SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metronidazole Tablets 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains metronidazole 500 mg.

Excipients with known effect:
Each tablet contains 50.0 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole is active against a wide range of pathogenic micro-organisms, notably species of *Bacteroids, Fusobacteria, Clostridia, Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.
It is also active against *Trichomonas vaginalis, Entamoeba histolytica, Gardia lamblia*, *Balantidium coli* and *Helicobacter pylori*.

Metronidazole is indicated in adults and children for the following indications:
1) Prevention of post-operative infections due to anaerobic bacteria, particularly species of *bacteroids* 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 (T*richomonas vaginalis*), and in man.
4) Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or *Gardnerella vaginalis*).
5) All forms of amoebiasis (intestinal and extra-intestinal disease and asymptomatic cyst passers).
6) Giardiasis.
7) Acute ulcerative gingivitis.
8) Acute dental infections (*eg* acute pericoronitis and acute apical infections)
9) Anaerobically-infected leg ulcers and pressure sores.
10) Treatment of *Helicobacter pylori* infection associated with peptic ulcer as part of triple therapy.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Metronidazole Tablets should be taken during or after meals, swallowed with water and NOT CHEWED.

Elderly: Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Hepatic impairment: Caution is advised in patients with hepatic encephalopathy. One third of the daily dose given once a day should be considered (see section 4.4).

1) Anaerobic infections:
Treatment for 7 days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician may decide to prolong treatment, *eg* for eradication of infection from sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or genital tract.
Children > 8 weeks to 12 years of age: The usual daily 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.
In newborns with a gestation age <40 weeks, accumulation of metronidazole can occur during the first week of life, why the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.
Children under 10 years: A more suitable dosage form should be used for this age group.

Prophylaxis against anaerobic infection - chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.
Adults: 1g stat dose 24 hours pre-operatively, followed by 400mg at 8 hourly intervals during the 24 hours preceding operation followed by post-operative iv or rectal administration until the patient is able to take tablets.
Children < 12 years: 20-30 mg/kg as a single dose given 1-2 hours before surgery.
Newborns with a gestation age <40 weeks: 10 mg/kg body weight as a single dose before operation.
Children under 10 years: A more suitable dosage form should be used for this age group.

2) Treatment of established infections:
Adults and children over 10 years: 800mg followed by 400mg 8 hourly.
Children under 10 years: A more suitable dosage form should be used for this age group.

3) Urogenital trichomoniasis:
Where reinfection is likely, sexual partners should be treated concomitantly.
Adults and adolescents: 2000 mg as a single dose or 200 mg 3 times daily for 7 days or 400 mg twice daily for 5-7 days.
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.
Children under 10 years: A more suitable dosage form should be used for this age group.

4) Bacterial vaginosis
Adults: 400mg twice daily for 7 days, or 2g as a single dose for one day only.
Adolescents: 400 mg twice daily for 5-7 days or 2000 mg as a single dose.

5) Amoebiasis
Adults> 10 years: 400 to 800 mg 3 times daily for 5-10 days.
Children 7 to 10 years: 200 to 400 mg 3 times daily for 5-10 days.
Children 3 to 7 years: 100 to 200 mg 4 times daily for 5-10 days.
Children 1 to 3 years: 100 to 200 mg 3 times daily for 5-10 days.
Alternatively, doses may be expressed by body weight:
35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day.
Children under 7 years: A more suitable dosage form should be used for this age group.

6) Giardiasis:
Adults > 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 to 10 days.
Children 7 to 10 years: 1000 mg once daily for 3 days.
Children 3 to 7 years: 600 to 800 mg once daily for 3 days.
Children 1 to 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.

Children under 7 years: A more suitable dosage form should be used for this age group.

7) Acute ulcerative gingivitis (for 3 day duration):
Adults and children over 10 years: 200mg three times daily.
Children under 10 years: A more suitable dosage form should be used for this age.

8) Acute dental infections (for 3-7 day duration):
Adults and children over 10 years: 200mg three times daily.

9) Leg ulcers and pressure sores (for 7 day duration):
Adults and children over 10 years: 400mg three times daily.

10) Treatment of Helicobacter pylori in infected patients
As a part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.

Method of Administration
For oral administration.

4.3 Contraindications

- Known hypersensitivity to nitroimidazoles, metronidazole or to any of the excipients listed in 6.1.
- Pregnancy - metronidazole should not be used in the first trimester in patients with trichomoniasis or bacterial vaginosis (see section 4.6).
- Breast feeding should be discontinued for 12-24 hours when single high dose (e.g. 2g) therapy is used (see section 4.6).

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 metronidazole for longer treatment than usually required should be carefully considered.
- *Neuropathy (central and peripheral):* Regular clinical and laboratory monitoring (especially leukocyte count) are advised if administration of metronidazole 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.
- Patients should abstain from alcohol for at least 48 hours following discontinuation of therapy with metronidazole. A disulfiram-like reaction with hypotension and flushing has occurred (see section 4.5).
- Caution in patients with epilepsy or those who have had seizures as high doses of Metronidazole can induce seizures.
- Consideration of the therapeutic benefit against the risk of peripheral neuropathy is advised with continuous therapy for chronic conditions.
- *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, metronidazole treatment must be immediately discontinued.

Interference with laboratory tests
Metronidazole may interfere with certain types of blood test determinations in blood (aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to false negative or an abnormally low result. These analytical determinations are based on a decrease in ultraviolet absorbance, a fact that occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidised to nicotinamide adenine dinucleotide (NAD). The interference is due to the similarity in the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Excipients
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take metronidazole as this product contains lactose.

Information on sodium content
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

- *Alcohol:* Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours after because of the possibility of a disulfiram-like (antabuse effect) reaction.
- *Disulfiram:* Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.
- *Oral anticoagulant therapy (warfarin type):* 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:* 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 concentration of lithium, creatinine, and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.
- *Phenytoin and phenobarbital:* Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours. Primidone accelerates the metabolism of Metronidazole causing reduced plasma concentrations.
- *5-fluorouracil:* Metronidazole reduces the clearance of 5-fluorouraciland can therefore result in increased toxicity of 5-fluorouracil.
- *Ciclosporin:* Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.
- *Busulfan:* Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.
- *Drugs that prolong QT interval:* QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

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 metronidazole, like other medicines, should not be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dosage regimens are not recommended.

Pregnancy

Metronidazole is contraindicated in the first trimester (see section 4.3) and should be used with caution in the second and third trimester when used to treat trichomoniasis or bacterial vaginosis (see section 4.4).

For all other indications Metronidazole should only be used if the benefits outweigh the risks or no other alternative is available especially in the first trimester.

Breast-feeding
It is advisable to stop breast feeding until 12 – 24 hours after Metronidazole therapy has been discontinued (see section 4.3).

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for drowsiness, dizziness, vertigo, confusion, hallucinations, convulsions 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.

System organ class	Frequency	Adverse event
Blood and lymphatic system disorders	Very rare	Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
	Not known	Leucopenia
Immune system disorders	Rare	Anaphylaxis
	Not known	Angioedema, 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, 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
Cardiac disorders	Not known	QT prolongation has been reported (particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval)
Gastrointestinal disorders	Not known	Taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea
Hepatobiliary disorders	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 (AGEP), pruritus, flushing
	Not known	Erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), 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)

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).

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 the 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

Features:
Nausea, vomiting, diarrhoea, anorexia, metallic taste, headache, dizziness and occasionally insomnia and drowsiness. Transiently increased liver enzyme activities have been reported rarely.

Transient epileptiform seizures have been reported following intensive or prolonged therapy. Other adverse effects occurring in these circumstances include peripheral motor neuropathy, blood dyscrasias and liver damage.

The combination of alcohol and metronidazole has been said to cause disulfiram type reactions in about 10% of individuals with sudden onset of excitement, giddiness, flushing, nausea, headache, hypotension and dyspnoea. However the mechanism of this reaction has been questioned.

Treatment:
Unlikely to be required.

Disulfiram type reactions should be treated with intravenous fluids and plasma expanders if necessary. Symptomatic and supportive.

In more serious cases:
1. Single brief convulsions do not require treatment. If frequent or prolonged control with intravenous diazepam (10-20mg in adults; 0.1-0.3mg/kg body weight) or lorazepam (4mg in an adult and 0.05mg/kg in a child). Give oxygen and correct acid base and metabolic disturbances as required.

2. Other measures as indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Nitroimidazole derivatives*
ATC Code: P01A B01

Mechanism of action
Metronidazole has antiprotozoan and antibacterial actions and it is effective against *Trichomonas vaginalis, Gardnerella vaginalis* and other protazoa including *Entamoeba histolytica, Gardia lamblia* and against anaerobic bacteria.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for metronidazole and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx.

5.2 Pharmacokinetic properties

Absorption
Metronidazole is readily absorbed following administration by mouth and bioavailability is 90-100%. Peak plasma concentrations occur after 20 minutes to 3 hours. Absorption may be delayed, but is not reduced overall, by administration with food.

Distribution
Metronidazole is widely distributed. It appears in most body tissues and fluids. It also crosses the placenta and rapidly enters foetal circulation. No more than 20% is bound to plasma proteins.

Biotransformation
Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The half-life of metronidazole is 6.5 ± 2.9 hours. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease.

Elimination
The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces. 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

Lactose, maize starch, povidone, magnesium stearate, carmellose sodium, microcrystalline cellulose, purified water, methylhydroxypropylcellulose, macrogol 400, titanium dioxide (E-171).

6.2 Incompatibilities

None.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Polyethylene container with pilfer-proof polyethylene closure,
pack sizes of 50, 100, 250 and 500 tablets.
Amber glass bottles,
pack sizes of 50, 100, 250 and 500 tablets.
Blister pack (aluminium (20 µm)/PVC (250 µm)),
pack sizes of 14 and 21 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0694

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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