AUSTRALIAN PRODUCT INFORMATION – SIMPLOTAN® (TINIDAZOLE)

1. NAME OF THE MEDICINE

Tinidazole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Simplotan tablets contain 500 mg of tinidazole.

3. PHARMACEUTICAL FORM

White, round, biconvex, film coated oral tablets engraved with "FAS 500" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Simplotan is indicated for the oral treatment of:

(a) *Trichomonas vaginalis* infections of the genito-urinary tract in both female and male patients. When infection with *Trichomonas vaginalis* has been confirmed or is suspected, simultaneous treatment of the consort is recommended.

(b) Giardiasis.

(c) Amoebic Dysentery and Amoebic Liver Abscess.

(d) Acute Giardiasis and Acute Amoebic Dysentery and Amoebic Liver disease in children.

(e) The prevention of infection of the surgical site which may be contaminated or potentially contaminated with anaerobic organisms, for example during colonic, gastro-intestinal and gynaecological surgery.

4.2 Dose and method of administration

Dosage

Trichomoniasis

Adult: 2 g (4 x 500 mg tablets) orally as a single stat dose.

Giardiasis

Adult: 2 g orally as a single stat dose.

Children: 50 mg/kg of body weight given as a single dose, up to a maximum of 2 g. It may be necessary to repeat this dose once in some cases.

Acute Amoebic Dysentery

Adult: 2 g orally as a single dose for 2 to 3 days. (In the occasional instance when a three day course is ineffective, treatment may be continued for ten days).

Children: 50 mg/kg of body weight up to a maximum of 2 g, given as a single daily dose on each three successive days.

Amoebic Liver Abscess

Adult: 2 g orally as a single daily dose for 3 days. (In the occasional instance when a three day course is ineffective, treatment may be continued for five days).

Total dosage varies according to the virulence of the *Entamoeba histolytica* between 4.5 to 10 g.

Children: 50 mg/kg of body weight, up to a maximum of 2 g, given as a single daily dose on each of five successive days.

In amoebic involvement of the liver the aspiration of pus may be required in addition to therapy with Simplotan.

Prevention of Postoperative Infections

Adult: A single oral dose of 2 g approximately 12 hours before surgery.

Children: There is no data available to allow dosage recommendations for children below the age of 12 in the prophylaxis of anaerobic infections.

Dosage adjustment

Use in Renal Impairment

Dosage adjustments in patients with impaired renal function are generally not necessary. However, because tinidazole is easily removed by haemodialysis, patients may require additional doses of tinidazole to compensate.

Method of administration

Administration with Food

It is recommended that tablets be taken during or after a meal.

4.3 Contraindications

Simplotan is contraindicated in patients with the following conditions:

1. Hypersensitivity to tinidazole, other 5-nitroimidazole derivatives, or any component of the tablet.

2. Blood dyscrasias or with a history of blood dyscrasias.

3. Active organic diseases of the central nervous system.

4. First trimester of pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy).

5. Nursing mothers, as Simplotan (tinidazole) is present in breast milk (see Section 4.6 Fertility, pregnancy and lactation - Use in lactation).

4.4 Special warnings and precautions for use

Haematological Effects

Simplotan may produce mild transient leukopenia and neutropenia. It is therefore recommended that total and differential leukocyte counts be done before and after treatment with the drug if a second course of therapy is necessary.

Disulfiram-like Reaction

Alcoholic beverages should be avoided during therapy with Simplotan and for at least 72 hours after discontinuing Simplotan because of the possibility of a disulfiram-like reaction (abdominal cramps, vomiting, tachycardia and flushing).

Neurological Effects

If, during therapy with Simplotan, abnormal neurological signs develop, therapy should be promptly discontinued (see Section 4.8 Adverse effects (undesirable effects)).

Bacterial Overgrowth

During treatment with closely related chemical compounds, vaginal and intestinal monilial overgrowth has been reported and may necessitate treatment with nystatin.

Interactions with Anticoagulants

Closely related chemical compounds enhance the activity of warfarin and if Simplotan is to be given to patients receiving this or other anticoagulants, the dosage of the latter should be recalibrated (see Section 4.5 Interactions with other medicines and other forms of interactions).

Administration with Food

It is recommended that tablets be taken during or after a meal.

Use in renal impairment

Because the drug is excreted in the urine caution should be exercised in patients with impaired renal function if administering a second or additional doses.

Use in the elderly

No data available.

Paediatric use

Experience in treating paediatric patients with this drug is relatively limited and information on safety is still incomplete.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Alcohol

Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided (see Section 4.4 Special warnings and precautions for use - Disulfiram-like Reaction).

Anticoagulants

Drugs of similar chemical structure have been shown to potentiate the effects of oral anticoagulants. Prothrombin times should be closely monitored and adjustments to the dose of the anticoagulant should be made as necessary (see Section 4.4 Special warnings and precautions for use - Interactions with Anticoagulants).

4.6 Fertility, pregnancy and lactation

Effects on fertility

As with other agents in the 5-nitroimidazole class, tinidazole has been reported to produce testicular and spermatogenic adverse effects in male rats.

Use in pregnancy – Pregnancy Category B3

Tinidazole crosses the placental barrier and enters the foetal circulation. Simplotan is contraindicated during the first trimester of pregnancy. Animal studies suggest that tinidazole may have teratogenic potential. Benefit and risk from its use should, therefore, be carefully assessed and the drug may be used during the second and third trimester with caution and discretion and only if in the judgement of the attending physician the expected benefits outweigh the potential risk.

Use in lactation

Tinidazole is secreted in breast milk. In view of its mutagenic potential, breast feeding is not recommended. Tinidazole may continue to appear in breast milk for more than 72 hours after administration. Women should not breast feed until at least three days after having discontinued Simplotan.

4.7 Effects on ability to drive and use machines

The effect of tinidazole on the ability to drive or operate heavy machinery has not been studied.

4.8 Adverse effects (undesirable effects)

Mild adverse reactions have been reported in about 15% of patients of which the most common were gastrointestinal. Reported mild side effects have generally been infrequent and self-limiting.

All adverse reactions are presented in the table below by system organ class and frequency.

System Organ Class	Common ≥1/100 to <1/10	Frequency not known (cannot be estimated from available data)
Blood and the lymphatic system disorders		Leukopenia, neutropenia
Immune system disorders		Drug hypersensitivity
Metabolism and nutrition disorders	Decreased appetite	
Nervous system disorders	Headache	Convulsions, neuropathy peripheral, paraesthesia, hypoaesthesia, sensory disturbances, ataxia, dizziness, dysgeusia
Ear and labyrinth disorders	Vertigo	
Vascular disorders		Flushing
Gastrointestinal disorders	Vomiting, diarrhoea, nausea, abdominal pain	Glossitis, stomatitis, constipation, tongue discolouration
Skin and subcutaneous tissue disorders	Dermatitis allergic, pruritis	Angioedema, urticaria
Renal and urinary disorders		Chromaturia
General disorders and administration site conditions		Pyrexia, fatigue, malaise
Investigations		Blood urea increased, aspartate aminotransferase increased, eosinophil count increased, haemoglobin decreased, blood bilirubin increased

CIOMS III categories: Common ≥1/100 to <1/10 (≥1% and <10%), Not known: frequency cannot be estimated from available data

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and Symptoms

Reports of overdoses in humans with tinidazole are anecdotal and do not provide consistent data regarding the signs and symptoms of overdose.

Treatment of Overdosage

There is no specific antidote for the treatment of overdosage with tinidazole. Treatment is symptomatic and supportive. Tinidazole is easily dialysable.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Microbiology

Simplotan (tinidazole) has been shown to be effective against *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*. Minimum inhibitory concentration (MIC) values for *Trichomonas vaginalis* ranged from 1.25 to 10 µg/mL when the organism was incubated with tinidazole for 6 hours and 0.12 - 1.25 µg/mL when the incubation period was 3 days. Minimum cidal concentration (MCC) for the same organism ranged from 1.25 to 40 µg/mL and 1.25 - 2.5 µg/mL in the two studies respectively.

The MIC for tinidazole against *Entamoeba histolytica* trophozoites after 48 hours incubation in Locke's medium was 40 µg/mL. An MIC of 6.25 µg/mL has been established for *Entamoeba histolytica*.

In the absence of suitable laboratory techniques the MIC/MCC for *Giardia lamblia* is not known.

Simplotan (tinidazole) has also been shown to be effective against anaerobic bacteria including *Bacteroides fragilis*, other species of *Bacteroides* and *Fusobacteria* spp. Other organisms for which tinidazole is also bactericidal belong to species such as *Peptococcus* spp., *Peptostreptococcus* spp., *Clostridium* spp. (except *C. difficile*), and *Eubacteria* spp. Aerobic and facultative aerobic bacteria, *Arachnia, propionibacteria*, and *actinomycetes* are resistant to tinidazole.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Following oral administration the drug is rapidly absorbed. In healthy female volunteers given a single oral 2 g dose of tinidazole, peak serum levels of 51 µg/mL were obtained 2 hours post-administration. At 24 hours mean serum concentration of tinidazole was 19 µg/mL; at 48 hours, 4 µg/mL and at 72 hours, 1.3 µg/mL. The serum half-life of tinidazole is approximately 12.7 hours.

Distribution

There is suggestive evidence that peak serum levels may be lower and serum half-life shorter in males than in females. The concentrations of tinidazole in various tissues and fluids of the female genital tract of gynaecological patients after a single 2 g oral dose have been reported. The concentrations in peritoneal fluid obtained at operation 8.5 – 15 hours after drug intake ranged between 16 – 40 µg/mL. Fallopian tube specimens yielded 15 – 26 µg/g tissue. Similar levels were obtained in specimens from myometrium, endometrium, vaginal secretions, cervix and omental fat. Cerebrospinal fluid (C.S.F.) concentrations in subjects without meningitis, were approximately 88% of the simultaneous serum concentrations.

Tinidazole is bound to plasma proteins to the extent of approximately 12%.

Metabolism and Excretion

It is excreted in the urine primarily as unchanged drug. Approximately 20% of the unchanged drug appears in the urine in 24 hours.

5.3 Preclinical safety data

Genotoxicity

In vitro mutagenicity results with tinidazole were mixed (positive and negative). Tinidazole is mutagenic in the Ames test and was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

Carcinogenicity

Animal carcinogenic studies are inadequate to exclude tumorigenic potential. However, as other drugs of this class have been shown to be tumorigenic in animals, the benefits and risks from the use of tinidazole should be carefully assessed in each case, particularly in relation to the severity of the disease, the age of the patient or if a longer than usual treatment period is required.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose

alginic acid

maize starch

magnesium stearate

sodium lauryl sulfate

hypromellose

propylene glycol

titanium dioxide

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

blister packs of 4.

6.6 Special precautions for disposal

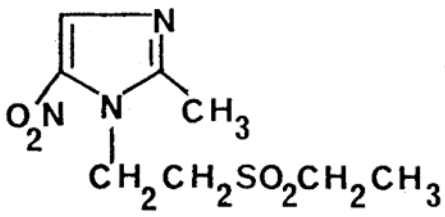
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Simplotan contains the active ingredient tinidazole. Simplotan (tinidazole) is a derivative of the substituted imidazole group of compounds. It is a pale yellow crystalline solid that is insoluble in water, but soluble in methanol and chloroform.

Chemical structure

The structural formula of tinidazole is shown below:



Chemical name: 1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole

Molecular formula: $C_8H_{13}N_3O_4S$

Molecular weight: 247.3

CAS number

19387-91-8.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine).

8. SPONSOR

Pfizer Australia Pty Ltd
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9. DATE OF FIRST APPROVAL

2 April 1993.

10. DATE OF REVISION

22 November 2019

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
All	All sections reformatted in line with the new form

2; 3; 4; 5; & 6	Editorial
8	Sponsor details updated