SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

VAGINYL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole BP 400.00mg

3 PHARMACEUTICAL FORM

Tablet

4.1 Therapeutic indications

Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause. Metronidazole is active against a wide range of pathogenic micro-organisms, notably species of *Bacteroides*, *Fusobacteria*, *Clostridia*, *Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.
It is also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia*, *Balantidium coli.*
Metronidazole is indicated in adults and children for the following indications:

1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of Bacteroides and anaerobic streptococci.
2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.
3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male. The male consort of females suffering from urogenital trichomoniasis should be treated concurrently.
4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).
5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).
6. Giardiasis.

7. Acute ulcerative gingivitis.
8. Anaerobically-infected leg ulcers and pressure sores
9. Acute dental infections (e.g. acute pericoronitis and acute apical infections). Considerations should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Metronidazole tablets should be swallowed, without chewing, with half a glassful of water during or after meals.

Posology

1. Prophylaxis against anaerobic infection:

Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery

Adults: 400 mg 8 hourly during 24 hours immediately preceding operation followed by postoperative intravenous or rectal administration until the patient is able to take tablets.

Paediatric population

Children < 12 years: 20-30mg/kg as a single dose given 1-2 hours before surgery *Newborns with a gestation age < 40 weeks*: 10mg/kg body weight as a single dose before operation

2. Anaerobic infections:

The duration of a course of metronidazole treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.

Treatment of established anaerobic infection:

Adults: 800 mg followed by 400 mg 8 hourly.

Paediatric population

Children: *>8 weeks to 12 years of age:* The usual dose is 20-30 mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children: <8 weeks of age: 15 mg/kg as a single dose daily or divided into 7.5 mg/kg every 12 hours.

Newborns with a gestation age <40 weeks: accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

3. Protozoal and other infections:

- *Urogenital trichomoniasis:*

  Adults and adolescents:

200 mg, 3 times daily for 7

days; or 400 mg, twice daily for

5-7 days; or 2000mg as a single

dose for 7 days

To prevent re-infection, the consort should receive the same course of treatment concurrently.

Children:

<10 years: 40 mg/kg orally as a single dose; or 15-30

mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000

mg/dose

- *Bacterial vaginosis*:

  Adults and adolescents:

  400 mg, twice daily for 5-7

  days; or 2000 mg as a single

  dose

- *Amoebiasis:*

  Adults and children over 10 years:

  a) Invasive intestinal disease in susceptible subjects, 800 mg three times daily for 5 days, or 2000 mg once daily for three days.

  b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis, 400 mg three times daily for 5-10 days or 2000 mg once daily for 2 days.

  c) Amoebic liver abscess, also forms of extra-intestinal amoebiasis, 400 mg three times daily for 5 days or 2000 mg once daily for two days.

  d) Symptomless cyst passers. The upper ranges of dosage and duration of treatment seem to be necessary in temperate climate countries. 400-800 mg three times daily for 5-10 days Children:

  7-10 years: 200-400 mg 3 times daily for 5-10 days
  3-7 years: 100-200 mg 4 times daily for 5-10 days
  1-3 years: 100-200 mg 3 times daily for 5-10 days

  Alternatively, dose may be expressed by body weight: 35-50 mg/kg daily in 3 divided doses for 5-10 days, not to exceed 2400 mg/day

- *Giardiasis*:

  Adults and children over 10 years: 2000

  mg once daily for 3 days or 400 mg

  three times daily for 5 days or 500 mg

  twice daily for 7-10 days Children:

  7-10 years: 1000 mg once daily for 3 days
  3-7 years: 600-800 mg once daily for 3 days

1-3 years: 500 mg once daily for 3 days

Alternatively, as expressed in mg per kg of body weight: 15-40 mg/kg/day divided in 2-3 doses

- *Acute ulcerative gingivitis*:

  Adults and adolescents: 200 mg, 3 times daily for 3 days
- *Acute dental infections*:

  Adults and adolescents: 200 mg, 3 times daily for 3-7 days.
- *Leg ulcers and pressure sores*:

  Adults and adolescents: 400 mg, 3 times daily for 7 days.

Children and infants weighing less than 10 kg should receive proportionally smaller dosages.

Elderly: Metronidazole is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.

4. Eradication of Helicobacter pylori in paediatric patients:

As a part of a combination therapy, 20mg/kg/day not to exceed 500 mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.

To be taken orally.

4.3 Contraindications

- Known hypersensitivity to nitromidazoles, metronidazole, or any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

There is a possibility that after Trichomonas vaginalis has been eliminated a gonococcal infection might persist.

Patients should be warned that metronidazole may darken urine. For information on renal and hepatic insufficiency, please see section 4.2,

Due to inadequate evidence on the mutagenicity risk in humans (see section 5.3), the use of Vaginyl for longer treatment than usually required should be carefully considered.

Neuropathy (central and peripheral)

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Vaginyl for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions, such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, vertigo, convulsive seizures).

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to the risk of neurological aggravation.

Hepatotoxicity in patients with Cockayne syndrome

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should not be used unless the benefit is considered to outweigh the risk and if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole. (see section 4.8)

Skin and subcutaneous tissue disorders

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, Vaginyl treatment must be immediately discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should be advised not to take alcohol during therapy and for at least 48 hours afterwards because of possibility of a disulfiram-like (antabuse effect) reaction. Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.
Some potentiation of anticoagulant therapy has been reported when Metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.
Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and Metronidazole. Lithium treatment should be tapered or withdrawn before administering Metronidazole

Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive Metronidazole.

Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

Metronidazole reduces the clearance of 5 fluorouracil and can therefore result in increased toxicity of 5 fluorouracil.

Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when co-administration is necessary.

Plasma levels of busulfan may be increased by Metronidazole which may lead to severe busulfan toxicity.

4.6 Fertility,Pregnancy and lactation

There is inadequate evidence of the safety of Metronidazole in pregnancy, but it has been in wide use for many years without apparent ill consequence.

Nevertheless Vaginyl, like other medicines, should not be given during pregnancy or during lactation unless the physician consider it essentail: in these circumstances short-term high-dosage therapy is not recommended.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness, drowsiness, vertigo, confusion, convulsions, hallucinations or transient visual disorders and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The frequency of adverse events listed below is defined 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)

Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

<u>Blood and lymphatic system disorders</u>:

Very rare: agranulocytosis, neutropenia, thrombocytopenia, and pancytopenia

Not known: leucopenia.

Immune system disorders:

Rare: anaphylaxis

Not known: angiodema, urticaria, fever.

Metabolism and nutrition disorders:

Not known: anorexia.

Psychiatric disorders:

Very rare: psychotic disorders, including confusion and hallucinations.

Not known: depressed mood

Nervous system disorders:

Very rare:

- encephalopathy (e.g. confusion, fever, vertigo, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.
- drowsiness, dizziness, convulsions, headaches

Not known:

- during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.
- aseptic meningitis
- vertigo

Eye disorders:

Very rare: vision disorders such as diplopia and myopia, which in most cases is transient.

Not known: optic neuropathy/neuritis

Ear and labyrinth disorders:

Not known: hearing impaired/hearing loss (including sensorineural), tinnitus.

Gastrointestinal disorders:

Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastrointestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.4).

Very rare:

- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis, and hepatocellular liver injury, jaundice and pancreatitis which is reversible on drug withdrawal.
- cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders:

Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis, pruritis, flushing

Not known: erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption.

Musculoskeletal, connective tissue and bone disorders:

Very rare: myalgia, arthralgia.

Renal and urinary disorders:

Very rare: darkening of urine (due to Metronidazole metabolite).

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professional are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomitting, ataxia and slight disorientation. There is no specific antidote for Metronidazole overdosage. In cases of suspected massive overdose, symptomatic and supportive treatment should be instituted.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01X D01

Metronidazole has antiprotozoal and antibacterial actions and is effective against *Trichomonas vaginalis* and other protozoa including, *Entamoeba histolytica* and *Giardia lamblia* and against anaerobic bacteria.

5.2 Pharmacokinetic properties

Metronidazole is rapidly and almost completely absorbed on administration of Vaginyl: peak plasma concentrations occur after 20 min to 3 hours.
The half-life of metronidazole is 8.5 ± 2.9 hours. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis.
Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.

Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro as well as in rodent or humans in vivo, there was inadequate evidence of a mutagenic effect of metronidazole with some studies reporting mutagenic effects, while other studies were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dicalcium phosphate
Povidone K25
Maize starch
Crospovidone
Magnesium stearate

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a dry place below 25°C in well closed containers. Protect from light.

6.5 Nature and contents of container

High density polystyrene or polypropylene securitainer type containers with lids for polythene or polypropylene with polythene bellows and/or polyurethane wads and/or polythene film.

Pack sizes:
28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 140, 150, 168, 180, 500, 1000, 5000, 50 000

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited

Boumpoulinas 11, 3RD Floor

Nicosia

Cyprus

P.C. 1060

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0065

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st June 1972 / 4th December 1998

10 DATE OF REVISION OF THE TEXT

20/04/2023

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)