DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

December 22, 1998

TRANSMITTED BY FACSIMILE

Jonah Shacknai
Chairman of the Board and CEO
Medicis Pharmaceutical Corporation
4343 East Camelback Road, Suite 250
Phoenix, AZ 85018

RE: **ANDA #63-181 (50 mg. Capsule)**
ANDA #63-065 (100 mg capsule)
Dynacin (minocycline HCl capsules, USP)
MACMIS # 6797

WARNING LETTER

Dear Mr. Shacknai:

This Warning Letter concerns Medicis Pharmaceutical Corporation's (Medicis) dissemination of advertising and labeling materials to promote Dynacin (minocycline HCl capsules, USP). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials as part of our monitoring and surveillance program. From its review, DDMAC has determined that these materials[1] contain statements or suggestions that are false or misleading in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 352(a), 352(n), 331(a), 331(b) and applicable regulations.

Background

Minocycline HCl Capsules, USP is a multisource product, i.e., it is commercially available from more than one manufacturer. "Dynacin" is a brand name used by Medicis Pharmaceutical Corporation to market and distribute minocycline HCl capsule, USP products that are manufactured by Danbury Pharmacal Inc.,a subsidiary of Schein Pharmaceuticals, Inc., under

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[1] These materials include DYN14697, DYN21098, DYN13797, DYN24498R, DYN21098, DYN190697R, DYN19697, DYN24498R, DYN21098, DYN03796, DYN03996, DYN21698, DYN14097, DYN18697, DYN13797, DYN13897, DYN14097, DYN14697, DYN21698AAD, DYN24498, DYN24498R DYN23498, DYN1969TR, and DYN19697. The materials cited are illustrative of the wide variety of violative promotional materials disseminated by Medicis.

ANDAs 63-065 and 63-191. Danbury's minocycline HCl capsule, USP products are distributed by other companies, including Schein, under the generic name.

Danbury's minocycline was approved for marketing based on information in the ANDAs submitted to the Food and Drug Administration (FDA) by Danbury that its minocycline HCl capsule products are bioequivalent and therapeutically equivalent to Minocin. Accordingly, Danbury's minocycline HCl products are AB rated to Minocin.[2] Other generic minocycline HCl capsule USP products such as those manufactured or marketed by Teva and Warner Chilcott are rated AB to Minocin. All of the AB rated minocycline HCl capsule products are therapeutically equivalent. In view of this determination, FDA believes that these products can be substituted for each other with the full expectation by health care providers and consumers that they will have the same clinical effect and safety profile as Minocin.

In its promotional claims, Medicis states that its AB-rated generic minocycline HCl product is superior in safety or effectiveness to Minocin, or to other generic products that are AB-rated to Minocin. Such claims are false or misleading and in direct conflict with the information presented by the applicant in its ANDAs and the decision reached by the Agency during the generic drug approval process. Although some sponsors, such as Medicis, choose to market their AB rated generic products using a brand name, these products are not distinguishable in safety or effectiveness from Minocin or from other generic products that are AB-rated to Minocin. Therefore, any claims by Medicis that its generic minocyline HCl capsules USP are superior in safety or effectiveness to any other AB-rated minocyline HCl capsule USP product are false or misleading and misbrand Dynacin.[3]

**APPEARS THIS WAY
ON ORIGINAL**

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2 Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), 18th Edition, 1998, p. 3-224 et seq.

3 This Warning Letter is not limited to the specific claims or advertising and promotional materials referred to herein. It is also directed to any other advertising and promotional materials for Dynacin that contain similar themes or statements.

Current Violations

A. Claims of Superiority Over Minocin

Medicis' claims that Dynacin is superior to Minocin are false or misleading. In its ANDA, Danbury submitted information that demonstrated that its generic minocycline HCl capsule USP product (that Medicis markets as Dynacin) was therapeutically equivalent to Minocin. Thus, statements that Dynacin is superior in safety or effectiveness contradict the information in the applications upon which this product is marketed and are false or misleading. Medicis' promotional statements that its generic product is superior to Minocin include the following:

- A recent study shows Dynacin outperforms Minocin in *P. acnes* reduction;[4]
- At 3 weeks, the reduction of *P. acnes* was 5 times greater than by Minocin. This difference was statistically significant;[5]
- The superior reduction of *P. acnes* produced by Dynacin may well be related to enhanced bioavailability and excellent dermal absorption;[6] and
- To our knowledge, no other manufacturer or marketer of branded or generic minocycline has represented itself as having specifications of identity, strength, quality, purity or potency which varies from that of Lederle's Minocin.... Evidence of superiority to the originator brand also provides superior performance to the generic products.[7]

B. Claims of Superiority to Other AB-Rated Generics

Medicis claims that Dynacin is superior to other AB-rated generic minocycline HCl capsule products are false or misleading. Medicis distributed promotional materials containing claims that Dynacin is superior in safety or effectiveness

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4 Brochures DYN14697, DYN21098, and DYN06596.

5 Brochure DYN14697. A footnote in the brochure states that the "Precise correlation between in vivo antimicrobial activity and clinical outcome has not been established." This disclosure does not correct the misleading messages presented in the brochure.

6 Brochure DYN14697.

7 Letter DYN24498R.

to other AB rated generic minocycline HCl capsule, USP products in (1) reducing *P. Acnes* more effectively; (2) demonstrating a lowered incidence of CNS or other adverse effects; (3) achieving greater clinical efficacy; and (4) having higher potency standards than the USP standard. For example, Medicis distributed promotional materials that stated:

- Thus excellent dissolution and bioavailability coupled with fast follicular absorption and outstanding kill of *P. acnes* within the follicle are prerequisites for excellent results and patient satisfaction. DYNACIN is the only brand of minocycline that has actually been proven to deliver all these actions."[8]

- Recent study shows Dynacin over five times less likely to cause vestibular symptoms than Vectrin [Warner Chilcott's minocycline HCl capsules, USP].[9]

- Superior Tolerance to Vectrin and Certain Generic Brands of Minocycline: ...The results showed Vectrin produced significantly higher levels (over five times higher) of the common vestibular side effects, dizziness and vertigo, in terms of incidence, severity and duration, compared with DYNACIN.[10]

- Here are the facts...Only DYNACIN and Minocin have demonstrated complete bioavailability with fasted and dairy-fed patients;[11]

- Evidence of superiority to the originator brand also provides evidence of superior performance to the generic products.[12]

- Based on these studies, we believe that we have supplied significant and meaningful evidence regarding the differences between DYNACIN and generic minocyclines. These are differences, which have caused Dermatologists to trust and prescribe DYNACIN.[13]

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8 Letter DYN24498 (p.1) (April 2, 1998)

9 Brochure DYN21098, Letter DYN190697R, and Letter DYN19697.

10 Letter DYN24498R (p.2) (April 2, 1998)

11 Letter DYN19697R (November 24, 1997)

12 Letter DYN24498R (June 10, 1998)

13 Letter DYN24498R (June 10, 1998)

- DYNACIN is manufactured under the MEDSURE quality assurance program. MEDSURE prescribes specifications that are more stringent than those of the United States Pharmacopoeia (USP), although USP standards are adopted by most manufacturers. Included under the MEDSURE program are tighter potency standards than those of the USP (95% vs. 90%), rapid dissolutions (90% release after 45 minutes vs. 75%), and batch-to-batch uniformity.[14]

- We believe there are well controlled studies which document the differences between DYNACIN and the branded or generic products made to the specifications of the originator drug and the USP specifications. MEDICIS has established separate, more stringent standards for the manufacture of DYNACIN compared to the Schein generic versions of minocycline.[15] [As noted above, Danbury is a subsidiary of Schein and is the manufacturer of the Schein product under ANDAs 63-181 and 63-065].

- To our knowledge, no other manufacturer or marketer of branded or generic minocycline has represented itself as having specifications of identity, strength, quality, purity or potency which varies from that of Lederle's Minocin.[16]

These claims are false or misleading by stating or suggesting that Dynacin is safer or more effective than other minocycline HCl products FDA has determined were therapeutically equivalent.

In addition, it is our understanding that Medicis' representatives have been promoting Dynacin by disseminating promotional materials containing a chart comparing "Dynacin vs. Generics" and "Dynacin vs. Vectrin" on the basis of alleged benefits. This chart contains superiority claims for Dynacin on a variety of parameters including "Consistency", and "Comparable Biopharmaceutic Profiles to Minocin Pellets." Although Dynacin is a generic product, Medicis presents comparisons between Dynacin and "generic" products and Dynacin and "Vectrin" (another generic minocycline marketed under a brand name). Although all of these products are generic, therapeutic equivalent products, Medicis alleges that the "generic" products are neither consistent nor bioequivalent to Minocin. Medicis also questions whether Vectrin is bioequivalent to Minocin. However, all minocycline HCl capsules, USP that are AB-rated are therapeutic equivalents, and all of these

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14 Letters DYN24498 (April 2, 1998), and DYN24498R (June 10, 1998.)

15 Letter DYN24498R (June 10, 1998)

16 *Id.*

minocycline products must meet the same well-established standards for consistency. Thus, Medicis' claims are false or misleading.

Under the Post-Marketing Reporting Requirements, all promotional materials are required to be submitted to the Agency for review at the time of initial dissemination. Our records indicate that this comparative chart has not been submitted for review as required under the provisions 21 C.F.R. §314.81(b)(3)(i).

C. Claims of Superiority over Other Forms of Tetracyclines

1. Use of In-Vitro Data to Suggest Clinical Efficacy

Medicis' claims that Dynacin is superior to other minocyclines, doxcyclines, or tetracyclines is false or misleading. Medicis distributed promotional materials containing the claim that "[s]tudies show DYNACIN significantly outperforms Minocin, Monodox, and Sumycin in reducing *P acnes.*[17] However, Medicis has not referred to substantial evidence to support its claim or to demonstrate a clinically significant difference in safety or effectiveness between Dynacin and other minocyclines, doxycyclines or tetracyclines.[18] Medicis presents its misleading superiority claims in a large, prominent, graphic presentation, but includes as a very small footnote at the bottom of the page the following disclaimer: "Precise correlation between *in vivo* antimicrobial effect and clinical outcome has not been established." The inclusion of this footnote does not remedy the misleading impression of superiority presented by the brochure.

2. Superiority Based on Increased Resistance to Doxycycline

Medicis claims that Dynacin exhibits superior clinical efficacy to doxycycline because *P. acnes* has shown increased resistance to doxycycline. One example of this claim is a Medicis postcard that states: "*Doxycycline's Ability to Protect Diminishes As Resistance has Built [--] Rx DYNACIN (minocycline* HCl)."[19] Another post-card states: "*DYNACIN: The path of least resistance.*"[20] These presentations misleadingly suggest that Dynacin is more effective because doxycycline, has lost or is losing its effectiveness against *P. acnes.* It also misleadingly suggests that *P. acnes* has the least resistance to Dynacin

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17 Advertisement DYN21098

18 *Id.*

19 Postcard DYN03796

20 Postcard DYN03996

as compared to all other oral antibiotics, including other AB-rated generic minocycline HCl capsules and Minocin.

D. Failure to Provide Fair Balance

Medicis' promotional materials contain inadequate risk information and, thus, are lacking in fair balance or otherwise misleading. These materials fail to present information relating to contraindications, warnings, precautions, and adverse effects with a prominence and readability reasonably comparable to the presentation of information relating to effectiveness. The approved product labeling for Dynacin states that minocycline is a member of the tetracycline-class of antibiotics. The labeling for Dynacin is similar to other tetracycline products and contains many of the contraindications, warnings and precautions associated with tetracycline antibiotics. However, Medicis fails to disclose this important risk information in its promotional materials.

For example, Medicis disseminated a display panel[21] that contains effectiveness claims but fails to include adequate risk information associated with the use of Dynacin. On this panel, Medicis claims that Dynacin is "SAFE" in very large type. The panel does not present any risk information, although a very small footnote at the bottom of the panel, directs the reader to "see references and full prescribing information at booth." The reference to a display booth or other site where the information may be located does not remedy the lack of risk disclosure.

In other materials, Medicis uses graphics that suggest the safe use of Dynacin in young children. However, the approved product labeling for Dynacin contains significant warnings about use in children under the age of 8. [22]

E. Overstatement of Superiority Based on Market Share

Medicis' promotional materials also present claims that Dynacin is the #1 oral antibiotic. These claims are false. For example, statements such as: "Rx: the #1 oral antibiotic brand DYNACIN (minocycline HCl),"[23] suggest that Dynacin may be the top-selling oral antibiotic in the United States. According to well-known published data, amoxicillin, is the most prescribed oral antibiotic. Dynacin was not included in the

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21 Ad DYN21698ADD

22 Letter DYN24398, Postcard DYN 14097, and Ad DYN18697.

23 Ad DYN 18697

top 200 drug prescriptions dispensed nationally during 1997.[24] Moreover, Medicis has not referred to or presented supporting evidence for the claim that Dynacin is #1 in sales, prescriptions, safety or efficacy.

F. Failure to Include Complete Prescribing Information with Labeling

All promotional labeling for prescription drugs, including Dynacin, must be accompanied by the approved product labeling and all advertising must be accompanied by a brief summary relating to side effects, contraindications and effectiveness.[25] Medicis has failed to comply with this regulatory requirement by disseminating promotional labeling materials with a brief summary instead of the full prescribing information.[26]

G. Repetitive Conduct

Many of the issues raised in this Warning Letter are not new issues for Medicis. These and similar issues have been addressed by DDMAC in untitled letters to Medicis dated December 16, 1992, January 11, 1993, and August 29, 1996. Nonetheless, Medicis has continued to disseminate advertising and labeling materials containing false or misleading claims that its generic minocycline HCl capsules USP are superior in safety or effectiveness to the reference product or to other AB-rated generic products.

H. Conclusions and Requested Actions

The actions of Medicis have resulted in the dissemination of false and misleading information about its product, Dynacin. Accordingly, Medicis should propose an action plan to correct these violations. As part of its action plan, Medicis should:

1. Immediately cease the use of any advertising and promotional labeling materials that are discussed in this letter, and all materials that contain the same or similar claims.

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24 "IMS and PT Present: Top 200 Drugs of 1997 – 33rd Ann. Ed.," *Pharmacy Times,* April 1998.

25 21 C.F.R.§201.56, §202.1(e)(4)(i).

26 DYN21098, DYN13797, DYN13897, DYN14097, DYN14697, DYN21698AAD, DYN24498, DYN23498, DYN19697, and DYN12097. This list is not exhaustive and only represents a sample of labeling disseminated without full prescribing information.

2. Submit in writing its intent to comply with "1" above.

3. Propose its plans for accomplishing corrective action.

4. Provide a complete listing of all advertising and promotional materials in current use and those materials that will be discontinued.

5. Submit a proposed "Dear Health Care Provider Letter" that will correct the false or misleading promotional claims Medicis has disseminated.

Because of the scope of Medicis' violative promotional campaign, the Dear Healthcare Professional letter and Medicis' action plan should be submitted to DDMAC for approval. After such approval, the letter should be disseminated by both direct mail and through a paid advertisement in all journals that contained advertisements for Dynacin during the 12 months prior to the date of this letter.

The violations discussed in this letter are not intended to be a complete listing. We are evaluating other aspects of Medicis' promotional campaign for Dynacin and additional violations may be identified. Consequently, DDMAC may determine that further remedial measures may be necessary at a later date to fully correct the false impressions resulting from Medicis' improper conduct.

Please respond in writing by January 11, 1999, regarding the steps taken in response to the instructions above.

If you have any questions in regard to this Warning Letter, please contact Dr. Jo Ann Spearmon, Patricia Kuker Staub, Esq., or Norman A. Drezin, Esq., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Medicis that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #6797.

Failure to respond to this letter may result in further regulatory action including seizure or injunction, without further notice.

Sincerely,

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising, and Communications