JUL 1 9 1999

NDA 50-168/S-073
NDA 50-218/S-047

Monarch Pharmaceuticals
Attention: R. Henry Richards, M.D.
Executive Vice-President, Medical Affairs
355 Beecham Street
Bristol, TN 37620

Dear Dr. Richard:

Please refer to your supplemental new drug application(s) dated September 30, 1996, received October 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cortisporin® Ointment (neomycin and polymyxin B sulfates, bacitracin zinc, and hydrocortisone ointment, USP)[NDA 50-168] and Cortisporin® Cream (neomycin and polymyxin B sulfates and hydrocortisone acetate cream, USP)[NDA 50-2 18]. We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submission(s) dated March 21, 1997. The submissions of March 21, 1997, constituted a complete response to our January 8, 1997 action letter.

These supplemental new drug applications provide for revision of the Pediatric Use subsection in response to the Federal Register statement of December 13, 1994. Additionally, in the January 8 1997, action letter, additional changes were requested in the following sections of the draft labeling: **CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION.**

We have completed the review of these supplemental applications, 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 submitted draft labelings. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labelings (FPL's) must be identical to the submitted draft labelings (package inserts submitted March 21, 1997).

Please submit 20 copies of the FPL as soon as they are available, in no case more than 30 days after they are printed. Please individually mount ten of the copies on heavy-weight paper or similar material for each NDA. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-168/S-073" and "FPL for approved supplement NDA 50-218/S-047." Approval of these submissions by FDA is not required before the labelings are used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. 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 for each NDA 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 these drug products (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:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of each drug product when they are 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 Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

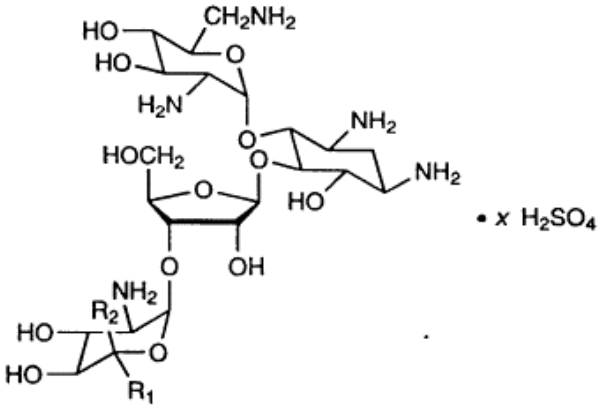
Sincerely,

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures - [CORTISPORIN® Ointment and CORTISPORIN® Cream draft labelings identifying the changes to the sections outlined above]

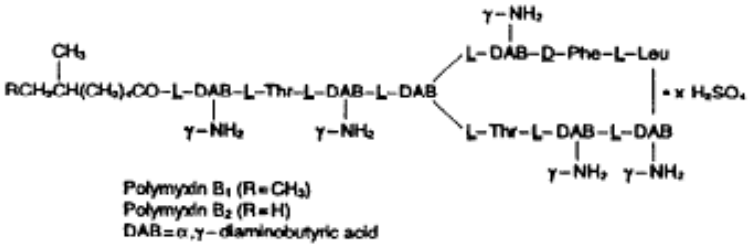
CORTISPORIN® Ointment
(neomycin and polymyxin B sulfates, bacitracin zinc, and hydrocortisone ointment USP)

DESCRIPTION:CORTISPORIN Ointment (neomycin and polymyxin B sulfates, bacitracin zinc, and hydrocortisone ointment, USP) is a topical antibacterial ointment. Each gram contains: neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 5,000 polymyxin B units, bacitracin zinc equivalent to 400 bacitracin units, hydrocortisone 10 mg (1%), and white petrolatum, qs.
Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae* Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600 mcg of neomycin standard per mg, calculated on an anhydrous basis. The structural formulae are:

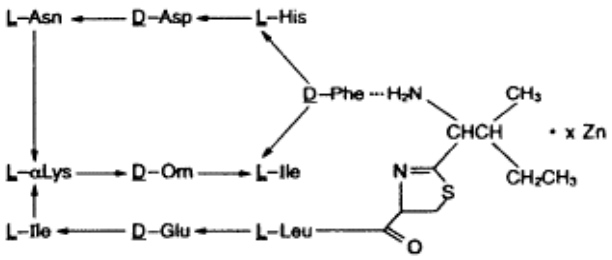


Neomycin B (R_1 = H, R_2 = CH_2NH_2)
Neomycin C (R_1 = CH_2NH_2, R_2 = H)

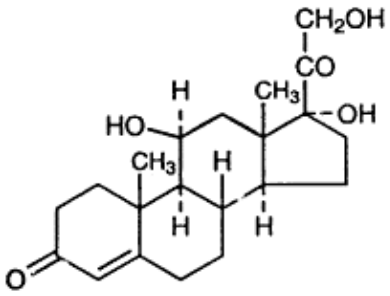
Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. The structural formulae are:



Bacitracin zinc is the zinc salt of bacitracin, a mixture of related cyclic polypeptides (mainly bacitracin A produced by the growth of an organism of the licheniformis group of *Bacillus subtilis* (Fam. Bacillaceae). It has a potency of not less than 40 bacitracin units per mg. The structural formula is:



Hydrocortisone, 11β,17,21-trihydroxypregn-4-ene-3, 20-dione, is an anti-inflammatory hormone. Its structural formula is:



CLINICAL PHARMACOLOGY: Corticoids suppress the inflammatory response to a variety of agents and they may delay healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case.
The anti-infective components in the combination are included to provide action against specific organisms susceptible to them. Polymyxin B sulfate, bacitracin zinc, and neomycin sulfate together are considered active against the following microorganisms*: Staphylococcus aureus*, streptococci, including *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae, Klebsiella-Enterobacter* species*, Neisseria* species, and *Pseudomonas aeruginosa*.
The product does not provide adequate coverage against Serratia marcescens.
The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.

INDICATIONS AND USAGE: For the treatment of corticosteroid-responsive dermatoses with secondary infection. It has not been demonstrated that this steroid-antibiotic combination provides greater benefit than the steroid component alone after 7 days of treatment. (See WARNINGS.)

CONTRAINDICATIONS: Not for use in the eyes or in the external ear canal if the eardrum is perforated. This product is contraindicated in tuberculous, fungal, or viral (for example, herpes simplex or varicella zoster) lesions of the skin. This product is contraindicated in those individuals who have shown

hypersensitivity to any of its components.

WARNINGS:
Neomycin can induce permanent sensorineural hearing loss due to cochlear damage mainly destruction of hair cells in the organ of Corti. The risk of ototoxicity is greater with prolonged use.
Therapy with this product should be limited to 7 days of treatment. (See INDICATIONS AND USAGE.)
Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known. Discontinue promptly if sensitization or irritation occurs.
When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling, and itching: it may be manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

PRECAUTIONS:
General: As with other antibiotic preparations, prolonged use may result in the—overgrowth of nonsusceptible organisms, including fungi. Treatment should not be continued for longer than 7 days. If the infection is not improved after 1 week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed. Allergic cross-reactions may occur which could prevent the use of any or all of the aminoglycoside antibiotics for the treatment of future infections,
Use of steroids on infected areas should be supervised with care as anti-inflammatory steroids may encourage spread of infections. If this occurs, steroid therapy should be stopped and appropriate antibacterial drugs used. Generalized dermatological conditions may require systemic corticosteroid therapy.
Signs and symptoms of exogenous hyperadrenocorticism can occur with the use of topical corticosteroids, including adrenal suppression. Systemic absorption of topically applied steroids will be increased if extensive body surface areas are treated or if occlusive dressings are used. Under these circumstances, suitable precautions should be taken when long-term use is anticipated.
Information for Patients: If redness, irritation, swelling, or pain persists or increases, discontinue use and notify physician. Do not use in the eyes.
Laboratory Tests: Systemic effects of excessive levels of hydrocortisone may include a reduction in the number of circulating eosinophils and a decrease in urinary excretion of 17-hydroxycorticosteroids.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals (rats, rabbits, mice) showed no evidence of carcinogenicity attributable to oral administration of corticosteroids.
Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Corticosteroids have been shown to be teratogenic in rabbits when applied topically at concentrations of 0.5% on days 6 to 18 of gestation and in mice when applied topically at a concentration of 15% on days 10 to 13 of gestation. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: Hydrocortisone appears in human milk following oral administration of the drug. Since systemic absorption of hydrocortisone may occur when applied topically, caution should be exercised when CORTISPORIN Ointment is used by a nursing woman.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established..
Sufficient percutaneous absorption of hydrocortisone can occur in infants and children during prolonged use to cause cessation of growth, as well as other signs and symptoms of hyperadrenocorticism.

ADVERSE REACTIONS: Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported. (See WARNINGS.) Adverse reactions have occurred with topical use of antibiotic combinations including neomycin, bacitracin, and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in two of

2,175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]
The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.
When steroid preparations are used for long periods of time in intertriginous areas or over extensive body areas, with or without occlusive non-permeable dressings, striae may occur; also there exists the possibility of systemic side effects when steroid preparations are used over large areas or for a long period of time.

DOSAGE AND ADMINISTRATION: Therapy with this product should be limited to 7 days. A thin film is applied 2 to 4 times daily to the affected area.

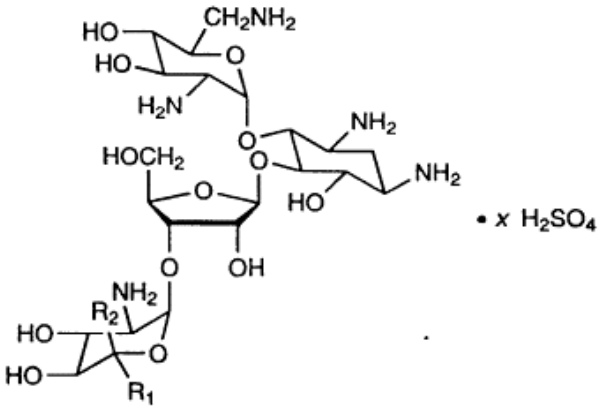
HOW SUPPLIED: Tube of 1/2 oz with applicator tip (NDC 0173-0196-88).
Store at 15° to 25°C (59° to 77°F).

REFERENCES:
1. Leyden JJ, Kligman AM. Contact dermatitis to neomycin sulfate. JAMA. 1979;242:1276-1278.
2. Prystowsky SD, Allen AM, Smith RW, et al. Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. Arch Dermatol. 1979;115:959-962.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

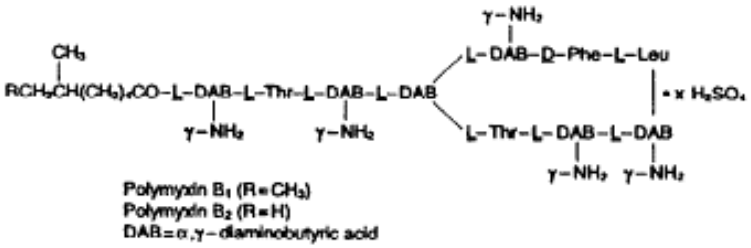
CORTISPORIN® Cream
(neomycin and polymyxin B sulfates and hydrocortisone acetate cream USP)

DESCRIPTION:CORTISPORIN Cream (neomycin and polymyxin B sulfates and hydrocortisone cream, USP) is a topical antibacterial cream. Each gram contains: neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and hydrocortisone acetate 5 mg (0.5%). The inactive ingredients are liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene poloxypropylene compound, emulsifying wax, purified water, and 0.25% methylparaben added as a preservative. Sodium hydroxide or sulfuric acid may be added to adjust pH. Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae* Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600 mcg of neomycin standard per mg, calculated on an anhydrous basis. The structural formulae are:

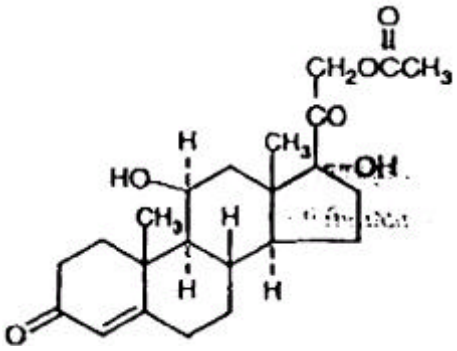


Neomycin B (R_1 = H, R_2 = CH_2NH_2)
Neomycin C (R_1 = CH_2NH_2, R_2 = H)

Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. The structural formulae are:



Hydrocortisone acetate is the acetate ester of hydrocortisone, an anti-inflammatory hormone. Its chemical name is 21-(acetyloxy)-11β,17,-dihydroxypregn-4-ene-3, 20-dione. Its structural formula is:



The base is a smooth vanishing cream with a pH of approximately 5.0.

CLINICAL PHARMACOLOGY: Corticoids suppress the inflammatory response to a variety of agents and they may delay healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case.
The anti-infective components in the combination are included to provide action against specific organisms susceptible to them. Polymyxin B sulfate and neomycin sulfate together are considered active against the following microorganisms*: Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella-Enterobacter* species*, Neisseria* species, and *Pseudomonas aeruginosa*. This product does not provide adequate coverage against Serratia marcescens and streptococci, including *Streptococcus pneumoniae.*
The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.
The acid pH helps restore normal cutaneous acidity.

INDICATIONS AND USAGE: For the treatment of corticosteroid-responsive dermatoses with secondary infection. It has not been demonstrated that this steroid-antibiotic combination provides greater benefit than the steroid component alone after 7 days of treatment. (See WARNINGS.)

CONTRAINDICATIONS: Not for use in the eyes or in the external ear canal if the eardrum is perforated. This product is contraindicated in tuberculous, fungal, or viral (for example, herpes simplex or varicella zoster) lesions of the skin. This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS:
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Therapy with this product should be limited to 7 days of treatment. (See INDICATIONS AND USAGE.)
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manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

PRECAUTIONS:

General: As with other antibiotic preparations, prolonged use may result in the—overgrowth of nonsusceptible organisms, including fungi. Treatment should not be continued for longer than 7 days. If the infection is not improved after 1 week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed. Allergic cross-reactions may occur which could prevent the use of any or all of the aminoglycoside antibiotics for the treatment of future infections.

Use of steroids on infected areas should be supervised with care as anti-inflammatory steroids may encourage spread of infections. If this occurs, steroid therapy should be stopped and appropriate antibacterial drugs used. Generalized dermatological conditions may require systemic corticosteroid therapy.

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Information for Patients: If redness, irritation, swelling, or pain persists or increases, discontinue use and notify physician. Do not use in the eyes.

Laboratory Tests: Systemic effects of excessive levels of hydrocortisone may include a reduction in the number of circulating eosinophils and a decrease in urinary excretion of 17-hydroxycorticosteroids.

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Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Corticosteroids have been shown to be teratogenic in rabbits when applied topically at concentrations of 0.5% on days 6 to 18 of gestation and in mice when applied topically at a concentration of 15% on days 10 to 13 of gestation. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Hydrocortisone appears in human milk following oral administration of the drug. Since systemic absorption of hydrocortisone may occur when applied topically, caution should be exercised when CORTISPORIN Cream is used by a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established..

Sufficient percutaneous absorption of hydrocortisone can occur in infants and children during prolonged use to cause cessation of growth, as well as other signs and symptoms of hyperadrenocorticism.

ADVERSE REACTIONS: Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported. (See WARNINGS.) Adverse reactions have occurred with topical use of antibiotic combinations including neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in two of 2,175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]

The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

When steroid preparations are used for long periods of time in intertriginous areas or over extensive body areas, with or without occlusive non-permeable dressings, striae may occur; also there exists the possibility of systemic side effects when steroid preparations are used over large areas or for a long period of time.

DOSAGE AND ADMINISTRATION: Therapy with this product should be limited to 7 days. A thin film is applied 2 to 4 times daily to the affected area. The cream should, if conditions permit, be gently rubbed into the affected areas.

HOW SUPPLIED: Tube of 7.5 g with applicator tip (NDC 0173-0185-98).
Store at 15° to 25°C (59° to 77°F).

REFERENCES:
1. Leyden JJ, Kligman AM. Contact dermatitis to neomycin sulfate. JAMA. 1979;242:1276-1278.
2. Prystowsky SD, Allen AM, Smith RW, et al. Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. Arch Dermatol. 1979;115:959-962.

GlaxoWellcome

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Research Triangle Park, NC 27709