Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metronidazole Solution for Infusion 5 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 5mg Metronidazole

For excipents, see 6.1

3 PHARMACEUTICAL FORM

Solution for infusion.

150 ml PVC infusion bag containing 100 ml of a clear pale yellow, sterile non pyrogenic aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metronidazole Infusion is indicated for the treatment of the following:

In the treatment of severe infections due to anaerobic bacteria, particularly species of *Bacteroides*, anaerobic *Streptococci*, etc. and for prophylaxis against such infections in patients for whom oral medication is not practicable.

4.2 Posology and method of administration

Intravenous infusion.

Adults and children over 12 years:

For treatment 100 ml (500 mg metronidazole) should be administered by intravenous infusion eight hourly. For prevention 100ml (500mg metronidazole) should be administered immediately before, during or after operation and repeated eight hourly thereafter.

Children under 12 years:

For treatment 7.5mg metronidazole per kg body weight should be administered by intravenous infusion eight hourly. For prevention 7.5mg metronidazole per kg body weight should be administered immediately before, during or after operation and repeated eight hourly thereafter.

In the case of children whose weights are below those usual for their age, or for infants below 10kg in weight, dosage of metronidazole should be reduced proportionately.

4.3 Contraindications

1) Patients with evidence, or a history, of blood dyscrasias, should not receive metronidazole since upon occasion a mild leucopenia has been observed during its administration. However, no persistent haematological abnormalities have been observed in animal or clinical studies.

2) Active organic disease of the central nervous system.

3) Pregnancy (first trimester), or lactation, unless the physician considers the benefits to outweigh the potential risk.

4) Hypersensitivity to metronidazole.

4.4 Special warnings and precautions for use

Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.

Reversible peripheral neuropathy has been reported with intensive or prolonged therapy with metronidazole. Its use should be avoided if possible in patients with active neurological disease.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: disulfiram-like reaction.

Anticoagulants: effect of micoumalone and warfarin enhanced. No interactions have been reported with parenteral anticoagulants of the heparin type. However, anti-coagulant activity should be routinely monitored with these products.

Antiepileptics: metronidazole inhibits the metabolism of phenytoin (increased plasma-phenytoin concentration); phenobarbitone accelerates metabolism of metronidazole (reduced plasma-metronidazole concentration).

Disulfiram: psychotic reaction.

Ulcer-healing Drugs: cimetidine inhibits metabolism (increased plasma metronidazole concentration).

4.6 Pregnancy and lactation

Use in Pregnancy:

There are no adequate or well-controlled studies to date using metronidazole in pregnant women, and the drug should be used during pregnancy only when clearly needed. Use of the drug during the first trimester of pregnancy is contra-indicated.

Because no therapy other than metronidazole currently has been shown to produce an adequate response in the treatment of trichomoniasis, oral metronidazole should be used to treat this infection in pregnant women only when severe symptoms cannot be controlled with local palliative treatment and only during the second and third trimester.

Use in Lactation:

Metronidazole is distributed into milk. Due to the tumorigenic potential of metronidazole in mice and rats, a decision

should be made whether to discontinue nursing or the drug, considering the relative importance of the drug to the woman.

If trichomoniasis in lactating women is treated with metronidazole, the drug should be administered as a single, oral 2 g dose and breast-feeding should be interrupted for at least 24 hours after administration of the drug.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Side effects and adverse reactions: Adverse reactions are relatively infrequent. There have been reports of rash, pruritus, urticaria, nausea, anorexia, furry tongue, dry mouth, nasal congestion, abdominal discomfort, glossitis, stomatitis (which may be associated with Candida overgrowth), metallic or unpleasant taste in the mouth, headache, dizziness.

Instances of a darkened urine have also been reported (almost certainly due to a metabolite of metronidazole).

There have been a few reports of peripheral neuropathy and transient epileptiform seizures during associated intensive and/or prolonged metronidazole therapy. In most cases the neuropathy disappeared after treatment was reduced or stopped.

There have been reports of bone marrow depression disorders such as agranulocytosis, neutropenia, thrombocytopenia and pancytopenia which may be reversed on drug withdrawal, although fatalities have been reported. Abnormal liver function tests, cholestatic hepatitis and jaundice may occur; these may be reversed upon drug withdrawal. Metronidazole may also be associated with erythema multiforme which may be reversed on drug withdrawal. Anaphylaxis may occur rarely.

4.9 Overdose

There is no specific treatment, but early gastric lavage is recommended following overdosage by mouth. Uneventful recovery has followed attempts at suicide with oral doses up to 12 g. Metronidazole is readily removed from plasma by hemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antimicrobial Effects:

Metronidazole is bactericidal, amoebicidal and trichomonacidal in action.

5.2 Pharmacokinetic properties

Metronidazole is readily absorbed following administration by mouth and bioavailability approaches 100%. Peak plasma concentrations of approximately 5 and 10µg per ml are achieved an average of one hour after single doses of 250 and 500mg respectively. Some accumulation and consequently higher concentrations occur when multiple doses are given. Concentrations may vary according to the type of assay used. Absorption may be delayed, but it is not reduced overall by administration with food.

Following the intravenous administration of metronidazole, peak steady-state plasma concentrations of about 25µg per ml with trough concentrations of about 18µg per ml have been reported in patients given a loading dose of 15mg per kg bodyweight followed by 7.5mg per kg every 6 hours.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast-milk, cerebral abscesses, cerebrospinal fluid, liver and liver abscesses, saliva, seminal fluid and vaginal secretions and achieves concentrations similar to those seen in plasma.

It also crosses the placenta and rapidly enters the foetal circulation. No more than 20% is bound to plasma proteins.

The plasma elimination half-life of metronidazole is about 8 hours. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease; that of the hydroxy metronidazole is prolonged in patients with renal failure.

The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces. Depending on the assay method used, up to 80% of a dose has been recovered in the urine within 48 hours.

The liver is the main site of metabolism and the principal metabolites result from oxidation of side chains and formation of glucuronides. Small quantities of reduced metabolites; including ring-cleavage products are formed in the gut flora. The urine in some patients may be reddish-brown due to the presence of unidentified pigments derived from the drug.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Disodium Hydrogen Phosphate Dodecahydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

It is generally recommended that no other drug be added to infusions of metronidazole ready-to-use. If administration is to be made through the tubing of an ongoing primary infusion, the primary infusion should be stopped, if possible, during metronidazole administration.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in the original container.

6.5 Nature and contents of container

150ml PVC bag containing 100ml of a clear pale yellow, sterile and non-pyrogenic aqueous solution. The infusion container is sealed in a polythene extruded plastic pouch.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.

Discard any unused portion.

Do not reconnect partially used bags.

7 MARKETING AUTHORISATION HOLDER

Gambro Northern Ireland Limited
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Old Belfast Road
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Larne
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8 MARKETING AUTHORISATION NUMBER

PA 1317/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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