1. NAME OF THE MEDICINAL PRODUCT

Avrogyl Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Avrogyl Suspension contains 200mg Metronidazole in each 5ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Suspension

4. Clinical particulars

4.1 Therapeutic indications

Metronidazole is active against a wide range of pathogenic micro-organisms, notably species of *Bacteroids, Fusobacteria, Clostridia, Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

It is also active against *Trichomonas vaginalis, Entamoeba histolytica, Gardia lamblia*, *Balantidium coli* and *Helicobacter pylori*.

Metronidazole is indicated in adults and children for the following indications:

1) Prevention of post-operative infections due to anaerobic bacteria, particularly species of *bacteroids* and anaerobic streptococci.

2) The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis and post-operative wound infections from which pathogenic anaerobes have been isolated.

3) Urogenital trichomoniasis in the female (T*richomonas vaginalis*), and in man.

4) Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or *Gardnerella vaginalis*).

5) All forms of amoebiasis (intestinal and extra-intestinal disease and asymptomatic cyst passers).

6) Giardiasis.

7) Acute ulcerative gingivitis.

8) Acute dental infections (*eg* acute pericoronitis and acute apical infections)

9) Anaerobically-infected leg ulcers and pressure sores.

10) Treatment of *Helicobacter pylori* infection associated with peptic ulcer as part of triple therapy.

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

4.2 Posology and method ofadministration

Method of administration

Oral use.

Posology

	DURATION OF DOSAGE (DAYS)	7 – 10 YERAS	3 – 6 YEARS	1 – 2 YEARS
AMOEBIOASIS 1. Acute invasive intestinal disease in susceptible patients.	5	10ml three times daily	5ml four times daily	5ml three times daily
2. Intestinal disease in less susceptible patients with chronic amoebic hepatitis	5 - 10	5ml three times daily	2.5ml four times daily	2.5ml three times daily

3. Other forms of amoebiasis including amoebic liver abscess	5	5ml three times daily	2.5ml four times daily	2.5ml three times daily
4. Symptomless cyst passers	5 - 10	5ml-10ml three times daily	5ml-10ml three times daily	2.5ml-5ml three times daily
UROGENITAL TRICHOMONIASIS In cases of likely reinfection, a second course of treatment should be done concurrently.	2	5ml-10ml three times daily	5ml-10ml three times daily	2.5ml-5ml three times daily
GIARDISIS If necessary, repeat treatment after 2 weeks	3	25ml once daily	15ml once daily	10ml once daily
ACUTE ULCERATIVE GINGIVITIS	3	2.5ml three times daily	2.5ml two times daily	1.2ml three times daily

1. Urogential trichomoniasis
Adults and children over 10 years:
2000mg as a single dose or 200 mg 3 times daily for 7 days or 400mg twice daily for 5-7 days
Children < 10 years:
40mg/kg orally as a single dose or 15 -30 mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000mg/dose

2. Acute ulcerative gingivitis
Adults & Children over 10 years: 600 mg daily in 3 divided doses for 3 days.
Children:
Aged 7 to 10 years: 300 mg daily in 3 divided doses for 3 days.
Aged 3 to 7 years: 200 mg daily in 2 divided doses for 3 days.
Aged 1 to 3 years: 150 mg in 3 divided doses for 3 days.

3. Amoebiasis
Adults and children over 10 years: 400 to 800mg 3 times daily for 5-10 days.
Children:
Aged 7 to 10 years: 200 to 400 mg 3 times daily for 5-10 days
Aged 3 to 7 years: 100 to 200 mg 4 times daily for 5-10 days
Aged 1 to 3 years: 100 to 200mg 3 times daily for 5-10 days.
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 2400 mg/day

4. Giardiasis
Adults and children over 10 years:2000 mg once daily for 3 days, or 400mg three times daily for 5 days, or 500mg twice daily for 7 to 10 days.
Children:
Aged 7 to 10 years:1000 mg once daily for 3 days.
Aged 3 to 7 years:600 mg to 800mg once daily for 3 days.
Aged 1 to 3 years:500 mg once daily for 3 days.
Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.

5. Anaerobic infections Treatment
Adults: 800 mg followed by 400 mg 8 hourly.
Children:
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, therefore the concentrations of metronidazole in serum should preferably be monitored after a few days therapy.

Prophylaxis against postoperative infections caused by anaerobic bacteria:
Adults: 400 mg at 8 hourly intervals during the 24 hours immediately preceding operation, followed post operatively by intravenous or rectal administration until oral dosing can be resumed.
Children:
Children < 12 years: 20-30 mg/kg as a single dose given 2-3hours before surgery
Newborns with a gestation age <40 weeks: 10mg/kg body weight as a single dose2-3 hours before operation

Eradication of helicobacter pylori in paediatric patients:
As part of a combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days.
Official guidelines should be consulted before initiating therapy.

6. Dental Infections
The usual total daily dose is 600 to 800 mg in divided doses. Treatment should generally be continued for 3 to 7 days.

7. Chronic pressure sores and ulcers
Adults: 1200 mg daily in 3 divided doses.

8. Bacterial Vaginitis
Adults and Adolescents: A single dose of 2000mg may be used or 400 mg twice daily for 5-7 days.

Adjustment of dosage does not appear necessary in patients with renal impairment.
In the case of children whose weights are below those usual for their age, or of infants below 10 kg in weight, dosage of metronidazole should be reduced proportionately.
Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Elderly:
Caution is advised particularly at high doses. No information is available on modification of dosage.

Hepatic Encephalopathy:
Daily dosage should be reduced to one third and may be given once daily (see precautions).

4.3 Contraindications

- Known hypersensitivity to nitroimidazoles, metronidazole or to any of the excipients listed in 6.1.
- Pregnancy - metronidazole should not be used in the first trimester in patients with trichomoniasis or bacterial vaginosis (see section 4.6).
- Breast feeding should be discontinued for 12-24 hours when single high dose (e.g. 2g) therapy is used (see section 4.6).
- Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.

4.4 Special warnings and precautions for use

The use of Avrogyl for prolonged treatment duration should be carefully weighed. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. It is recommended that haematological tests be carried out regularly and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures).

High dosage regimens have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Metronidazole and a metabolite have been shown to be mutagenic in some tests with non-mammalian cells. Intensive or prolonged metronidazole therapy should be conducted only under

conditions of close surveillance for clinical and biological effects and under specialist direction.

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit using metronidazole to treat trichomoniasis in such patients should be carefully considered.

Avrogyl should be administered with caution to patients with hepatic encephalopathy. Cases of severe bullous skin reactions, sometimes fatal, such as Stevens-Johnson syndrome(SJS), toxic epidermal necrolysis (TEN) or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole (see Section 4.8). The majority of cases of SJS reported occurred within 7 weeks of starting treatment with metronidazole. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms of SJS, TEN or AGEP (e.g. flu-like symptoms, progressive skin rash often with blisters or mucosal lesions) are present; treatment must be immediately discontinued (see 4.8 Undesirable Effects).

Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite).

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

4.5 Interaction with other medicinal products and other forms of interaction

nteractions to be used with caution:

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

• *Anticoagulants:* Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. No interactions have been reported with anticoagulants of the heparin type. However, anticoagulant activity should be routinely monitored with these products.

• *Alcohol:* Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours after because of the possibility of a disulfiram-like reaction.

• *Disulfiram:* Psychotic reactions have been reported.

• *Immunosuppressants:* Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Pharmacokinetic interactions:

• *Antiepileptics:* Patients receiving phenobarbital metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours. Metronidazole inhibits metabolism of phenytoin (increases plasma-phenytoin concentration). Primidone accelerates the metabolism of Metronidazole causing reduced plasma concentrations.

• *Cytotoxics:* Metronidazole inhibits metabolism of fluorouracil. Therefore, increased toxicity of fluorouracil can result. Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

• *Ulcer-healing drugs:* Cimetidine inhibits the metabolism of metronidazole (increases plasma-metronidazole concentration).

• *Oestrogens:* broad spectrum antibiotics possibly reduce the contraceptive effect. See local/national guidelines or BNF for specific advice.

• *Drug-lab modifications:* Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole, depending on the method used.

4.6 Pregnancy and Lactation

Pregnancy
There is inadequate evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. As with all medicines, metronidazole should not be given during pregnancy or during lactation unless it is considered essential, and in these circumstances the short, high-dosage regimens are not recommended.

Pregnancy
Metronidazole is contraindicated in the first trimester (see section 4.3) and should be used with caution in the second and third trimester when used to treat trichomoniais or bacterial vaginosis (see section 4.4).

For all other indications Metronidazole should only be used if the benefits outweigh the risks or no other alternative is available especially in the first trimester.

Breast-feeding
It is advisable to stop breast feeding until 12 – 24 hours after Metronidazole therapy has been discontinued (see section 4.3).

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

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).

Serious adverse reactions occur rarely with standard recommended regimens.

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

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, pancytopenia
Not known	Leucopenia, bone marrow depression disorders such as aplastic

	anaemia
Immune system class:	
Rare	Anaphylaxis
Not known	Angiodema, urticaria, 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 (eg. confusion, fever, headache, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve in discontinuation of the drug, drowsiness, dizziness, convulsions, headaches
Not known	Depression, paraesthesia, 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. Incoordination of movement, aseptic meningitis
Eye disorders:	
Very rare	Diplopia, myopia
Not known	Optic neuropathy/neuritis
Ear and labyrinth disorders:	
Not known	Hearing impaired/hearing loss (including sensorineural), tinnitus
Gastrointestinal disorders:	
Not known	Unpleasant taste in the mouth, taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances, diarrhoea, abdominal pain, anorexia
Hepatobiliary disorders:	
Very rare	Abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is 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
Skin and subcutaneous tissue disorders:	
Very rare	Skin rashes, pustular eruptions, pruritus, flushing
Not known	Erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption
Musculoskeletal, connective tissue and bone disorders:	
Very rare	Myalgia, arthralgia
Renal and urinary disorders:	
Very rare	Darkening of urine (due to metronidazole metabolite)

- *Gastrointestinal disorders*- epigastricpain, nausea, vomiting, malaise, diarrhoea.

- *Oral mucositis, taste disorders*- dry mouth, anorexia.-reversible cases of pancreatitis.-tongue discolouration/furry tongue.

- *Immune system disorders*- angioedema anaphylactic shock.Nervous system disorders-peripheral sensory neuropathy, paraesthesia-headache, convulsions, dizziness.

- *Reports of encephalopathy*- (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve with discontinuation of the drug.

- *Aseptic meningitis*

- *Psychiatric disorders*- psychotic disorders including confusion, hallucinations-depressed mood

- *Eye disorders*- transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision.-Optic neuropathy/neuritis.

- *Ear and labyrinth disorders*-hearing impaired/hearing loss (including sensorineural)-tinnitus

- *Blood and lymphatic system disorders*- cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.

- *Hepatobiliary disorders*- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.

- *Cases of liver failure*- requiring liver transplant have been reported in patients treated with metronidazole mostly when used in combination with other antibiotic drugs.

- *Skin and subcutaneous tissue disorders*-rash, pruritus, flushing, urticaria-pustular eruptions, acute generalised exanthematous pustulosis

- *Fixed drug eruption*- Stevens-Johnson syndrome, toxic epidermal necrolysis.

- *General disorders and administration site conditions*- fever

4.9 Overdose

Features:

Nausea, vomiting, diarrhoea, anorexia, metallic taste, headache, dizziness and occasionally insomnia and drowsiness. Transiently increased liver enzyme activities have been reported rarely.

Transient epileptiform seizures have been reported following intensive or prolonged therapy. Other adverse effects occurring in these circumstances include peripheral motor neuropathy, blood dyscrasias and liver damage.

The combination of alcohol and metronidazole has been said to cause disulfiram type reactions in about 10% of individuals with sudden onset of excitement, giddiness, flushing, nausea, headache, hypotension and dyspnoea. However the mechanism of this reaction has been questioned.

Treatment:

Unlikely to be required.

Disulfiram type reactions should be treated with intravenous fluids and plasma expanders if necessary. Symptomatic and supportive.

In more serious cases:

1. Single brief convulsions do not require treatment. If frequent or prolonged control with intravenous diazepam (10-20mg in adults; 0.1-0.3mg/kg body weight) or lorazepam (4mg in an adult and 0.05mg/kg in a child). Give oxygen and correct acid base and metabolic disturbances as required.

2. Other measures as indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: *Nitroimidazole derivatives*
ATC Code: P01A B01

Mechanism of action
Metronidazole has antiprotozoal and antibacterial actions including activity against anaerobic bacteria and entamoeba histolytica. It is effects against *Trichomonas vaginalis, Gardnerella vaginalis* and other protazoa including *Entamoeba histolytica, Gardia lamblia* and anaerobic bacteria.

5.2 Pharmacokinetic properties

Absorption
Metronidazole is readily absorbed following administration by mouth and bioavailability is 90-100%. Peak plasma concentrations occur after 20 minutes to 3 hours. 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.

Biotransformation
Metronidazole is metabolized in the liver by side-chain oxidation and glucuronide formation. The half-life of metronidazole is 6.5 ± 2.9 hours. 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. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. 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.

5.3 Preclinical safety data
Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear 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 others studies were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sucrose
Polysorbate 80
Methyl Paraben
Lemon Flavour
Propylene Glycol
Glycerol
Avicel RC 581
Deionised Water

6.2 Incompatibilities
None.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C. Protect from light.

6.5 Nature and contents of container
Amber bottle with Ropp aluminium screw cap, fitted with an inner plastic measuring cap.
Pack size 60 ml.

6.6 Special precautions for disposal
No special requirements.

7 . APPLICANT/MANUFACTURER

Avro Pharma Limited
Daid House, Plot 2, Block J, Limca Way,
Isolo Industrial Estate, Oshodi-Apapa Expressway
Isolo, Lagos State.
Tel: +234(1)2913955
Email: info.avropharma@gmail.com