# Prescribing Information

# PrCORTISPORIN® OINTMENT

Neomycin and Polymyxin B Sulfates, Bacitracin Zinc
and Hydrocortisone Ointment USP

**Anti-inflammatory and antibacterial**

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# Prescribing Information

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**Anti-inflammatory and antibacterial**

## Clinical Pharmacology

Corticosteroids suppress the inflammatory response to a variety of agents and they may delay healing. Since corticosteroids 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.*

When used topically, bacitracin zinc, polymyxin B sulfate and neomycin sulfate are rarely irritating and are not absorbed systemically in significant amounts through intact skin or mucous membrane, but the possibility of significant absorption exists when extensive raw

areas are being treated. The incidence of skin sensitization to this combination has been shown to be low on normal skin. Since these antibiotics are seldom used systemically, the patient is spared sensitization to those antibiotics which might later be required systemically.

Hydrocortisone is partially absorbed through intact skin and this absorption is enhanced when the skin is broken or occluded.

The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.

## Indications and Clinical Use

CORTISPORIN® (Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydrocortisone Ointment USP) Ointment is indicated for the treatment of skin infections and inflammation.

**Not for use <u>in</u> the eyes.**

## Contraindications

CORTISPORIN® (Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydrocortisone Ointment USP) Ointment should not be used to treat otitis externa in the presence of a perforated tympanic membrane because of the risk of ototoxicity.

The use of CORTISPORIN® Ointment is contraindicated in patients who have demonstrated allergic hypersensitivity to any of the components of the preparation or to cross-sensitizing substances such as aminoglycosides and other related antibiotics.

The presence of pre-existing nerve deafness is a contra-indication to the use of CORTISPORIN® Ointment in circumstances in which significant systemic absorption could occur.

Due to the known ototoxic and nephrotoxic potential of neomycin sulfate, the use of CORTISPORIN® in large quantities or on large areas for prolonged periods of time is not recommended in circumstances where significant systemic absorption may occur.

Viral, tuberculous, primary bacterial and fungal infections of the skin are contra-indications to the use of CORTISPORIN® Ointment.

A possibility of increased neomycin absorption exists in very young children, thus CORTISPORIN® Ointment is not recommended for use in neonates and infants (up to 2 years). In neonates and infants, absorption by immature skin may be enhanced and renal function may be immature.

## Warnings

The concurrent use of other aminoglycoside antibiotics is not recommended in circumstances where significant systemic absorption of neomycin sulfate following topical application could occur.

Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known.

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 manifested 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.

Following significant systemic absorption: aminoglycosides such as neomycin can cause irreversible ototoxicity; neomycin sulfate, polymyxin B sulfate and bacitracin zinc have nephrotoxic potential; polymyxin B sulfate has neurotoxic potential.

**Gastrointestinal**

**Clostridium difficile-associated disease:**

*Clostridium difficile*-associated disease (CDAD) has been reported with use of many antibacterial agents. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases

## Precautions

### General

As with any antibiotic preparation, prolonged use may result in the overgrowth of non-susceptible organisms, including fungi. The possibility of persistent fungal infections of the cornea and ear should be considered after prolonged steroid dosing. Appropriate measures should be taken if this occurs.

The use of CORTISPORIN® (Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydrocortisone Ointment USP) Ointment should not be continued for more than 7 days in the absence of any clinical improvement. If the infection is not improved after one 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.

Hydrocortisone may mask the allergic effects produced by any component of

Signs and symptoms of exogenous hyperadrenocorticism, including adrenal suppression, can occur with the use of topical corticosteroids. Systemic absorption of topically applied steroids will be increased if extensive body suface areas are treated or if occlusive dressings are used. Under these circumstances, suitable precautions should be taken when long-term use is anticipated.

Avoid introduction of CORTISPORIN® ointment into the eye. If CORTISPORIN® ointment is accidentally introduced into the eye, the eye should be rinsed thoroughly with cold water.

CORTISPORIN® ointment should be kept out of reach of children.

## Use in the Elderly

CORTISPORIN® Ointment is suitable for use in elderly patients. Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of neomycin sulfate may occur (see Dosage and Administration section).

## Use in Children

CORTISPORIN® Ointment is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus CORTISPORIN® Ointment is not recommended for use in neonates and infants (<2 years) (see Contraindications and Dosage and Administration sections).

## Use in Pregnancy

There is little information to demonstrate the possible effect of topically applied neomycin in pregnancy. However, neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity, thus use of CORTISPORIN® Ointment is not recommended in pregnancy.

## Nursing Mothers

There is little information to demonstrate the possible effect of topically applied neomycin in lactation. Thus use of CORTISPORIN® Ointment is not recommended in nursing mothers.

## Patients with Special Diseases and Conditions

In renal impairment the plasma clearance of neomycin is reduced (see Dosage and Administration).

## Drug Interactions

Following significant systemic absorption, both neomycin sulfate and polymyxin B sulfate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents. However, the neuromuscular blocking activity of neomycin sulfate and polymyxin B sulfate is unlikely to present a hazard during use of CORTISPORIN® Ointment.

## 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.

**Carcinogenicity**

Long-term studies in animals (rats, rabbits, mice) showed no evidence of carcinogenicity attributable to oral administration of corticosteroids.

## Adverse Reactions

Adverse reactions have occurred with topical use of antibiotic combinations containing 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. In another study, the incidence was found to be approximately 1%.

Neomycin occasionally causes skin sensitization. There is, however, an increased incidence of hypersensivity to neomycin sulfate in certain selected groups of patients in dermatological practice, in particular venous stasis eczema and ulceration, and chronic otitis externa.

Allergic hypersensitivity to neomycin following topical use may manifest itself as an eczematous exacerbation with reddening, scaling, swelling and itching of the affected skin, or as a failure of the lesion to heal.

Allergic hypersensitivity reactions following the topical administration of bacitracin zinc, hydrocortisone and polymyxin B sulfate are rare events.

Anaphylactic reactions following the topical application of bacitracin zinc have been reported, but are rare events.

Topically applied hydrocortisone may produce skin atrophy such as telangiectasiae and striae.

However, this effect only occurs following prolonged use, high dosage, occlusion of the topical site (for example by plastic or by natural occlusion as in the groin), and particularly applies to infants and young children. The possibility of systemic adverse effects when steroid preparations are used over larger areas or for a long period of time also exists.

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.

**Postmarketing Data**

Immune System Disorders

Application site hypersensitivity

General Disorders and Administration Site Conditions

Headache, application site reaction including pain, erythema, irritation, edema, burning sensation

Skin and Subcutaneous Tissue Disorders:

Exfoliative dermatitis, skin atrophy, telangiectasia, striae, exacerbation of underlying skin conditions including eczema.

## Symptoms and Treatment of Overdosage

No information is available concerning accidental ingestion of CORTISPORIN® (Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydrocortisone Ointment USP) Ointment.

### Symptoms

No specific symptoms or signs have been associated with excessive use of CORTISPORIN® Ointment. However, consideration should be given to significant systemic absorption (see Contraindications, Warnings, and Precautions sections).

### Treatment

Use of the product should be stopped and the patient's general status, hearing acuity, renal and neuromuscular functions should be monitored.

Blood levels of neomycin sulfate and bacitracin zinc should also be determined, and hemodialysis may reduce the serum level of neomycin sulfate.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

## Dosage and Administration

CORTISPORIN® ointment is for topical skin administration only. Treatment should not be continued for more than 7 days without medical supervision.

Dilution of CORTISPORIN® (Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydrocortisone Ointment USP) Ointment is not recommended; reduction of the antibiotic concentrations may reduce their therapeutic efficacy.

### Use in Adults

Prior to treatment, remove any debris such as pus, crusts etc. from the affected area; apply a thin film to the affected area two to four times per day, depending on the clinical condition.

**Do not use in the eyes.**

### Use in Children

CORTISPORIN® Ointment is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus CORTISPORIN® Ointment is not recommended for use in neonates and infants (<2 years) (see Contraindications and Precautions sections).

### Use in the Elderly

CORTISPORIN® Ointment is suitable for use in elderly patients. Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of neomycin sulfate may occur (see Warnings, and Precautions sections).

### Dosage in Renal Impairment

Dosage should be reduced in patients with reduced renal function (see Warnings and Precautions sections).

## Pharmaceutical Information

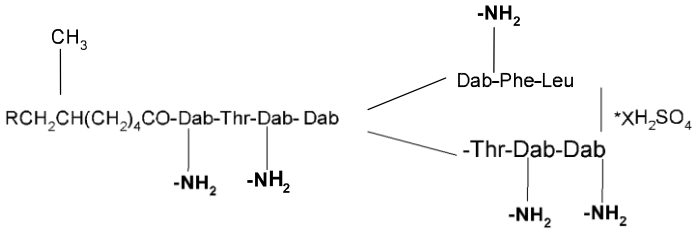
### Drug Substance

CORTISPORIN® (Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydrocortisone Ointment USP) Ointment is an antibacterial and anti- inflammatory ointment for topical use.

***Polymyxin B Sulfate***

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).

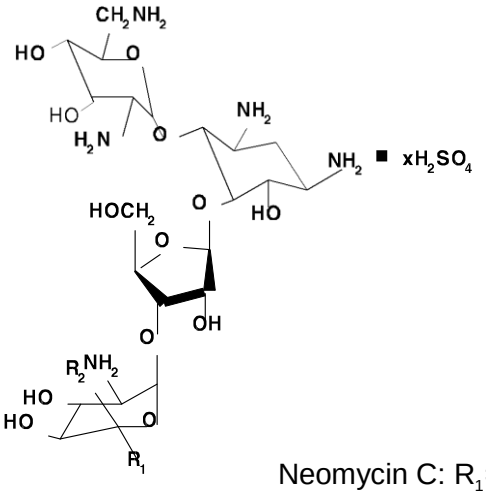
It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. The structural formulae are:




Polymyxin $B_1$: R=$CH_3$ Polymyxin $B_2$: R=H DAB = $\alpha$, $\gamma$-diaminobutyric acid

***Neomycin Sulfate***

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 μg of neomycin standard per mg, calculated on an anhydrous basis. The structural formulae are:



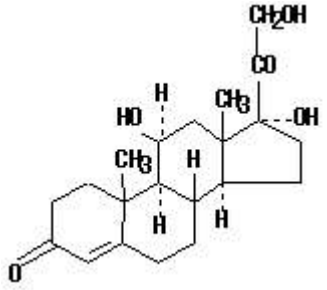
Neomycin B: $R_1$=H, $R_2$=$CH_2NH_2$ Neomycin C: $R_1$=$CH_2NH_2$, $R_2$=H

***Bacitracin Zinc***

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 lichenformis group of *Bacillus subtilis* (Fam. Bacillaceae). The structural formula is not known.

***Hydrocortisone***

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



## Composition

Each gram contains polymyxin B sulfate 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg and hydrocortisone 10 mg in a low melting point petrolatum.

## Stability and Storage Recommendations

Store between 15° and 25°C.

# Availability of Dosage Forms

Tubes of 15 g.

# References

1. Leyden JJ, Kligman AM. Contact dermatitis to neomycin sulfate. JAMA 1979;242(12):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.