Product Information

Metronidazole Gel

Composition:

A sterile gel containing Metronidazole BP 0.5% w/w, the pH of the gel is 4.5 to 6.0.

Description:

Metronidazole is 2-(2-methyl-5-nitroimidazol-l-yl)ethanol.

$C_6H_9N_3O_3$ MW= 171.2

CAS Number = 443-48-1

Metronidazole is a white or yellowish, crystalline powder. It is slightly soluble in water, in alcohol, in acetone and in dichloromethane. It is very slightly soluble in ether. It darkens on exposure to light and should be protected from light.

Excipients:

Sodium phosphate dibasic anhydrous, citric acid – anhydrous, propylene glycol, hydroxyethylcellulose, purified water.

Pharmacology:

Metronidazole is a synthetic nitroimidazole derivative. It is an anaerobic antibacterial agent and an antiprotozoal (trichomoniasis, amoebiasis, giardiasis). However, the mechanisms by which Metronidazole Gel acts in reducing inflammatory lesions of rosacea are unknown, but may include an antibacterial and/or anti-inflammatory effect.

Pharmacokinetics:

The absorption of metronidazole following topical administration is negligible. Studies using Rozex Gel, another metronidazole (0.75%) gel preparation, have shown that following topical administration of 1 gram of a metronidazole gel (containing 7.5 mg of metronidazole) to the face of 10 rosacea patients, serum concentrations of metronidazole ranged from undetectable to a maximum of 66 nanograms per mL. This concentration is approximately 100 times less than concentrations afforded by a single 250 mg tablet. The serum metronidazole concentrations were below the detectable limits of the assay at the majority of time points in all patients. Three of the patients had no detectable serum concentrations of metronidazole at any time point. The mean dose of the gel applied during clinical studies was 600 mg which represents 4.5 mg of metronidazole per application. Therefore, under normal usage levels, the formulation affords minimal serum concentrations of metronidazole.

Indications:

Metronidazole Gel is indicated for the treatment of inflammatory papules and pustules of rosacea.

Contra-indications:

Metronidazole is contra-indicated in individuals with a history of hypersensitivity to metronidazole, other nitroimidazole derivatives, or any of the other ingredients in the formulation.

Precautions:

Metronidazole Gel is for external use only.

Topical metronidazole preparations have been reported to cause watery or tearing eyes when applied too close to the eyes. Contact with the eyes should therefore be avoided.

If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use.

Adverse haematological effects have not been reported to date with topical metronidazole. However, metronidazole is a nitroimidazole and should be used with care in patients with evidence of or history of blood dyscrasia.

Patients should be advised to avoid or minimise exposure of areas treated with metronidazole gel to sunlight or other sources of UV light (See **Carcinogenicity and mutagenicity**).

Unnecessary or prolonged use of this medication should be avoided as the long term safety of topical metronidazole is unknown (See **Carcinogenicity and mutagenicity**).

Use in Pregnancy: Category B2

The potential adverse effects of Metronidazole Gel in pregnancy have not been determined, however oral metronidazole readily crosses the placenta and rapidly enters the foetal circulation.

There is no conclusive evidence of fetotoxicity or teratogenicity in animal studies with metronidazole, nor has clinical experience to date with the use of metronidazole in pregnant women revealed evidence of fetotoxic or teratogenic effect of the drug. Because there are no well controlled studies of therapy with Metronidazole gel in pregnant women, Metronidazole gel should not be used during pregnancy.

Australian categorisation definition of Category B2:

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Use in Lactation:

Following oral administration, metronidazole is excreted in breast milk in concentrations similar to those found in the plasma. Metronidazole blood levels from topical application are significantly lower than those achieved after oral metronidazole. A decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children:

The safety and efficacy of topical preparations of metronidazole in children have not been established.

Carcinogenicity and Mutagenicity:

Animal studies with oral metronidazole showed increased incidences of tumour in the lung, liver, testes, reticulum, mammary gland and pituitary gland in certain rodent species. Evidence of photocarcinogenicity of metronidazole has also been reported in mice. Although there is no evidence to date of a carcinogenic effect in humans, it is prudent to avoid unnecessary and prolonged use of Metronidazole gel, and to avoid exposure of sites treated with Metronidazole Gel to the sun (See **Precautions**).

Oral metronidazole has shown evidence of mutagenic activity in several bacterial systems. In addition, a dose response increase in the frequency of micronuclei was observed in mice after intraperitoneal injection and an increase in chromosomal aberrations has been found in human lymphocyte cultures. Oral Metronidazole caused hypospermatogenesis, infertility and abnormal spermatozoa in mice and rats with a NOEL in rats being about 200 times the estimated human metronidazole dose contained in this gel based on body surface area. In patients with Crohn's disease, oral metronidazole increased the chromosome abnormalities in circulating lymphocytes. The benefit/ risk ratio should therefore be carefully assessed in each case particularly in relation to the severity of the disease and the age of the patient.

Carcinogenicity (including dermal or photocarcinogenicity) studies have not been performed using topical metronidazole.

Interactions with Other Drugs:

Only relatively small amounts of metronidazole are absorbed through the skin or mucous membranes. Drug interactions are therefore less likely to occur following topical administration, compared to oral administration. However, the following interactions should be kept in mind when prescribing Metronidazole Gel.

Coumarin Anticoagulants

Metronidazole should be used with caution in patients receiving anticoagulant drugs. Systemic metronidazole potentiates the effects of oral anticoagulants, resulting in prolongation of the prothrombin time. While only small amounts of metronidazole are absorbed from topical preparations through the skin or mucous membranes at usual dosages, the possibility that anticoagulant effects may be potentiated should be considered when topical metronidazole is used in patients receiving oral anticoagulant therapy.

Alcohol

Disulfiram-like reactions have occurred in some patients who ingested alcohol while receiving oral or IV metronidazole. These reactions have not been reported to date in patients receiving topical application of metronidazole to the skin.

Effects on laboratory tests:

Systemic metronidazole may interfere with serum AST (SGOT), ALT (SGPI), LDH, triglycerides and glucose determinations.

Adverse Reactions:

Topically applied metronidazole is generally well tolerated. Because of the minimal absorption of metronidazole and consequently its insignificant plasma concentration after topical administration, the adverse experiences reported with the oral form of the drug have not been reported with topical metronidazole. There have been no adverse reports for this product, however, non serious adverse experiences have been reported with other higher strength products including contact dermatitis/allergic reaction: local irritation, redness, itching, burning: treatment failure (worsening of rosacea): watery eyes : metallic taste: tingling or numbness in the extremities: nausea: other (zoster lesion, pustules on the nose and vesicular bullous eruptions). The causal relationship with topical Metronidazole has not been unequivocally established for these adverse experiences. Serious and unexpected events with the higher strength metronidazole cream include skin cancer (2 reports), peripheral neuropathy and hypomagnesaemia (1 report) and abnormal liver function test (1).

Local Effects

Adverse reactions reported with topical metronidazole are mainly local reactions. They included transient redness and mild dryness, pruritus, aggravated rosacea or acne, burning, irritation and stinging. These reactions occurred in less than 3% of patients.

Topical metronidazole preparations have also caused eye irritation (watering or tearing) if the gel is applied too closely to the eyes. Conjunctivitis associated with topical use of metronidazole on the face has also been reported.

Systemic Effects

Since only minimal amounts of topical metronidazole preparations are absorbed systemically following application to the skin, abnormal haematologic, renal or hepatic function test results have not been reported.

However, other adverse systemic effects including metallic taste, nausea, and tingling or numbness of the extremities, have been reported in patients receiving topical metronidazole.

Dosage and Administration:

General Instructions:

Areas to be treated should be cleansed before application of Metronidazole Gel. To minimize the risk of local irritation, application of the gel can be delayed for 15-20 minutes after cleansing of the skin. Patients may use cosmetics after application of the gel. A moisturiser can also be used if the skin is dry.

Adults & Elderly:

For the treatment of inflammatory lesions (papules and pustules) of rosacea, a thin film of Metronidazole Gel should be applied and rubbed in to the cleansed, affected areas twice daily. Clinical improvement usually occurs within three weeks. Patients should be monitored to ensure clinical benefit continues and that no local or systemic events occur. In the absence of a clear clinical improvement therapy should be stopped.

Children: Not recommended.

Overdosage:

There is no human experience with overdosage of Metronidazole Gel. The acute oral toxicity of the Metronidazole Gel formulation was determined to be greater than 5 g/kg (the highest dose given) in albino rats.

Presentation:

AUST R 10846: Tube (Sterile, tamper proof): 10 g

Storage:

Store below 25°C

Schedule:

All States and A.C.T. - S.4 (Prescription only Medicine)

Sponsor:

ORION Laboratories Pty Ltd

25 – 29 Delawney Street

Balcatta WA 6021

TGA approved: 9th January 2004

Date of last amendment: 14th June 2006

Code: MET01523_2_PI