SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Metronidazole 5 mg/ml Solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for infusion contains 5mg metronidazole.
Each 100ml of solution for infusion contains 500mg metronidazole.
Excipients:
Each ml of solution for infusion contains 0.1384 mmol (3.2602mg) sodium.
Each 100ml of solution for infusion contains 13.84 mmole (or 326.02 mg) sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for infusion
A clean, bright, pale yellow sterile isotonic solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Metronidazole 5mg/ml solution for infusion is indicated in adults and children when oral medication is not possible in:
- The prophylaxis of pre/postoperative infections due to sensitive anaerobic bacteria particularly species of Bacteroides and anaerobic Streptococci, during abdominal, gynaecological, gastrointestinal or colorectal surgery which carries a high risk of occurrence of this type of infection. The solution may also be used in combination with an antibiotic active against aerobic bacteria.
- The treatment of severe intra-abdominal and gynaecological infections in which sensitive anaerobic bacteria particularly Bacteriodes and anaerobic Streptococci have been identified or are suspected to be the cause.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
4.2 Posology and method of administration

Method of administration:
Metronidazole 5mg/ml solution for infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bag infused over 20 to 60 minutes). Oral medication should be substituted as soon as feasible.

Prophylaxis against post-operative infection caused by anaerobic bacteria:
Primarily in the context of abdominal (especially colorectal) and gynaecological surgery.
Antibiotic prophylaxis duration should be short, mostly limited to the post operative period (24 hours but never more than 48 hours). Various schedules are possible.

Adults: Intravenous injection of single dose of 1000mg-1500mg, 30-60 minutes preoperatively or alternatively 500mg immediately before, during or after operation, then 500mg 8-hourly.

Children: < 12 20 - 30 mg/kg as a single dose given 1-2 hours before surgery.

Newborns with a gestation age < 40 weeks: 10 mg/kg of body weight as a single dose before operation.

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

Anaerobic infections
Intravenous route is to be used initially if patients’ symptoms preclude oral therapy.
Various schedules are possible.

Adults: 1000mg - 1500mg daily as a single dose or alternatively 500mg every 8 hours

Children > 8 weeks to 12 years of age: The usual daily dose is 20 -30mg/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 the 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 the drug might occur during the first week of life, which is why the concentrations of Metronidazole in serum should preferably be monitored after a few days of therapy.

Bacterial vaginosis
Adolescents: 400 mg twice daily for 5-7 days or 2000 mg as a single dose

Urogenital trichomoniasis
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
Giardiasis
> 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.

Amoebiasis
> 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

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

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

Oral medication could be given, at the same dose regimen. Oral medication should be substituted as soon as feasible.

Duration of Treatment

Treatment for seven to ten days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician might decide to prolong treatment e.g. for the 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.

Patients with renal failure
Routine adjustments of the dosage of Metronidazole are not considered necessary in the presence of renal failure.
No routine adjustment in the dosage of Metronidazole needs to be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD). However dosage reduction may be necessary when excessive concentrations of metabolites are found.
In patients undergoing haemodialysis, Metronidazole should be re-administered immediately after haemodialysis.

Patients with advanced hepatic insufficiency
In patients with advanced hepatic insufficiency a dosage reduction with serum level monitoring is necessary.
4.3 Contraindications

Known hypersensitivity to Metronidazole or other imidazole derivatives or any of the excipients (see 6.1 List of excipients).

Metronidazole is contraindicated in the first trimester of pregnancy.

Use of Metronidazole is contraindicated in patients with end stage liver damage, hematopoietic disorders and uncontrolled diseases of the central or peripheral nervous system.

4.4 Special warnings and precautions for use

Liver disease:

Metronidazole is mainly metabolized by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit ratio of using Metronidazole to treat trichomoniasis in such patients should be carefully considered (for dosage adjustment see section 4.2). Plasma levels of Metronidazole should be closely monitored.

Active Central Nervous System disease:

Metronidazole should be used with caution in patients with active disease of the Central Nervous System. The treatment should be withdrawn in case of ataxia, dizziness, or confusion. The risk of aggravation of the neurological state should be considered in patients suffering from severe central and peripheral neurological diseases, fixed or progressive paraesthesia and epilepsy. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Renal Disease:

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Sodium restricted patients:

May be harmful to patients on a low sodium diet.

Alcohol:

Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like effect (flushing, vomiting, tachycardia). See Section 4.5.

Intensive or prolonged Metronidazole therapy:

As a rule, the usual duration of therapy with i.v Metronidazole or other imidazole derivatives is usually less than 10 days. This period may only be exceeded in individual cases after a very strict benefit-risk assessment. Only in the rarest possible case should the treatment be repeated. Limiting the duration of treatment is necessary because damage to human germ cells cannot be excluded.
Intensive or prolonged Metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible.

In case of prolonged treatment, occurrence of undesirable effects such as paraesthesia, ataxia, dizziness and convulsive crises should be checked. High dose regimes have been associated with transient epileptiform seizures.

Monitoring:
Regular clinical and laboratory monitoring (including leukocyte formula) are advised in cases of high-dose or prolonged treatment, in case of antecedents of blood dyscrasia, in case of severe infection and in severe hepatic insufficiency.

General:
Patients should be warned that Metronidazole may darken urine (due to Metronidazole metabolite).

4.5 Interaction with other medicinal products and other forms of interaction
Not recommended concomitant therapy:
Alcohol: Disulfram-like effect (warmth, redness, vomiting, tachycardia).
Alcohol beverage and drugs containing alcohol should be avoided. Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).

Concomitant therapy requiring special precautions:
Oral anticoagulants (warfarin): increase of the effects of oral anticoagulants and the risk of haemorrhage (decrease in its liver catabolism). Prothrombin time should be monitored more frequently. The dose of oral anticoagulants should be adjusted during the treatment with Metronidazole and 8 days after withdrawal. A large number of patients have been reported showing an increase in oral anticoagulant activity whilst receiving concomitant antibiotic therapy. The infectious and inflammatory status of the patient, together with their age and general well-being are all risk factors in this context. However, in these circumstances it is not clear as to the part played by the disease itself or its treatment in the occurrence of prothrombin time disorders. Some classes of antibiotics are more likely to result in this interaction, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins.
Vecuronium (non depolarizing curaremimetic): Metronidazole can potentialise the effects of vecuronium.

Combinations to be considered:
5 Fluoro-uracile: increase in the toxicity of 5 fluoro-uracile due to a decrease of its clearance.

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.

Barbiturates - Phenobarbital might induce the metabolism of Metronidazole, which could lead to decreased efficacy of Metronidazole.
Cholestyramine may delay or reduce the absorption of Metronidazole.
Concomitant administration of phenytoin and Metronidazole may affect the metabolism of Metronidazole.
Cimetidine inhibits the metabolism of Metronidazole.

Cyclosporine - Case reports indicate that concomitant treatment with Metronidazole and Cyclosporine might lead to increased serum levels of cyclosporine. Cyclosporine concentrations and creatinine levels should be monitored.

Laboratory tests:
Metronidazole may immobilize Treponema and thus may lead to falsely positive Nelson's test.

4.6 Pregnancy and lactation
Clinical data on a large number of exposed pregnancies and animal data did not show a teratogenic or foetotoxic effect. However unrestricted administration of nitroimidazolene to the mother may be associated with a carcinogenic or mutagenic risk for the unborn or newborn child.

Therefore Metronidazole should not be given during pregnancy unless clearly necessary. Metronidazole is contraindicated in the first trimester of pregnancy.
Metronidazole is excreted in breast milk. During lactation either breastfeeding or Metronidazole should be discontinued.

4.7 Effects on ability to drive and use machines
No studies have been performed following intravenous treatment with Metronidazole on the ability to drive and use machines. Therefore it is recommended that patients should not drive or use machines.

4.8 Undesirable effects
Common undesirable effects (>1/100 <1/10):
Gastrointestinal tract: diffuse symptoms of intolerance (like nausea, vomiting), metallic taste, stomatitis and glossitis and dry mouth; myalgia.

Uncommon undesirable effects (>1/1000, <1/100):
Leucopenia, headaches and weakness.

Rare undesirable effects (>1/10,000, <1/1000):
General: fever, skin rashes, urticaria, erythema multiforme anaphylactic shock, Quincke oedema, pustolosis.
Neurology: drowsiness, dizziness, ataxia, peripheral neuropathy or transient epileptiform seizures, hallucinations
Blood: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia. Blood dyscrasia is generally reversible but fatal cases have been reported.
Liver: Abnormal function tests, cholestatic hepatitis jaundice, pancreatitis; rare and reversible cases of pancreatitis are reported.
Gastrointestinal: Mucositis, epigastralgia, nausea, vomiting, diarrhoea, anorexia.
Urine: darkening of urine.
Eyes: diplopia, myopia.
Herxheimer reaction.
Changes in the blood picture as well as peripheral neuropathy observed after prolonged treatment or high dosages generally abate after treatment withdrawal.
Frequency, type and severity of adverse reactions in children are the same as in adults.

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.

4.9 Overdose

Symptoms
In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting, ataxia and slight disorientation. In a preterm newborn, no clinical or biological sign of toxicity developed.

Treatment
There is no specific treatment for Metronidazole overdose. Metronidazole infusion should be discontinued. Patients should be treated symptomatically.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metronidazole is an anti-infectious drug belonging to the pharmacotherapeutic group of nitroimidazole derivatives, which have effect mainly on strict anaerobes. This effect is probably caused by interaction with DNS and different metabolites.

Pharmacotherapeutic group: Anti bacterials for systemic use: imidazole derivatives

ATC Code: J01XD01

and

Pharmacotherapeutic group: Anti-protozoals: nitroimidazole derivatives

ATC Code: P01 AB0 1.

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

Anti-Microbial Spectrum:

The MIC breakpoints separating susceptible from intermediately susceptible and intermediately susceptible from resistant organisms are as following:

\[ S \leq 4 \text{ mg/l} \quad \text{and} \quad R > 4 \text{ mg/l} \]

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to Metronidazole or not.

<table>
<thead>
<tr>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUSCEPTIBLE</strong></td>
</tr>
<tr>
<td>Gram negative aerobes <em>Helicobacter pylori</em></td>
</tr>
<tr>
<td>Anaerobes</td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
</tr>
<tr>
<td><em>Bifidobacterium</em> resistant (70%)</td>
</tr>
<tr>
<td>Bilophila</td>
</tr>
</tbody>
</table>
Cross-resistance with tindazol occurs.

### 5.2 Pharmacokinetic properties

**Distribution:** After administration of a single 500 mg dose, mean Metronidazole peak plasma concentrations of ca. 14-18 µg/ml are reached at the end of a 20 minute infusion. 2-hydroxy-metabolite peak plasma concentrations of ca..3 µg/ml are obtained after a 1 g single i.v. dose. Steady state Metronidazole plasma concentrations of about 17 and 13 -µg/ml are reached after administration of Metronidazole every 8 or 12 hours, respectively.

Plasma protein binding is less than 10%, and the volume of distribution 1.1 ± 0.4 l/kg.

**Metabolism:** Metronidazole is metabolised in the liver by hydroxylation, oxidation and glucuronidation. The major metabolites are a 2-hydroxy- and an acetic acid metabolite.

**Elimination:** More than 50% of the administered dose is excreted in the urine, as unchanged Metronidazole (ca. 20% of the dose) and its metabolites. About 20% of the dose is excreted with faeces. Clearence is 1.3 ± 0.3 ml/min/kg, while renal
clearance is about 0.15 ml/min/kg. The plasma elimination half-life of Metronidazole is ca. 8 hours, and of the 2-hydroxy-metabolite ca. 10 hours.

Special patient groups: The plasma elimination half-life of Metronidazole is not influenced by renal impairment, however this may be increased for 2-hydroxy- and an acetic acid metabolite. In the case of haemodialysis, Metronidazole is rapidly excreted and the plasma elimination half-life is decreased to ca. 2.5 h. Peritoneal dialysis does not appear to affect the elimination of Metronidazole or its metabolites.

In patients with impaired liver function, the metabolism of Metronidazole is expected to decrease, leading to an increase in the plasma elimination half-life. In patients with severe liver impairment, clearance may be decreased up to ca. 65%, resulting in an accumulation of Metronidazole in the body.

5.3 Preclinical safety data
Metronidazole has been shown to be non-mutagenic in mammalian cells *in vitro* and *in vivo*.

Metronidazole and a metabolite have been shown to be mutagenic is some tests with non mammalian cells.

Although Metronidazole has been shown to be carcinogenic in certain species of mice, it was not carcinogenic in either rats or guinea pigs. There is no suspicion of carcinogenicity in man.

Further preclinical data on repeated toxicity and toxicity to reproduction add no relevant knowledge for the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric acid Monohydrate,
Anhydrous Disodium Hydrogen Phosphate,
Sodium Chloride
Water for Injections
6.2 Incompatibilities

Metronidazole 5 mg/ml solution for Infusion should not be mixed with cefamandole nafate, cefoxitin sodium, dextrose 10% w/v, and compound sodium lactate injection, penicillin G potassium.

6.3 Shelf life

Glass bottle containing 100 ml - 36 months

Plastic bag containing 100 ml - 36 months

6.4 Special precautions for storage

100 ml glass bottle: Store below 30°C. Do not refrigerate or freeze. Keep vial in the outer carton in order to protect from light.

100 ml plastic bag: Store below 25°C. Do not refrigerate or freeze. Keep bag in the original package in order to protect from light.

6.5 Nature and contents of container

Metronidazole 5 mg/ml Infusion (100 ml) is available in type II glass bottles closed with a bromobutyl rubber closure.

Metronidazole 5 mg/ml Infusion is available in 100ml PVC bag.

6.6 Special precautions for disposal

The containers are for single use only. Discard any unused portion. Do not reconnect partially used containers.

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

7 MARKETING AUTHORISATION HOLDER

Claris Lifesciences UK Limited
Crewe Hall,
Crewe,
Cheshire,
CW 1 6UL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
PL 20568/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/03/2009

10 DATE OF REVISION OF THE TEXT
14/08/2015