DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: DEC 29 2003

From: Division of Dietary Supplement Products, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Pre-market Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Spermine and Spermidine (Spermelene)

Firm: Nokomis Research Inc.

Date Received by FDA: May 6, 2003

90-Day Date: August 5, 2003

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day pre-market notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Tanya L. Jackson

Attachments

95S-0316

RPT191

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, Maryland 20740

JUL 18 2003

Mr. Richard Bendera
Nokomis Research Inc.
87 Burnhamthorpe Road
Toronto, Ontario M9A 1H3

Dear Mr. Bendera:

This is to inform you that the notification, dated May 1, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on May 6, 2003. Your notification identified the substances spermine and spermidine as the substances that you intend to market as new dietary ingredients in the product Spermelene.

The description in the notification of the dietary supplement Spermelene states that the level of the new dietary ingredients in the supplement will be in the range of 2.5 mg-2.7 mg of spermine and 2.5 mg-2.7 mg of spermidine per pill or capsule. The notification states that "the minimum recommended use for humans is 90 continuous days in order to cover an entire spermatogenesis period."

Under 21 U.S.C. 350b(a)(2), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has reviewed the information included in the notification for the new dietary ingredients, spermine and spermidine, and concludes that the notification does not provide evidence supporting the safe use of the ingredients or supplement containing it in the general population. Neither the supplement product Spermelene nor the ingredients spermine and spermidine are adequately identified or characterized. Specifically, your general statement that "spermine and spermidine (Spermelene) is [sic] a compound that can be isolated from corn, cucumber, oat and radish leaves and stems or any other natural source, but may also include any portion of the compounds which provide the biological activity of maintaining male fertility and libido and reducing inflammation and easing of pain in human males with prostatitis" fails to adequately identify or characterize the new dietary ingredients or their source(s).

FDA is unable to determine whether the scientific studies you cite provide an adequate basis for a conclusion that the dietary supplement Spermelene will reasonably be expected to be safe because it is unclear how the information submitted relates qualitatively and quantitatively to the proposed supplement.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that spermine and spermidine in the Spermelene product, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

You also indicate in your submission that your product is useful for "maintaining fertility and libido and reducing inflammation and easing of pain in human males with prostatitis." Under 21 U.S.C. 321(g)(1)(B), a drug is defined as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The information in your submission suggests that your product is intended to be used to treat medical conditions and is subject to regulation as a drug under 21 U.S.C. 321(g)(1)(B) and is not a dietary supplement. See 21 CFR 101.93(g). If you wish Spermelene to be evaluated for its use in the treatment of these medical conditions, you should contact FDA's Center for Drug Evaluation and Research (CDER).

Your notification will be kept confidential for 90 days after the filing date of May 6, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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May 1, 2003

RECEIVED
MAY 05 2003

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

To Whom it May Concern:

Pursuant to the Federal Food, Drug, and Cosmetic Act, notification is hereby provided of a new dietary ingredient, SPERMELENE. Accordingly, enclosed please find an original signed copy and two (2) copies of this notification.

1. Name and complete address of manufacturer and distributor of the new dietary ingredient:

Nokomis Research Inc.
c/o Nokomis Group Inc.
Box #2
King City, Ontario L7B 1A4
Canada

(courier address)
87 Burnhamthorpe Road
Toronto, Ontario M9A 1H3
Canada

2. Name of the new dietary ingredients:

SPERMINE
SPERMIDINE

To be used in combination under the trade name SPERMELENE*

3. A description of the dietary supplements that contain the new dietary ingredient.

It is anticipated that SPERMELENE will be used in the following formats: pills and/or capsules, and as an additive to various foods or other dietary supplements. It is also anticipated that Selenium and/or Vitamin E (accepted dietary ingredients) will be added to the new supplement.

Spermine and spermidine are both known as polyamines.

Polyamines are organic cations of low molecular weight which are present in prokaryotic and eukaryotic cells. The major polyamines in mammals are putrescine, spermidine and spermine (Calandra et al. 46:209-222 (1996) Apptla).

Polyamines are ubiquitous chemicals that occur in every living cell. They fulfil an array of roles in cellular metabolism and are involved in many steps of protein, RNA and DNA synthesis, from the control and initiation of translation to the regulation of its fidelity (Dunshea and King, 73:819-828 (1995).

The polyamines, spermine and spermidine have been studied in connection with sperm for a considerable period of time (see for example, Colandra, R.S. et al. Physio. Pharmaco. Ther. Latinoan. 1996:46(4):209-22).

Many food stuffs and vegetables -- such as Chinese cabbage, endive, iceberg lettuce, wheat, apple leaves, spinach, and radishes -- have been found to contain varying levels of the aforementioned polyamines.

Spermine and spermidine (SPERMELENE) is a compound that can be isolated from corn, cucumber, oat, and radish leaves and stems, or any other natural source, but may also include any portion of the compounds which provide the biological activity of maintaining male fertility and libido and reducing inflammation and easing of pain in human males with prostatitis.

Also included in the meaning of the terms spermine and spermidine are any and all synthetic analogs of the naturally occurring polyamines, or biologically active portions thereof, howsoever prepared.

A chemical analysis has been performed in respect of corn namely the chemical constituents of *Zea mays L. (Poaceae)*, cucumber namely the chemical constituents of *Cucumis sativus L. (Cucurbitaceae)*, oats namely the chemical constituents of *Avena sativa L. (Poaceae)*, and radishes namely the chemical constituents of *Raphanus sativas L. (Brassicaceae)* (The Clinicians' Handbook of Natural Healing by Gary Null, Kensington Publishing, New York, 1997). Over 90 different chemicals and compounds are identified in the list of constituents. Vitamin E (alpha-tocopherol) is an antioxidant that protects the body's cells against damage by reactive chemical compounds known as free radicals. Vitamin E and selenium have similar actions (Merck Manual of Medical Information, Pocket Books, New York, 1997). The present product has identified spermine, spermidine, selenium and or Vitamin E as constituents which can help maintain male fertility and libido -- within normal limits -- and help provide a reduction in inflammation and an easing of pain for those male humans with prostatitis.

Spermidine and spermine are phytochemicals derived from green plant materials. Phytochemicals are substances found in edible plants that exhibit potential benefits in the prevention and treatment of disease. According to the Journal of the American Dietetic

Association (April '95): *It is the position of the ADA that specific substances in foods (e.g. phytochemicals) may have a beneficial role in health as part of a varied diet.* Although, it is possible to produce synthetic or recombinant spermine, spermidine, selenium, and or vitamin E, it is preferably derived from corn, cucumber, oats, lettuce, lentil seeds, radish leaves, radish seeds, cabbage.(Bardocz, s. et al., J. Nut. Biochem, 1993 vol 4) and (Smith, T.A., Phytochemistry, 1970, vol 9, pp.1479-1486).

Both spermine and spermidine, when ingested, are transported from inside the intestine into the blood stream with only **30%** of the ingested amount being metabolically degraded. Therefore about **70%** of what is ingested is metabolically available for the body to use in various cellular processes.

It has been reported that selenium, and like-wise vitamin E, provided to males as a supplement can improve sperm motility. However, it is believed that spermine, spermidine, selenium and or vitamin E in combination has not previously been used to help inhibit male infertility. It has been found that that the use of selenium and or vitamin E in a formulation *in combination with spermine and spermidine* may provide a surprisingly effective composition for maintaining male fertility and libido and for reducing inflammation and easing pain for those human males with prostatitis.

Accordingly the present composition, comprising spermine, spermidine, selenium and or vitamin E, may be effective in maintaining male fertility and libido and reducing inflammation and easing of pain for those human males with prostatitis.

"Effective amount" as used herein is the amount required at dosages and periods of time necessary to achieve the specified desired result.

3.1 Level of the new dietary ingredient in the product.

The normal daily intake of dietary polyamines in humans is 350-500 pmol/day.

Fresh radish sprouts, as example, have the highest polyamine concentrations reported in the literature at about 1500 ug/g (Simón-Sarkadi and Holzapefel 1995), (Bardocz et al. 1993), and (Smith, T.A. 1996).

Previous patented research showed that a human daily intake was 4500 ug.

Based on body mass scaling, the following dosages were determined.

Where mice are the mammals, a dose that should produce positive results would be at least 5ug of spermine (2.5ug) and spermidine (2.5ug), and 0.04 ml/kg of selenium and vitamin E.

Where human males are the mammals, a dose that should produce positive results would be **5mg – 5.4mg of spermine (2.5mg – 2.7mg) and spermidine (2.5mg – 2.7mg), and 55micrograms of selenium and or 10mg of vitamin E.**

Minimum recommended use for humans is **90 continuous days**, in order to cover an entire spermatogenesis period.

The composition of the present product when administering spermine, spermidine, selenium and or vitamin E preferably contains suitable pharmaceutical carriers or dilutants as appropriate. Suitable pharmaceutical carriers and methods of preparing pharmaceutical dosage farms are described in Remington's Pharmaceutical Sciences, Mack Publishing Company,

3.2 Conditions of use of the product.

The foregoing examples illustrate that a composition of the present product including spermine, spermidine or including spermine, spermidine and selenium, or including spermine, spermidine, and vitamin E, or including spermine, spermidine, selenium, and vitamin E may result in maintaining sexual health in males, including an increase in libido, and improvement in sperm count, sperm motility, as well as improved sperm quality, and enhanced fertility. In addition, the anti-inflammatory and resulting pain reduction effects of the composition may be very effective in the treatment of the male prostate conditions.

3.3 History of use or other evidence of safety.

Both the natural and the purified compounds have been found to be safe at the amounts required. In addition, it is important to note that the active ingredients are naturally occurring chemicals in both plants and animals. These compounds are normally synthesized in various tissues in the body and in plants. As well, the ingredients are commercially available as purified powders; ;there is, therefore, an existing database on biological safety of these compounds. Most importantly, in none of the following studies, was there any evidence of detrimental effects on mammal health, growth or wellbeing.

1) Human Studies: Soft science human studies showed a ***36% increase in sperm count*** in men with low/low normal sperm counts. Data from family physician observations was sufficiently complete to perform a scientifically sound statistical analysis. The results showed that one to four months of therapeutic administration culminated in a significant increase in sperm concentration. Median sperm concentration doubled. Most importantly, these results were also associated with a **50% improvement of sperm motility**.

2) Equine Studies (Standard Bred): A pilot study on four horses* with normal sperm counts showed evidence for a small increase in sperm count on two animals. More importantly, ***sperm count and motility did not decrease*** in any of the animals at a time when they were normally expected to do so (i.e. End of the

breeding season). This is significant in that it greatly expands the breeding season and dramatically enhances economic potential.

3) Mice Studies: Carefully controlled studies on three groups of mice using only spermine and spermidine (10 mice per group: placebo-controlled, liquid product, spermine and spermidine – positive control) showed a **42.8% increase** in sperm count at the end of the six weeks. The magnitude of the increase varied considerably among the mice, with some mice showing a doubling of sperm count, and others showing a smaller increase. Based on the variability seen here, a group of 20 mice per treatment would have resulted in more statistically significant results. However, the magnitude of increase clearly ***indicates a clear physiological significance and importance.***

4) Mice Studies: A controlled laboratory study using 40 B6D2F-1 male mice treated with the three S compound were set up in 1:1 matings with 300 non-treated B6C3F-1 females resulting in a **"clearly higher embryo production"**

5) Equine Studies (Thoroughbreds): Elite thoroughbreds exhibiting either libido and/or infertility problems are being tested with the product's compounds on an ongoing basis with positive results. Conducted by a world-renowned theriogenologist and two senior veterinarians skilled in the equine field, the tests have shown that the ***"sexual behavior of the low-libido stallions were enhanced following treatment"*** **and that a** ***"positive improvement in stimulating stallions with low libido"*** has been seen. Although the evaluation of sub-fertile stallions is still continuing, there has been ***"encouragement in its effect on the enhancement of sperm quality"*** **and an indication that** ***"sperm production is up".*** Overall, those involved in the equine market feel that the product is ***"good for the industry and good for the owners".***

6) Continuing Equine Studies: The product has been used for the past three years in continued research. Over **25,000** doses have been administered with no reported detrimental effects.

7) Soft Science Canine Studies: These studies have shown ***an increase in sperm production.***

8) Mice Studies: In an additional research, three groups of spermine-deficient GY mice were studied in order to further evaluate the effects of the product for treating infertility in males. According to the study director, ***"there is definitely something happening ... it seems that it*** **(the product)** ***works".*** Most notably, the ***"results were consistent with testing done on regular mice"*** **with** ***"both sperm count and motility up".***

The accumulated evidence has provided convincing proof that the products may increase sperm count and quality as well as enhancing libido in male mammals -- with no detrimental effects..

3.3.1 Reference to published materials

Araujo, J.F., A.S. Righini, J.J. Fleury, M.C. Caldas, J.B. Costa-Neto and N. Marques. 1996. Seasonal rhythm of semen characteristics of a Brazilian breed ("mangalarga") stallion. *Chronobiology International* 13:477-485.

Bardocz, Susan, et al., 1993. Polyamines in Food-Implications for growth and health. *J. Nutr. Biochem* Vol 4., April.

Calandra, R.S., Rulli, S.B., Frungieri, M.B., Suescun, M.O.,Gonzalez-Calvar, S.I., 1996. Polyamines in the Male Reproductive System. *Acta Physiol Pharmacol Ther Latinoam* 46(4):209-22.

Dunshea, F.R., King, R.H. 1995. Response to Homeostatic Signals in Ractopamine-Treated Pigs. *Br.J. Nutri* June;73(6):809-18

Jasko, D.J. 1992. Evaluation of stallion semen. *Veterinary Clinics of North America: Equine Practice* 8:129-148.

Jasko, D.J., T.V. Little, D.H. Lein and R.H. Foote. 1992. Comparison of spermatozoa movement and semen characteristics with fertility in stallions: 64 cases (1987-1988). *Journal of the American Veterinary Medical Association* 7:979-985.
Kovacs, A., Simon-Sarkadi, L., Ganzler, K., 1999. Determination of biogenic amines by capillary electrophoresis. *J. Chromatogr. A.*Mar 26;836(2):305-13.

Magistrini, M.P. Chanteloube and F. Palmer. 1987. Influence of season and frequency of ejaculation on production of stallion semen for freezing. *Journal of Reproduction and Fertility* (Supplement) 35: 127-133

Null, Gary, 1997. The Clinician's Handbook of Natural Healing, Kensington Publishing, New York.

Simon-Sarkadi, L., Holzapfel, W. H.,1994. Determination of biogenic amines in leafy vegetables by amino acid analyser, *Z. Lebensm Unters Forsch,* Mar;198(3):230-3.

Simon-Sarkadi, L., Holzapfel, W. H., 1995. Biogenic Amines and microbial quality of sprouts. *Z. Lebensm Unters Forsch,*Apr;200(4):261-5.

Smith, T.A., 1969. Putrescine, Spermidine and Spermine in Higher Plants, *Phytochemistry,* Vol.9,pp.1479-1486.

Stewart, B.L. and J.F. Roser, 1998. Effects of age, season, and fertility status on plasma and intratesticular immunoreactivity (IR) inhibit concentrations in stallions. *Domesticated Animal Endocrinology* 15: 129-130.

3.3.2 Other reference materials.

Medical Definitions: Gould's Medical Dictionary 1943
Merck Index

Dr. Duke's Phytochemical and Ethnobotanical Databases, Agricultural Research Services

Singer, R., et al, 1989. The influence of seminal plasma and polyaminic substances on the motility of isolated human sperm. *Int J Fertil,* May;34(3):224-230.

Melendrez, C.S., et al. 1992, Polyamines in ejaculated ram spermatozoa and their relationship with sperm motility. *J. Androl,* Jul;13(4):293-296.

Cross, N.L., 1996. Human seminal plasmaprevents sperm from becoming acrosomally responsive to the agonist, progesterone: cholesterol is the major inhibitor. *Bio. Reprod.,*Jan;54(1):138-145

Quemener, V., 1992. Depletion in nuclear spermine during human spermatogenesis, a natural process of cell differentiation. *Amer. J. Physiol,* Aug;263(2pt1):C343-C347.

Breitbart, H., Rubenstein, S., Lax, Y.1997. Regulatory mechanisms in acrosomal exocystosis. *Rev. Reproduction,* Sep;2(3):165-174.

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Lorenz, B. et al. 1998. Spermine deficiency in Gy mice caused by deletion of the Spermine synthase gene, *Hum Mol Genet,* Mar;7(3):541-547.

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Baze, P.E., et al. 1985. Distribution of polyamines in human epidermis. *Br. J. Dermatol,* Apr;112(4):393-396.

Karacagil, M., 1989. The effect of spermine, spermidine and kallikrein on the triple adenosine triphosphatase enzyme activity of spermatozoa in males with oligoasthenozoospermia. *Br. J. Urol.,* Jan;63(1):84-6.

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Breitbart, H, Rubinstein, S., Lax, Y., 1997. Regulatory mechanisms in acrosomal exocytosis. *Rev.Reprod.*, Sep;2(3):165-174.

Lenz, S., 2003. Fertility supplementation with sperm-aide (polyamine modulator). *Conf. Paper.*

4. Designated contact:

Rick Bendera
87 Burnhamthorpe Road
Toronto, Ontario M9A 1H3
Tel# (416) 236-0846
Fax# (416) 236-7087
Cwmgmt@aol.com

R. Bendera **Date** May 1/03

Please note that under separate correspondence sent February 25, 2003, (see attached) a request was sent to the FDA requesting clarification and direction. As an addendum to this letter, please be advised that a patent (#6,555,140) has been issued by the United States Patent and Trademark Office (April 29, 2003)

Thank you in advance for considering the above.

Yours truly,

R. Bendera

Rick Bendera

February 25, 2003

Division of Standards & Labeling Regulations
Office of Nutritional Products, Labelling, & Dietary
Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food & Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

Attention: Susan Aitken

As a follow up to our telephone conversation of today, I am requesting clarification and direction as to:

1. Whether spermine and spermidine (both naturally extracted and synthetic format) are considered to be a Dietary Supplement or a New Dietary Ingredient?

2. Is there a difference, in how these products are viewed by the FDA, if they are either naturally extracted or a synthetic?

Overview:

As discussed we have received acknowledgement that the U.S. patent office has verbally approved our patent. COMPOSITION & METHOD FOR ENHANCING MALE FERTILITY & LIBIDO. We also have patents pending in Canada and Europe.

Using normal amounts (those concentrations found in vegetables, fruits, cereals, milk products, & meat) of spermine and spermidine in a composition, we have been able to enhance male fertility.

From our research and our testing plus countless literature searches, we have results that are extremely positive and most beneficial.

Spermine and Spermidine have been known for years as referenced in Gould's Medical Dictionary (1943), the Merck Index, CAS NUMBER's 71-44-3 & 124-20-9 & articles dated December 1969 & 1993.(see attached).

May 14, 2003

Division of Standards & Labeling Regulations
Office of Nutritional Products, Labelling, & Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food & Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

RECEIVED 5/19/03 HFS-811

Attention: Robert J. Moore

First and foremost thank you for your response to my original February 25, 2003 letter.

As a follow up to your letter dated May 8, 2003, I would like to provide the following information as feedback to your letter and for further consideration.

With respect to extracted or purified forms of spermine and spermidine, we will move forward with our project based upon your response.

However, with respect to synthetic versions of spermine and spermidine, we would like you to consider the following:

We have consulted with Dr. Patrick Woster, Professor, Pharmaceutical Sciences at Wayne State University, Detroit , MI. [(313) 577-1523], a renowned expert in the field of polyamines, most specifically spermine and spermidine.

According to Dr. Woster,

- Both vitamins and minerals, elements of food, can and are synthetically produced and used for human consumption.

- Sodium Chloride, a common salt, which is a constituent of animal fluids and tissue and of food, is synthetically manufactured and used as a part of our diet.

- Spermine and Spermidine are polyamines found in our food and in bodily fluids, and can be synthetically produced.

- Polyamines are metabolites of botanicals.

- Our expressed usage of naturally extracted and/or synthetic spermine and spermidine will not exceed the daily human consumption of polyamines in one's diet.

Under a separate letter dated May 1, 2003 (Nokomis Research/Richard Bendera) and acknowledged by your department as having been received May 5, 2003, we have requested your approval in considering SPERMINE and SPERMIDINE as new dietary ingredients under the trade name *SPERMELENE.*

With this submission, we have provided references which we believe are supportive of our request.

Attached to this correspondence please find copies of our original letter, your response to our letter, and two papers that provide evidence of the magnitude of spermine and spermidine in foods that we eat, and evidence that a synthetic version of these two polyamines falls within the same category as the vitamins and minerals that are synthetically produced to replicate their presence in food stuffs.

We would ask that you add this letter to our submission for a new dietary ingredient, and as well reconsider your response of May 8, 2003 to include synthetic spermine and spermidine in light of this additional information.

Thank you in advance for your additional consideration of this matter.

Yours truly,

Richard Bendera
87 Burnhamthorpe Road
Toronto, Ontario
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