Public Assessment Report

Decentralised Procedure

Metronidazole 5mg/ml Solution for Infusion

(metronidazole)

UK/H/4504/001/DC

UK licence numbers: PL 00289/1466

Teva UK Limited
LAY SUMMARY

On 15 May 2012, the MHRA granted Teva UK Limited a Marketing Authorisation (licence) for the medicinal product, Metronidazole 5mg/ml Solution for Infusion (PL 00289/1466). This is a prescription-only medicine (POM).

Metronidazole is an antibiotic. It works by killing the bacteria that cause infections in your body. It can be used to:

- treat infections of the blood, brain, lung, bones, genital tract, pelvic area and stomach
- prevent infections after surgery

Based on the data submitted by Teva UK Limited, Metronidazole 5mg/ml Solution for Infusion was considered to be a generic version of the reference product, Flagyl 500mg/100ml Solution for Infusion (PL 17780/0515, Winthrop Pharmaceuticals UK Limited).

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Metronidazole 5mg/ml Solution for Infusion outweigh the risk; hence a Marketing Authorisation has been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure Page 4

Module 2: Summary of Product Characteristics Page 5

Module 3: Product Information Leaflet Page 14

Module 4: Labelling Page 20

Module 5: Scientific discussion during initial procedure Page 24

   I Introduction Page 24
   II About the product Page 26
   III Scientific Overview and discussion Page 27
      III.1 Quality aspects Page 27
      III.2 Non-clinical aspects Page 30
      III.3 Clinical aspects Page 30
   IV Overall conclusions and benefit-risk assessment Page 33

Module 6: Steps taken after initial procedure Page 34
## Module 1

### Information about Initial Procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Metronidazole 5mg/ml Solution for Infusion</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<tr>
<td>Active Substances</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Form</td>
<td>Solution for Infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>5 mg/ml</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG UNITED KINGDOM</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member State (CMS)</td>
<td>Belgium, Denmark, Germany, Greece, Hungary, Ireland, Luxembourg, Slovakia</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/4504/001/DC</td>
</tr>
<tr>
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</table>
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Metronidazole 5mg/ml Solution for Infusion (PL 00289/1466) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Metronidazole 5mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5mg of Metronidazole
Each 100ml of solution contains 500mg of Metronidazole
This product contains 318mg Sodium per 100ml bag.
For a full list of excipients see 6.1

3 PHARMACEUTICAL FORM

Solution for Infusion
A clear, slightly greenish yellow solution for intravenous infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole is indicated for the treatment of the following infections caused by metronidazole susceptible anaerobic micro-organisms in adults and children (see sections 4.4 and 5.1)

- The prophylaxis of postoperative infections where anaerobic bacteria are expected to be causative pathogens.
- The treatment of peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, and post-operative wound infections

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Prophylaxis of postoperative infections caused by anaerobic bacteria
Primarily in the context of abdominal (especially colorectal) and gynaecological surgery.
Antibiotic prophylaxis duration should be short and limited to the peri-operative period.

Adults:
500mg 1-2 hours before surgery, repeated after 8 and 16 hours. Oral medication should be substituted as soon as feasible.

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

Newborn Infants with a gestational age less than 40 weeks:
A single dose of 10 mg/kg of body weight preoperatively.

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

Treatment of infections due to anaerobic bacteria.
Intravenous route is to be used initially if patients symptoms preclude oral therapy.

Adults:
500mg every 8 hours.
Children >8 weeks to 12 years of age:
A single dose of 20 to 30mg/kg/day or alternatively divided into 3 doses of 7.5 mg/kg given every 8 hours. The daily dose may be increased to 40mg/kg, depending on the severity of the infection.

New-borns and Infants less than 8 weeks of age:
A single dose of 15 mg/kg of body weight daily or divided into 2 doses of 7.5 mg/kg every 12 hours.

Pre-Term Newborn Infants with a gestational age less than 40 weeks:
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.

Patients with renal failure (see section 4.4)
Limited data are available in this population. These data do not indicate the need for dose reduction. (see section 5.2.)
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 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.

Patients with severe hepatic insufficiency
A reduction of the daily dose in patients with severe hepatic impairment will be necessary. In patients with hepatic encephalopathy the daily dosage should be reduced to one third and may be administered once daily (see section 4.4)

Duration of Treatment (see section 4.3 and 5.3)
Usual treatment duration is 7 days (see sections 4.4 and 5.3).

Method of administration (see section 6.6)
Metronidazole 500mg/100ml Intravenous 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.
Metronidazole 500mg/100ml Intravenous Infusion is for single use only (see section 6.6)

4.3 Contraindications
Hypersensitivity to Metronidazole or other imidazole derivatives or any of the excipients (see 6.1 List of excipients).

4.4 Special warnings and precautions for use
Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Liver disease:
In patients with severe liver damage, metronidazole should only be used if its expected benefits clearly outweigh potential hazards.
Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant accumulation 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.

Central Nervous System disease:
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.
Convulsive seizures, myoclonus and peripheral neuropathy, the latter mainly characterized by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurological signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

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

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:
The duration of therapy with i.v Metronidazole or other imidazole derivatives is usually 7 days and should generally not exceed 10 days. This period may be exceeded in individual cases only after a very careful benefit-risk assessment. Metronidazole and a metabolite have been shown to be mutagenic in some tests with non mammalian cells an increase of certain tumors was noted in animal experiments. Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. Regular clinical and laboratory monitoring (including full blood count) 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. Patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures). These effects are normally reversible. High dosage regimes have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess.

General:
Patients should be warned that Metronidazole may darken urine. Aspartate amino transferase assays may give spuriously low values in patients being treated with metronidazole depending on the method used. This medicinal product contains 318mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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 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 have been reported when metronidazole has been used with the warfarin type of anticoagulants. Prothrombin time should be monitored more frequently and the dose of oral anticoagulants adjusted.

5 Fluoro-uracile:
Increase in the toxicity of 5 fluoro-uracile due to a decrease of its clearance.
Busulfan:
Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity. Fatal cases have been reported. Therefore, this combination should be avoided.

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.

Phenytoin  
Concomitant administration of phenytoin and Metronidazole may affect the metabolism of Metronidazole.

Cimetidine  
Cimetidine may reduce the elimination of metronidazole and subsequently lead to increased metronidazole concentrations in serum.

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.

Carbamazepine  
Metronidazole may inhibit the metabolism of carbamazepine and raise the plasma concentrations as a consequence.

Tacrolimus  
Concomitant administration with metronidazole leads to increased blood concentrations of tacrolimus. The inhibition of hepatic metabolism of tacrolimus via CYP-450 3A4 is suspected. Frequent monitoring of tacrolimus blood levels and renal function is required particularly at the initiation or the end of the therapy with metronidazole in patients who are stabilized on their tacrolimus regimen.

Amiodarone  
Prolongation of the QT-interval and Torsade de pointes has been reported during concomitant treatment with metronidazole and amiodarone. It is recommended to monitor the QT-interval on the ECG in patients receiving this combination therapy. Patients treated on an outpatient basis should be advised to contact immediately the doctor if symptoms of Torsade de pointes occur such as dizziness, palpitations, and syncope.

Mycophenolat mofetil  
Substances that alter the gastrointestinal flora (e.g., antibiotics) may reduce the oral bioavailability of mycophenolic acid products. Close clinical and laboratory monitoring for evidence of diminished immunosuppressive effect of mycophenolic acid is recommended during concomitant therapy with anti-infective agents.

Contraceptive drugs  
Some antibiotics can, in exceptional cases, decrease the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the intestine and hereby reduce the re-absorption of unconjugated steroid. Therefore the plasma levels of the active steroid decrease. This unusual interaction can occur in women with a high excretion of steroid conjugates through the bile. About 60 pregnancies have reported in English women using contraceptive pills that concomitantly have taken antibiotics, e.g. ampicillin, amoxicillin and tetracyclines. There are negative studies for trimetoprim-sulpha, roxitromycin and clarithromycin but the amount of data is very small.

Laboratory tests:  
Metronidazole may immobilize Treponema and thus may lead to falsely positive Nelson’s test. Aspartate amino transferase assays may give spuriously low values in patients being treated with metronidazole depending on the method used.

4.6 Fertility, Pregnancy and lactation

Fertility  
Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus following treatment with metronidazole. However higher doses of metronidazole (about 30 times higher than the maximum oral human dose) caused infertility and marked testicular toxicity in mice and rats.
Pregnancy
Clinical data on a large number of exposed pregnancies and animal data did not show a teratogenic or fetotoxic 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.

Lactation
Metronidazole is excreted in breast milk. Breastfeeding should be stopped if treatment with Metronidazole is necessary. After the end of the therapy with metronidazole, breastfeeding should not be resumed before another 2–3 days because of the prolonged elimination period of metronidazole.

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 are advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects
Adverse effects occur mainly at high doses or during prolonged treatment. The most commonly observed adverse effects include nausea, perverted taste and the risk of development of neuropathies during prolonged use.

In assessing side effects, the following convention has been used for classifying frequency:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1/10</td>
<td>≥1/100 to &lt;1/10</td>
<td>≥1/1,000 to &lt;1/100</td>
<td>≥1/10,000 to &lt;1/100</td>
<td>&lt;1/10,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders:</td>
<td></td>
<td>agranulocytosis, neutropenia, thrombocytopenia, pancytopenia</td>
<td>leucopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders:</td>
<td>anaphylaxis</td>
<td>angiodema, urticaria, fever.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td>anorexia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders:</td>
<td>psychotic disorders, including confusion and hallucinations.</td>
<td>depressed mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders:</td>
<td>encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysarthria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug. Drowsiness, dizziness, convulsions, headaches 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. Aseptic Meningitis</td>
<td></td>
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</tr>
</tbody>
</table>
Eye disorders: vision disorders such as diplopia and myopia, which, in most cases, is transient. optic neuropathy / neuritis

Gastrointestinal disorders: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastrointestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders: abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is reversible on drug withdrawal.

Skin and subcutaneous tissue disorders: skin rashes, pustular eruptions, pruritis, flushing erythema multiforme.

Musculoskeletal, connective tissue and bone disorders: myalgia, arthralgia.

Renal and urinary disorders: darkening of urine (due to metronidazole metabolite).

4.9 Overdose

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. The clinical symptoms were usually limited to nausea, vomiting, ataxia and slight disorientation.

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

Pharmacotherapeutic group: Anti bacteria for systemic use: imidazole derivatives
ATC Code: J01XD01

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.

PK/PD relationship
Metronidazole acts in a concentration dependent manner.

Mechanism of action
Metronidazole is taken up into bacterial and human cells. Under anaerobic conditions, metronidazole is converted to reduction products that interact with DNA to cause destruction of helical DNA leading to a protein synthesis inhibition and cell death in susceptible organisms.

Breakpoints
European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below. EUCAST clinical MIC breakpoints for metronidazole (2011-01-05, v 3.1)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptible (S) (mg/l)</th>
<th>Resistant (R) (mg/l)</th>
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<tbody>
<tr>
<td>Gram positive anaerobes, except Cl. difficile</td>
<td>≤4</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>
The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

5.2 Pharmacokinetic properties

Distribution: After administration of a single 500 mg dose, mean Metronidazole peak plasma concentrations of ca. 14 – 18 \( \mu \)g/ml are reached at the end of a 20 minute infusion. 2-hydroxy-metabolite peak plasma concentrations of ca. 3 \( \mu \)g/ml are obtained after a 1 g single i.v. dose. Steady state Metronidazole plasma concentrations of about 17 and 13 \( \mu \)g/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 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.

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 evidence of carcinogenicity in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride  
Citric acid monohydrate  
Sodium dihydrogen phosphate dihydrate  
Sodium hydroxide  
Water for injections
6.2 **Incompatibilities**
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 **Shelf life**
2 Years

6.4 **Special precautions for storage**
Keep container in the outer carton in order to protect from light. Store below 25 °C. Do not freeze.

6.5 **Nature and contents of container**
Polycine infusion bags fitted with a polypropylene SFC (Single Function Connection) port. The port is sealed with a synthetic isoprene rubber stopper and a polypropylene snap-cap. The infusion bags are contained in a clear plastic or aluminium overpouch.

*Pack sizes*
100 ml bags (500 mg metronidazole) in packs of 5, 10 or 30 bags

6.6 **Special precautions for disposal**
Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following the insertion of infusion set.

Do not remove unit from overpouch until ready for use.

The inner bag maintains the sterility of the product.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

In patients maintained on intravenous fluids, Metronidazole 500mg/100ml Intravenous Infusion may be diluted with appropriate volumes of 0.9% sodium chloride solution, dextrose 5% - 0.9% sodium chloride solution, dextrose 5% w/v or potassium chloride infusions (20 and 40 mmol/litre).

Using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In the case of adverse reaction, infusion must be stopped immediately.

The product should be used immediately after opening.
Discard after single use.
Discard any unused portion.
Do not reconnect partially used bags.

7 **MARKETING AUTHORISATION HOLDER**
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex, BN22 9AG
UNITED KINGDOM

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00289/1466
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/05/2012

10 DATE OF REVISION OF THE TEXT
15/05/2012
Module 3

Patient Information Leaflet – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Metronidazole 5 mg/ml Solution for Infusion

Read all of this leaflet carefully before you start using 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 IS AND WHAT IT IS USED FOR
2. BEFORE YOU ARE GIVEN METRONIDAZOLE
3. HOW YOU WILL BE GIVEN METRONIDAZOLE
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE METRONIDAZOLE
6. FURTHER INFORMATION

1. WHAT METRONIDAZOLE IS AND WHAT IT IS USED FOR

Metronidazole 5 mg/ml Solution for Infusion (called Metronidazole in this leaflet) contains an ingredient called metronidazole. This belongs to a group of medicines called antibiotics.

It works by killing the bacteria that cause infections in your body.

It can be used to:
- Treat infections of the blood, brain, lung, bones, genital tract, pelvic area and stomach
- Prevent infections after surgery

If you need any further information on your illness, speak to your doctor.

2. BEFORE YOU ARE GIVEN METRONIDAZOLE

You must NOT be given Metronidazole if you are:
- allergic (hypersensitive) to metronidazole or any of the other ingredients of Metronidazole (see section 6).
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
Do not have Metronidazole if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before receiving your medicine.

Take special care with Metronidazole and check with your doctor before being given your medicine if:
- you have or have ever had a liver problem
- you are having kidney dialysis (see section 3: ‘People having dialysis’).

If you are not sure if any of the above apply to you, talk to your doctor before receiving your medicine. Do this even if they have applied in the past.
Before you are given Metronidazole
Tell your doctor or pharmacist if you are:
- suffering from disease of the nervous system
- pregnant or breast-feeding, or think you might be pregnant
- undergoing kidney dialysis
- taking any other medicines. Some medicines may change the way metronidazole works, e.g. warfarin, lithium, phenobarbital, colestyramine, phenytoin cimetidine and cyclosporine. Always tell your doctor about any other medicine you are taking whether on prescription or bought by yourself.

If you have to go to a doctor, dentist or hospital for any reason, tell them that you are receiving metronidazole.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Metronidazole can affect the way some other medicines work. Also, some other medicines can affect the way Metronidazole works.

In particular tell your doctor if you are taking any of the following medicines:
- Medicines used to thin the blood such as warfarin
- Lithium for mental illness
- Phenobarbital for epilepsy
- 5 fluorouracil for cancer
- Busulfan for leukaemia (cancer of the blood cells)
- Cimetidine for heartburn or stomach ulcers
- Ciclosporin used to prevent the rejection of organs after transplant.
- Carbamazepine for epilepsy and bipolar
- Tacrolimus, an immunosuppressant
- Amiodarone for irregular heart beat
- Mycophenolate mofetil, an immunosuppressant used following transplant surgery
- Contraceptive drugs

If you are not sure, talk to your doctor before receiving your medicine.

Using Metronidazole with food and drink
Do NOT drink any alcohol while receiving Metronidazole, and for 48 hours after finishing your course. Drinking alcohol whilst you are being treated might cause unpleasant side effects, such as feeling sick (nauses), being sick (vomiting), stomach pain, hot flushes, very fast or uneven heart rate (tachycardia), and headache.

Pregnancy and breast-feeding
Tell your doctor before receiving Metronidazole if:
- you are pregnant, might become pregnant or think you may be pregnant. Metronidazole should not be given during pregnancy unless considered absolutely necessary
- you are breast-feeding. It is better not to use Metronidazole if you are breast-feeding. This is because small amounts may pass into the mother’s milk.

Driving and using machines
While taking Metronidazole you may feel sleepy, dizzy, confused, see or hear things that are not there (hallucinations), have fits (convulsions) or temporary eyesight problems (such as blurred or double vision). If this happens, do not drive or use any machinery or tools.

Tests
Your doctor may wish to carry out some tests if you have been having this medicine for more than 10 days.
Important information about some of the ingredients of Metronidazole

- Sodium: This medicinal product contains 318 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW YOU WILL BE GIVEN METRONIDAZOLE

How your medicine will be given
Your medicine will be administered to you by a doctor or nurse. The length of your course of treatment will depend on your needs and the illness being treated.

- Metronidazole is administered into a vein using a drip at a rate of 5ml/minute
- The dose of Metronidazole will depend on your needs and the illness being treated
- The length of your treatment will depend on the type of infection you have and how bad it is
- As soon as possible after starting your treatment with Metronidazole, your doctor will suggest changing to a medicine taken by mouth.

The usual dose for adults and children is given below:

To treat bacterial infection
Adults
- You will be given a dose of 500 mg (100 ml) Metronidazole every 8 hours

Children > 2 months old
- Your doctor will work out how much your child should be given depending on their weight, usually 20-30 mg/kg
- The dose will be repeated every 8 hours

To prevent infections from happening after surgery
Adults
- You will be given 500 mg (100 ml) Metronidazole shortly before your operation
- The dose may be repeated twice at 8 hourly intervals

Children
- Your doctor will work out how much your child should be given depending on their weight, usually 20-30 mg/kg
- Your child will receive the first dose shortly before their operation
- The dose may be repeated twice at 8 hourly intervals

People having dialysis
Kidney dialysis removes Metronidazole from your blood. If you are having kidney dialysis you must have this medicine after your dialysis.

People with liver problems
Your doctor may lower your dose or use the medicine less often.

If you are given more Metronidazole than you should
It is unlikely that your doctor or nurse will give you too much medicine. Your doctor or nurse will monitor your progress and check how much medicine you are given. If you think you have been given too much medicine, tell your doctor or nurse, who will know what to do. Always ask if you are not sure why you are being given a medicine.

If you are not given Metronidazole at the right time
Your doctor or nurse will have instructions about when to give you your medicine. It is unlikely that you will not be given the medicine as it has been prescribed. If you think that you may have missed a dose, then talk to your doctor or nurse.
If you stop having Metronidazole
Keep having Metronidazole until your doctor tells you to stop. Do not stop having Metronidazole just because you feel better. It is important for you to keep having Metronidazole infusions until your doctor decides to stop them. If you stop, your infection may get worse again.

If you have any further questions on the use of this product, ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

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

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

Tell your doctor straight away if:
- you have an allergic reaction. The signs may include: swelling of the hands, feet, ankles, a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. You could also notice an itchy, lumpy rash (hives) or nettle rash (urticaria)
- you get a high fever, headache, see or hear things that are not there, feel clumsy or have difficulty in controlling your movements, are confused, more sensitive to light than usual, notice a stiff neck, unusual behaviour or eye movements or have problems with speaking. This could be a serious but very rare condition called encephalopathy.

Talk to your doctor straight away if you notice any of the following side effects:

Very Rare (affects less than 1 in 1,000 people)
- Yellowing of the skin and eyes. This could be due to a liver problem (jaundice)
- Unexpected infections, mouth ulcers, bruising, bleeding gums, or severe tiredness. This could be caused by a blood problem
- Severe stomach pain which may reach through to your back (pancreatitis).

Tell your doctor if any of the following side effects gets serious or lasts longer than a few days:

Very Rare (affects less than 1 in 10,000 people)
- Low white blood cell count
- You may feel weak, bruise more easily and get more infections than usual. This could be because of a blood problem called 'pancytopenia'
- Headache
- Confusion, hallucinations
- Feeling of weakness.
- Feeling sleepy or dizzy
- Fits (convulsions)
- Clumsiness or poor coordination
- Difficulties speaking
- Problems with your eyesight such as blurred or double vision
- Darkening of the urine
- Itching, inflammation or swelling of the skin, or skin rashes, all of which may sometimes be severe
- Pain in the muscles or joints
- Abnormal liver function tests, hepatitis (inflammation of the liver)
Not Known:

- Fever
- Angioedema (swelling of face and/or neck which may affect breathing and swallowing)
- Feeling sick (nausea), being sick (vomiting), upset stomach or diarrhoea
- Depressed mood
- Numbness, tingling, pain, or a feeling of weakness in the arms or legs
- Unpleasant taste in the mouth
- Mouth sores; inflammation of the mouth and tongue, dry mouth
- Skin rash (erythema multiforme)
- You may get more infections than usual. This could be because of a blood problem called ‘leucopenia’
- Mental problems such as feeling confused and seeing or hearing things that are not there (hallucinations)
- Meningitis (inflammation of the tissues surrounding the brain)
- Inflammation of the optic nerve which may affect your eyesight
- Loss of appetite

Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE METRONIDAZOLE

Keep this medicine out of the sight and reach of children.

This medicine will be kept by your doctor or pharmacist in a safe place where children cannot see or reach it.

Store in original packaging to protect from light. Do not store above 25°C. Do not freeze.

Do not use Metronidazole after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Do not use Metronidazole if you notice particulates in solution, or leakage from the bag.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Metronidazole contains:

- Each ml of solution for infusion contains 5 mg metronidazole as the active substance
- Each 100 ml of solution for infusion contains 500 mg metronidazole as the active substance
- The other ingredients are: sodium chloride, sodium dihydrogen phosphate dihydrate, citric acid monohydrate, sodium hydroxide and water for injections.

What Metronidazole looks like and contents of the pack
Metronidazole is a clear, slightly greenish-yellow solution for infusion.
Metronidazole is available in infusion bags containing 100 ml of solution.

Marketing Authorisation Holder
Teva UK Limited, Eastbourne, BN22 9AG, UK
Manufacturer
TEVA Pharmaceutical Works Private Limited Company, H-2100 Gödöllő, Táncsics Mihály út 82, Hungary

This leaflet was last revised in April 2012.

PL 00289/1466
Module 4

Labelling – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING</th>
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<tr>
<td>Infusion Bag</td>
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<tr>
<td>Al Overpouch</td>
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</table>

1. NAME OF THE MEDICINAL PRODUCT

Metronidazole 5 mg/ml Solution for Infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution contains 5 mg Metronidazole  
Each 100 ml of solution contains 500 mg Metronidazole  
500mg/100ml

3. LIST OF EXCIPIENTS

Sodium Chloride, Citric Acid Monohydrate, Sodium Dihydrogen Phosphate Dihydrate, Sodium Hydrosulphide, Water for Injections.

Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for Infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.  
For single use only. Discard any remaining solution.  
Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
9. SPECIAL STORAGE CONDITIONS

Keep container in the outer carton to protect from light. Store below 25°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1466

13. BATCH NUMBER

Batch no:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

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

   Metronidazole 5 mg/ml Solution for Infusion

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each ml of solution contains 5 mg Metronidazole
   Each 100 ml of solution contains 500 mg Metronidazole
   500mg/100ml

3. **LIST OF EXCIPIENTS**

   Sodium Chloride, Citric Acid Monohydrate, Sodium Dihydrogen Phosphate Dihydrate, Sodium Hydroxide, Water for Injections.

   Please see the enclosed leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for Infusion
   5 x 100 ml infusion bags
   10 x 100 ml infusion bags
   30 x 100 ml infusion bags

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For intravenous use.
   For single use only. Discard any remaining solution.
   Please read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP (MM/YYYY)
9. **SPECIAL STORAGE CONDITIONS**

Keep container in the outer carton to protect from light. Store below 25°C. Do not freeze.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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PL 00289/1466

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Batch no:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor

16. **INFORMATION IN BRAILLE**

Metronidazole 5 mg/ml Solution for Infusion
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Teva UK Limited a Marketing Authorisation for the medicinal product, Metronidazole 5mg/ml Solution for Infusion (PL 00289/1466, UK/H/4504/001/DC) on 15 May 2012. The product is a prescription-only medicine.

This is a generic application for Metronidazole 5mg/ml Solution for Infusion, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK product, Flagyl 500mg/100ml Solution for Infusion, originally licensed to May & Baker Limited (PL 00012/0107) on 26 June 1991. The licence for the reference product underwent a Change of Ownership (CoA) procedure and was authorised to the current Marketing Authorisation Holder, Winthrop Pharmaceuticals UK Limited (PL 17780/0515) on 03 March 2010. The reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in this Decentralised Procedure, Teva UK Limited applied for a Marketing Authorisation for Metronidazole 5mg/ml Solution for Infusion in Belgium, Denmark, Germany, Greece, Hungary, Ireland, Luxembourg and Slovakia.

Metronidazole is indicated for the treatment of the following infections caused by metronidazole susceptible anaerobic micro-organisms in adults and children (see SmPC sections 4.4 and 5.1):

- prophylaxis of postoperative infections where anaerobic bacteria are expected to be causative pathogens
- treatment of peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, and post-operative wound infections

The product is also indicated for the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Consideration should be given to official guidance on the appropriate use of antibacterial agents. The solution should be administered with sterile equipment using an aseptic technique.

Metronidazole has antibacterial and antiprotozoal actions and is effective against anaerobic bacteria and against Trichomonas vaginalis and other protozoa including Entamoeba histolytica and Giardia lamblia. Metronidazole acts in a concentration dependent manner. It is taken up into bacterial and human cells. Under anaerobic conditions, metronidazole is converted to reduction products that interact with DNA to cause destruction of helical DNA leading to a protein synthesis inhibition and cell death in susceptible organisms.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application cross-refers to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Metronidazole 5mg/ml Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anti bacteria for systemic use: imidazole derivatives (J01XD01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Solution for Infusion 5mg/ml</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4504/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>BE, DE, DK, ES, HU, IE, LU, SK</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00289/1466</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG UNITED KINGDOM</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Metronidazole

Nomenclature:

INN: Metronidazole

Chemical names: 2-(2-methyl-5-nitroimidazol-1-yl)ethanol

2-(5-nitro-2-methylimidazol-1-yl)ethanol

Structure:

![Chemical structure of metronidazole]

Molecular formula: C₆H₉N₃O₃

Molecular weight: 171.2 g/mol

CAS No: 443-48-1

Physical form: White to pale yellow crystalline powder

Solubility: Sparingly soluble in water, in alcohol and in chloroform; slightly soluble in ether

The active substance, metronidazole, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

All aspects of the manufacture and control of metronidazole are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of metronidazole for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description and Composition

Metronidazole 5mg/ml Solution for Infusion is presented as a clear, slightly greenish yellow solution for intravenous infusion. Each ml of solution contains 5 mg of the active ingredient, metronidazole. The solution should be administered with sterile equipment using an aseptic technique.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, citric acid monohydrate, sodium dihydrogen phosphate dihydrate, sodium hydroxide and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective Ph. Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed products. None of the excipients are sourced from genetically modified organisms.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, generic formulation pharmaceutically equivalent to the reference product, Flagyl 500mg/100ml Solution for infusion (Winthrop Pharmaceuticals UK Limited), with the same dosage form, strength and route of administration.

A comparison of the physiochemical properties of the test and reference products has been provided. Comparative impurity data were provided for batches of test and reference products and were satisfactory.

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 studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished product specification

Finished product specifications are provided for release and shelf life and are 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. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Metronidazole 5mg/ml Solution for Infusion is supplied in 100 ml (500 mg metronidazole) polycine infusion bags fitted with polypropylene SFC (Single Function Connection) ports.
The ports are sealed with synthetic isoprene rubber stoppers and polypropylene snap-caps. The infusion bags are contained in clear plastic or aluminium overpouches in pack sizes of 5, 10 or 30 bags.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 2 years, with storage instructions ‘Keep container in the outer carton in order to protect from light. Store below 25 °C. Do not freeze’. The product should only be used if the solution is clear, without visible particles and if the container is undamaged. The product should be used immediately after opening, following insertion of the infusion set. For full details concerning use, dilution and disposal of the medicinal product, refer to section 6.6 of the SmPC.

**Quality Overall Summary**

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The PIL text is in line with the SmPC and is satisfactory. User-testing of the PIL text has been evaluated and accepted.

**Conclusion**

The quality grounds for this application are considered adequate. There are no objections to approval of Metronidazole 5mg/ml Solution for Infusion from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that this is an application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of metronidazole, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK product, Flagyl 500mg/100ml Solution for Infusion (Winthrop Pharmaceuticals UK Limited).

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the product.

There are no objections to approval of Metronidazole 5mg/ml Solution for Infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INTRODUCTION

Metronidazole is a 5-nitroimidazole that has selective activity against anaerobic microorganisms, including bacteria and protozoa. Intravenous metronidazole has been approved for the treatment of serious anaerobic bacterial infections.

Metronidazole has a limited spectrum of activity that includes various protozoans and most Gram-negative and Gram-positive anaerobic bacteria. Metronidazole appears to selectively produce cytotoxic effects in anaerobes by a reduction reaction, depriving the organism of required reduction equivalents. The complete mode of action of metronidazole has not been fully elucidated. The cytotoxic property of metronidazole is specific for anaerobic organisms and is thought to be due to intermediate or final products of reduction of the nitro-group of metronidazole. Preferential reduction of the 5-nitro group may occur by a ferrodoxin-like system and an anaerobic environment is required for reduction to proceed. Although the drug readily diffuses into both aerobic and anaerobic organisms it remains unchanged in aerobic bacteria. The nitro reduction which takes place in anaerobic bacteria creates a diffusion gradient resulting in a greater uptake of metronidazole by these organisms. The specific degradation product of metronidazole responsible for the therapeutic effect is not known. The most probable product is the hydroxylamine derivative, although other investigators postulate that the amino derivative with the imidazole ring cleaved is more likely the cause.

The reduction reaction is a pyruvate phosphoroclastic reaction important to the electron transport proteins, ferredoxins, commonly found in anaerobes. The redox potential of the metronidazole reduction is only slightly above that of the electron transport redox potential, thus extensive reduction of metronidazole occurs. This is not possible in aerobic systems, in which the redox potential is well above that necessary to promote this reaction. Anaerobic organisms are thus deprived of required reduction equivalents, resulting in loss of the helical structure of DNA, strand breakage, and associate impairment of the ability of DNA to function as a template. Metronidazole and the nitroimidazoles are thought to produce their bactericidal activity through 4 phases:

(i) entry into the bacterial cell
(ii) nitro group reduction
(iii) action of the cytotoxic byproducts
(iv) production of inactive end products.

Bactericidal activity appears to be dependent on the formation of a redox intermediate metabolite in the bacterium. This toxic metabolite may interact primarily with DNA, RNA or intracellular proteins; however, its main effect is DNA strand breakage, inhibited repair and ultimately disrupted transcription and cell death. Additional mechanisms may be present in polymicrobial infections. The addition of facultative anaerobes such as Escherichia coli to cultures of Bacteroides fragilis results in faster bactericidal activity of metronidazole. The mechanism may be the formation by E. coli of a bactericidal intermediate metabolite.

INDICATIONS

Metronidazole is indicated for the treatment of the following infections caused by metronidazole susceptible anaerobic micro-organisms in adults and children (see SmPC sections 4.4 and 5.1):

- prophylaxis of postoperative infections where anaerobic bacteria are expected to be causative pathogens
- treatment of peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, and post-operative wound infections

The product is also indicated for the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Consideration should be given to official guidance on the appropriate use of antibacterial agents. The solution should be administered with sterile equipment using an aseptic technique.

The indications are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is satisfactory.

CLINICAL PHARMACOLOGY

The clinical pharmacology of metronidazole is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

Clinical efficacy

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of metronidazole is well-established from its extensive use in clinical practice.

Metronidazole 5mg/ml Solution for Infusion is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the reference product, Flagyl 500mg/100ml Solution for Infusion (Winthrop Pharmaceuticals UK Limited). Thus, in accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1), Appendix II Parenteral solutions, the applicant is not required to submit a bioequivalence study.
Clinical safety

No new safety data have been submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of metronidazole is well-known.

CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is acceptable.

Product Information Leaflet (PIL)

The final PIL text is in line with the approved SmPC and is satisfactory.

Labelling

The labelling text is satisfactory.

CONCLUSIONS

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Metronidazole 5mg/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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview.

The applicant’s Metronidazole 5mg/ml Solution for Infusion has been demonstrated to be a generic version of the UK reference product, Flagyl 500mg/100ml Solution for Infusion (Winthrop Pharmaceuticals UK Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

The PIL text is in line with the SmPC and is satisfactory. The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling text complies with statutory requirements.

The MAH has submitted text versions only for the PIL and labelling and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Metronidazole 5mg/ml Solution for Infusion is a generic version of the UK reference product, Flagyl 500mg/100ml Solution for Infusion (Winthrop Pharmaceuticals UK Limited). Extensive clinical experience with metronidazole is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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