peach B 2/036550(17) (Dragoco)
Fruitapone Pineapple B 2/036000(18) (Dragoco)
Neo Extrapone Chamomile Liquid 2/070350(19) (Dragoco)
Neo Extrapone Chamomille 2/060350(20) (Dragoco)
Phytoconcentrol Camomile, Oil Soluble 2/066310(21) (Dragoco)
Ultraspheres-7900(22) (Lipoid)

International Cosmetic Ingredient Dictionary and Handbook, 8th Edition, Printed Edition Page Number: 147

Cross References: [Cosmetic Ingredient Review] (23)[International Buyers' Guide] [CTFA List of Japanese Cosmetic Ingredients] (24) These hypertext links will activate when associated electronic books are purchased.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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MATERIAL SAFETY DATA SHEET

NOT Hazardous according to criteria of Worksafe Australia

Date of Issue : Nov 1997

1. IDENTIFICATION

General

Product Name : ALPHA-BISABOLOL

Other Names :

UN No. : N/A

Dangerous Goods Class : C.1

Subsidiary Risk : None Allocated

Hazchem Code : N/A

Pack Group : 0

: N/A

Poisons Schedule : N/A

Uses :

Antiphlogistic active agent for the cosmetic industry.

1.1 Physical Description / Properties

Appearance : Clear, colourless to faint yellow liquid with faint, floral, sweetish odour.

Formula : C15 H26 O

Boiling Point : 287 deg C

Melting Point : N/A deg C

Vapour Pressure : 0.16 mm Hg (1 atmosphere)

Specific Gravity : 0.92 (water = 1)

Flash Point : Test Unknown 148

: N/A ()

Solubility in water : N/A g/l (25 deg C)

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Flammability Limits (as percentage volume in air)

Lower Explosion Limit : 0.8

Upper Explosion Limit : 3.8

1.2 Other Properties

Autoignition temperature = 250 deg C Stable up to approximately 330 deg C Sparingly soluble in water. Soluble in many organic solvents.

1.3 Ingredients

Chemical Entity	CAS No.	Proportions (%)
ALPHA-BISABOLOL	[515-69-5]	>85

2. HEALTH HAZARD INFORMATION

2.1 Health Effects - Acute

Swallowed

Adverse effects are not expected.

Eye

Eye contact with product is not expected to cause irritation.

Skin

Skin contact with product is not expected to cause irritation.

Inhaled

Inhalation overexposure is not expected at ambient temperatures.

2.2 Health Effects - Chronic

Chronic effects are not known.

2.3 First Aid

Swallowed

Rinse mouth and then drink plenty of water.

Eye

Wash affected eyes for at least 15 minutes under running water with eyelids held open. Seek medical attention if irritation persists.

Skin

Wash thoroughly with soap and water. Remove contaminated clothing.
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Inhaled

Keep patient calm and remove to fresh air.

First Aid Facilities

Ensure an eye bath and safety shower are available and ready for use.

2.5 Advice to Doctor

Treat symptomatically based on judgement of doctor and individual reactions of patient.

2.6 Toxicity Data

Oral LD50 = >5000 mg/kg (Rat) Acute skin irritation : non-irritant (Rabbit) (Draize Test) Acute eye irritation : non-irritant (Rabbit) (Draize Test) Acute inhalation hazard : no mortalities after 7h exposure in a highly enriched and/or saturated atmosphere at 20 deg C (Rat)

---

3. PRECAUTIONS FOR USE

3.1 Exposure Standards

An exposure standard has not been established for this product.

Engineering Controls

Ensure workplace is well ventilated.

3.3 Personal Protection

Protective glasses with side-shields. protective gloves. Protective overalls. Wash hands and face thoroughly after handling and before work breaks, eating, drinking, smoking and using toilet facilities.

3.4 Flammability

Combustible liquid. Flash point 148 deg C.

SAFE HANDLING INFORMATION

4.1 Storage / Transport

Not classified as a dangerous good for storage or transport. Store in accordance with all regulations relevant to combustible liquids. Keep tightly closed in a dry and cool place. Not subject to hazardous substances labelling.

4.2 Packaging / Labelling

UN No. N/A

Class C.1

Sub Risk None Allocated Records processed under FOIA Request #2015-7714; Released by CDRH on 02-01-2016.

Hazchem Code N/A

Pack Group 0

EPG No. N/A

Shipping Name ALPHA-BISABOLOL

Hazard

Risk Phrases

Safety Phrases

4.3 Spills and Disposal

Spills

Clean-up personnel should wear protective overalls with goggles and gloves. Do not let product enter drains.

Contain and soak up all spills with absorbent material. Place waste in labelled containers for disposal.

Disposal

Must be disposed of in accordance with all Local, State and Federal regulations to an approved landfill or incinerated.

FIRE AND EXPLOSION HAZARD

Fire / Explosion

Combustible liquid. Stable up to approximately 330 deg C.

Extinguishing Media

Fire-fighters should wear full protective clothing including self-contained breathing apparatus. In case of fire use powder or foam type extinguishers. Use equipment/media appropriate to surrounding fire conditions. Dispose of fire debris and contaminated extinguishing water in accordance with all regulations.

---

5 OTHER INFORMATION

Other Information

Inhibition of degradation activity in activated sludge is not to be anticipated during correct introduction of low concentrations. Do not discharge product to water courses without effluent treatment. The product is biodegradable. Degradability : >60% BOD of the ThOD [OECD 301C] Toxicity to bacteria : EC/LC10 >10,000 mg/L/0.5h (Pseudomonas putida) EC/LC50 >10,000 mg/L/0.5h (Pseudomonas putida) EC/LC90 >10,000 mg/L/0.5h (Pseudomonas putida) Toxicity limit concentration >10,000 mg/L Toxicity to fish : EC/LC50 >4.6 <10 mg/L/96h (Leuciscus idus) EC/LC0 5 mg/L/48h (Leuciscus idus) Theoretical OD value : 3027 mg/g Biochemical Oxygen Demand : 2200 mg/g

Contact Points

Records processed under FOIA Request #2015-7714; Released by CDRH on 03-01-2016.

Organisation	Location	Telephone	Ask For
Redox Chemicals Pty Ltd	Wetherill Park NSW	02-97255155	Technical Officer
Poisons Information Centre	Westmead	131129	
		1800-251525	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Appendix D

OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

PIROCTONE OLAMINE AND ITS MONOETHANOLAMINE SALT

Colipa n° P59

adopted by the SCCNFP during its 19th plenary meeting
of 27 February 2002

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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. Terms of Reference

1.1 Context of the question

Cosmetic products marketed in the EU may only contain those preservatives which are listed in Annex VI of the Cosmetics Directive 76/768/EEC, "List of preservatives which cosmetic products may contain".

The preamble of the Annex states that preservatives marked with the symbol (+) may also be added to cosmetic products in concentrations other than those laid down in the Annex for other specific purposes apparent from the presentation of the products.

Piroctone olamine and its monoethanolamine salt bears the symbol (+) and can therefore be used in cosmetics at much higher concentrations, as long as they are not employed as preservatives.

In its opinion of 17 February 1999 concerning the restrictions on materials listed in Annex VI of Directive 76/768/EEC on cosmetic products, the SCCNFP stated that those substances indicated by (+) in Annex VI, when incorporated into cosmetic formulations for non-preservative functions, should be subjected to the same restrictions in usage levels and warnings as when used for preservative effects.

If a preservative marked with the symbol (+) is added for non-preservative purpose to a cosmetic product in a concentration other than that laid down in the Annex VI, data to substantiate its safety should be submitted to the SCCNFP.

1.2 Request to the SCCNFP

The SCCNFP was requested to review the data submitted to support the safety of piroctone olamine and its monoethanolamine salt when used at concentrations other than those laid down in Annex VI to Directive 76/768/EEC for non-preservative purposes apparent from the presentation of the products and to answer the following question :

* Can piroctone olamine and its monoethanolamine salt safely used for non-preservative purposes in face care products (leave on) at a maximum concentration of 1.0% ?

1.3 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.
The extend to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

1.4. Definitions of terms where appropriate

Piroctone Olamine (PO) has been already subject for evaluation on the background of earlier submissions.

Submission I : February 1980
Submission II : January 1985

The result of the respective evaluation and the opinion of the Scientific Committee of Cosmetology (SCC) is laid down in Reports of the SCC, sixth series, EUR 11139 EN, 1987.

PO had been approved for use in cosmetic products at a maximal concentration of 1 % (rinse-off products) or 0.5 % in other products.

PO is non-sensitising , non-genotoxic, non-teratogenic and the systemic toxicity has been measured in a 90-day oral test NOEL in rats: 100 mg/kg/day; in 90-day topical application NOEL in rabbits: 16 mg/kg/day (one dose test).

The percutaneous penetration rate in rats was in the order to 4.5 % of a topically applied dose. Since 1983, no reports have appeared in the literature indicating that the substance could be attributed to unwanted adverse effects.

In HRIPT, the test cpd. PO at 0.5 % in a vehicle did not induce irritation or sensitisation. In a human use test 0.2 % or 1.0 % in shampoos provided no evidence of adverse reactions. Rabbit irritation tests indicated that PO was slightly irritating to the skin (at 1 %) and eye (0.5 %).

In "other uses" (within the EU) and outside the EU, the cpd. PO obviously has widely used in skin creams (up to 1 %) already for a long time without any user complaints or even reports in literature.

Submission III (January 2001) has been presented in order to defend the use of Piroctone Olamine (P59) as for "other use" in face care products (leave on products) at a concentration of 1 %. Submission III is primarily dealing with skin and ocular tolerance of PO at higher concentrations as 1 %, namely 2 % and 3 %.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118. 140

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2. Toxicological Evaluation and Characterisation

By lack of appropriate and validated in vitro test methods the new experiments have been carried out using in vivo models according to modern test protocols following GLP rules.

2.1. General

2.1.1. Primary name

Piroctone Olamine (INCI)

2.1.2. Synonyms

1-Hydroxy-4-methyl-6(2,4,4-trimethylpentyl)2-pyridon and its monoethanolamine salt

2.1.3. Trade names and abbreviations

Octopirox

2.1.4. CAS number

68890-66-4

2.1.5. Structural formula

/

2.1.6. Empirical formula

Emp. Formula : $C_{14}H_{23}NO_2 . C_2H_7NO$
Mol weight : 298.48

2.1.7. Purity, composition and substance codes

/

2.1.8. Physical properties

Appearance : /
Melting point : /
Boiling point : /
Density : /

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Rel. vap. dens. : /
Vapour Press. : /
Log P_{ow} : /

2.1.9. Solubility

/

2.2. Function and uses

Piroctone Olamine has been approved for use in cosmetic products at a maximal concentration of 1 % (rinse-off products) or 0.5 % (other products).

TOXICOLOGICAL CHARACTERIZATION

Only the results of the new investigations from submission III (January 2001) are listed under the respective position number of the SCCNFP standard form. The investigations reported in Submission I (1980) and II (1985) have been proven satisfactorily as to conduct and scientific interpretation and thus the results could be taken under consideration for this safety evaluation.

2.4. Irritation & corrosivity

2.4.1. Irritation (skin)

OECD 404

Three New Zealand White rabbits were treated topically with concentrations of 2.0 % (left flank) or 3.0 % (right flank). Exposure time was 4 hours. The test compound was kept in contact with the skin by semi-occlusive dressing. Cutaneous reactions were observed and scored 1 hour, 24, 48 and 72 hours after removal of the dressing.
Result: No cutaneous reactions were observed in the study. The test substance was rated to be non-irritant to the skin of rabbits at concentrations up 3.0 %.

Ref. : 48

2.4.2. Irritation (mucous membranes)

OECD 405

The eyes of three New Zealand White rabbits were treated with 0.1 ml concentrations of 2.0 % (left eye) or 3.0 % (right eye). The eyes were not rinsed after application of the test substance. Ocular reactions were observed and scored 1 hour, 24, 48 and 72 hours after administration.
Result: With the exception of a single case of a slight and transient corneal opacity (3.0 %, day 2), ocular reactions were limited to the conjunctiva (redness, chemosis and discharge).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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At 2.0 % very slight to moderate conjunctival reactions were observed in all animals and persisted up to day nine of the study. At 3.0 %, very slight to moderate conjunctival reactions (redness; chemosis, discharge) and a single case of mild, transient corneal opacity (day 2 only) was observed in all animals and persisted up to day three. On the basis of the irritation scores, the test substance was rated to be a slight irritant in rabbits.

Ref. : 49

2.10. Special investigations

2.10.1. Human Data

In a double-blind study in humans (report in French language) the tolerance of two cream formulations, i.e. 47JP12 and 47JP2, containing 1.0 % and 0.5 % octopirox (piroctone olamine, PO), respectively. With the exception of the different content of PO, the formulation ingredients were identical.
The creams were applied once a day, morning or evening, to the face of 65 volunteers, 5 times a week, for a total of four weeks.
Result: No difference was noted in the tolerance of these formulations. Both creams showed a good acceptance and tolerance. These data support the tolerance of 1.0 % PO in face creams.

Ref. :

2.11. Safety evaluation

CALCULATION OF SAFETY MARGIN

Piroctone Olamine (Octopirox)

Based on a usage volume of X ml, containing at maximum X %

Maximum amount of ingredient applied	**I (mg)**	=	
Typical body weight of human		=	**60 kg**
Maximum absorption through the skin	**A (%)**	=	
Dermal absorption per treatment	**I x A**	=	
Systemic exposure dose (SED)	**I x A / 60 kg**	=	
No observed adverse effect level (mg/kg)	**NOAEL**	=	

Margin of Safety	**NOAEL / SED**	=

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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2.12. Opinion

The Committee is of the opinion that the information submitted is insufficient to allow an adequate risk assessment to be carried out.

Before any re-assessment, a complete dossier up-to-modern-standards would be required not only on piroctone olamine but also on its monoethanolamine salts.

2.13. References

Submission III

44. Freeberg FE, Griffith JF, Bruce RD, Bay PHS. Correlation of animal tests methods with human experience for household products. J. Toxicol. – Cut. and Ocular Toxicol. 1 (3), 53-64, 1984.
45. N° 57: hydroxy-4-methyl-6(2,2,4-trimethylpentyl)2-pyridon and its monoethanolamine salt. Reports of the Scientific Committee on Cosmetology, sixth series, EUR 11139 EN, 1987.
46. Patil, SM, Patrick E, Maibach HI. Animal, human, and in vitro test methods for predicting skin irritation. In: Dermatoxicology, fifth edition., pp. 411-436, Eds. Marzulli FN and Maibach HI. Taylor and Frances, London, 1996.
47. Manciaux X. 52883 – Acute dermal irritation in rabbits. Study number 20306 TAL, Centre International de Toxicology, Evreux, France, unpublished report, Sept. 22, 2000.
48. Manciaux X. 2848 - Acute eye irritation in rabbits. Study number 20307 TAL, Centre International de Toxicology, Evreux, France, unpublished report, Sept. 22, 2000.
49. Lemaitre M. Etude en double aveugle de l'efficacité et de tolerance de la creme 47JP12 contre 47JP2 dans la dermie seborreique du visage, unpublished report, August 1997.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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Appendix E

VITIS VINIFERA (GRAPE) SEED EXTRACT

CAS No.
84929-27-1

EINECS No.
284-511-6

Definition: Vitis Vinifera (Grape) Seed Extract is an extract of the seeds of the grape, *Vitis vinifera*.

Regulatory and Ingredient Use Information for Botanicals(1)

Chemical Class(es): Biological Products

Function(s): Anticaries Agent; Antidandruff Agent; Antifungal Agent; Antimicrobial Agent; Antioxidant; Oral Care Agent; Oral Health Care Drug; Sunscreen Agent; Ultraviolet Light Absorber

Technical/Other Name(s):
Extract of Grape Seed
Extract of Vitis Vinifera Seed
Grape Seed Extract
Vitis Vinifera (EU)
Vitis Vinifera Seed Extract

Trade Name(s):
ActiVin (Interhealth Nutraceuticals)
Leucocyanidins (Indena SpA)
Leucocyanidins of Grape Seed Extract (981016) (Euromed)
Leucoselect (Indena SpA)
OPC pepin de raisin (Berkem)

Trade Name Mixture(s):
Glycosphere-PCO(2) (Kobo sarl)
Grape Seed Extract(3) (Collaborative Labs)
Leucocyanidins Phytosome(4) (Indena SpA)

International Cosmetic Ingredient Dictionary and Handbook, 8th Edition, Printed Edition Page Number: 1562

Cross References: [International Buyers' Guide] (5) These hypertext links will activate when associated electronic books are purchased.

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Biolab SGS srl
Centro di analisi & ricerche biologiche

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20090 Vimodrone (Milano)
Tel. (02) 2650039
Telex 322202
Telefax (02) 2504333

TOXICOLOGY LABORATORY

Date: 25.02.91

Protocol n.: 0575/1

Study n.: 91/168

PRIMARY SKIN IRRITATION
ACUTE EYE IRRITATION

Sponsor: INDENA

Product: LEUCOCIANIDINE LAV. 22694/9 B.A. 75377

Toxicology laboratory

MEMBRI DEL GRUPPO SGS (SOCIETE GENERALE DE SURVEILLANCE)

CAPITALE SOCIALE L. 80.000.000 i.v.
ISCR. TRIBUNALE DI MONZA REG. SOC. N. 40131
C.C.I.A.A. MILANO N. 966696
COD. FISC. N. 03765750157 - PART. IVA N. 00782140969

Questions? Contact CDER/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118

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Protocol n. 0575/1 Study N. 91/168

PRIMARY SKIN IRRITATION

Sponsor: INDENA

Product: LEUCOCIANIDINE LAV. 22694/9 B.A. 75377

Species and Strains: White New Zealand Rabbits Sex:Males

Cutaneous reaction	Skin	Observation time	Rabbit N. 1	2	3	4	5	6	Mean value
Erythema & Eschar	Intact	24 h	0	0	0	0	0	0	0,0
		72 h	0	0	0	0	0	0	0,0
		5 gg	0	0	0	0	0	0	0,0
		7 gg	0	0	0	0	0	0	0,0
	Abraded	24 h	0	0	0	0	0	0	0,0
		72 h	0	0	0	0	0	0	0,0
		5 gg	0	0	0	0	0	0	0,0
		7 gg	0	0	0	0	0	0	0,0
A) Subtotal									0,0
Oedema	Intact	24 h	0	0	0	0	0	0	0,0
		72 h	0	0	0	0	0	0	0,0
		5 gg	0	0	0	0	0	0	0,0
		7 gg	0	0	0	0	0	0	0,0
	Abraded	24 h	0	0	0	0	0	0	0,0
		72 h	0	0	0	0	0	0	0,0
		5 gg	0	0	0	0	0	0	0,0
		7 gg	0	0	0	0	0	0	0,0
B) Subtotal									0,0
C) Total (A + B)									0,0
PRIMARY SKIN IRRITATION SCORE (C:4)									0,0

Conclusions

The product above mentioned is considered non irritant for the skin.

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ACUTE EYE IRRITATION

Protocol N.: 0575/1 Date: 25.02.91

Product: LEUCOCIANIDINE LAV. 22694/9 B.A. 75377 Study N°: 91/168

Sponsor: INDENA

Tissue	Time		individual scores 1	2	3	4	5	6	daily mean (x) 60'	24h	48h	72h	7g
1) Cornea	60'	a	0	0	0	0	0	0					
		b	0	0	0	0	0	0	0.0				
	24 h	a	0	0	0	0	0	0					
		b	0	0	0	0	0	0		0.0			
a= opacity	48 h	a	0	0	0	0	0	0					
b= area		b	0	0	0	0	0	0			0.0		
	72 h	a	0	0	0	0	0	0					
		b	0	0	0	0	0	0				0.0	
x= (Summ. a x b x 5) / 6	7 d	a	0	0	0	0	0	0					
		b	0	0	0	0	0	0					0.0
2) Iris	60'	c	0	0	0	0	0	0	0.0				
c= congestion	24 h	c	0	0	0	0	0	0		0.0			
	48 h	c	0	0	0	0	0	0			0.0		
x= (Summ. c x 5) / 6	72 h	c	0	0	0	0	0	0				0.0	
	7 d	c	0	0	0	0	0	0					0.0
3) Conjunctivae	60'	d	2	2	2	2	2	2					
		e	1	1	2	2	1	2	11.0				
		f	2	2	2	2	2	2					
	24 h	d	2	1	2	1	1	2					
d= redness		e	1	1	1	1	1	1		9.00			
e= chemosis		f	2	2	2	2	2	2					
f= discharge	48 h	d	1	1	1	1	1	1					
		e	1	1	1	1	1	1			6.67		
		f	2	1	2	1	1	1					
	72 h	d	1	1	1	1	1	1					
		e	1	1	1	1	1	1				6.00	
		f	1	1	1	1	1	1					
	7 d	d	1	1	1	1	1	1					
		e	0	0	0	0	0	0					4.00
x= Summ. (d + e + f)x2 / 6		f	1	1	1	1	1	1					
Mean daily total scores: (1 + 2 + 3)									11.0	9.0	6.67	6.0	4.0

Conclusions : The results indicate that the product can be considered non irritant.

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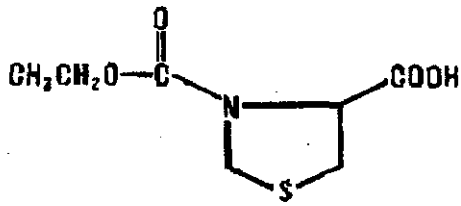
Appendix F

TELMESTEINE

CAS Nos.: 122946-43-4; 127657-29-8

Empirical Formula:
$C_7H_{11}NO_4S$

Definition: Telmesteine is the heterocyclic organic compound that conforms to the formula:



Chemical Class(es): Esters ; Heterocyclic Compounds ; Thio Compounds

Function(s): Not Reported

Technical/Other Name(s):
3,4-Thiazolidinedicarboxylic Acid, 3-Ethyl Ester

Trade Name(s):
Telmesteina (Yason)

International Cosmetic Ingredient Dictionary and Handbook, 8th Edition, Printed Edition Page Number: 1481

Cross References: [International Buyers' Guide] (1) These hypertext links will activate when associated electronic books are purchased.

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SOLCHEM
SOLCHEM ITALIANA S.P.A.

MATERIAL SAFETY DATA SHEET

Product: **TELMESTEINE**

Date of issue : 30.10.2002 **revision date:**

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

SOLCHEM ITALIANA S.p.A.
Via Della Vittoria,89
26837 Cassino d'Alberi Mulazzano (MILANO)
+2-988882.1
e-mail : info@solchem.it

Product identification: TELMESTEINE

2.COMPOSITION / INFORMATION ON INGREDIENTS

Chemical name: N-carbethoxy-4-thiazolidin-carboxylic acid
Synonym: N-Ethoxycarbonyl-L-Thiazolidine-4-Carboxilic acid
How Supplied: bulk substance
Product Use :pharmaceutical manufacturing
Chemical Family : amino acids derivative
Molecular Formula : C7 H11 N O4 S
CAS # : 122946-43-4
EINECS No :

COMPONENTS	*HAZARDOUS*	*CONCENTRATION*	*CAS #*	*MOLECULAR WEIGHT*
Telmesteine	no	100 %	122946-43-4	205.23

3. HEALTH HAZARDS IDENTIFICATON

no data available

15t

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SOLCHEM
SOLCHEM ITALIANA S.P.A.

4. FIRST AIDS AND MEASURES

General Instructions : The usual precautions taken when handling chemicals should be observed

Eye contact : flush with copious amounts of water for at least 15 minutes. Call a physician.

Skin contact : flush with soap and copious amounts of water for at least 15 minutes. Remove contaminated clothing and shoes. Call a physician

Ingestion : wash out mouth with water provided person is conscious, call a physician

Inhalation : remove to fresh air. If breathing became difficult, call a physician

5. FIRE FIGHTING MEASURES

Extinguishing media : carbon dioxide, dry chemical powder or appropriate foam

Special fire-fighting procedures: wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.

Unusual fire and explosions hazards: emits toxic fumes under fire conditions

6. ACCIDENTAL RELEASE MEASURES

Wear self-contained breathing apparatus, rubber boots and heavy rubber gloves.
Sweep up, place in a bag and hold for waste disposal.
Avoid raising dust
Ventilate area and wash spill site after material pick up is complete.

7. HANDLING AND STORAGE

Handling : approved respirator. Compatible chemical-resistant gloves. Chemical safety goggles. Mechanical exhaust required.

Storage : store in well-closed containers, protected from light and humidity. Place in a well ventilated area.

8. EXPOSURE CONTROL AND PERSONAL PROTECTION

8.1: protective clothing or equipment	appropriate laboratory apparel
8.2: control of threshold limits	not applicable
8.3 personal protection	protect exposed skin
8.3.1 respiratory protection	wear approved respirator
8.3.2 hand protection	rubber gloves
8.3.3 eye protection	protective goggles

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9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance /Physical State / Colour/Odour : white crystalline powder, odourless
Boiling Point: not applicable
Evaporation rate (degree C) : not applicable
Flash point : no data available
Freezing point : no data available
Melting point : about 98°C
Density: no data available
Vapour pressure: not applicable
Viscosity : not applicable
Water solubility : soluble
pH Values: 2.4 (1% solution) pKa : 3.0
Auto-flammability: no data available
Explosive properties : no data available
Ignition temperature : no data available

10. STABILITY AND REACTIVITY

Stability : stable from a safety point of view
Incompatibilities: no data available
Hazardous combustion or decomposition products: carbon monoxide, carbon dioxide, nitrogen oxides, sulphur oxides
Hazardous polymerisation : no data available

11. TOXICOLOGICAL INFORMATION

LD 50 (oral rat / mouse) : > 4000 mg/kg

12. ECOLOGICAL INFORMATION

General notes : Do not allow product to reach ground water , water bodies or sewage system.

13. DISPOSAL CONSIDERATION

Incinerate in an approved facility after dissolving in a suitable solvent.
Dispose in accordance with all state and local regulations.

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14. TRANSPORT REGULATION

It is not subject to the current regulations for transportation of hazardous goods for the transport on land or by air /sea

15. REGULATORY INFORMATION

16. OTHER INFORMATION

These statements solely describe the safety demands of the product and base according to the best of our belief on our today's knowledge. They , however, do not represent any assurance towards properties of the product within the sense of liability , resp. guaranty regulation and thus are given without obligation.

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Appendix G

STUDY TITLE:

ISO CLOSED PATCH SENSITIZATION STUDY

TEST ARTICLE:

Wound and Skin emulsion

TEST FACILITY:

NAMSA
2261 Tracy Road
Northwood, OH 43619-1397

SPONSOR:

MIKE KILLEEN
SINCLAIR PHARMACEUTICALS
1825 GARRETT DRIVE
CARROLL, TX 75010

NAMSA
Ensuring Medical Device Safety and Compliance™

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Affiliates: France • Germany • Israel • Taiwan • United Kingdom

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SUMMARY

A study was conducted in the guinea pig to evaluate the potential for delayed dermal contact sensitization of Wound and Skin emulsion. The study was conducted based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization.

The test article was occlusively patched for 6 to 8 hours to the intact skin of 10 guinea pigs, three times a week, for a total of nine induction treatments over a 3 week period. The control article was similarly patched to 5 guinea pigs. Following a recovery period, the 10 test and 5 control animals received a challenge patch of the test article and the test article diluent. All sites were observed for evidence of dermal reactions at approximately 24, 48, and 72 hours after patch removal.

Under the conditions of this study, the test article showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

Study and Supervisory Personnel:

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Jennifer N. Moritz, BA
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Approved by: Cherise M. McCoy for — 3-7-03

Joshua D. Moninger, BS
Technical Reviewer

Date Completed

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INTRODUCTION

The test article described below was evaluated for the potential to cause delayed dermal contact sensitization following repeated occlusive patching in the guinea pig. The study was conducted based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization. The test article was received on January 9, 2003. The first patch was applied on January 15, 2003, and the observations were concluded on February 20, 2003. The susceptibility of the Hartley guinea pig strain to a known sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB), has been substantiated at NAMSA with this method under lab number 02T-12300-00 completed on November 15, 2002.

MATERIALS

The sample provided by the sponsor was identified and handled as follows:

Test Article:	Wound and Skin emulsion
Identification No:	Not Supplied
Storage Conditions:	Room temperature
Control Article:	Hill Top Chamber®
Preparation:	The test article was dosed as received.

METHODS

Test System:

Species:	Guinea pig (*Cavia porcellus*)
Strain:	Hla®:(HA)CVF®
Source:	Hilltop Lab Animals, Inc.
Sex:	Female (nulliparous)
Body Weight Range:	375 grams to 426 grams the day prior to first treatment
Age:	No particular age was prescribed for this test
Acclimation Period:	Minimum 5 days
Number of Animals:	15
Identification Method:	Ear punch

Justification of Test System:

The Hartley albino guinea pig has been used historically for sensitization studies. Repeated patching of the test material to fur-clipped intact skin will be employed. Topical applications are related to the human exposure route and will permit the evaluation of dermal contact and/or absorption of potential sensitizers during induction and challenge phases. Reactions directly under the topical application site can be observed. The susceptibility of the Hartley strain to a know sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB), has been substantiated at NAMSA with this method.

Animal Management:

Husbandry:	Conditions conformed to Standard Operating Procedures which are based on the "Guide for the Care and Use of Laboratory Animals."
Food:	PROLAB® Guinea Pig Diet was provided daily.

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Water: Freely available, municipal (Toledo, OH) water was delivered through an automatic watering system.

Contaminants: Reasonably expected contaminants in feed or water supplies did not have the potential to influence the outcome of this test.

Housing: Animals were housed in groups in stainless steel suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, animal code and first treatment date.

Environmental: The room temperature was monitored daily. The temperature range for the room was within a range of 64-79°F.

The room humidity was monitored daily. The humidity range for the room was 30-70%.

The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark).

Facility: NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.

Personnel: Associates involved were appropriately qualified and trained.

Selection: Only healthy, previously unused animals were selected.

Experimental Procedure:

On the day prior to the first induction treatment, each animal was weighed and identified. The hair was removed with an electric clipper from the left flank of 10 guinea pigs designated as test animals and 5 guinea pigs designated as control animals. Each animal was observed daily for general health.

Induction:

The following day, the nonwoven cotton disk contained inside a Hill Top Chamber® was saturated with 0.3 ml of the test article and applied to the appropriate animal. The chamber was then secured with hypoallergenic tape to the intact skin. A dry Hill Top Chamber® was similarity patched to each control guinea pig. To maintain the occluded patch in position, the trunk of each guinea pig was wrapped with an elastic band.

At 6 to 8 hours, the wraps and patches were removed. The sites were wiped with dry gauze after patch removal to remove any material residue from the skin. Observations for dermal responses were recorded 24 hours following the completion of each test article exposure (see DEVIATION). Prior to scoring, the sites were wiped with 35% isopropyl alcohol saturated gauze.

The application procedure was repeated three times each week (e.g. Monday-Wednesday-Friday) for 3 weeks until nine applications were made to the left flank of the animals. The hair was clipped the day prior to each application to provide a clear site. Due to test animal numbered 48 showing a reaction of well-defined erythema at the sixth induction patch number, the patch for this animal was placed on a virgin site for the following patch application (see RESULTS).

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Challenge:

At 13 days after the final induction patch, the hair of each guinea pig was removed with an electric clipper from the right flank area. On the following day, the nonwoven cotton disk inside a Hill Top Chamber® was removed and a 0.3 ml portion of the test article was applied to the chamber and then topically secured with hypoallergenic tape to the intact skin on the ventral flank of each test and control guinea pig. A dry Hill Top Chamber® was similarly patched to the dorsal flank of each test and control guinea pig. The trunk of each guinea pig was wrapped with an elastic band to hold the occluded patches in place.

All wraps and patches were removed 6 to 8 hours later. The sites were wiped with dry gauze after patch removal. At 24 hours after patch removal, the challenged sites and surrounding area were shaved. Observations for dermal reactions were conducted at 2-4 hours following the shave and at 48 and 72 hours after challenge patch removal. Sites were wiped with 35% isopropyl alcohol saturated gauze before scoring at each interval. Evaluations for both the induction and challenge phases were based on dermal reactions which were scored as outlined below:

ERYTHEMA (ER)		EDEMA (ED)	
Reaction	Numerical Grading	Reaction	Numerical Grading
No erythema	0	No edema	0
Slight erythema	1	Slight edema	1
Well-defined erythema	2	Well-defined edema	2
Moderate erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

Following the challenge patch, any test animal exhibiting a dermal reaction greater than that observed in the challenge control conditions was considered as showing delayed contact sensitization to the test article. Pattern and duration of reactions was also considered in the final evaluation.

DEVIATION

Observations for dermal responses 24 hours following the fifth induction patch were not conducted. This deviation was not believed to have adversely affected the outcome of the study.

RESULTS

Clinical Observations: Individual body weights are presented in Appendix 1. All animals appeared clinically normal throughout the study.

Dermal Observations: Individual results of dermal scoring for the induction and challenge phases appear in Appendices 2 and 3. During induction scoring, several of the test animals exhibited scores from no erythema to well-defined erythema, and from no edema to slight edema. During the challenge 24 hour scores, three animals exhibited scores of slight erythema on the test sites. These scores were not indicative of delayed dermal contact sensitization. Therefore, no evidence of sensitization was observed.

Results of the rechallenge appear in Appendix 4.

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and ISO 17025.

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CONCLUSION

Under the conditions of this study, the test article showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

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APPENDIX 1

INDIVIDUAL BODY WEIGHTS AND CLINICAL OBSERVATIONS

Animal Number/ Group	Individual Observation	
	Pretreatment Body Weight (g)	Clinical Observations
46 Test	388	Animal appeared clinically normal throughout the study.
47 Test	380	Animal appeared clinically normal throughout the study.
48 Test	387	Animal appeared clinically normal throughout the study.
49 Test	426	Animal appeared clinically normal throughout the study.
50 Test	391	Animal appeared clinically normal throughout the study.
51 Test	414	Animal appeared clinically normal throughout the study.
52 Test	375	Animal appeared clinically normal throughout the study.
53 Test	403	Animal appeared clinically normal throughout the study.
54 Test	405	Animal appeared clinically normal throughout the study.
55 Test	398	Animal appeared clinically normal throughout the study.
56 Control	407	Animal appeared clinically normal throughout the study.
57 Control	392	Animal appeared clinically normal throughout the study.
58 Control	391	Animal appeared clinically normal throughout the study.
59 Control	395	Animal appeared clinically normal throughout the study.
60 Control	405	Animal appeared clinically normal throughout the study.

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APPENDIX 2

GUINEA PIG SENSITIZATION

DERMAL REACTIONS - INDUCTION

Animal Number/ Group	Induction Patch Number																	
	1		2		3		4		*		6		7		8		9	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
46 Test	0	0	0	0	0	0	0	0			1	0	1	0	1√	0	1	0
47 Test	0	0	1	0	0	0	0	0			1	0	1	0	1	0	1	0
48 Test	0	0	1	0	0	0	1	0			2•	0	1	0	1√	0	1	0
49 Test	0	0	1	0	1	0	1	0			1	0	1	0	1	0	1	0
50 Test	0	0	0	0	0	0	1	0			0	0	1	0	1	0	1	0
51 Test	0	0	1	0	1	0	1	0			1	0	1	0	1	0	1	0
52 Test	0	0	0	0	0	0	0	0			1	0	1	0	1	0	1	0
53 Test	0	0	0	0	0	0	0	0			1	0	1	0	1	0	1	0
54 Test	0	0	0	0	0	0	1	0			1	0	1	0	1	1	1	0
55 Test	0	0	1	0	1	0	1	0			1	0	1	0	1	0	1	0
56 Control	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0
57 Control	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0
58 Control	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0
59 Control	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0
60 Control	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0

* = No scores conducted (see DEVIATION)
√ = Animals #46 and 48 appeared to have small scabbed areas at the test sites.
• = Animal #48 repatched at virgin site for IND 7.
Test = Test article
Control = Dry Hill Top Chamber®
ER = Erythema
ED = Edema

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APPENDIX 3

GUINEA PIG SENSITIZATION

DERMAL REACTIONS - CHALLENGE

Animal Number/ Group	Hours After Patch Removal											
	24				48				72			
	Test Site		Control Site		Test Site		Control Site		Test Site		Control Site	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
46 Test	0	0	0	0	0	0	0	0	0	0	0	0
47 Test	0	0	0	0	0	0	0	0	0	0	0	0
48 Test	0	0	0	0	0	0	0	0	0	0	0	0
49 Test	1	0	0	0	0	0	0	0	0	0	0	0
50 Test	0	0	0	0	0	0	0	0	0	0	0	0
51 Test	1	0	0	0	0	0	0	0	0	0	0	0
52 Test	0	0	0	0	0	0	0	0	0	0	0	0
53 Test	0	0	0	0	0	0	0	0	0	0	0	0
54 Test	1	0	0	0	0	0	0	0	0	0	0	0
55 Test	0	0	0	0	0	0	0	0	0	0	0	0
56 Control	0	0	0	0	0	0	0	0	0	0	0	0
57 Control	0	0	0	0	0	0	0	0	0	0	0	0
58 Control	0	0	0	0	0	0	0	0	0	0	0	0
59 Control	0	0	0	0	0	0	0	0	0	0	0	0
60 Control	1	0	0	0	0	0	0	0	0	0	0	0

ER = Erythema
ED = Edema

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Appendix H

STUDY TITLE:

ISO SKIN IRRITATION STUDY

TEST ARTICLE:

Wound and Skin emulsion

TEST FACILITY:

NAMSA
2261 Tracy Road
Northwood, OH 43619-1397

SPONSOR:

MIKE KILLEEN
SINCLAIR PHARMACEUTICALS
1825 GARRETT DRIVE
CARROLL, TX 75010

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SUMMARY

The test article, Wound and Skin emulsion, was evaluated for primary skin irritation in accordance with the guidelines of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization. Two 25 mm x 25 mm sections of the test article and control article were topically applied to the skin of each of three rabbits and left in place for 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application.

Under the conditions of this study, well-defined erythema and no edema were observed on the skin of the rabbits. The Primary Irritation Index for the test article was calculated to be 1.1. The response of the test article was categorized as slight.

Study and Supervisory Personnel:

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1-24-03
Date Completed

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INTRODUCTION

The test article identified below was evaluated for primary skin irritation in accordance with the guidelines of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization. The purpose of this study was to determine the potential for a single topical application of the test article to irritate skin of the rabbit. The test article was received on January 9, 2003. Patches were applied on January 18, 2003, and the observations were concluded on January 21, 2003.

MATERIALS

The sample provided by the sponsor was identified and handled as follows:

Test Article:	Wound and Skin emulsion
Identification No.:	Not Supplied
Storage Conditions:	Room temperature
Control Article:	Four-ply gauze supplied by the test facility, was cut into 25 mm x 25 mm sections, moistened with 0.5 ml of saline per section and backed with polyethylene plastic.
Preparation:	The test article was cut into 25 mm x 25 mm sections of 4-ply gauze were moistened with 0.5 ml of the test article and applied to the akin of the rabbit.

METHODS

Test System:

Species:	Rabbit (*Oryctolagus cuniculus*)
Breed:	New Zealand White
Source:	Myrtle's Rabbitry, Inc.
Sex:	Male
Body Weight Range:	2.2 kg to 2.5 kg at selection
Age:	Young adult
Acclimation Period:	Minimum 5 days
Number of Animals:	Three
Identification Method:	Ear tag

Justification of Test System:

The rabbit is specified as an appropriate animal model for evaluating potential skin irritants by the current ANSI/AAMI/ISO testing standards. The rabbit is widely used for this purpose and relative ranking of irritant scores can be determined.

Animal Management:

Husbandry:	Conditions conformed to Standard Operating Procedures which are based on the "Guide for the Care and Use of Laboratory Animals."
Food:	PROLAB® High Fiber Rabbit Diet was provided daily.

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Water:	Freely available, municipal (Toledo, OH) water was delivered through an automatic watering system.
Contaminants:	Reasonably expected contaminants in feed or water supplies did not have the potential to influence the outcome of this test.
Housing:	Animals were individually housed in stainless steel suspended cages identified by a card indicating the lab number, animal number, test code, sex, and date dosed.
Environmental:	The room temperature was monitored daily. The temperature range for the room was 61-72°F.
	The room humidity was monitored daily. The humidity range for the room was 30-70%.
	The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark).
Facility:	NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.
Personnel:	Associates involved were appropriately qualified and trained.
Selection:	Only healthy, previously unused, animals free from irritation or other dermatological lesions that could interfere with the test were selected.

Experimental Procedure:

On the day prior to treatment, the fur on each rabbit's back was clipped with an electric clipper. On the day of treatment, four sites, two on each side of the back and positioned cranially and caudally, were designated on each rabbit. The sites were free of blemishes that could interfere with the interpretation of results. Each rabbit received four, parallel epidermal abrasions with a sterile needle. The sites on the left side of the back remained intact.

A 25 mm x 25 mm section of the test article was moistened with 0.5 ml of saline, and applied to each cranial site (two sites per rabbit) by introduction under a 4 ply gauze layer to an area of skin approximately 25 mm x 25 mm square. The patches were backed with plastic and covered with a nonreactive tape. The control sample was similarly applied to the caudal sites. The trunk of each animal was wrapped with an elastic binder to maintain the test patches in position. Animals were returned to their cages after treatment.

After the 24 hour exposure, the binders, tape, and patches were removed. The sites were gently wiped with a gauze sponge dampened with deionized water in an attempt to remove any remaining residue. Dermal observations for erythema and edema were recorded at 1, 24, 48 and 72 hours after patch removal in accordance with the criteria in Appendix 2.

The Primary Irritation Index of the test was calculated following test completion for each animal. The erythema and edema scores obtained at the 24, 48 and 72 hour intervals were added together and divided by the total number of observations. This calculation was conducted separately for the test and control article for each animal. The score for the control was subtracted from the score for the test article to obtain the Primary Irritation Score. The Primary Irritation Score for each rabbit was added together and divided by the number of rabbits to obtain the Primary Irritation Index. The Primary Irritation Index was characterized based on the definitions outlined in Appendix 1.

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RESULTS

Individual results of dermal scoring appear in Appendix 1. Well-defined erythema and no edema reactions resulted in an overall evaluation of slight irritation to the skin of the rabbits. The time of onset of the Maximum Irritation Response was at 1 hour and the time to Maximum response was 1 hour. The Primary Irritation Index of the test article was calculated to be 1.1. The irritation calculations are shown below:

Rabbit Number	Test Score Average	-	Control Score Average	Individual Primary Irritation Score	Combined Primary Irritation Score (CPIS)	Primary Irritation Index (CPIS ÷ 3)	Response Category
32585	1.0	-	0.0	1.0	3.3	1.1	Slight
32586	1.0	-	0.0	1.0			
32587	1.3	-	0.0	1.3			

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and ISO 17025.

CONCLUSION

Under the conditions of this study, well-defined erythema and no edema were observed on the skin of the rabbits. The Primary Irritation Index for the test article was calculated to be 1.1. The response of the test article was categorized as slight.

RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

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APPENDIX 1

DERMAL OBSERVATIONS

Rabbit Number/ Gender	Weight (kg)	Group	Observation	Interval (hours)							
				1		24		48		72	
				Left	Right	Left	Right	Left	Right	Left	Right
32585 Male	2.5	Test	Erythema	1	1	1	1	1	1	1	1
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
32586 Male	2.3	Test	Erythema	1	1	1	1	1	1	1	1
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
32587 Male	2.2	Test	Erythema	2	2	2	2	1	1	1	1
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0

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APPENDIX 2

CLASSIFICATION SYSTEM FOR SKIN REACTION

REACTION	NUMERICAL GRADING
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond exposure area)	4
Total possible score for irritation	8

NOTE: Other adverse changes at the skin sites shall be recorded and reported

IRRITATION RESPONSE CATEGORIES IN THE RABBIT

RESPONSE CATEGORY	MEAN SCORE
Negligible	0.0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

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Appendix I

CLINICAL REPORT ON PATCH AND PHOTO-PATCH TESTS WITH XCLAIR®

SUMMARY

Xclair® is a product in development by Sinclair Pharmaceuticals. In order for development to proceed into human efficacy clinical studies, this product was tested for any potential skin reaction when applied alone or in combination with UV rays.
In this report, the results of patch and photo-patch tests with this product are reported.

INTRODUCTION

The objectives of this study were to use *in vivo* models for screening the irritant, allergic, photo-irritant and photo-allergic capability of Xclair® (Sinclair Pharmaceuticals), that was applied to human skin of volunteers.

SUBJECTS AND METHODS

1) Subjects

Twenty-two Caucasian, healthy volunteers were subjected to patch and photo-patch tests with Xclair®.
The subjects were 5 males (22.7%) and 17 females (77.3%), with an age ranging from 24 to 80 years (mean age: 47.5 years).
Patients' characteristics are reported in Table 1.

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1a) Inclusion criteria

Inclusion criteria were:
- Adult and healthy males and females;
- Skin photo-type: II-III;
- Subjects with healthy skin;
- Subjects who agreed not to wet the product application site and who agreed to avoid intensive physical activity;
- Subjects who agreed to fill in a file in which personal data, dermatological notes and dates regarding the tests were reported;
- Subjects who agreed to sign a written informed consent form.

1b) Exclusion criteria

Exclusion criteria were:
- Female subjects who were pregnant or breast feeding;
- Subjects with tattoos, scars, sunburn, … on the test site which could interfere with scoring;
- Subjects who were under therapy for a systemic or a skin disease that required the use of systemic (antihistamines, corticosteroids, non steroidal anti-inflammatory drugs, beta-blockers) or topical drugs or that could interfere with the test products evaluation;
- Subjects with a history of hypersensitivity to any of the formulations components;

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- Subjects with a history of any significant systemic disease;
- Subject who were not able to meet the study attendance requirements.

2) Patch and photo-patch tests

2a) Single patch test

The product was applied on the right volar forearm under occlusion for 48 hours.

2b) Single photo-patch test

The product was applied on the left volar forearm under occlusion for 24 hours. After removal of the patch, UVA rays were applied (14 J/cm2) on the same test site.

2c) Assessment

Reading was made visually after 30 minutes, 24 and 48 hours after patch removal.
Visual reading of patch test was based on the following scale:

0: no reaction
1: weak erythema
2: weak erythema and micro-vesicles
3: erythema, micro-vesicles and weak oedema
4: erythema, micro-vesicles and oedema

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Visual reading of photo-patch test was based on the following scale:

0: no reaction
1: weak erythema
2: considerable erythema
3: erythema, oedema and weak exudation
4: vesicles and/or blisters
5: erosions

RESULTS

Twenty-two volunteers were subjected to patch and photo-patch tests with Xclair®.

1) Patch test

Patch test results are reported in Table 1.
Three subjects (13.6%) developed a 2+ local reaction and 6 subjects (27.3%) a 1+ local reaction.
In 13 subjects (59.1%) no reaction was observed.
Neither diffuse/generalized nor systemic reactions were reported by the subjects or observed by the investigator.

2) Photo-patch test

Photo-patch tests results are reported in Table 1.
Two subjects (9.1%) developed a 2+ local reaction and 4 subjects (18.2%) a 1+ local reaction.
In 16 subjects (72.7%) no reaction was observed.
Neither diffuse/generalized nor systemic reactions were reported by the subjects or observed by the investigator.

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COMMENT

1) Patch tests

On the basis of the results previously mentioned, Xclair® seems to have an irritant potential (6 subjects with a 1+ local reaction out of 22 = 27.3%).

2) Photo-patch tests

The four subjects (18.2%) with a 1+ local reaction would suggest a mild photo-irritant capability of Xclair®.

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TABLE 1. Patients' characteristics and results of patch and photo-patch tests.

PTS		Sex	Birth (year)	Patch t.	Photo-patch t.
1	EA	F	1931	++	–
2	LA	F	1974	++	+
3	SB	F	1979	–	–
4	FB	F	1976	–	–
5	MB	F	1955	–	–
6	LB	F	1923	+	–
7	SB	F	1976	–	–
8	MGB	F	1946	+	–
9	CB	F	1962	–	–
10	FD	F	1972	+	+
11	IF	F	1928	+	–
12	MLG	F	1960	–	–
13	LG	F	1961	–	–
14	EL	M	1943	+	+
15	MN	F	1967	–	++
16	IP	F	1948	–	–
17	PDP	M	1952	++	+
18	MS	F	1965	–	++
19	RS	F	1959	–	–
20	AV	M	1960	–	–
21	SV	M	1957	–	–
22	VV	M	1926	+	–

LEGENDS: PTS = patients.

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CLINICAL REPORT ON PATCH AND PHOTO-PATCH TESTS WITH XCLAIR®

Study Site :
Istituto Dermatologico Europeo - Milan/Italy

Investigator :
Prof. Stefano Veraldi

Co-Investigator
Prof. Paolo Pigatto

Scientific Director
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Milan, February 18, 2003

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