SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zyomet 0.75%w/w Gel

Metronidazole 0.75%w/w Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole 0.75% w/w.

Excipient(s) with known effect*:*

Propylene glycol	30mg/g
Benzyl alcohol	10mg/g

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel for cutaneous use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole Gel is indicated for the treatment of acute inflammatory exacerbations of acne rosacea.

4.2 Posology and method of administration

Posology

The average period of treatment varies according countries. It is usually of three to four months. The recommended duration of treatment should not be exceeded. However, if a clear benefit has been demonstrated continued therapy for a further three to four months period may be considered by the prescribing physician depending upon the severity of the condition. In clinical studies, topical metronidazole therapy for rosacea has been continued for up to 2 years. In the absence of a clear clinical improvement, therapy should be stopped.

Elderly

The dosage does not need to be adjusted for elderly patients

Paediatric population

Metronidazole is not recommended for use in children due to a lack of data on safety and efficacy.

Method of administration

Metronidazole should be applied in a thin layer to the affected areas of the skin twice daily, morning and evening. Areas to be treated should be washed with a mild cleanser before application. Patients may use non comedogenic and non astringent cosmetics after application of metronidazole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Metronidazole Gel has been reported to cause lacrimation of the eyes, contact with eyes and mucous membranes should be avoided.

If eye contact does occur the gel should be washed out carefully with water.

If irritation does occur the patient should be advised to use metronidazole less frequently or to stop temporarily and to seek medical advice if necessary. The UV exposure (sunbathing, solarium, sunlamp) should be avoided during the therapy with metronidazole. Metronidazole transforms into inactive metabolite due to UV exposure, therefore its efficacy decreases significantly. Phototoxic side-effects haven't been reported in clinical trials in relation to metronidazole.

Metronidazole is a nitro imidazole and should be used with caution in patients with an evidence of, or history of blood dyscrasia. Unnecessary and prolonged use of this medication should be avoided. Evidence suggests that metronidazole is carcinogenic in certain animal species. There is no evidence to date of a carcinogenic effect in human (see section preclinical safety data)

Avoid drinking alcohol while using Metronidazole Gel.

Excipients

This medicine contains 30 mg propylene glycol in each gram. Propylene glycol may cause skin irritation.

This medicine contains 10 mg benzyl alcohol in each gram. Benzyl alcohol may cause allergic reactions. Benzyl alcohol may also cause mild local irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with systemic medication is unlikely because absorption of metronidazole following cutaneous application is low. Nevertheless, it should be mentioned that disulfiram-like reactions has been reported in small number of patients taking metronidazole and alcohol concomitantly.

Oral metronidazole has been reported to potentiate the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin is not known. However, very rare cases of modification of the INR values have been reported with concomitant use of metronidazole and coumarin anticoagulants.

4.6 Fertility, pregnancy and lactation

Pregnancy

There has been no experience to date with the use of topical metronidazole in pregnant patients.

In case of oral administration, metronidazole crosses the placental barrier and enters the foetal circulation rapidly.

No foetotoxicity was observed after oral metronidazole in either rats or mice.

However because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents this drug should be used in pregnancy only if clearly needed.

Breast-feeding

After oral administration, Metronidazole is excreted in breast milk in concentrations similar to those found in the plasma. Even through blood levels are significantly lower with cutaneous application of metronidazole than those achieved after oral metronidazole in nursing mothers, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility

There are no data on the effects on human male or female fertility.

See section 5.3 Preclinical safety data

4.7 Effects on ability to drive and use machines

Based upon the pharmacodynamic profile and clinical experience performance related to driving and using machines should not to be affected.

4.8 Undesirable effects

The following spontaneous adverse experiences have been reported, and within each system organ class, are ranked by frequency, using the following convention:

Very common (≥1/10)

Common (≥1/100 to, < 1/10)

Uncommon (≥1/ 1,000 to,< 1/100)

Rare (≥1/10,000 to,< 1/1,000)

Very rare (<1/10,000),

Not known (cannot be estimated from the available data)

Nervous system disorders:

Uncommon: hypothesia, paraesthesia, dysgeusia (metallic taste)

Eye disorders:

Not known: watery eyes if applied too closely to this area.

Gastrointestinal disorders:

Uncommon: nausea

Skin and subcutaneous tissue disorders:

Common: dry skin, erythema, pruritus, skin discomfort (burning, pain of skin/stinging), skin irritation, worsening of rosacea.

Not known: contact dermatitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

No data exists about overdosage in humans. Acute oral toxicity studies with a topical gel formulation containing 0.75% w/w metronidazole in rats have shown no toxic action with doses of up to 5 g of finished product per kilogram body weight, the highest dose used. This dose is equivalent to the oral intake of 12 tubes of 30g packaging Metronidazole Gel for an adult weighing 72 kg, and 2 tubes of Gel for a child weighing 12 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoal and antibacterial agent which is active against a wide range of pathogenic micro-organisms. ATC Code: D06BX01

Mechanism of action

The mechanisms of action of metronidazole in rosacea are unknown but available evidence suggests that the effects may be antibacterial and/or anti-inflammatory.

5.2 Pharmacokinetic properties

Metronidazole is rapidly and nearly totally absorbed after oral administration. The drug is not significantly bound to serum proteins and distributes well to all body compartments with the lowest concentration found in the fat. Metronidazole is excreted primarily in the urine as parent drug, oxidative metabolites and conjugates.

Bioavailability studies with metronidazole gel in rosacea patients treated with 7.5 mg metronidazole applied topically to the face resulted in maximum serum concentrations of 66 ng/ml which is approximately 100 times less than those attained after a single oral dose of 250 mg. In most patients at most time points after metronidazole gel application, serum concentrations of metronidazole were below the detectable limits of the assay (25 ng/ml).

5.3 Preclinical safety data

The toxicity studies conducted with the Metronidazole 0.75% Topical Gel formulation demonstrate that the product is non-toxic in rats after acute oral administration 5g/kg and produced no ocular irritation in rabbit eyes. The formulation

produced no observable effects in rabbits after dermal application of 13 mg /kg for 90 days.

No compound-related dermal or systemic effects were observed in a 13-week cutaneous route toxicity study, in which metronidazole gel containing Metronidazole 0.75% w/w was applied daily to rabbits at doses ranging between 0.13 and 13 mg/kg.

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters.

One study showed a significant enhancement of UV induced skin tumours in hairless mice treated with Metronidazole intraperitoneally (15μg per g body weight and per day for 28 weeks). Although the significance of these studies to man is not clear, patients should be advised to avoid or minimise exposure of metronidazole treated sites to sun.

Metronidazole has shown mutagenic activity in several in vitro bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injection and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200 to 1200mg/day of metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol

Disodium Edetate

Hydroxyethylcellulose

Benzyl Alcohol

Purified Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

a) For the product as packaged for sale - 3 years

b) After first opening the container - Comply with expiry date.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate.

6.5 Nature and contents of container

5g, 15g. 30g, 50g and 60g HDPE tubes.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd,

Dashwood House,

69 Old Broad Street,

London, EC2M 1QS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL: 12762/0025.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th September 1998.

10 DATE OF REVISION OF THE TEXT

24/10/2023