# Metronidazole 5 mg/ml Solution for infusion

**PL 20568/0006**

**UKPAR**

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METRONIDAZOLE 5 MG/ML SOLUTION FOR INFUSION

PL 20568/0006

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Metronidazole 5 mg/ml Solution for infusion (product licence number: 20568/0006). This solution for infusion is only available on prescription.

Metronidazole 5 mg/ml Solution for infusion contains 5 mg/ml of the antibiotic metronidazole. Metronidazole is used to prevent or treat infections caused by anaerobic bacteria (bacteria that can live without oxygen). Metronidazole infusion is used when metronidazole cannot be taken by mouth.

Metronidazole is used to:

- Prevent pre and/or post operative infections caused by sensitive bacteria in surgical procedures with a high risk of occurrence of this type of infection.

- Treat severe abdominal and gynaecological infections where sensitive bacteria are suspected to be the cause.

Metronidazole infusion may also be used in combination with other antibiotics.

Metronidazole 5 mg/ml Solution for infusion raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
METRONIDAZOLE 5 MG/ML SOLUTION FOR INFUSION

PL 20568/0006

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Metronidazole 5 mg/ml Solution for infusion to Claris Lifesciences UK Limited on 18 March 2009.

This is a standard abridged application submitted under article 10(1) of Directive 2001/83/EC, as amended. The applicant claims that this product is a generic version of Flagyl Injection 0.5%w/v (PL 00012/0107), which was licensed to May & Baker Limited on 14 March 1978.

Metronidazole 5mg/ml solution for infusion is indicated 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.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
All aspects of the manufacture and control of metronidazole are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of metronidazole for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting the shelf life.

DRUG PRODUCT

Composition of the finished product
Metronidazole 5mg/ml solution for infusion contains the excipients citric acid monohydrate, anhydrous disodium hydrogen phosphate, sodium chloride and water for injections. Appropriate justification for the inclusion of each excipient has been provided. Certification confirms that none of the excipients contain material of animal or human origin.

All excipients used comply with their respective Ph. Eur. monograph. Satisfactory certificates of analysis have been provided for all excipients.

There were no novel excipients used and no overages.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Metronidazole 5 mg/ml Infusion is available in either type II glass bottles closed with a bromobutyl rubber closure or a 100ml PVC bag. Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set for this product, both when stored in the glass bottle and the plastic bag. Storage conditions are “Store below 30°C. Do not refrigerate or freeze. Keep vial in the outer carton in order to protect from light” for product stored in the glass bottle and “Store below 25°C. Do not refrigerate or freeze. Keep bag in the original package in order to protect from light” for product stored in the plastic bag. This is satisfactory.
Product literature
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Assessor’s Overall Conclusions
A Marketing Authorisation may be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.
CLINICAL ASSESSMENT

INTRODUCTION
Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa. It is available in oral, intravenous and rectal formulations.

Indications
Prophylaxis and treatment of infection in which anaerobic bacteria have been identified or are suspected to be the cause.

Dose and Dose Regimen
These are in line with the reference product.

Good Clinical Practice (GCP) Aspects
No clinical trials were necessary for this application hence no GCP certificate/statement is needed.

Paediatric Development Programme
Doses in children should be adjusted by body weight.

CLINICAL PHARMACOLOGY

Pharmacokinetics
Metronidazole is widely distributed in body tissues after injection. At least half the dose is excreted in the urine as metronidazole and its metabolites, including an acid oxidation product, a hydroxy derivative and glucoronide. Metronidazole diffuses across the placenta, and is found in the breast milk of nursing mothers in concentrations equivalent to those in serum, having a volume of distribution of 1.1 ± 0.4 litres/kg and a plasma protein binding of about 10%. The half-life is about 8.5 hours and the clearance 1.3 ml/min/kg.

Assessor’s overall conclusions on pharmacokinetics
The pharmacokinetic characteristics of metronidazole have been well studied in the past. There are no particular concerns for this generic formulation.

Bioequivalence
Since this is an aqueous intravenous formulation, no bioequivalence study is required.

Pharmacodynamics
Metronidazole undergoes reductive metabolism in anaerobes forming a metabolite that interferes with nucleic acid synthesis. It has antiprotozoal and antibacterial actions and is effective against Trichomonas vaginalis and other protozoa, including Entamoeba histolytica and Gardia lambila and against anaerobic bacteria.

Assessor’s overall conclusions on pharmacodynamics
The pharmacodynamic characteristics of metronidazole have been well studied in the past. There are no particular concerns for this generic formulation.
CLINICAL EFFICACY
Metronidazole is active against a wide range of pathogenic microorganisms, notably species of Bacteroides, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci and Gardnerella vaginalis, as well as protozoa. It has been proven useful in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

The applicant requests a waiver for the clinical information based on the following:
1. This is an abridged application for a generic product
2. Both the reference and the applicant’s products have the same route of administration
3. The proposed product is presented as an injectable solution

Assessors’ overall conclusions on clinical efficacy
As there are no pharmaceutical/quality concerns, the waiver can be granted.

CLINICAL SAFETY
The safety aspects of metronidazole are well covered in the SPC which mimics that of the reference product.

PRODUCT LITERATURE
The Summary of Product Characteristics, Patient Information Leaflet and labels for this product are medically satisfactory.

OVERALL CONCLUSION
A Marketing Authorisation may be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Metronidazole 5 mg/ml Solution for infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of metronidazole is well established. The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Metronidazole 5 mg/ml Solution for infusion. The risk benefit ratio is therefore considered to be acceptable.
**METRONIDAZOLE 5 MG/ML SOLUTION FOR INFUSION**

**PL 20568/0006**

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 11 October 2005</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 2 November 2005</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 16 December 2005 and the quality dossier on 5 January 2007</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 11 May 2007 and the quality dossier on 14 May 2007</td>
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<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 2 November 2007 and the clinical dossier on 14 November 2007</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 28 November 2007 and the clinical dossier on 7 January 2008</td>
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<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 30 January 2008</td>
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<td>8</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 12 February 2008</td>
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<tr>
<td>9</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 3 March 2008 and the quality dossier on 14 March 2008</td>
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<td>10</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality and clinical dossiers on 16 June 2008</td>
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<tr>
<td>11</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 12 November 2008</td>
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<td>12</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 17 December 2008</td>
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<td>13</td>
<td>The application was determined on 18 March 2009</td>
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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 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.
"Official guidance with respect to the proper use and prescription of antimicrobial agents should be taken into account."

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 of surgical pre/post-operative infection
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: Intravenous injection of single dose of 20 to 30 mg/kg, 30-60
minutes preoperatively or alternatively 7.5mg/kg given immediately before,
during or after surgery, repeated every 8 hours thereafter.
Pre-Term Newborn Infants with a gestational age less than 40 weeks: A single
dose of 10 mg/kg of body weight preoperatively.

Treatment of infections due to anaerobic bacteria.

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: A single dose of 20 to 30mg/kg/day or alternatively divided into 3
doses of 7.5 mg/kg given every 8 hours.

New born Infants less than 8 weeks of age: A lower dose of 15 mg/kg of body
weight once daily or 7.5 mg/kg every 12 hours.

Pre-Term Newborn Infants with a gestational age less than 40 weeks of age:
Accumulation of the drug might occur during the first week of life. Serum
concentrations should be controlled after a few days of therapy.

The 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 disulfiram-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: Disulfiram-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 disulfiram-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.

H kernheimer reaction.

Changes in the blood picture as well as peripheral neuropathy observed after prolonged treatment or high dosages generally abate after treatment withdrawal.

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 bacteria 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 ≤ 4 mg/l and R > 4 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>
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<tr>
<td><strong>SUSCEPTIBLE</strong></td>
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<tr>
<td>Gram negative aerobes Helicobacter pylori</td>
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<tr>
<td>Anaerobes</td>
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<tr>
<td>Bacteroides fragilis</td>
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<tr>
<td>Bifidobacterium&gt;&gt;resistant (70%)</td>
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<td>Bilophila</td>
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<td>Clostridium</td>
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<td>Clostridium difficile</td>
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<td>Clostridium perfringens</td>
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<td>Eubacterium Fusobacterium</td>
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<td>Peptostreptococcus</td>
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<td>Prevotella</td>
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<td>Porphyromonas</td>
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<td>Veillonella</td>
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<tr>
<td><strong>RESISTANT</strong></td>
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<td>Gram positive aerobes</td>
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<td>Actinomyces</td>
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<td>Anaerobes</td>
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<td>Mobiluncus</td>
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<td>Propionibacterium acnes</td>
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<td><strong>ANTIPARASITIC ACTIVITY</strong></td>
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<tr>
<td>Entamoeba histolytica</td>
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<tr>
<td>Giardia intestinalis</td>
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<td>Trichomonas vaginalis</td>
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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. Clearance 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 in 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 AUTHORITY HOTELDER**
Claris Lifesciences UK Limited
Crewe Hall,
Crewe,
Cheshire,
CW 1 6UL,
United Kingdom.

8 **MARKETING AUTHORIZATION NUMBER(S)**
PL 20568/0006

9 **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
18/03/2009

10 **DATE OF REVISION OF THE TEXT**
18/03/2009
Package Leaflet: Information For The User

Metronidazole 5 mg/ml Solution for infusion

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this Leaflet
1. What Metronidazole infusion is and what it is used for
2. Before you are given Metronidazole infusion
3. How you are given Metronidazole infusion
4. Possible side effects
5. How to store Metronidazole infusion
6. Further information

1. WHAT METRONIDAZOLE INFUSION IS AND WHAT IT IS USED FOR

Metronidazole infusion is a solution for infusion (into a vein). It contains 5 mg/ml of the active ingredient metronidazole. Metronidazole is an antibiotic.

Metronidazole is used to prevent or treat infections caused by anaerobic bacteria (bacteria that can live without oxygen). Metronidazole infusion is used when metronidazole cannot be taken by mouth

Metronidazole is used to:
- Prevent pre- and/or post operative infections owing to sensitive bacteria in surgical procedures with a high risk of occurrence of this type of infection.
- Treat severe abdominal and gynaecological infections where sensitive bacteria are suspected to be the cause.

Metronidazole infusion may be used in combination with other antibiotics.

2. BEFORE YOU ARE GIVEN METRONIDAZOLE INFUSION

Do not take Metronidazole infusion if you:
- are allergic (hypersensitive) to metronidazole or any of the other ingredients of Metronidazole infusion (see list of ingredients in Section 6). An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue.

Take special care with Metronidazole infusion (and talk to your doctor) if you:
- are having dialysis treatment (metronidazole should be re-administered immediately after dialysis)
- have a liver disorder (the dose of your metronidazole may need to be adjusted)
- are having blood tests of liver functions (metronidazole may interfere with results of some of the tests)
- have a disease of the brain or nervous system
- have had alcohol (Do not take alcohol during Metronidazole treatment and for at least 48 hours afterwards as this might cause unpleasant side effects, such as nausea and vomiting, abdominal pain, hot flushes, palpitations and headache).

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription. This is especially true of the following medicines as they may interact with your Metronidazole infusion:
- oral anticoagulants (medicines to prevent blood clots).
- lithium (a treatment for mental illness)
- phenobarbital (a sedative or treatment for epilepsy)
- 5-fluorouracil (a treatment for cancer or skin diseases)
- ciclosporin (a drug used to prevent rejection after a transplant)
- cholesterol (a drug used to reduce cholesterol levels in blood)
- clopidogrel (a drug used in healing stomach ulcers)

It may still be all right for you to be given Metronidazole infusion and your doctor will be able to decide what is suitable for you.

Pregnancy and breast-feeding
You should not be given Metronidazole infusion while pregnant or breast-feeding unless your doctor tells you to. Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines
Metronidazole infusion may cause drowsiness, dizziness, confusion, hallucinations, convulsions or temporary visual disorders. If you have any of these symptoms you should not drive or operate machinery.
3. HOW YOU ARE GIVEN METRONIDAZOLE INFUSION

The solution will be administered into a vein using a drip. It will be given at a rate of 5 ml / minute. As soon as possible after being given the injection your treatment will be continued using oral medication. Your doctor will decide when you can start to take oral medication instead of the drip. The amount of metronidazole you will be given will depend on the reason it is being prescribed for you.

To prevent infection before or after abdominal or gynaecological surgery, adults will usually receive a single dose of 1000 mg - 1500 mg up to one hour before surgery or 500 mg (100 ml) immediately before, during or after the operation. A 500 mg dose will then usually be repeated every 8 hours as necessary. Oral medication, given 8 hours later, will then replace the drip as soon as feasible.

To treat established infections, in the event that you are unable to take medicine by mouth, adults may be given 1000 - 1500 mg daily as a single dose or 500 mg of metronidazole (100 ml) every 8 hours.

Children will receive a smaller dose which is calculated from their body weight as either a single dose of 20-30 mg/kg up to one hour before surgery or 7.5 mg/kg immediately before, during or after the operation and then repeated every 8 hours.

Newborn infants born prematurely will receive a single dose of 10 mg/kg of body weight prior to surgery.

For newborn infants less than 6 weeks old, 15 mg/kg of body weight as a single dose, or 7.5 mg/kg every 12 hours will be given.

Metronidazole will be administered to the elderly with caution, especially where high doses are required.

Duration of treatment for ongoing infections is usually 7-10 days.

This product contains 7.90 mg/ml Sodium chloride and 0.476 mg/ml Anhydrous Disodium Hydrogen Phosphate corresponding to 13.84 mmoles (or 326.02 mg) of sodium per 100 ml.

This should be taken into consideration for patients on a low sodium diet.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Metronidazole infusion can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions, although serious allergic reactions are very rare. Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

The following side effects have been reported:

- Numbness, tingling, pain, or a feeling of weakness, in the arms or legs
- Convulsions or fits
- Mental problems, including confusion and hallucinations
- Temporary effects to your eyesight, such as blurred or double vision
- Unpleasant taste in the mouth
- Furred tongue
- Nausea (feeling sick)
- Vomiting
- Upset stomach
- Loss of appetite
- Itching, inflammation or swelling of the skin, or skin rashes, which may sometimes be severe
- Severe abdominal (tummy) pain
- Fever, headache or sore throat
- Yellowing of the skin and eyes (jaundice)
- Darkening of the urine
- Unexpected infections, mouth ulcers, bruising, bleeding gums, or severe tiredness
- Drowsiness, or dizziness
- Clumsiness, or poor coordination
- Pains in the muscles or joints
- Blood disturbances
- Abnormal liver tests.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE METRONIDAZOLE INFUSION

Your doctor or pharmacist knows how to store Metronidazole infusion.

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

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

6. FURTHER INFORMATION

What Metronidazole infusion contain:

The active substance is Metronidazole.

The other ingredients are: Citric acid, Disodium Hydrogen Phosphate, Sodium Chloride and Water for Injections

What Metronidazole infusion looks like and contents of the pack:

Metronidazole 5 mg/ml Infusion (100 ml) is in glass bottles closed with a rubber stopper.

Metronidazole 6 mg/ml Infusion is also available in 100 ml plastic bag.

This leaflet was last revised in March 2009

Clarity Healthcare UK Limited

Crew Hall, Crews, Cheshire, CW6 6UL, United Kingdom

Manufacturer:

Provon Pharmaceuticals Ltd

Crew Hall, Crews, Cheshire, CW6 6UL, United Kingdom
LABELLING

Each 100ml of solution for infusion contains 500mg Metronidazole

Metronidazole 5 mg/ml Solution for infusion

100 ml

Other Ingredients
Citric Acid Monohydrate
Anhydrous Disodium Hydrogen Phosphate
Sodium Chloride
Water for Injections

For dosage and directions for use, see package insert.
Store below 30°C. Do not refrigerate or freeze.
Keep vial in the outer carton in order to protect from light.
Use as directed by doctor.

Do not use if container is damaged or solution is not clear. The Containers are for single use only. Discard any unused portion.
Do not reconnect partially used containers.
Sterile, single dose container.

Claris

Each ml of solution for infusion contains 5mg Metronidazole
Excipients:
Citric Acid Monohydrate
Anhydrous Disodium Hydrogen Phosphate
Sodium Chloride
Water for Injections

Dosage: For dosage and directions for use, see package insert.
Storage: Store below 25°C.
Do not refrigerate or freeze. Keep bag in the original package in order to protect from light.
Use as directed by doctor.

POM

Code: GUJ/DRUGS/GLP-5
M. A. No.: PL 20568/0006
Sterile, single dose container.

Caution: Squeeze and inspect inner bag which maintains product sterility. Discard if leaks are found.
Do not use if solution is not clear. The Containers are for single use only. Discard any unused portion.
Do not reconnect partially used containers.

Keep out of the reach and sight of children.

Marketing Authorisation Holder:
Claris Lifesciences UK Limited
Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom.

Metronidazole 5 mg/ml Solution for infusion
For Intravenous (I.V.) use only.

Each 100ml of solution for infusion contains 500mg Metronidazole

POM