SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metronidazole 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of Metronidazole.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film –coated tablet

White to off white colored, caplet shaped (14.20 x 5.70 mm) film-coated tablets, debossed “200” on one side and plain on other side.

4. CLINICAL PARTICULARS

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 (see sections 4.4 and 5.1).

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 and Balantidium coli.*

Metronidazole is indicated in adults and children for the following indications:
1) Prevention of post-operative infections due to anaerobic bacteria particularly species of *Bacteroides* and *anaerobic streptococci*
2) Urogenital trichomoniasis in the female (trichomonal vaginitis) and in man.
3) Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis)
4) 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.
5) All forms of amoebiasis (intestinal and extra-intestinal disease and asymptomatic cyst passers).
6) Acute ulcerative gingivitis.

7) Giardiasis.
8) Acute dental infections (e.g. 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

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.

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

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.

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, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

Protozoal and other infections

Dosage is given in terms of metronidazole or metronidazole equivalent					
	Duration of dosage in days	Adults and children over 10 years	**Children**		
			7 to 10 years	**3 to 7 years**	**1 to 3 years**
Urogenital trichomoniasis Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently	7 Or 5-7	2000mg as a single dose or 200 mg three times daily or 400mg twice daily	40mg/kg orally as a single dose or 15- 30 mg/kg/day divided in 2-3 doses; not to exceed 2000mg/dose		
Bacterial vaginosis	5-7 or	400 mg twice daily			
	1	2000mg as a single dose			
Amoebiasis *(a) Invasive intestinal disease in susceptible subjects* *(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis*	5 5-10	800 mg three times daily 400 mg three times a day	400 mg three times daily 200 mg three times daily	200 mg four times daily 100 mg four times daily	200 mg three times daily 100 mg three times daily
c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(d) Symptomless cyst passers	5-10	400-800 mg three times daily	200-400 mg three times daily	100-200 mg four times daily	100-200 mg three times daily
	Alternatively, doses may be expressed by body weight 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day				

Giardiasis	3	2000mg once daily or	1000mg once daily	600-800 mg once daily	500 mg once daily
	5	400mg three times daily or			
	7-10	500mg twice daily			
	Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.				

	Duration of dosage in days	Adults and children over 10 years	Children		
			7 to 10 years	3 to 7 years	1 to 3 years
Acute ulcerative gingivitis	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
Acute dental infections	3-7	200 mg three times daily			
Leg ulcers and pressure sores	7	400 mg three times daily			

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

Eradication of Helicobacter pylori in paediatric 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 use.

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

4.3 Contraindications

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

4. CLINICAL PARTICULARS

4.4 Special warnings and precautions for use

Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria.

Neuropathy (central and peripheral)

Regular clinical and laboratory monitoring (especially leucocyte 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.

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 therefore be used after careful benefit-risk assessment and only 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.

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.

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

In patients undergoing haemodialysis Metronidazole and metabolites are efficiently removed during an eight hour period of dialysis. Metronidazole should therefore be re-administered immediately after haemodialysis.Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of Metronidazole may contribute to the symptoms of the encephalopathy. Metronidazole should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one

third and may be administered once daily.

Patients should be warned that Metronidazole may darken urine. For information on renal and hepatic insufficiency, please see section 5.2.

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.

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.

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

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

5-fluorouracil: Metronidazole reduces the clearance of 5 fluorouracil and 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

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. CLINICAL PARTICULARS

4.8 Undesirable effects

Frequency type and severity of adverse reactions in children are the same as in adults.

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.

Frequency, type and severity of adverse reactions in children are the same as in adults.

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.

Blood and lymphatic system disorders:	
Very rare	agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known	Leucopenia, bone marrow depression disorders such as aplastic anaemia
Immune system class:	
Rare	anaphylaxis
Not known	angiodema, urticaria, fever

Metabolism and nutrition disorders:	
Not known	Anorexia
Psychiatric disorders:	
Very rare	Psychotic disorders, including hallucinations and confusion
Not known	depressed mood
Nervous system disorders;	
Very rare	• Encephalopathy (eg. Confusion, vertigo, fever, headache, hallucinations paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. Ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve in discontinuation of the drug. • Drowsiness, dizziness, convulsions, headaches

Not known	• Depression, paresthesia, 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. Incoordination of movement • Aseptic meningitis • vertigo • PT Cerebellar syndrome: Cerebellar syndrome (eg. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve upon discontinuation of the drug, have been observed with Pylera. • posterior reversible encephalopathy syndrome (PRES)
Eye disorders:	
Very rare	vision disorders such as diplopia, myopia which, in most cases, is transient.
Not known	optic neuropathy/neuritis
Gastrointestinal disorders:	
Not known	unpleasant taste in the mouth, taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea, abdominal pain, anorexia
Hepatobiliary disorders:	
Very rare	• abnormal liver function tests, 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. • 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).
Skin and subcutaneous tissue disorders:	
Very rare	skin rashes, pustular eruptions, pruritus, flushing, acute generalised exanthematous (AGEP) pustulosis,
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)
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

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 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 vomiting, 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. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Antibacterials for systemic use*
ATC Code: *J01X D01*

Mechanism of action
Metronidazole itself is ineffective. It is a stable compound able to penetrate into microorganisms.

Under anaerobic conditions nitroso radicals acting on DNA are formed from metronidazole by the microbial pyruvate-ferredoxin-oxidoreductase, with oxidation of ferredoxin and flavodoxin. Nitroso radicals form adducts with base pairs of the DNA, thus leading to breaking of the DNA chain and consecutively to cell death.

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.

PK/PD relationship
Metronidazole acts in a concentration dependent manner. The efficacy of metronidazole mainly depends on the quotient of the maximum serum concentration (c_{max}) and the minimum inhibitory concentration (MIC) relevant for the microorganism concerned.

Breakpoints
For the testing of metronidazole usual dilution series are applied. The following minimum inhibitory concentration have been established to distinguish susceptible from resistant microorganisms:

EUCAST (EUCAST: Clinical Breakpoint Tables) breakpoints separating susceptible (S) from resistant organisms (R) are as follows:

Organism	Susceptible	Resistant
Clostridium difficile[1]	≤ 2 mg/l	> 2 mg/l
Other Gram-positive anaerobes	≤ 4 mg	> 4 mg/l
Gram-negative anaerobes	≤ 4 mg	> 4 mg/l

[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.

List of susceptible and resistant organisms.

Commonly susceptible species
Anaerobes
Clostridium difficile°
Clostridium perfringens°$^{\Delta}$
Fusobacterium spp.°
Peptoniphilus spp.°
Peptostreptococcus spp.°
Porphyromonas spp.°
Prevotella spp.
Veillonella spp.°
Bacteroides fragilis
Other micro-organisms
Entamoeba histolytica°
Gardnerella vaginalis°
Giardia lamblia°
Trichomonas vaginalis°

Species for which acquired resistance may be a problem
Gram-negative aerobes
Helicobacter pylori
Anaerobes

Inherently resistant organisms

All obligate aerobes
Gram-positive micro-organisms
Enterococcus spp.
Staphylococcus spp.
Streptococcus spp.
Gram-negative micro-organisms
Enterobacteriaceae
Haemophilus spp.

° At the time of publication of these tables, no up-to-date data were available. In primary literature, standard reference books and therapy recommendations susceptibility of the respective strains is assumed.
$^{\Delta}$ Only to be used in patients with allergy to penicillin

Mechanisms of resistance to metronidazole
The mechanisms of metronidazole resistance are still understood only in part. Strains of Bacteroides being resistant to metronidazole possess genes encoding nitroimidazole reductases converting nitroimidazoles to aminoimidazoles. Therefore, the formation of the antibacterially effective nitroso radicals is inhibited.

There is full cross resistance between metronidazole and the other nitroimidazole derivatives (tinidazole, ornidazole, nimorazole). The prevalence of acquired resistance of individual species may vary, depending on region and time. Therefore, especially for the adequate treatment of severe infections specific local information regarding resistance should be available. If there is doubt about the efficacy of metronidazole due to the local resistance situation, expert advice should be sought.

Especially in the case of severe infections or failure of treatment, microbiological diagnosis including determination of species of the microorganism and its susceptibility to metronidazole is required.

5.2 Pharmacokinetic properties

Absorption:
Metronidazole is readily absorbed from the gastrointestinal tract and the oral bioavailability is > 90%. Consequently, the same mg dose will result in similar exposure (AUC) when switching between intravenous and oral dosing. Metronidazole is rapidly and almost completely absorbed on administration of metronidazole tablets; 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

Distribution:
Metronidazole is widely distributed in body tissues after injection. It also diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum. Protein binding is less than 20 %, the apparent volume of distribution is 36 litres.

Metronidazole appears in most body tissues and fluids including bile, bone, cerebral abscess, cerebrospinal fluid, liver, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma.

Biotransformation:
Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. Its metabolites include an acid oxidation product, a hydroxy derivative and glucuronide. The major metabolite in the serum is the hydroxylated metabolite, the major metabolite in the urine is the acid metabolite.

Elimination:
Approximately 80% of the substance is excreted in urine with less than 10% in the form of the unchanged drug substance. Small quantities are excreted via the liver. Elimination half-life is 8 (6-10) hours.

Characteristics in special patient groups:
Renal insufficiency delays excretion only to an unimportant degree. The elimination half-life of metronidazole remains unchanged in the presence of renal failure, however such patients retain the metabolites of metronidazole. The clinical significance of this is not known at present.

Delayed plasma clearance and prolonged serum half-life (up to 30 h) is to be expected in severe liver disease.

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 others studies were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Anhydrous calcium hydrogen phosphate

Maize starch

Povidone

Crospovidone

Microcrystalline cellulose

Colloidal anhydrous silica

Magnesium stearate

Film coat:

Hypromellose

Polyethylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-PVC/PVDC blisters of 20 and 21 film-coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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