CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Medicis Phaarmaceutical Corporation
Attention: Joseph Cooper
Senior Vice President
4343 East Camelback Road
Phoenix, Arizona 85018-2700

APR 30 1999

Dear Mr. Cooper:

Please refer to your supplemental new drug application dated December 31, 1998, received January 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ovide®, (malathion) Lotion).5%.

We acknowledge receipt of your submissions dated February 26, March 17, and April 22, 1999.

This supplemental new drug application provides for labeling revisions to update the label.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18613/S-010." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

/S/ 4/30/99

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

FINAL PRINTED LABELING

APPROVED

APR 3 0 1999

NDC 99207-650-02

Ovide® (malathion) Lotion, 0.5%

Rx Only

For topical use only. Not for oral or ophthalmic use.

DESCRIPTION

OVIDE Lotion contains 0.005 g of malathion per mL in a vehicle of isopropyl alcohol (78%), terpineol, dipentene and pine needle oil. The chemical name of malathion is (±)-[(dimethoxyphosphinothioyl)-thio] butanedioic acid diethyl ester. Malathion has a molecular weight of 330.36. represented by $C_{10}H_{19}O_6PS_2$. and has the following chemical structure:

CHEMICAL STRUCTURE HERE

CLINICAL PHARMACOLOGY

Malathion is an organophosphate agent which acts as a pediculicide by inhibiting cholinesterase activity in vivo. Inadvertent transdermal absorption of malathion has occurred from its agricultural use. In such cases, acute toxicity was manifested by excessive cholinergic activity, i.e., increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia (see OVERDOSAGE). Because the potential for transdermal absorption of malathion from Ovide Lotion is not known at this time, strict adherence to the dosing instructions regarding its use in children, method of application, duration of exposure, and frequency of application is required.

INDICATIONS AND USAGE

OVIDE Lotion is indicated for patients infected with *Pediculus humanus capitis* (head lice and their ova) of the scalp hair.

CONTRAINDICATIONS

OVIDE Lotion is contraindicated for neonates and infants because their scalps are more permeable and may have increased absorption of malathion. OVIDE Lotion should also not be used on individuals known to be sensitive to malathion or any of the ingredients in the vehicle.

WARNINGS

1. OVIDE Lotion is **flammable**. The lotion and wet hair should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers. Do not smoke while applying lotion or while hair is wet. Allow hair to dry naturally and to remain uncovered after application of OVIDE Lotion.
2. OVIDE Lotion should only be used on children under the direct supervision of an adult.
3. If OVIDE Lotion comes into contact with the eyes, flush immediately with water. Consult a physician if eye irritation persists.
4. If skin irritation occurs, discontinue use of product until irritation clears. Reapply the OVIDE Lotion and, if irritation reoccurs, consult a physician.
5. Slight stinging sensations may occur with the use of OVIDE Lotion.

General: Keep out of reach of children. Close eyes tightly during product application. If accidentally placed in the eye, flush immediately with water. Use only on scalp hair.

Information to Patients

1. OVIDE Lotion is **flammable**. The lotion and hair wet with lotion should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers. Do not smoke while applying lotion or while hair is wet. The person applying OVIDE Lotion should wash hands after application. Allow hair to dry naturally and to remain uncovered after application of OVIDE Lotion.
2. OVIDE Lotion should only be used on children under the direct supervision of an adult. Children should be warned to stay away from lighted cigarettes, open flames, and electric heat sources while the hair is wet.
3. In case of accidental ingestion of OVIDE Lotion by mouth, seek medical attention immediately.

4. If you are pregnant or nursing, you should contact your physician before using OVIDE Lotion.
5. If OVIDE Lotion comes into contact with the eyes, flush immediately with water. Consult a physician if eye irritation persists or if visual changes occur.
6. If skin irritation occurs, wash scalp and hair immediately. If the irritation clears, OVIDE Lotion may be reapplied. If irritation reoccurs, consult a physician.
7. Slight stinging sensations may be produced when using OVIDE Lotion.
8. Apply OVIDE Lotion on the scalp hair in an amount just sufficient to thoroughly wet hair and scalp. Pay particular attention to the back of the head and neck when applying OVIDE Lotion. Anyone applying OVIDE Lotion should wash hands immediately after the application process is complete.
9. Allow hair to dry naturally and to remain uncovered. Shampoo hair after 8 to 12 hours, again paying attention to the back of the head and neck while shampooing.
10. Rinse hair and use a fine-toothed (nit) comb to remove dead lice and eggs.
11. If lice are still present after 7-9 days, repeat with a second application of OVIDE Lotion.
12. Further treatment is generally not necessary. Other family members should be evaluated by a physician to determine if infested, and if so, receive treatment.

Laboratory Tests: There are no special laboratory tests needed in order to use this medication.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Although carcinogenesis, mutagenesis and impairment of fertility have not been studied with Ovide Lotion, malathion, has been shown to be genotoxic in a number of *in vitro* and *in vivo* mutation and clastogenicity assays. However, there was no evidence of a carcinogenic effect following long-term oral administration of malathion in F344 rats after 2 years feeding with up to 0.4% (approximately 200-400 mg/kg/day) nor was it tumorigenic in Osborne-Mendel rats or B6C3F1 mice after similar feeding for 80 weeks with 0.8% (approximately 400-600 mg/kg/day) or 1.6% (approximately 1000-2000 mg/kg/day), respectively. Based on body surface area,
doses tested are approximately 4 to 40 fold greater than those anticipated in humans (assuming 100% bioavailabiltiy).

Reproduction studies performed with malathion in rats at doses approximately 30 fold greater than those anticipated in humans (based on body surface area and assuming 100% bioavailability) revealed no evidence of impaired fertility.

Pregnancy: Pregnancy Category B. There was no evidence of teratogenicity in studies in rats and rabbits at doses up to 900 mg/kg/day and 100 mg/kg/day malathion, respectively. A study in rats failed to show any gross fetal abnormalities attributable to feeding malathion up to 2,500 ppm (approximately 200 mg/kg/day) in the diet during a three-generation evaluation period. These doses were approximately 2 to 10 times higher than the anticipated human dose (based on body surface area and assuming 100% bioavailability). Because animal reproduction studies are not always predictive of human responses, this drug should be used (or handled) during pregnancy only if clearly needed.

Nursing Mothers: Malathion in an acetone vehicle has been reported to be absorbed through human skin to the extent of 8% of the applied dose. However, percutaneous absorption from the Ovide Lotion formulation has not been studied, and it is not known whether malathion is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ovide Lotion is administered to (or handled by) a nursing mother.

Pediatric Use: The safety and effectiveness of OVIDE Lotion in children less than 6 years of age has not been established via well-controlled trials.

ADVERSE REACTIONS

Malathion has been shown to be irritating to the skin and scalp. Accidental contact with the eyes can result in mild conjunctivitis.

It is not known if OVIDE Lotion has the potential to cause contact allergic sensitization.

OVERDOSAGE

Consideration should be given, as part of the treatment program, to the high concentration of isopropyl alcohol in the vehicle.

Malathion, although a weaker cholinesterase inhibitor than some other organophosphates, may be expected to exhibit the same symptoms of cholinesterase depletion after accidental ingestion orally. If accidentally swallowed, vomiting should be induced promptly or the stomach lavaged with 5% sodium bicarbonate solution.

Severe respiratory distress is the major and most serious symptom of organophosphate poisoning requiring artificial respiration, and atropine may be needed to counteract the symptoms of cholinesterase depletion.

Repeat analyses of serum and RBC cholinesterase may assist in establishing the diagnosis and formulating a long-range prognosis.

DOSAGE AND ADMINISTRATION

1. Apply OVIDE Lotion on **DRY** hair in amount just sufficient to thoroughly wet the hair and scalp. Pay particular attention to the back of the head and neck while applying OVIDE Lotion. Wash hands after applying to scalp.
2. Allow hair to dry naturally - use no electric heat source, and allow hair to remain uncovered.
3. After 8 to 12 hours, the hair should be shampooed.
4. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs.

5. If lice are still present after 7-9 days, repeat with a second application of OVIDE Lotion.

Further treatment is generally not necessary. Other family members should be evaluated by a physician to determine if infested, and if so, receive treatment.

Clinical Studies

Two controlled clinical trials evaluated the pediculicidal activity of OVIDE Lotion. Patients applied the lotion to the hair and scalp in quantities, up to a maximum of 2 fl. oz, sufficient to thoroughly wet the hair and scalp. The lotion was allowed to air dry and was shampooed with Prell shampoo 8 to 12 hours after application. Patients in both the OVIDE Lotion group and in the vehicle group were examined immediately after shampooing, 24 hours after, and 7 days after for the presence of live lice. Results are shown in the following table:

Number of Patients Without Live Scalp Lice

Treatment	Immediately After	24 Hrs. After	7 Days After
OVIDE Lotion	129/129	122/129	114/126
OVIDE Vehicle	105/105	63/105	31/105

The presence or absence of ova at day 7 was not evaluated in these studies. The presence or absence of live lice or ova at 14 days following treatment was not evaluated in these studies. The residual amount of malathion on hair and scalp is unknown.

HOW SUPPLIED

OVIDE (malathion) Lotion, 0.5%, is supplied in bottles of 2 fl oz (59 mL) NDC 99207-650-02.
Store at controlled room temperature 20°-25°C (68°-77°F).
Flammable. Keep away from heat and open flame.

Rx Only

Medicis logo
Manufactured for:
Medicis, The Dermatology Company®
by: West Pharmaceutical Services
Lakewood, NJ 08701

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

CHEMISTRY REVIEW(S)

APR 30 1999

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 18-613 **CHEM.REVIEW#**: 1 **REVIEW DATE**: April 30, 1999

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCM-009	31-DEC-98	05-JAN-99	06-JAN-99

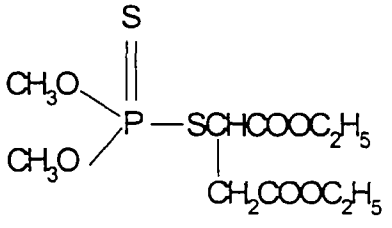
NAME & ADDRESS OF APPLICANT: Medicis Pharmaceutical Corp.
4343 Camelback Road
Phoenix, AZ 85018-2700

Joseph Cooper
Senior Vice President
602-808-8800

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of head lice and their ova.

DOSAGE FORM: Lotion
STRENGTHS: 0.5%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ R_x _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLC. FORMULA, MOLC. WT:



Molecular Formula: $C_{10}H_{19}O_6PS_2$
Molecular Weight: 330.35
CAS No.: 121-75-5

NDA 18-613
Medicus Pharmaceutical Corp.
Ovide (malathion) Lotion, 0.5%

REMARKS/COMMENTS:

N.B. This supplement was originally submitted as NDA 18-613/SCM-009. The purpose of this supplement was to:

1). Add a new manufacturing site, [redacted]

2). Add an alternate analytical testing site, [redacted]

3). Approve the carton and labeling for Ovide (malathion) Lotion, 0.5%

The rationale for these changes are as follows. Medicis acquired this NDA (18-613) from [redacted] in December 1997. At that time, the NDA was inactive; that is, marketing of Ovide Lotion was discontinued in 1994. At the present time [1999] Medicis wishes to reintroduce Ovide into the market. Medicis submitted a supplement containing the above three changes. The supplement was administratively split into two supplements: **NDA 18-613/SCM-009** and **NDA 18-613/SLR-010**.

This is the review of **NDA 18-613/SLR-009**, the *new manufacturing facility as well as an updated review of the NDA*.

Note: For ease of review, the entire NDA review template was imported into the [supplement] form. The rationale for this was that it would be easier to identify, and review, new information for the NDA but actually submitted in the supplement.

NDA 18-613
Medicus Pharmaceutical Corp.
Ovide (malathion) Lotion, 0.5%

CONCLUSIONS & RECOMMENDATIONS:

The supplement application is recommended for approval.

/S/

W.C. Timmer, Ph. D.
Review Chemist

cc: Orig. NDA 17-426
HFD-540/Division File
HFD-540/ProjMan/MWright
HFD-540/Chem/WCTimmer
HFD-540/TeamLdr/WHDeCamp /S/ 4/20/99

filename:

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology and Toxicology Data

APR 14 1999

Key Words: Malathion; Pediculicide; Cholinesterase Inhibitor

Reviewer: Lynnda Reid, Ph.D.
Division: Dermatologic and Dental Drug Products, HFD-540
Date: April 12, 1999

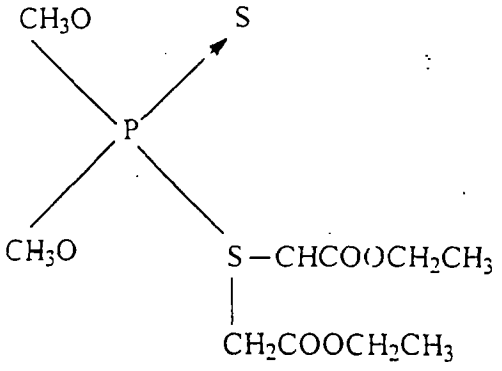
NDA No: 18-613
Submissions: S-010, dated January 7, 1999; and
SLR-010, dated March 17, 1999

Information to Sponsor: Yes ( ) No (X)

Sponsor: Medicis Pharmaceutical Corp., The Dermatology Company®
4343 East Camelback Road
Phoenix, AZ 85018-2700
(602) 808-8800

Drug:

Generic Name: Malathion 0.5% Lotion
Trade Name: Ovide® Lotion 0.5%
Chemical Names: (1) Butanedioic acid, [(dimthoxyphosphinothioyl)-thio]-, di-ethyl ester; (2) diethyl mercaptosuccinate, S-ester with O,O-dimethyl phosphorodithioate
CAS Number: CAD 121-75-5
Molecular Formula: 330.37
Molecular Weight: $C_{10}H_{19}O_6PS_2$
Structure:



Drug Class: Pediculicide

Indication: Treatment of Head Lice

APPEARS THIS WAY
ON ORIGINAL

Clinical Formulation:

Ingredients	% v/v
Malathion	
Terpineol	
Dipentene	
Pine Needle Oil	
Isopropyl Alcohol	

Ovide® Lotion 0.5% Is supplied in 2 fl oz (59 ml) bottles containing mg malathion.

Route of Administration: Topical

Proposed Clinical Protocol or Use: The drug is applied to dry scalp and hair until thoroughly moistened, then allowed to dry naturally. After 8 to 12 hours, the hair is shampooed. The drug product may be applied a second time in 7 to 9 days, if needed.

Previous Clinical Experience: Ovide® has been marketed under the tradename Prioderm® in Europe (1972), Australia (1976) and the US (1982).

INTRODUCTION

Malathion is classified as an organophosphorous pesticide and has been used in the United States since 1952. Malathion acts primarily on the nervous system induces by inhibition of cholinesterase activity and subsequent accumulation of acetylcholine. The carboxylic acid ester groupings in malathion can be hydrolyzed by mammalian carboxyesterases to metabolites which do not inhibit cholinesterase. However, carboxyesterase activity is low in susceptible insects, therefore increasing their susceptibility and accounting for the increased sensitivity of insects when compared to mammalian species.

Supplement S-010 provides for a change in manufacturing and packaging site for Ovide® Lotion 0.5% to To reflect this change in manufacturing site, revised labeling has been submitted which includes the new manufacturer and other minor CMC information.

Supplement SLR-010 was submitted in response to an informational request for submission of literature, accompanied by a comprehensive review, regarding any new information relevant to the evaluation of 1) the genotoxic potential of malathion and its metabolite malaoxon, 2) carcinogenic potential, and 3) reproductive/developmental effects of malathion. Appropriate labeling revisions should be submitted for the labeling section entitled 'Carcinogenesis, Mutagenesis and Fertility'. If no such studies have been reported in the literature since the last labeling revision, the Sponsor should indicate that a literature search was conducted and that there is no new information at this time.

INDEX OF SUBMITTED LITERATURE

1. CENTER FOR DISEASE CONTROL, 10 October 1997, 7(41):1 ff, ISSN 1350-9357.
2. H-W Leung. and D.J. Paustenbach, 1993, Percutaneous Toxicity. In: General and Applied Toxicology (Chapter 21), B. Ballantyne, T. Marrs and P. Turner, editors, Stockton Press, New York, NY, page 473.
3. W.J. Hayes, A.M. Mattson, J.G. Short and R.F. Witter, 1960, Safety of Malthion Dusting Powder for Louse Control. Bulletin of the World Health Organization 22:503-514.
4. DATA MANUAL MALATHION CHEMICAL, Cheminova Agro A/S/ Denmark, 98 pages, March, 1998

TOXICOLOGY REVIEW FOR LABELING PURPOSES

The labeling proposed by the Sponsor and the information submitted in support of the labeling does not reflect the extent of currently available information in the areas of genotoxicity, carcinogenicity, and reproductive effects of malathion. In regards to genotoxicity, the present labeling states that "Tests for mutagenicity have not been conducted." A cursory search of the MED LINE database revealed many peer-reviewed publications reporting the results of genotoxicity assays conducted with malathion and other organophosphorous pesticides. Many of these studies appear to indicate that malathion may be genotoxic although the carcinogenicity studies in rats and mice were negative. Mammalian *in vivo* and *in vitro* studies of technical and/or commercial grade malathion and its major metabolite malaoxon show a pattern of induction of chromosome damage, as measured by increases in chromosome aberrations, sister chromatid exchanges, and micronuclei.

Genotoxicity:

Dose-dependent increases in chromosomal aberrations and sister-chromatid exchanges, and decreases in mitotic indices were observed in human peripheral leukocytes following treatment with malathion at concentrations of 0.02, 0.2 2.0 and 20 µg/ml added to the culture medium at 0, 24 and 48 hours after culture initiation (Balaji and Sasikala, 1993). Similar *in vitro* results have been reported by other investigators (Pluth et al., 1996; Venkat et al., 1995; Waters et al., 1988; Chen et al., 1981; Shiau et al., 1980). In addition, *in vivo* assays with malathion and malaoxon have also reported patterns of induction of chromosome damage, as measured by chromosome aberrations, sister chromatid exchanges, and micronuclei (Flessel et al., 1993; Dzwonkowska and Hubner, 1986).

Mice exposed dermally to malathion, high concentrations were associated with the induction of chromosome aberrations in somatic (bone marrow) and germ cells (primary spermatocytes) (Salvadori et al., 1988). However, in a study designed to investigate the cytogenetic and genetic effects of subchronic exposure to organophosphorus insecticides, male mice received 8 ppm malathion in their drinking water 5 days/wk for 7 weeks. At the end of the treatment, no chromosome damage was observed in bone marrow cells, spermatogonia, or primary spermatocytes, and the subsequent dominant lethal mutation assays performed in pre- and postimplantation fetuses were negative (Degraeve et al., 1984).

References:

Balaji M and Sasikala K. (1993) Cytogenetic Effect of Malathion in *in vitro* Culture of Human Peripheral Blood. Mutat Res 301(1):13-7.

Chen HH, Hsueh JL. Sirianni SR and Huang CC. (1981) Induction of Sister-Chromatid Exchanges and Cell Cycle Delay in Cultured Mammalian Cells Treated with Eight Organophosphorus Pesticides. Mutat Res 88(3):307-16.

Degraeve N, Chollet MC and Moutschen J. (1984) Cytogenetic and Genetic Effects of Subchronic Treatment with Organophosphorus Insecticides. Arch Toxicol 56(1):66-7.

Dzwonkowska A and Hubner H. (1986) Induction of Chromosomal Aberrations in the Syrian Hamster by Insecticides Tested *in vivo*. Arch Toxicol 58(3):152-6.

Flessel P, Quintana PJ and Hooper K. (1993) Genetic Toxicity of Malathion: A Review. Environ Mol Mutagen 22(1):7-17.

Pluth JM, Nicklas JA. O'Neill JP and Albertini RJ. (1996) Increased Frequency of Specific Genomic Deletions Resulting from *in vitro* Malathion Exposure. Cancer Res. 56(10):2393-9.

Salvadori DM, et al. (1988) Cytogenetic Effects of Malathion Insecticide on Somatic and Germ Cells of Mice. Mutat Res 204:283-7.

Shiau SY, Huff RA. Wells BC and Felkner IC. (1980) Mutagenicity and DNA-Damaging Activity for Several Pesticides Tested with *Bacillus subtilis* Mutants. Mutat Res 71(2):169-79.

Waters MD, Bergman HB and Nesnow S. (1988) The Genetic Toxicology of Gene-Tox Non-Carcinogens. Mutat Res 205(1-4):139-82.

Venkat JA, Shami S. Davis K, Nayak M, Plimmer JR. Pfeil R, and Nair PP. (1995) Relative Genotoxic Activities of Pesticides Evaluated by a Modified SOS Microplate Assay. Environ Mol Mutagen 25(1):67-76.

Carcinogenicity: Long-term carcinogenicity studies utilizing technical-grade malathion in the feed were conducted in Osborne-Mendel rats and B6C3F1 mice by the National Cancer Institute (TR-192, 1978). Rats were treated with time-weighted average doses of 4,700 or 8,150 ppm malathion, and mice were treated with 8,000 or 16,000 ppm for 80 weeks followed by an observation period of 14-15 weeks. In female rats, there was a statistically significant (P=0.026) dose-related trend in the number of follicular-cell neoplastic lesions (Table 1). However, the results of the Fisher exact test for direct comparison between the dosed and control groups were not significant. More dosed males than dosed females had either tumors or hyperplasia of the follicular cells of the thyroid; however, because of the higher incidence of tumors among the male controls, none of the results of the statistical tests were significant. These thyroid tumors were not considered by NTP to be associated with the administration of malathion.

In male mice, hepatocellular carcinomas and neoplastic nodules were observed (Table 2). However statistical analysis did not reveal any evidence in either male or female mice of drug related tumorigenic activity.

Table 1: Incidence of thyroid follicular cell neoplastic lesions in female Osborne-Mendel rats administered malathion over an 80 week period.

Neoplastic Lesion	Control	4,700 ppm	8,150 ppm
Follicular-Cell Carcinomas	0		3/50
Follicular-Cell Adenomas	0		1/50
Follicular-Cell Hyperplasia	0	3/50	

Table 2: Incidence of neoplastic lesions in male B6C3F1 mice administered malathion over an 80 week period.

Neoplastic Lesion	Control	8,000 ppm	16,000 ppm
Hepatocellular Carcinoma	5/49	7/48	11/49
Neoplastic Nodules	3/49		6/49

It was concluded that under the conditions of this study, there was no clear evidence of the association of the tumor incidence with the administration of malathion to Osborne-Mendel rats or B6C3F1 mice.

In a second study 2-year carcinogenicity study was performed by the National Cancer Institute in F344 rats, animals (49 or 50/sex/group) were fed diets containing 0, 2,000 or 4,000 ppm malathion for 203 weeks and then observed for an additional 2 or 3 weeks (TR-192, 1979). No tumors occurred in the dosed groups of rats of either sex at incidences that could be related clearly to administration of the malathion. Compound-related toxic effects were not observed in female rats, but males experienced dose related decreased mean body weights, increased mortality, gastritis, and gastric ulcers. It was concluded that under the conditions of this study, malathion was not carcinogenic in F344 rats, but that females may not have received a maximum tolerated dose.

In a third study (TR-135) a bioassay with malaxon, the major metabolite of malathion, was performed by the National Cancer Institute in F344 rats to further investigate any possible carcinogenicity related to malathion. As observed with malathion, no clear evidence was obtained to associate the administration of time-weighted average dietary concentrations of 500 or 1,000 ppm malaoxon with oncogenic activity.

References:

1) National Cancer Institute, Bioassay of Malathion for Possible Carcinogenicity, Technical Report No. 24, DHEW Publication No. (NIH) 78-824, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD, 1978.

2) National Cancer Institute, Bioassay of Malathion for Possible Carcinogenicity, Technical Report No. 192, DHEW Publication No. (NIH) 79-1748, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 1979.

3) National Cancer Institute, Bioassay of Malaoxon for Possible Carcinogenicity, Technical Report No. 135, DHEW Publication No. (NIH) 79-1390, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 1979.

Reproductive and Developmental Toxicity: Labeling approved for the original label for Ovide Lotion indicated that there was no evidence of teratogenicity, reproductive or developmental effects observed in rats with preparations containing up to 900 mg/kg malathion or in a multi-generational feeding study with up to 2,500 ppm malathion in the diet.

Teratogenicity studies in rats and rabbits were negative with repeat oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively, administered during gestation (Bisti et al., 1994; Machin and McBride, 1989; Lechner and Abdel-Rahman, 1984; Khera et al., 1978; Dobbins, 1967; Kalow and Marton, 1961). Various reproductive effects have been reported as follows: reduced neonatal survival was reported in the multi-generational study performed by Kalow and Marton (1961); decreased fetal weights and increases resorptions were reported by Dobbins (1967) after dams were administered at least 200 mg/kg malathion; and Lechner and Abdel-Rahman (1984), reported increased incidences of hemorrhagic spots on the upper back of fetuses following administration of 50 mg/kg/day malathion to Sprague Dawley female rats for 3 months prior to mating through gestation day 19. These anomalies occurred only at high doses or after prolonged exposures to malathion and do not suggest that there is any substantial hazard with regard to the use of malathion at ordinary levels of exposure normally associated with use of pesticides.

References:

Bisti GA, Singh K, Khan SU et al. (1994) Fate of Wheat Bound Malathion Residues in Rats During Gestation. Chemosphere 29:451-5.

Dobbins PK. (1967) Organic Phosphate Insecticides as Teratogens in the Rat. J Fla Med Assoc 54:452-6.

Kalow and Marton. (1961) Second-Generation Toxicity of Malathion in Rats. Nature 192:464-465.

Kimbrough RD and Gaines TB. (1968) Effect of Organic Phosphorus Compounds and Alkylating Agents on the Rat Fetus. Arch Environ Health 16:805-808.

Khera KS, Whalen C and Trivett G. (1978) Teratogenicity Studies on Linuron, Malathion, and Methoxychlor in Rats. Toxicol Appl Pharmacol 45:435-444.

Lechner DMW and Abdel-Rahman MS. (1984) A Teratology Study of Carbaryl and Malathion Mixtures in Rat. J Toxicol Environ Health 14:267-278.

Machin MG and McBride WG. (1989) Teratological Study of Malathion in Rabbit. J Toxicol Environ Health 26:249-53.

SUMMARY AND DISCUSSION

Each bottle of Ovide Lotion contains [redacted] mg malathion, which will remain in contact with the hair and scalp over an 8 to 12 hour period. Assuming 100% absorption following topical application (or accidental ingestion) would result in systemic doses of up to approximately 15 mg/kg of malathion for a 20 kg child and 5 mg/kg malathion for a 60 kg adult.

The equivalent doses in mg/kg/day, and adult human equivalent doses in mg/kg/day have been calculated based on body surface area and are presented for the highest doses evaluated for carcinogenicity potential (Table 1) and reproductive and developmental toxicity (Table 2).

Table 1: Dose equivalents for the average high dose administered in the feed during chronic carcinogenicity testing of malathion.

Species	High Dose (ppm)	Duration	Average Dose* mg/kg/day	Adult Human Equivalent Dose
Osborne-Mendel Rats	12,000 8,000	3 wks 77 wks	800 1,200	130 mg/kg/day 200 mg/kg/day
Fischer 344 Rats	4,000	105-106 wks	400 – 200 (young – old)	66 – 33 mg/kg/day
B6C3F1 Mice	16,000	80 wks	2,400	200 mg/kg/day

*Calculated by Dr. Harold Carlin: Pharm/Tox Review dated August 9, 1991.

Table 2: Dose equivalents for the average doses administered during subacute and subchronic nonclinical investigations of reproductive and developmental toxicity potential of malathion.

Species	High Dose	Duration	Adult Human Equivalent Dose
NZ White Rabbits	100 mg/kg/day	Gestation Days 7-12	33 mg/kg/day
Rats (Various Species)	50 - 300 mg/kg/day	Gestation	8 - 50 mg/kg/day
Rats*	2,500 ppm/day (100 to 250 mg/kg/day)	3-Generation	20 to 40 mg/kg/day

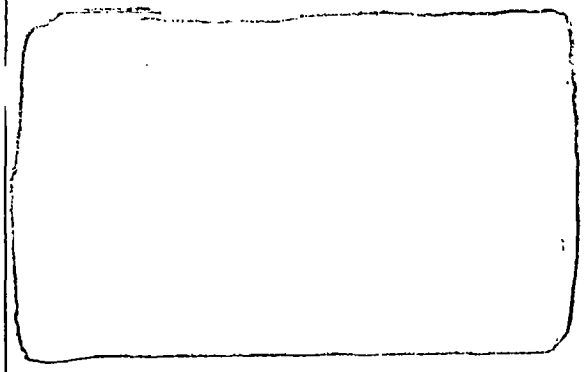
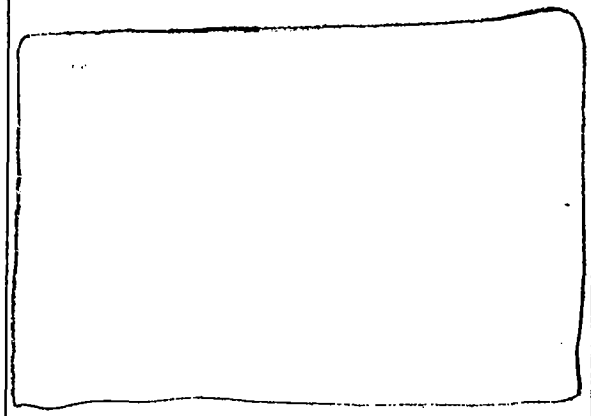
* Based on average food consumption of 40 to 100 g/kg/day.

Dermal absorption is estimated to be less than 10% of the applied dose (<1.5 mg/kg), producing an additional 10 fold safety factor resulting in maximal human exposures 10 to 100 times less than the oral levels of malathion which were administered to animals. In addition, the above studies represent subacute to chronic testing periods whereas no effects (reproductive or physiological) were reported following acute i.p. injections of up to 900 mg/kg malathion.

Recommendations: Based on information in the literature, I recommend the following labeling changes.

LABELING

ORIGINAL APPROVED LABEL	*LABELING SUBMITTED WITH SLR-010*	*PROPOSED LABELING*
Carcinogenesis, Mutagenesis and Fertility - Malathion is neither carcinogenic in male or female F344 rats after 2 years feeding with up to 4000 ppm (0.4%) nor is it tumorigenic in Osborne-Mendel rats or B6C3F1 mice after a similar feeding for 80 weeks with 8,000 ppm (0.8%) and 16,000 ppm (1.6%) respectively. Tests for mutagenicity have not been conducted.	[redacted]	**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Carcinogenesis, mutagenesis and impairment of fertility have not been studied with Ovide Lotion. Malathion, the active ingredient in Ovide Lotion, has been shown to be genotoxic in a number of *in vitro* and *in vivo* mutation and clastogenicity assays. However, there was no evidence of a carcinogenic effect following long-term oral administration of malathion in F344 rats after 2 years feeding with up to 0.4% (~200-400 mg/kg/day) nor was it tumorigenic in Osborne-Mendel rats or B6C3F1 mice after similar feeding for 80 weeks with 0.8% (~400-600 mg/kg/day) or 1.6% (~1000-2000 mg/kg/day), respectively. Based on body surface area, doses tested are approximately 4 to 40 fold greater than those anticipated in humans (assuming 100% bioavailabiltiy). Reproduction studies performed with malathion in rats at doses approximately 30 fold greater than those anticipated in humans (based on body surface area and assuming 100% bioavailability) revealed no evidence of impaired fertility.

Pregnancy Category B – There was no evidence of teratogenicity in studies utilizing single i.p. injections of malathion at 600 and 900 mg/kg in pregnant rats or oral dosing with up to 300 mg/kg on days 6 through 15 of gestation. A reproduction study in rats failed to show any gross fetal abnormalities attributable to feeding malathion up to 2,500 ppm in the diet during a three generation evaluation period. These studies employed at least 50 to 70 times the adult human topical dose. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.		**Pregnancy:** Pregnancy Category B. There was no evidence of teratogenicity in studies in rats and rabbits at doses up to 900 mg/kg/day and 100 mg/kg/day malathion, respectively. A study in rats failed to show any gross fetal abnormalities attributable to feeding malathion up to 2,500 ppm (~200 mg/kg/day) in the diet during a three-generation evaluation period. These doses were approximately 2 to 10 times higher than the anticipated human dose (based on body surface area and assuming 100% bioavailability). Because animal reproduction studies are not always predictive of human responses, this drug should be used (or handled) during pregnancy only if clearly needed.
Nursing Mothers – Malathion in an acetone vehicle has been reported to be absorbed through human skin only to the extent of 8% of the applied dose. However, percutaneous absorption from the OVIDE Lotion formulation has not been studied and it is not known whether malathion is excreted in human milk. Caution should be exercised when OVIDE Lotion is administered to the nursing mother.		**Nursing Mothers:** Malathion in an acetone vehicle has been reported to be absorbed through human skin to the extent of 8% of the applied dose. However, percutaneous absorption from Ovide Lotion formulation has not been studied, and it is not known whether malathion is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ovide Lotion is administered to (or handled by) a nursing mother.

/S/ 4-12-99

Lynnda Reid, Ph.D. Date
Pharmacologist/Toxicologist

cc:
IND
HFD-540
HFD-540/Pharm/Reid
HFD-540/Pharm/Jacobs
HFD-540/CSO/Wright
HFD-540/MO/Cook
HFD-540/Chem/Timmer

For Concurrence Only:
HFD-540/DD/JWilkin 151 4/26/99
HFD-540/TL/AJacobs 4/14/99

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

STATISTICAL REVIEW(S)

APR 9 1999

STATISTICAL/CLINICAL REVIEW AND EVALUATION

NDA#: NDA 18-613

Applicant: Medicis Pharmaceutical Group

Name of Drug: Ovide (malathion) Lotion, 0.05%

Documents Reviewed: Briefing Package dated November 4, 1981

Type of Report: NDA review

Indication: Head lice treatment

Medical officer: Denise Cook, M.D. (HFD-540)

Introduction

Manufacturing of Ovide Lotion had stopped in 1994 and the drug had been delisted (but not for safety reasons) in 1995. Recently, the NDA 18-613 changed ownership. The new owner, Medicis, submitted the supplement with the request to remarket the product. The objective of this review is to examine whether the 1981 submission supports the claim that Ovide Lotion is safe and effective in treatment of head lice.

Efficacy

The 1981 submission had 5 efficacy studies. The first three studies had three arms: Ovide lotion, Ovide vehicle, and Kwell. Studies 4 and 5 had two arms: Ovide lotion and Ovide vehicle. As the Kwell arm has a limited regulatory utility, this review will consider only efficacy comparisons of Ovide versus vehicle. All studies were double blind and randomized. The sample sizes in Studies 1, 2, 3, 4, and 5 were 25, 83, 24, 119 and 119, respectively. Studies 4 and 5 will be considered pivotal because the number of subjects was larger than in the first 3 studies. Studies 1, 2, and 3 will be considered as supportive.

Studies 4 and 5 have the same design (protocol #79-1103). Subjects were school age children who had live lice and at least 10 viable nits prior to entering study. Prell shampoo was provided for washing out the medication after 12 hours. To compare the baseline **ovicidal** efficacy in treatment groups, 10 hair shafts with viable nits were placed in vials and incubated for 14 days. Examination of these nits were made at 7 and 14 days for hatching (these samples are called pre-treatment samples). The medication was then applied to the hair and scalp. The medication was removed after 12 hours. Nits were removed (these are post-treatment samples) and treated the same way as in the pre-treatment samples. Adult lice were collected at the same time and evaluated as to whether they were dead or alive. These collected lice were again evaluated at 2, 4 and 24 hours.

Seven days after the treatment, the patient's hair was rinsed with isopropyl alcohol to determine whether any lice were present due to newly hatched nits that were not killed during the treatment.

The primary efficacy variables in this review were:

1. The proportion of subjects free of live lice at day 7 after removal of the lotion (**cure rate**)
2. The proportion of ova hatching in the post-treatment sample (**ovicidal activity**)

To evaluate **baseline balance** relative to **oval hatching rate**, the corresponding samples of ova collected in the two treatment groups prior to treatment (pre-treatment samples), were compared after incubation for 7 days. A Chi-square test adjusted for continuity was used to compare cure rates or ova hatching rates.

EFFICAY RESULTS

Pivotal efficacy Studies 4 and 5

Analysis of the ***pre-treatment*** samples showed that there was a good balance between treatment groups relative to hatching rate before treatment. In Study 4, the proportion of hatched ova in the pre-treatment sample among all collected ova after 7 days was 381/680 in the Ovide group and 248/470 in the vehicle group (p= 0.30). In Study 5, the proportion of hatched ova among all collected ova after 7 days was 371/610 in the Ovide group and 365/580 in the vehicle group (p=0.49).

Cure rate. In Study 4, number of subjects free of live lice at day 7 after treatment was 52/61 in the Ovide group and 10/58 in the vehicle group (p=0.001).

In Study 5, number of subjects free of live lice at day 7 after treatment was 62/65 in the Ovide group and 21/47 in the vehicle group (p= 0.001).

In Studies 4 and 5 combined, number of subjects free of live lice at day 7 after treatment was 114/126 in the Ovide group and 31/105 in the vehicle group (p<0.001).

Ovicidal activity.

For the ***post-treated*** samples, in Study 4, the proportion of hatched ova among all collected ova after 7 days was 9/676 in the Ovide group and 109/457 in the vehicle group (p=0.001).

In Study 5, the proportion of hatched ova among all collected ova after 7 days was 145/610 in the Ovide group and 257/580 in the vehicle group (p= 0.001).

An analysis of actual data in the statistical review by Dr. Christine Waternaux, also showed that there was a statistically significant difference between the Ovide and vehicle groups relative to

the ovicidal activity in both Studies 4 and 5.

Supportive Efficacy Studies 1, 2, and 3.

Cure rate. In Study 1, proportion of subjects free of live lice at day 7 after treatment was 6/10 in the Ovide group and 3/5 in the vehicle group (p=1.0).
In Study 2, proportion of subjects free of live lice at day 7 after treatment was 26/36 in the Ovide group and 2/19 in the vehicle group (p=0.001).

In Study 3, proportion of subjects free of live lice at day 7 after treatment was 7/10 in the Ovide group and 1/5 in the vehicle group (p= 0.20).

Ovicidal activity.

For the ***post-treated*** samples, in Study 1, the proportion of hatched ova among all collected ova after 7 days was 9/100 in the Ovide group and 8/50 in the vehicle group (p=0.32).

In Study 2, the proportion of hatched ova among all collected ova after 7 days was 8/357 in the Ovide group and 59/201 in the vehicle group (p= 0.001).

In Study 3, the proportion of hatched ova among all collected ova after 7 days was 15/100 in the Ovide group and 16/50 in the vehicle group (p= 0.027).

EFFICACY CONCLUSIONS:

Both pivotal Studies 4 and 5 support the sponsor's claim that Ovide Lotion is statistically significantly more effective than vehicle relative to the primary efficacy variables: proportion of subjects free of live lice at day 7 after the treatment (p=0.001) and proportion of hatched lice 7 days after treatment (p=0.001).

Of the three secondary studies, Studies 2, and 3 support the claim that Ovide Lotion is statistically significantly more effective than vehicle relative to the proportion of hatched lice 7 days after treatment (p<0.02). Study 3 also supports the claim that Ovide Lotion is statistically significantly more effective relative to proportion of patients free of live lice after 7 day of treatment (p=0.001). In all other primary efficacy comparisons in the secondary studies, Ovide Lotion was numerically better than vehicle.

SAFETY RESULTS

No safety measurements were performed in the pivotal studies. Six safety studies were conducted. The largest of them, a contact sensitization study had 100 subjects treated with Ovide lotion and 94 subjects treated with vehicle. There were no reactions in the Ovide group. However, this study did not have sufficient sample size to observe reactions with the incidence

the ovicidal activity in both Studies 4 and 5.

Supportive Efficacy Studies 1, 2, and 3.

Cure rate. In Study 1, proportion of subjects free of live lice at day 7 after treatment was 6/10 in the Ovide group and 3/5 in the vehicle group (p=1.0).
In Study 2, proportion of subjects free of live lice at day 7 after treatment was 26/36 in the Ovide group and 2/19 in the vehicle group (p=0.001).

In Study 3, proportion of subjects free of live lice at day 7 after treatment was 7/10 in the Ovide group and 1/5 in the vehicle group (p= 0.20).

Ovicidal activity.

For the *post-treated* samples, in Study 1, the proportion of hatched ova among all collected ova after 7 days was 9/100 in the Ovide group and 8/50 in the vehicle group (p=0.32).

In Study 2, the proportion of hatched ova among all collected ova after 7 days was 8/357 in the Ovide group and 59/201 in the vehicle group (p= 0.001).

In Study 3, the proportion of hatched ova among all collected ova after 7 days was 15/100 in the Ovide group and 16/50 in the vehicle group (p= 0.027).

EFFICACY CONCLUSIONS:

Both pivotal Studies 4 and 5 support the sponsor's claim that Ovide Lotion is statistically significantly more effective than vehicle relative to the primary efficacy variables: proportion of subjects free of live lice at day 7 after the treatment (p=0.001) and proportion of hatched lice 7 days after treatment (p=0.001).

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SAFETY RESULTS

No safety measurements were performed in the pivotal studies. Six safety studies were conducted. The largest of them, a contact sensitization study had 100 subjects treated with Ovide lotion and 94 subjects treated with vehicle. There were no reactions in the Ovide group. However, this study did not have sufficient sample size to observe reactions with the incidence

rate of less than 1%. According to the Rule of Three, at least 300 subjects are needed for safety evaluations. This is a matter of the clinical judgement of the reviewing medical division to decide whether Ovide is safe in the treatment of children with head lice.

REVIEWER'S CONCLUTIONS (which may be conveyed to the sponsor)

Efficacy

Efficacy Studies 4 (N=119) and 5 (N=119) were considered pivotal. Studies 1 (N=25), 2 (N=83), and 3 (N=24) were considered secondary. **The primary efficacy variables** in this review were:

1. The proportion of subjects free of live lice at day 7 after the treatment (**cure rate**),
2. The proportion of hatched lice at day 7 in the post-treatment sample (**ovicidal activity**).

Pivotal studies 4 and 5 support the claim that Ovide Lotion is statistically significantly more effective than vehicle relative to the primary efficacy variables, proportion of subjects free of live lice at day 7 after the treatment (p=0.001) and proportion of hatched lice 7 days after treatment (p=0.001).

Secondary studies 2 and 3 support the claim that Ovide Lotion is statistically significantly more effective than vehicle relative to the proportion of hatched lice at day 7 after treatment (p<0.02). Study 3 also supports the claim that Ovide Lotion is statistically significantly more effective relative to proportion of patients free of live lice after 7 days of treatment (p=0.001). In all other primary efficacy comparisons in the secondary studies, Ovide Lotion was numerically better than vehicle.

The presence or absence of ova at day 7 after the treatment was not evaluated in these studies. The presence or absence of live lice at day 14 after the treatment was not evaluated in these studies.

Safety

No safety measurements were performed in the pivotal studies. Six safety studies were conducted. The largest of them, a contact sensitization study had 100 subjects treated with Ovide lotion and 94 subjects treated with vehicle. There were no reactions in the Ovide group. However, this study did not have sufficient sample size to observe reactions with the incidence rate of less than 1%. According to the Rule of Three, at least 300 subjects are needed for safety evaluations. This is a matter of the clinical judgement of the reviewing medical division to decide whether Ovide is safe in the treatment of children with head lice.

Overall Conclusions: The efficacy studies support the claim that Ovide Lotion is statistically significantly more effective than vehicle in treatment of head lice. As the safety data do not have large enough number of subjects, this is a matter of the clinical judgement of the reviewing

medical division to decide whether Ovide Lotion is safe in the treatment of children with head lice.

/S/ 04.9.99

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 04/09/'99

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 18-613
HFD-540
HFD-540/Mrs. Wright
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Cook
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Freidlin
HFD-344/Dr. Carreras
Chron.(HFD-725)
This review contains 5 pages.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-613/S-009

APR 30 1999

Medicis Pharmaceutical Corp.
Attention: Joseph Cooper
Senior Vice President
4343 Camelback Road
Phoenix, AZ 85018-2700

Dear Mr. Cooper:

Please refer to your supplemental new drug application dated December 31, 1998, received January 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ovide (malathion) Lotion, 0.5%.

We acknowledge receipt of your submission dated December 31, 1998.

This supplemental new drug application provides for (1) a new site for manufacturing, [redacted] and (2) an alternate testing site, [redacted]
The labeling changes originally submitted as part III of this supplement (pp. 225-229) have been redesignated as S-010, and will be acted upon separately.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

/S/ 4/30/99

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for the
Division of Dermatologic and Dental Drug Products,
(HFD-540)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

9 **Page(s) Redacted**

Draft

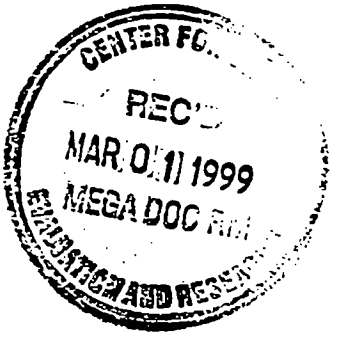
Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-613/S009/S010

CORRESPONDENCE

ORIGINAL



MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

NDA SUPPL AMENDMENT
S-010/RL

February 26, 1999

Jonathan K. Wilkin, MD
Division of Dermatological and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
HFD-540, Room 12B-06
5600 Fishers Lane
Rockville, MD 20857

RE: Amendment - Ovide® (malathion) Lotion 0.5%, NDA 18-613
S-010 - Draft Labeling

Dear Dr. Wilkin:

We hereby amend the subject NDA to provide for revised draft labeling as requested in the teleconference held between the Agency and Medicis on February 01, 1999.

Enclosed please find an updated diskette, Microsoft Word, and hard copies of the following labeling pieces;

- Package Insert (PI) - updated to the current labeling requirements per discussion on 02/01/99.
- Dosage and Administration section for the carton and bottle label. These changed because of the PI update.
- Color board of the front carton panel.

The panels of the carton and the label for the bottle, except for the Dosage and Administration section, will remain the same as the Supplement submitted on, December 31, 1998. Complete color copies of labeling are not available for this amendment.

Please feel free to contact me at (602) 808-3813 if you have any questions concerning this amendment.

Sincerely,

Lynn Hansen

Lynn Hansen
Regulatory Affairs
Medicis Pharmaceutical Corporation

OR Verbal Update Issued 4/30/99
/S/

Desk Copy: Ms. Millie A. Wright - HFD-540

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http: www.medicis.com
NYSE Symbol: MRX

(170)

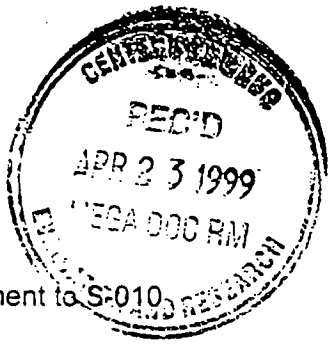
MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

ORIGINAL

NDA SUPPL AMENDMENT

April 22, 1999

Ms. Millie Wright
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatological and Dental Drug Products, HFD-540
Office of Drug Evaluation V
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 18-613 Ovide® (malathion) Lotion 0.05% - Amendment to S-010
Labeling Reference Copies

Dear Ms. Wright:

Enclosed please find the requested information, via our telephone conversations April 20 & 23, 1999 for the above stated subject.

The following are included in this Amendment:

Attachment 1: Proposed labeling for the carton.

Attachment 2: Proposed labeling for the bottle, front and back.

Attachment 3: Proposed package insert.

Attachment 4: Clinical Documents: Safety and Efficacy Summaries from NDA, including a chart listing the ages of the children listed in the studies.

Joe Cooper and I will be available all day on Friday, April 23, please feel free to call us at (602) 808-3813.

Regards,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

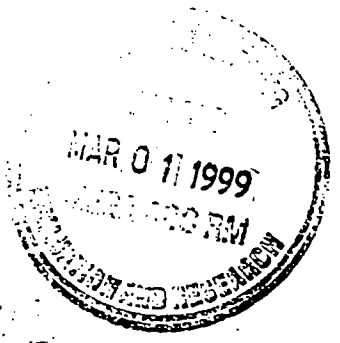
cc: Desk Copy to Ms. Wright

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http: www.medicis.com
NYSE Symbol: MRX

(15)

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

SUPPL NEW CORRESP



February 26, 1999

Ms. Millie Wright
Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard
Central Document Room-N243
Rockville, MD 20850

Dear Ms. Wright:

Enclosed please find the User Fee Cover Sheets (Form FDA 3397) for the Ovide® (malathion) Lotion 0.5% Supplements S-009 and S-010 as requested in the telephone call between Lynn Hansen (Medicis) and yourself.

If you should need anything further please contact Lynn Hansen at 602-808-3813.

Sincerely,

Rosa Hernandez

Rosa Hernandez
Regulatory Affairs Associate

Notes
No further actions needed
/S/

APPEARS THIS WAY
ON ORIGINAL

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http: www.medicis.com
NYSE Symbol: MRX

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-613/S-010

FEB 10 1999

Medicis Pharmaceutical Corporation
4343 East Camelback Road
Phoenix, AZ 85018-2700

Attention: Joseph P. Cooper, Senior Vice President

Dear Mr. Cooper:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Ovide® (malathion) Lotion 0.5%

NDA Number: 18-613

Supplement Number: S-010

Date of Supplement: December 31, 1998

Date of Receipt: January 7, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 8, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

2/9/99

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-613/S-009

JAN 14 1999

Medicis Pharmaceutical Corporation
4343 East Camelback Road
Phoenix, AZ 85018-2700

Attention: Joseph P. Cooper, Senior Vice President

Dear Mr. Cooper:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Ovide® (malathion) Lotion 0.5%

NDA Number: 18-613

Supplement Number: S-009

Date of Supplement: December 31, 1998

Date of Receipt: January 7, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 8, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research