1. NAME OF THE MEDICINAL PRODUCT

{(Metronidazole Suspension) Metronidazole BP 200mg/5ml Oral Suspension}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of the suspension contains Metronidazole Benzoate BP; Equivalent to Metronidazole BP 200mg.
{For a full list of excipients, see section 7.1}

3. PHARMACEUTICAL FORM

Oral Suspension

4. Clinical particulars

4.1 Therapeutic indications

{Metronidazole Suspension, metronidazole BP 200mg/5ml} is very active against protozoa and anaaerobic bacteria. It is recommended for the treatment of glardiasis, acute ulcerative gingivitis. Bacterial vaginosis, trichomonal vaginitis, amoebiasis, inflammatory bowel disease, dracunculiasis etc.

4.2 Posology and method ofadministration

Posology

Pediatric population

Children 1-3 years: ½ teaspoonful (2.5ml) three times a day

Children 3-7 years: 1 teaspoonful (5ml) three times a day

Children 7-10 years: 1-2 teaspoonfuls (5-10ml) three times a day

4.3 Contraindications

Metronidazole is contra-indicated in patients who are hypersensitive to metronidazole, in premature babies and neonates.

4.4 Special warnings and precautions for use

Alcohol should be avoided during treatment with metronidazole and it should not be administered during pregnancy of lactation. Great care should be taken when administered to patients with blood

dyscrasias or with active disease of the central nervous system. Usage must be discontinued if signs of peripheral neuropathy or central nervous system toxicity develops. Patients with severe liver disease are advised to take reduced doses.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not consume alcohol during and for at least 48 hours after metronidazole treatment because of a possible disulfiram-like (antabuse effect) reaction Metronidazole has been reported to enhance the anticoagulant effect of the warfarin and coumarin type anticoagulants, the dosage of which may therefore require reducing. Prothrombin times should be monitored. No interactions have been reported with the heparin-type anticoagulants. Simultaneous treatment with lithium and metronidazole may impair clearance of lithium, accompanied by evidence of possible renal damage. Lithium treatment should be withdrawn or gradually reduced before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients treated with both lithium and metronidazole. The rate of metabolism of metronidazole is increased in patients treated with pheno-barbitone, reducing metronidazole half-life to approximately 3 hours. Metronidazole may impair the clearance of phenytoin. Aspartate amino-transferase assays may give spuriously low values in patients treated with metronidazole, depending on the test method used. Metronidazole has anti-treponemal activity and may mask the immunological response seen in untreated early syphilis; contacts of syphilis receiving metronidazole should probably be screened for an additional 4 - 8 weeks. Metronidazole increases the toxicity of 5-fluorouracil by decreasing its renal clearance. Metronidazole potentiates the activity of vecuronium. Metronidazole may interact with disulfiram causing psychotic effects.

4.6 Pregnancy and Lactation

Metronidazole, like other medicines, should not be given during pregnancy or lactation unless the physician considers it essential; in these circumstances short high-dosage regimens are not recommended. Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

4.7 Effects on ability to drive and use machines

Patients should not drive or operate machinery if they become dizzy or drowsy

4.8 Undesirable effects

Serious adverse reactions occur rarely with the recommended dosage regimens. 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.

Thrombophlebitis may occur following intravenous administration of metronidazole.

Blood and lymphatic system disorders:

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

Not known: temporary moderate leucopenia

Immune system disorders:

Rare: anaphylaxis

Very rare: Steven-Johnson syndrome

Not known: angioedema, urticaria

Metabolism and nutrition disorders Not known: anorexia.

Psychiatric disorders:

Very rare: psychotic disorders, including hallucinations.

Not known: insomnia and changes in mood or mental state such as depression or confusion

Nervous system disorders:

Very rare: encephalopathy, (eg confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebella syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.)

- drowsiness, dizziness, convulsions, headache

Not known: during high-dosage or prolonged metronidazole treatment, 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.

Eye disorders:

Very rare: transient visual disorders such as diplopia and myopia

Gastrointestinal disorders:

Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastrointestinal disturbance,

antibiotic associated pseudomembranous colitis

Hepatobiliary disorders:

Very rare: abnormal liver function tests, cholestatic hepatitis, jaundice, and pancreatitis reversible on drug withdrawal

Skin and subcutaneous tissue disorders:

Very rare: skin rashes, pruritis, pustular eruptions

Not known: Erythema multiforme which may be reversed on drug removal.

Musculoskeletal, connective tissue and bone disorders:

Very rare: myalgia, arthralgia

Renal and urinary disorders:

Very rare: darkening of the urine (due to metronidazole metabolite).

4.9 Overdose

Evans Baroque metronidazole should be taken at least one hour before a meal. The duration of treatment ranges from 5 days to several weeks but always follow your physician's instructions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterial

Mechanism of action

Metronidazole diffuses into the organism, inhibits protein synthesis by interacting with DNA, and causes a loss of helical DNA structure and strand breakage. Therefore, it causes cell death in susceptible organisms. The mechanism of action of metronidazole occurs through a four-step process.

Step one is the entry into the organism by diffusion across the cell membranes of anaerobic and aerobic pathogens. However, antimicrobial effects are limited to anaerobes.

Step two involves reductive activation by intracellular transport proteins by altering the chemical structure of pyruvate-ferredoxin oxidoreductase. The reduction of metronidazole creates a concentration gradient in the cell that drives uptake of more drugs and promotes free radical formation that is cytotoxic.

Step three, interactions with intracellular targets, is achieved by cytotoxic particles interacting with host cell DNA resulting in DNA strand breakage and fatal destabilization of the DNA helix.

Step four is the breakdown of cytotoxic products. Metronidazole is also cytotoxic to facultatively anaerobic bacteria like *Helicobacter pylori* and *Gardnerella vaginalis*, but the mechanism of action to these pathogens is not well understood

Pharmacodynamic effects

Metronidazole is an antimicrobial agent of the nitro-5-imidazole family. It is active against a wide range of pathogenic micro-organisms in particular species of Bacteroides, Clostridia, Eubacteria, Fusobacteria, Gardnerella vaginalis,and anaerobic cocci. It is also active against Balantidium coli, Entamoeba histolytica, Giardia lamblia and Trichomonas. Metronidazole enters target cells of bacteria or protozoa probably by passive diffusion and is activated by reduction of the nitro group by pyruvate-ferredoxin oxidoreductase; the resultant unstable intermediate interacts with DNA effectively preventing replication

Metronidazole treats amebiasis, trichomoniasis, and giardiasis, exerting both antibacterial and antiprotozoal activities. Metronidazole is an effective treatment for some anaerobic bacterial infections. Metronidazole has shown antibacterial activity against the majority of obligate anaerobes, however, during in vitro studies, it does not demonstrate significant action against facultative anaerobes or obligate aerobes. The nitro group reduction of metronidazole by anaerobic organisms is likely responsible for the drug's antimicrobial cytotoxic effects, causing DNA strand damage to microbes. A note on convulsions and neuropathy and carcinogenesis. It is important to be aware of the risk of peripheral neuropathy and convulsions associated with metronidazole, especially at higher doses. If convulsions or numbness of an extremity occur, discontinue the drug immediately. Metronidazole has been found to be carcinogenic in mice and rats. The relevance to this effect in humans is unknown. It is advisable to only administer metronidazole when clinically necessary and only for its approved indications. Clinical efficacy and safety

Clinical Pharmacology of Metronidazole

Take this medicine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered. To help clear up your infection completely, keep using this medicine for the full time of treatment, even if you begin to feel better after a few days. If you stop using this medicine too soon, your infection may return. This medicine works best when there is a constant amount in the blood. To help keep the amount constant, do not miss any doses. Also, it is best to take the doses at evenly spaced times during the day. If you need help planning the best times to take your medicine, check with your doctor.

5.2 Pharmacokinetic properties

6. Metronidazole is metabolised mainly by hepatic oxidation and glucuronide formation. At least half of

the infused dose is recovered in urine after approximately 8 hours, as metronidazole but mainly as its principal metabolites: metabolite I (hydroxy form) present in plasma and urine and with 30 - 65% activity of metronidazole, and metabolite II (acid form) not detected in plasma but representing 40 - 50% of the substances in urine, with 5% activity of metronidazole. Metronidazole crosses the placenta and rapidly enters the foetal circulation. It is excreted in milk but the intake of a breastfed infant of a mother receiving the recommended dose would be considerably less than the therapeutic dose for infants. The half-life of metronidazole is reported to be longer in neonates and in patients with liver disease; that of the hydroxy metabolite is prolonged in patients with renal failure. After injection, metronidazole is widely distributed in most body tissues and fluids reaching concentrations similar to those in plasma; it crosses the placenta and rapidly enters the foetal circulation. No more than 20% metronidazole is bound to plasma proteins. Peak steady state plasma concentrations of approximately 25µg/ml with a trough concentration of 18µg/ml have been reported in patients given an intravenous loading dose of 15mg/kg body weight followed by 7.5mg/kg every 6 hours. Metronidazole may impair the clearance of phenytoin.

6.1 Preclinical safety data

No relevant information additional to that contained elsewhere in the SPC

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Polysorbate 80 (Tween 80)
Aerosil 200
Nipasept
Methyl Paraben
Propyl Paraben
Ethanol 96%
Metronidazole Benzoate
Banana Flavour (Liquid)
FD & C Yellow No. 10
Sodium Carboxyl Methyl Cellulose
Sugar Granulated BP
Deionised Water

7.2 Incompatibilities

Metronidazole solution must not be mixed with cefamandole nafate, cefoxitin sodium, 10%w/v dextrose infusion, compound sodium lactate infusion, penicillin G potassium.

7.3 Shelf life

3 years

7.4 Special precautions for storage

How to store Metronidazole Suspension
Store below 25°C, away from light, Keep all medicines out of the reach of children

7.5 Nature and contents of container <and special equipment for use, administration or implantation>

Plastic bottle with Evans baroque label on it, inserted in a carton with a leaflet for instruction on how to use.
Pack size: 60ml

7.6 Special precautions for disposal <and other handling>

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

8. <APPLICANT/MANUFACTURER>

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