Public Assessment Report

National Procedure

Metronidazole 200 mg/ 5 ml Oral Suspension

(Metronidazole)

UK licence no: PL 30684/0236

DAWA Limited
LAY SUMMARY
Metronidazole 200 mg/ 5 ml Oral Suspension  
(Metronidazole)

This is a summary of the public assessment report (PAR) for Metronidazole 200 mg/ 5 ml Oral Suspension (PL 30684/0236). It explains how Metronidazole 200 mg/ 5 ml Oral Suspension was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Metronidazole oral suspension in this lay summary for ease of reading.

For practical information about using Metronidazole oral suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Metronidazole oral suspension and what is it used for?
Metronidazole oral suspension is a ‘generic medicine’. This means that Metronidazole oral suspension is similar to a ‘reference medicine’ already authorised in the UK called Flagyl S 200mg/5ml Oral Suspension (Winthrop Pharmaceuticals UK Limited).

Metronidazole can be used for:
Adults and children over 1 year
- preventing infections after you have an operation
- treating infections including infections of the blood, brain, lungs, bones, lining of the abdomen, pelvis and infections following childbirth or around the area where patients had an operation
- treating trichomoniasis - a sexually transmitted infection, in both males and females
- treating amoebiasis - an infection of the intestine or liver caused by a parasite
- treating giardiasis - an infection that causes swelling of the intestines.

Adults and children over 10 years only
- treating vaginosis - an infection and swelling of the vagina
- treating swollen gums and ulcers in the mouth (gingivitis) and other dental infections
- treating ulcers and pressure sores on the leg.

Children
- It can also be used in children to treat a bacterial infection in the stomach (Helicobacter pylori).

How is Metronidazole oral suspension used?
Metronidazole oral suspension is taken orally.

The usual dose for adults and children are:

<table>
<thead>
<tr>
<th>What patients are taking the medicine for</th>
<th>Number of days patients will take the medicine for</th>
<th>How much to take – adults and children over 12 years of age</th>
<th>How much to take – Children under 12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of infections after surgery</td>
<td>1</td>
<td>10 ml (400 mg) three times a day on the day before the</td>
<td>A doctor will work out the right dose based on your child’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PAR Metronidazole 200 mg/ 5 ml Oral Suspension

<table>
<thead>
<tr>
<th>Bacterial infections</th>
<th>operation</th>
<th>weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>A 20 ml (800 mg) dose followed by 10 ml (400 mg) three times a day</td>
<td></td>
</tr>
</tbody>
</table>

**Other infections**

Adults and children over 10 years of age

<table>
<thead>
<tr>
<th>What patients are taking the medicine for</th>
<th>Number of days patients will take the medicine for</th>
<th>How much to take – Adults and children over 10 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichomoniasis</td>
<td>1</td>
<td>50 ml (2000 mg) once a day</td>
</tr>
<tr>
<td></td>
<td>5 to 7</td>
<td>A doctor or pharmacist will inform patients the dosage</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>A doctor or pharmacist will inform patients the dosage</td>
</tr>
<tr>
<td>Vaginosis</td>
<td>1</td>
<td>50 ml (2000 mg) once a day</td>
</tr>
<tr>
<td></td>
<td>5 to 7</td>
<td>10 ml (400 mg) twice a day</td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>5 to 10</td>
<td>10 ml (400 mg) to 20 ml (800 mg) three times a day</td>
</tr>
<tr>
<td>Giardiasis</td>
<td>3</td>
<td>50 ml (2000 mg) once a day</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10 ml (400 mg) to 20 ml (800 mg) three times a day</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>3</td>
<td>5 ml (200 mg) three times a day</td>
</tr>
<tr>
<td>Dental infections</td>
<td>3 to 7</td>
<td>5 ml (200 mg) three times a day</td>
</tr>
<tr>
<td>Leg ulcers and pressure sores</td>
<td>7</td>
<td>10 ml (400 mg0 three times a day</td>
</tr>
</tbody>
</table>

Children under 10 years of age

<table>
<thead>
<tr>
<th>What patients are taking the medicine for</th>
<th>Number of days patients will take the medicine for</th>
<th>How much to take – Children aged 7-10 years</th>
<th>How much to take – Children aged 307 years</th>
<th>How much to take – Children aged 1-3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichomoniasis</td>
<td>7</td>
<td>A doctor will work out the right dose based on the child’s weight. This should not exceed 2000 mg a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 to 10</td>
<td>5 ml (200 mg to 10 ml (400 mg) three times a day</td>
<td>2.5 ml (100 mg) to 5 ml (200 mg) four times a day</td>
<td>2.5 ml (100 mg) to 5 ml (200 mg) three times a day</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>25 ml (1000 mg) once a day</td>
<td>15 ml (600 mg) to 20 ml (800 mg) once a day</td>
<td>12.5 ml (500 mg) once a day</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2.5 ml (100 mg) three times a day</td>
<td>2.5 ml (100 mg) twice a day</td>
<td>1.25 ml (50 mg) three times a day</td>
</tr>
</tbody>
</table>
Metronidazole oral suspension can only be obtained on prescription from a doctor.

For further information on how Metronidazole oral suspension is used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How does Metronidazole oral suspension work?
Metronidazole oral suspension contains an active ingredient called metronidazole benzoate. This belongs to a group of antibiotics called antibacterials. This helps to treat bacterial infections.

How has Metronidazole oral suspension been studied?
As this product is an oral suspension; the applicant has not performed any clinical trials. No additional studies were needed as Metronidazole oral suspension is a generic medicine that is given orally and contains the same active substance and content as the reference medicine, Flagyl 200mg Tablets (Winthrop Pharmaceuticals UK Limited).

What are the benefits and risks of Metronidazole oral suspension?
As Metronidazole oral suspension is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Flagyl 200mg Tablets (Winthrop Pharmaceuticals UK Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Why is Metronidazole oral suspension approved?
It was concluded that, in accordance with EU requirements, Metronidazole oral suspension has been shown to have comparable quality and to be comparable to Flagyl 200mg Tablets. Therefore, the view was that, as for Flagyl 200mg Tablets, the benefit outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Metronidazole oral suspension?
A Risk Management Plan (RMP) has been developed to ensure that Metronidazole oral suspension is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Metronidazole oral suspension, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Metronidazole oral suspension
A Marketing Authorisation was granted in the UK on 28 March 2017.

The full PAR for Metronidazole oral suspension follows this summary. For more information about treatment with Metronidazole oral suspension, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2017.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted DAWA Limited, a Marketing Authorisation for the medicinal product Metronidazole 200 mg/ 5 ml Oral Suspension (PL 30684/0236) on 28 March 2017. The product is a prescription-only medicine (POM) indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected as the pathogen.

Metronidazole oral suspension is active against a wide range of pathogenic micro-organisms, notably *Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia, Balantidium coli* and other species of bacteroides, fusobacteria, eubacteria, clostridia and anaerobic cocci.

It is indicated in Adults, Children and Newborns with a gestation age of over 40 weeks for:
- The treatment of septicaemia, bacteraemia, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, peritonitis and post-operative wound infections from which one or more pathogenic anaerobes have been isolated.
- The prevention of post-operative infections caused by anaerobic bacteria particularly species of bacteroides and anaerobic streptococci.

Adults and Children over 10 years only for:
- Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginitis or *Gardnerella* vaginitis).
- Acute dental infections (e.g. acute pericoronitis and acute apical infections).
- Anaerobically infected leg ulcers and pressure sores.

Adults and Children for:
- The treatment of urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.
- All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers)
- Giardiasis
- Acute ulcerative gingivitis.

Children for
- Eradication of Helicobacter pylori

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Flagyl S 200mg/5ml Oral Suspension, which was originally authorised to May & Baker Limited (PL 00012/5256R) on 22 October 1985. This licence underwent a change of ownership procedures to Hawgreen Limited (PL 17077/0001) on 01 September 1998 and to the current Marketing Authorisation Holder (MAH), Winthrop Pharmaceuticals UK Limited (PL 17780/0275), on 03 January 2007.
The selective action of this compound against anaerobes and anoxic and hypoxic cells is due to the mode of action. The nitro group of metronidazole acts as electron acceptor and is thus reduced to a chemically reactive drug form. This produces biochemical lesions in the cells, thus causing death. The major site of action is believed to be DeoxyriboNucleic Acid (DNA), where it causes loss of the helical structure and inhibits synthesis.

A bioequivalence study has been submitted with this application, comparing the test formulation, Metronidazole 200 mg/ 5 ml Oral Suspension, and the reference formulation, Flagyl S 200mg/5ml Oral Suspension, under fasting conditions.

No new non-clinical studies were submitted, which is acceptable given that the application is a generic medicinal product of an originator product that has been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Metronidazole 200 mg/ 5 ml Oral Suspension outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction

The proposed formulation is an oral suspension. Each 5 ml of oral suspension contains metronidazole benzoate equivalent to 200 mg of metronidazole, as active ingredient. The excipients present are microcrystalline cellulose and carmellose sodium (90:10), carboxymethylcellulose sodium (E466), sucrose, sorbitol 70% (E420), sodium saccharin (E 954), polysorbate 80 (E433), propylene glycol (E1520), colloidal anhydrous silica, sodium dihydrogen phosphate dihydrate (E339) (for pH adjustment), sodium citrate dihydrate (E331) (for pH adjustment), methyl parahydroxybenzoate (E218), flavour lemon, flavour orange and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of flavour lemon and flavour orange which comply with an in-house specification.

The finished product is supplied in amber colored glass bottles (USP type III) with white child resistant caps containing 100 ml suspension.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Metronidazole
Chemical name(s): 2-(2-Methyl-5-nitro-1H-imidazol-1-yl) ethyl benzoate
Structure:

![Structure of Metronidazole]

Molecular formula: \( \text{C}_{12}\text{H}_{13}\text{N}_{3}\text{O}_{4} \)
Molecular weight: 275.3 g/mol
Appearance: A white or slightly yellowish crystalline powder or flakes.
Solubility: Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in alcohol.

Metronidazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, metronidazole, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious, oral suspension containing 200 mg metronidazole that is bioequivalent to the reference product Flagyl S 200 mg/5ml oral suspension (Winthrop Pharmaceuticals, UK).

A comparative dissolution profile has been presented for the proposed and reference products.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 36 months for unopened bottle with storage conditions ‘Do not store above 25°C’ and ‘Store the medicine in the original packaging in order to protect it from light’ are set. Once the bottle is opened the product must be used within 12 weeks.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This generic application has been submitted in accordance with Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of metronidazole are well known. As metronidazole is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology

No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics

No new data have been submitted and none are required for applications of this type.
III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
This is a generic application submitted under the Decentralised Procedure according to Article 10.1 of Directive 2001/83/EC, as amended, for Metronidazole 200 mg/5ml oral suspension.

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of metronidazole are well known. As metronidazole is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is considered appropriate.

With the exception of the bioavailability study, no new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study under fasting conditions.

This was a randomised, two-treatment, two-sequence, two-period, crossover single dose bioequivalence study comparing the pharmacokinetics of the test product Metronidazole 200 mg/5ml oral suspension with the reference product Flagyl 200 mg/5ml oral suspension (Winthrop Pharmaceuticals, UK) in 28 healthy male subjects under fasting conditions.

Blood samples were collected before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Results
Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters (C_{max} and AUC_{0-t}) of Metronidazole (N=28)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T) product</td>
<td>Reference (R) product</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>3487.4783</td>
<td>3536.0561</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>47054.9735</td>
<td>49048.6436</td>
</tr>
</tbody>
</table>
Conclusion
The 90% confidence intervals for \( C_{\text{max}} \) and AUC\( _{0-1} \) were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr*). Bioequivalence has been shown for the test formulation (Metronidazole 200 mg/5ml oral suspension) and the reference formulation (Flagyl 200 mg/5ml oral suspension) under fasting conditions.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Metronidazole 200 mg/5 ml Oral Suspension.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified risk: Hypersensitivity, anaphylaxis &amp; angioedema</td>
<td>Metronidazole may cause hypersensitive reactions such as rashes, urticaria (skin disease) and fever. Information is given in SmPC Section 4.3 Contraindication. Precaution given in PIL Section 2 as Do not take Metronidazole Oral Suspension and tell your doctor if: you are allergic (hypersensitive) to metronidazole or parabens.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Identified risk: Central &amp; peripheral neurotoxicity, including convulsions, aseptic meningitis, optic neuritis, subacute cerebellar syndrome, encephalopathy (and especially in patients with active or chronic severe peripheral &amp; central nervous system disease).</td>
<td>Patient having problem of CNS, Special warnings and precautions for use is mentioned in SmPC &amp; PIL. Metronidazole should be used with caution in patients having central nervous system disease. Some Undesirable effects are mentioned in SmPC section 4.8 such as: Very rare (Affecting fewer than 1 in 10,000 patients): - A brain disease (Encephalopathy) which symptoms may have confusion, fever, perception of objects with no reality usually arising, headache, light sensitivity, disturbances in sight and movement, stiff neck a sudden, violent, irregular movement of the body. Not known: (Very less frequency) - Long metronidazole therapy a few instances of damage nerves that carry messages to and from the brain and spinal cord from and to the rest of the body (peripheral neuropathy) have been reported. In most cases this nerve damage treatment was stopped or when dosage was reduced. Serous inflammation of the linings of the brain (Aseptic meningitis) has been reported. Possible side effects are mentioned in PIL Section 4: Tell your doctor or pharmacist if you notice any of the following side effects: - A serious but very rare side effect is a brain</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Disease (encephalopathy). Symptoms vary but you might get a fever, stiff neck, headache. • You develop symptoms such as abnormal sensitivity to light, abdominal pain, fever which revent to disease called meningitis.</td>
<td>None proposed</td>
<td></td>
</tr>
<tr>
<td>Identified risk: Hepatitis, pancreatitis &amp; hepatic failure</td>
<td>Special warnings and precautions given for use of metronidazole in patient having jaundice or liver problems. Metronidazole is mainly metabolised through liver (by hepatic oxidation). Liver disease may affect the excretion of metronidazole from body.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Undesirable effects mentioned in SmPC Section 4.8: Very rare (Affecting fewer than 1 in 10,000 patients): • Increase in liver enzymes results abnormal liver function tests due to swelling in liver (hepatitis), liver injury, yellowish discoloration of the skin (jaundice) and swelling in pancreas (pancreatitis) which shall be reversible on drug withdrawal. Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs. Some warnings and precautions mentioned in PIL Section 2 and section 4 as Talk to your doctor, pharmacist or nurse before taking Metronidazole Oral Suspension • if you have liver problems And tell your doctor or pharmacist straight away if you notice any of the following side effects: • Yellowing of the skin and eyes. This could be due to a liver problem (jaundice). Severe stomach pain which may reach through to your back (pancreatitis).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identified risks: Metronidazole accumulation &amp; toxicity in patients with advanced</td>
<td>Doses of Metronidazole should monitored in case of liver problems and lower dose shall be given. Special warnings and precautions given in SmPC &amp; PIL for use:</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
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<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>hepatic impairment, including those with hepatic encephalopathy</td>
<td>Significant accumulation may occur in patients with live disease and the resulting high level of metronidazole in blood may contribute to the drain related disease. Metronidazole oral suspension should be administered with caution to patients with brain dysfunction that occurs as a result of severe liver disease (hepatic encephalopathy). The daily dosage may be reduced to one third and may be administered once daily. Your doctor may prescribe a lower dose or to use the medicine less often.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Identified risks: Severe skin reactions (e.g. SJS, TEN, erythema multiforme)</td>
<td>There are skin related undesirable effects may occur due to Metronidazole or its excipients. information regarding skin reactions has given in SmPC as reported; Very rare (Affecting fewer than 1 in 10,000 patients): skin rashes, unpleasant sensation of the skin that provokes the urge to scratch (pruritus), raised bumps that are filled with a white, thick fluid (pustular eruptions) and markedly red in the face and often other areas of the skin (flushing). Not known (very less frequency): Redness of skin (Erythema multiforme) may occur, which may be reversed on drug withdrawal. A life-threatening skin condition (Stevens-Johnson syndrome or toxic epidermal necrolysis).</td>
<td>None proposed</td>
</tr>
<tr>
<td>Identified risk: Serious haematological effects (agranulocytosis, neutropenia, thrombocytopenia, pancytopenia)</td>
<td>Metronidazole may cause reduction in the number of red and white blood cells, as well as platelets as undesirable effects. Some reported undesirable effects mentioned in SmPC section 4.8; Very rare (Affecting fewer than 1 in 10,000 patients): Low white blood cell (agranulocytosis, neutropenia, thrombocytopenia and pancytopenia) which are reversible on drug withdrawal. A moderate Low white blood cell has been reported in some patients but the white cell</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Identified risk: Psychotic disorders including confusion, hallucinations &amp; depression</td>
<td>Special warning has been given in SmPC and possible side effects including effects on ability to drive and use machines: Patients should be warned about the potential for abnormally sleepy during day time, confusion, seeing or hearing things that are not there, irregular movement of body or visual disorders, and advised not to drive or operate machinery if these symptoms occur. Possible side effects informed in PIL Section 4: Very rare: may affect up to 1 in 10,000 people - Fits (convulsions) Mental problems such as feeling confused or seeing or hearing things that are not there (hallucinations)</td>
<td>None proposed</td>
</tr>
<tr>
<td>Identified risk: Drug interactions, including anticoagulants, lithium, disulfiram, phenytoin, 5-flourouracil, ciclosporin &amp; busulfan</td>
<td>Special precautions is given in PIL and in SmPC on using with other medicinal products. Metronidazole Oral Suspension can affect the way some other medicines work. Also, some medicines can affect the way Metronidazole Oral Suspension works. - Warfarin – used to thin your blood - Lithium - used to treat depression - Phenobarbital or phenytoin - used to treat epilepsy - 5-fluorouracil - used to treat cancer - Busulfan – used to treat leukaemia - Ciclosporine – used after organ transplants - Disulfiram - used to treat alcoholism</td>
<td>None proposed</td>
</tr>
<tr>
<td>Potential risks: Mutagenicity</td>
<td>Due to inadequate evidence on the genetic alteration (mutagenicity) risk in humans, the use of Metronidazole oral suspension for longer treatment than usually required should be carefully considered. Metronidazole has been shown to be causing cancer (carcinogenic) in the mouse and in the rat while humans have provided no evidence of an increased carcinogenic risk in humans.</td>
<td>None</td>
</tr>
<tr>
<td>Missing information: Use in pregnancy</td>
<td>Metronidazole oral suspension should not therefore be given during pregnancy or during</td>
<td>None</td>
</tr>
</tbody>
</table>

PL 30684/0236
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lactation unless the physician considers it essential, in these circumstances short, high dosage regimes are not recommended.</td>
<td></td>
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<tr>
<td></td>
<td>A significant amount of metronidazole is found in breast milk and breast feeding should be avoided after a large dose. This could give a bitter taste to the milk.</td>
<td></td>
</tr>
</tbody>
</table>

**IV.7 Discussion on the clinical aspects**

The grant of a Marketing Authorisation is recommended.

**V User consultation**

The package leaflet 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 language used for the purpose of user testing the patient information leaflet (PIL) was English.

The package leaflet 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*.

**VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION**

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with metronidazole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The currently approved labelling is listed below:
Metronidazole 200 mg/5 ml Oral Suspension

Each 5 ml of oral suspension contains metronidazole benzylate equivalent to 200 mg metronidazole. Also contains: polyvinyl alcohol, hydroxypropyl cellulose, sodium (98:10), sucrose, sorbitol 70%, E40, sodium E432, E433, E434, E435, E436, calcium phosphate dihydrate, propyl galllate, parahydroxybenzoate (E320), lemon flavour, orange flavour, and water.

Read the package leaflet before use. Use as directed by the doctor. For oral use only. Keep out of the sight and reach of children. Use within 12 weeks of opening.

PL 30684/0236
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/05/2018</td>
<td>Type 1B</td>
<td>To update sections 2, 4.1, 4.4, 4.8, 5.1, 6.1 and 6.3-6.5 of the SmPC in line with the reference product</td>
<td>Approved on 04/06/2018-see Annex 1</td>
</tr>
</tbody>
</table>
ANNEX 1

Our Reference: PL 30684/0236-0009
Product: Metronidazole 200 mg/ 5 ml Oral Suspension
Marketing Authorisation Holder: DAWA Limited
Active Ingredient(s): Metronidazole benzoate

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): Not applicable

Reason:
To update sections 2, 4.1, 4.4, 4.8, 5.1, 6.1 and 6.3-6.5 of the SmPC in line with the reference product.

Supporting Evidence
Revised SmPC fragments.

Evaluation
The proposed changes to the SmPC are in line with the reference product. The updated SmPC fragments have been incorporated into the Marketing Authorisation.

Conclusion
The proposed changes to the SmPC are acceptable.

Decision - Approved on 04 June 2018.