SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Metronidazole 200 mg/ 5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral suspension contains Metronidazole Benzoate equivalent to 200 mg of Metronidazole.

Excipient(s) with known effect:
Each 5ml of oral suspension also contains
2.50 g Sucrose,
0.09% w/v Methyl Parahydroxybenzoate and

See ‘section 4.4 special warnings and precautions for use’.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral suspension.
A white to cream-coloured suspension having sweet taste and orange- lemon flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Metronidazole oral suspension is 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 microorganisms, 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.

### 4.2 Posology and method of administration

For oral administration only.
A: **Prophylaxis**: against anaerobic infection—chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.

Dosage: 400mg at 8 hourly intervals during the 24 hours preceding the operation followed by postoperative intravenous or rectal administration until the patient is able to take Metronidazole oral suspension by mouth.

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

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

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

B: **Treatment of established anaerobic infection**:

800mg followed by 400mg at 8 hourly intervals.

Children > 8 weeks to 12 years of age: The usual daily dose is 20 –30mg/kg/day as a single dose or divided into 7.5mg/kg every 8 hours. The daily dose may be increased to 40mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children < 8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12 hours.

In newborns with a gestation age <40 weeks, accumulation of metronidazole can occur during the first week of life, which is why the concentrations of metronidazole in serum should preferably be monitored after a few days therapy.

C: **Treatment of Protozoal and Other Infections**:

*(See table)*

<table>
<thead>
<tr>
<th></th>
<th><strong>Duration of dosage in days</strong></th>
<th><strong>Adults and children over 10 years</strong></th>
<th><strong>Children</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>7-10 years</strong></td>
</tr>
<tr>
<td><strong>Urogenital Trichomoniasis</strong></td>
<td>7</td>
<td>200mg three times daily</td>
<td>40mg/kg orally as a single dose or 15 – 30mg/kg/day divided in 2 – 3 doses not to exceed 2000mg/dose</td>
</tr>
<tr>
<td>Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently</td>
<td>5-7</td>
<td>400mg twice daily</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2000mg as a single dose</td>
<td>--</td>
</tr>
</tbody>
</table>

*(See table)*
<table>
<thead>
<tr>
<th>Condition</th>
<th>Age Range</th>
<th>Initial Dose</th>
<th>Follow-Up Dose</th>
<th>Concomitant Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Vaginosis</td>
<td>5-7 or 1</td>
<td>400mg twice daily</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2000mg as a single dose</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>5-10</td>
<td>400 - 800mg three times daily</td>
<td>200 – 400mg three times daily</td>
<td>100 – 200mg four times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 – 200mg three times daily</td>
<td>100 – 200mg three times daily</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternatively, doses may be expressed by body weight 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giardiasis</td>
<td>3 or 5 or 7-10</td>
<td>2000mg once daily</td>
<td>1000mg once daily</td>
<td>600-800mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400mg three times daily</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500mg twice daily</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Acute Ulcerative Gingivitis</td>
<td>3</td>
<td>200mg three times daily</td>
<td>100mg three times daily</td>
<td>50mg three times</td>
</tr>
<tr>
<td>Acute Dental Infections</td>
<td>3-7</td>
<td>200mg three times daily</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Leg Ulcers and Pressure Sores</td>
<td>7</td>
<td>400mg three times daily</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Dosage is given in terms of metronidazole or metronidazole equivalent.

* Children and babies weighing less than 10Kg should receive proportionally smaller doses.

** Metronidazole oral suspension is well tolerated by the elderly, but a pharmacokinetic study suggests cautious use of high dosage regimen in this age group.
Eradication of Helicobacter pylori in paediatric patients:
As a part of combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.

4.3 Contraindications
Known hypersensitivity to Metronidazole and/or hydroxybenzoates.

4.4 Special warnings and precautions for use

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Metronidazole oral suspension for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures).

There is the possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.

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

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 oral suspension need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD).

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 encephalopathy.

Metronidazole oral suspension should be administered with caution to patients with hepatic encephalopathy. The daily dosage may be reduced to one third and may be administered once daily.
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.

Metronidazole oral suspension contains sucrose and sorbitol. Each 5ml contains 2.5g sucrose and 0.64g sorbitol. Patients with hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The sucrose content should be taken into account in patients with diabetes mellitus. It may also be harmful to teeth.

Methyl and propyl hydroxybenzoates are contained in this product which may cause allergic reactions (possibly delayed).

Patients should be warned that metronidazole may darken urine.

Due to inadequate evidence on the mutagenicity risk in humans (see section 5.3), the use of Metronidazole oral suspension for longer treatment than usually required should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction
Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiramlike (antabuse effect) reaction.

Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anti-coagulants. Dosage of the anticoagulant may require reducing. Prothrombin time should be monitored. No interactions have been reported of the heparin type.

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 concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Patients receiving phenobarbital metabolise metronidazole at a much greater rate than normally, reducing the half life to approximately three hours.
Increased serum carbamazepine levels and toxicity have been seen in patients given concomitant metronidazole.

Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole, depending on the method used.

Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods no longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

Metronidazole reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Patients receiving ciclosporin or tacrolimus with metronidazole are at risk of elevated ciclosporin / tacrolimus serum levels. Serum ciclosporin / tacrolimus and serum creatinine should be closely monitored when coadministration is necessary.

Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

4.6 Fertility, pregnancy and lactation

There is inadequate evidence of the safety of metronidazole in pregnancy. Metronidazole oral suspension should not therefore be given during pregnancy or during lactation unless the physician considers it essential, in these circumstances short, high dosage regimes are not recommended.

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.

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 advised not to drive or operate machinery if these symptoms occur.
4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:

- very common (≥1/10);
- common (≥1/100 to < 1/10);
- uncommon (≥1/1,000 to < 1/100);
- rare (≥1/10,000 to < 1/1,000);
- very rare (< 1/10,000);
- not known (cannot be estimated from the available data).

Frequency, type and severity of adverse reactions in children are the same as in adults.

Serious adverse reactions occur very rarely with standard recommended regimens. However, clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

**Blood and lymphatic system disorders:**

Very rare: agranulocytosis, neutropenia, thrombocytopenia and pancytopenia, often reversible on drug withdrawal, although fatalities have occurred.

Not known: A moderate leucopenia has been reported in some patients but the white cell count has always returned to normal before or after treatment has been completed.

**Immune system disorders:**

Rare: Anaphylaxis

Not known: urticaria, angioedema and fever

**Metabolism and nutrition disorders:**

Not known: anorexia

**Psychiatric disorders:**

Very rare: psychotic disorders, including confusion and hallucinations

Not known: depressed mood

**Nervous system disorders:**

Very rare:
- Encephalopathy (e.g. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and
tremor) have been reported very rarely which may resolve on discontinuation of
the drug

- Drowsiness, dizziness, convulsions, headache, ataxia, inco-ordination of
  movement
  Not known:

- During intensive and/or prolonged metronidazole therapy a few instances of
  peripheral neuropathy or transient epileptiform seizures have been reported. In
  most cases neuropathy disappeared after treatment was stopped or when dosage
  was reduced.

- Aseptic meningitis has been reported

Eye disorders:
Very rare: transient visual disorders such as diplopia and myopia have been reported
Not known: Optic neuropathy/neuritis has been reported

Gastrointestinal disorders:
Not known: Unpleasant taste in the mouth, oral mucositis, furred tongue, nausea,
vomiting, gastro-
  intestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:
Very rare:
- Abnormal liver function tests, increase in liver enzymes (AST, ALT, alkaline
  phosphatase), cholestatic or mixed hepatitis, and hepatocellular liver injury,
  jaundice and pancreatitis, reversible on drug withdrawal have been reported.
- Cases of liver failure requiring liver transplant have been reported in patients
  treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders:
Very rare: skin rashes, pustular eruptions, pruritus, flushing
Not known: Erythema multiforme may occur, which may be reversed on drug
withdrawal. Stevens-
  Johnson syndrome or toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia

Renal and urinary disorders:
Very rare: darkening of the urine (due to metronidazole metabolite)
The parahydroxybenzoates used in Metronidazole oral suspension may cause immediate or delayed hypersensitivity reactions.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals and patients are asked to report any suspected adverse reactions via the Yellow Card Reporting Scheme at www.mhra.gov.uk/yellowcard.

4.9 **Overdose**
Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. There is no specific antidote for metronidazole overdosage. In cases of suspected massive overdosage, a symptomatic and supportive treatment should be instituted.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

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 DNA, where it causes loss of the helical structure and inhibits synthesis.

5.2 **Pharmacokinetic properties**
Absorption - Metronidazole is readily absorbed following administration by mouth and bioavailability is 90-100%. Peak plasma concentrations of approximately 5µg/ml and 10µg/ml are achieved an average of 1-2 hours after single doses of 250mg and 500mg respectively. Some accumulation and consequently higher concentrations occur when multiple doses are given. Absorption may be delayed, but is not reduced overall, by administration with food.
Distribution - Metronidazole is widely distributed. It appears in most body tissues and fluids. It also crosses the placenta and rapidly enters foetal circulation. No more than 20% is bound to plasma proteins.

Metabolism - Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The plasma elimination half-life of metronidazole is about 6-9 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease.

Elimination - The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However, similar studies in the hamster have given negative results and epidemiological studies in humans have provided no evidence of an increased carcinogenic risk in humans.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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
Purified water.

6.2 Incompatibilities
Not applicable

6.3 Shelf life

Unopened: 36 months

Once opened: Use within 12 weeks

6.4 Special precautions for storage
Do not store above 25°C.
Store your medicine in the original packaging in order to protect them from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container
The product is supplied in amber colored glass bottles (USP type III) with 28 mm white child resistant caps containing 100 ml suspension.

6.6 Special precautions for disposal
Keep out of the sight and reach of children.
Shake the bottle well before use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
7 MARKETING AUTHORISATION HOLDER

DAWA Limited,
5 Sandridge Close,
Harrow, Middlesex - HA1 1XD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 30684/0236

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/03/2017

10 DATE OF REVISION OF THE TEXT
28/03/2017