

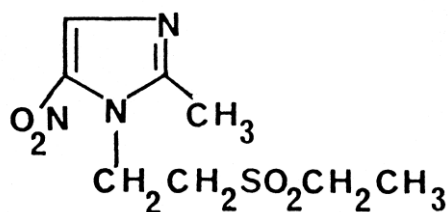
# PRODUCT INFORMATION

## SIMPLOTAN<sup>®</sup> (Tinidazole)

### NAME OF THE MEDICINE

Simplotan (tinidazole) 500 mg tablets.

Simplotan contains the active ingredient tinidazole. The structural formula of tinidazole is shown below:



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

Molecular formula: C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S

Molecular weight: 247.3

CAS registry number: 19387-91-8.

### DESCRIPTION

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.

Simplotan tablets contain 500 mg of tinidazole. The following ingredients are also present: microcrystalline cellulose, alginate acid, maize starch, magnesium stearate, sodium lauryl sulfate, hypromellose, propylene glycol and titanium dioxide.

### PHARMACOLOGY

#### 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.

## **Pharmacokinetics**

### ***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.

## **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.

## **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 PRECAUTIONS, Use in Pregnancy).
5. Nursing mothers, as Simplotan (tinidazole) is present in breast milk (see PRECAUTIONS, Use in Lactation).

## **PRECAUTIONS**

### **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 ADVERSE EFFECTS).

### **Bacterial Overgrowth**

During treatment with closely related chemical compounds, vaginal and intestinal monial 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 INTERACTIONS WITH OTHER MEDICINES).

### **Administration with Food**

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

### **Use in 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.

### **Paediatric Use**

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

### **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.

### **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.

## 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.

## 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.

## INTERACTIONS WITH OTHER MEDICINES

### Alcohol

Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided (see PRECAUTIONS, 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 PRECAUTIONS, Interactions with Anticoagulants).

## ADVERSE 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 $\geq 1/100$ 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

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

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

## **DOSAGE AND ADMINISTRATION**

### ***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.

### **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.

## **OVERDOSAGE**

### **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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

Simplotan is supplied as white, round, biconvex, film coated oral tablets engraved with “FAS 500” on one side and plain on the other, each containing 500 mg tinidazole base, in blister packs of 4.

### **Storage**

Store below 25°C.

## **POISON SCHEDULE OF THE MEDICINE**

S4 (Prescription Only Medicine).

## **NAME AND ADDRESS OF THE SPONSOR**

G P Laboratories  
Division of Pfizer Australia Pty Ltd  
ABN 50 008 422 348  
38-42 Wharf Road  
West Ryde NSW 2114

## **FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS**

2 April 1993.

## **DATE OF MOST RECENT AMENDMENT**

20 November 2013

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