SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metran 200 / Metronidazole Tablets 200 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole 200 mg.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Flat, white or creamy-white scored tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole Tablets 200mg is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Metronidazole Tablets 200mg 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 vaginalis* and other species of trichomonads, *Entamoeba histolytica, Giardia lamblia, Balantidium coli* and the causative organisms of acute ulcerative gingivitis.

Metronidazole Tablets 200mg is indicated in the oral treatment of:

The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci.

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.

Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male. The male consort of females suffering from urogenital trichomoniasis should be treated concurrently.

Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).

All forms of amoebiasis (intestinal and extra-intestinal disease, and that of symptomless cyst passers).

Giardiasis.

Acute ulcerative gingivitis.

Anaerobically-infected leg ulcers and pressure sores.

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

Posology
Anaerobic infections: The duration of a course of Metronidazole Tablets 200mg treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.

Prophylaxis against anaerobic infection: Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.

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

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

Treatment of established anaerobic infection:

Adults: 800mg followed by 400mg 8-hourly.

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

Children < 8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12hours. In newborns with a gestation < 40 weeks, accumulation of

metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferably 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 infection is likely in adults the consort should receive similar course of treatment concurrently	7 or 5-7	2000 mg as a single dose or 200 mg three times daily or 400 mg twice daily	40 mg/kg orally as a single dose or 15-30 mg/kg/day divided in 2-3 doses; not to exceed 2000 mg/day		
Bacterial vaginosis	5-7 or	400 mg twice daily			
	1	2000 mg as a single dose			
Amoebiasis (a) Invasive intestinal disease in susceptible subjects	5	800 mg three times daily	400 mg three daily mg times	200 mg four daily mg times	200 mg three times daily
(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5-10	400 mg three times daily	200 mg three times daily	100 mg four 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 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day				
Giardiasis	3	2000 mg once daily or	1000 mg once daily	600-800 mg once daily	500 mg once daily
	5	400 mg three			

		times daily or			
	7-10	500 mg twice daily			
	Alternatively, as expressed in mg per kg of body weight: 15-40 mg/kg/day divided in 2-3 doses.				
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, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.

Method of administration

For oral use.
Metronidazole Tablets 200mg should be swallowed without chewing, with half a glassful of water, during or after meals.

4.3 Contraindications

Hypersensitivity to nitroimidazoles, metronidazole or any of the excipients.

4.4 Special warnings and precautions for use

Regular clinical and laboratory monitoring (especially leukocyte count) are advised if administration of Metronidazole Tablets 200mg 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, 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.

The possibility that an accompanying gonococcal infection might persist in a symptomatic state after *Trichomonas vaginalis* has been eliminated should be borne in mind.

The elimination half-life of metronidazole remains unchanged in the presence of renal failure. The dosage of metronidazole therefore needs no reduction. Such patients however retain the metabolites of metronidazole. The clinical significance of this is not known at present.

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.

No routine adjustment in the dosage of Metronidazole Tablets 200mg needs to be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

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.

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.

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, Flagyl treatment must be immediately discontinued.

Patients should be warned that metronidazole may darken urine.

Patients with acute porphyria should not take this medicine.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Due to inadequate evidence on the mutagenicity risk in humans, the use of metronidazole for longer treatment than usually required should be carefully considered.

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 the possibility of a disulfiram-like (antabuse effect) reaction.

Concomitant administration of disulfiram has led to acute psychosis and confusional states.

The effects of warfarin type oral anticoagulants may be potentiated by metronidazole. The dose of warfarin type oral anticoagulants 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.

Phenobarbital and Phenytoin causes increased metabolism of metronidazole, reducing the half-life to about three hours.

Metabolism of metronidazole is accelerated by primidone.

Metronidazole inhibits the metabolism of phenytoin (increased plasma concentration).

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.

Metronidazole possibly reduces bioavailability of mycophenolate.

The metabolism of metronidazole is inhibited by cimetidine.

Antibacterials that do not induce liver enzymes possibly reduce the contraceptive effect of oestrogens.

4.6 Fertility, Pregnancy and lactation

As there is insufficient evidence on safety of use in pregnancy or lactation, metronidazole should not be given in these circumstances unless it is considered essential by the physician. If it is used, then 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 drowsiness, dizziness, 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 ($\geq 1/10$); common ($\geq 1/100$ to < 1/10); uncommon ($\geq 1/1,000$ to < 1/100); rare ($\geq 1/10,000$ to < 1/1000); 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 risk of peripheral neuropathy.

Blood and lymphatic system disorders:	

Very rare	Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia.
Not known	Leucopenia. White blood cell counts return to normal once treatment is completed.
Immune system class:	
Rare	Anaphylaxis
Not known	Urticaria, angioedema, 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 (e.g. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve on discontinuation of drug. Drowsiness, dizziness, convulsions, headaches
Not known	During intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. These usually disappear after treatment is stopped or dosage reduced. Aseptic meningitis
Eye disorders:	
Very rare	Diplopia and myopia (which in most cases are 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 (unpleasant taste in the mouth), oral mucositis, furred tongue, nausea, vomiting, gastrointestinal 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, pruritus, 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 a metabolite of metronidazole).

4.9 Overdose

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms are limited to vomiting, ataxia and slight disorientation. There is no specific treatment for gross over dosage of metronidazole. 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

Metronidazole is an antimicrobial agent acting against a wide range of anaerobic bacteria and protozoa including *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*.

5.2 Pharmacokinetic properties

Metronidazole is rapidly absorbed from the gastro-intestinal tract. Peak plasma concentrations occur between twenty minutes and three hours.

The elimination half-life 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

Lactose

Maize Starch

Pregelatinised Maize Starch

Sodium Starch Glycollate

Magnesium Stearate

6.2 Incompatibilities

None known.

6.3 Shelf Life

36 months (tub)
24 months (blister pack)

6.4 Special precautions for storage

Store in a dry place, below 25°C.

Keep container tightly closed, protect from light.

6.5 Nature and Contents of Container

High density polystyrene container with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane/polythene wads.
Pack sizes of 21, 28, 56 and 250 tablets.

Aluminium (foil layer)-PVC/PVDC (transparent base layer) blister pack of 21 tablets.

Not all pack sizes/types may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Esteve
Pharmaceuticals
Ltd
The Courtyard
Barns
Choke Lane
Cookham
Dean
Maidenhead

B
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SL6 6PT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17509/0073

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/11/95

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