SUMMARY OF PRODUCT CHARACTEISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Tinidazole Tablets 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated Tablet Contains:

Tinidazole BP…..500mg

Approved colours used in coating.

3. Pharmaceutical form

Film Coated Tablet

Yellow colored, elongated, biconvex, scored on one side, film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of the following infections:

1. Eradication of *Helicobacter pylori* associated with duodenal ulcers, in the presence of antibiotic and acid suppressant therapy.

2. Anaerobic infections such as:

Intraperitoneal infections: peritonitis, abscess.

Gynaecological infections: endometritis, endomyometritis, tube-ovarian abscess.

Bacterial septicaemia.

Post-operative wound infections.

Skin and soft tissue infections.

Upper and lower respiratory tract infections: pneumonia, empyema, lung abscess.

3. Non-specific vaginitis.

4. Acute ulcerative gingivitis.

5. Urogenital trichomoniasis in both male and female patients.

6. Giardiasis.

7. Intestinal amoebiasis.

8. Amoebic involvement of the liver.

9. Prophylaxis: The prevention of post-operative infections caused by anaerobic bacteria, especially those associated with colonic, gastro-intestinal and gynaecological surgery.

4.2 Posology and method of administration

Route: Oral administration during or after a meal.

Posology

Eradication of H. pylori associated with duodenal ulcers:

Adults: the usual dose of Fasigyn is 500mg twice daily coadministered with omeprazole 20mg twice daily and clarithromycin 250mg twice daily for 7 days.

Clinical studies using this 7 day regimen have shown similar *H. pylori* eradication rates when omeprazole 20mg once daily was used. For further information on the dosage for omeprazole see Astra data sheet.

Anaerobic infections*:*

Adults: an initial dose of 2g the first day followed by 1g daily given as a single dose or as 500mg twice daily. Treatment for 5 to 6 days will generally be adequate but clinical judgement must be used in determining the duration of therapy, particularly when eradication of infection from certain sites may be difficult. Routine clinical and laboratory observation is recommended if it is considered necessary to continue therapy for more than 7 days.

Children: < 12 years – there is no data available.

Non-specific vaginitis:

Adults: non-specific vaginitis has been successfully treated with a single oral dose of 2g. Higher cure rates have been achieved with 2g single doses on 2 consecutive days (total dose 4g).

Acute Ulcerative Gingivitis:

Adults: a single oral dose of 2g.

Urogenital trichomoniasis:

(when infection with *Trichomonas vaginalis* is confirmed, simultaneous treatment of the consort is recommended).

Adults: a single dose of 2g.

Children: a single dose of 50 to 75mg/kg of body weight. It may be necessary to repeat this dose.

Giardiasis:

Adults: a single dose of 2g.

Children: a single dose of 50 to 75mg/kg of body weight. It may be necessary to repeat this dose.

Intestinal Amoebiasis:

Adults: a single daily dose of 2g for 2 to 3 days.

Children: a single daily dose of 50 to 60mg/kg of body weight on each of 3 successive days.

Amoebic involvement in the liver:

Adults: total dosage varies from 4.5 to 12g, depending on the virulence of the *Entamoeba histolytica*.

For amoebic involvement of the liver, the aspiration of pus may be required in addition to therapy with Tinidazole

Initiate treatment with 1.5 to 2g as a single oral daily dose for three days. Occasionally when a three day course is ineffective, treatment may be continued for up to six days.

Children: a single dose of 50 to 60 mg/kg of body weight per day for five successive days.

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.

Prevention of post-operative infection:

Adults: a single dose of 2g approximately 12 hours before surgery.

Children: < 12 years – there is no data available.

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

Use in the elderly**:** there are no special recommendations for this age group.

Method of administration

Oral administration. Swallow tablet's whole with a glass of water during or after a meal.

"The scored is non-functional".

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

As with other drugs of similar structure, tinidazole is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal studies.

Tinidazole should be avoided in patients with organic neurological disorders.

Tinidazole, other 5-nitroimidazole derivatives or any of the components of this product should not be administered to patients with known hypersensitivity to the drug.

Use of tinidazole is contraindicated during the first trimester of pregnancy and in nursing mothers.

4.4 Special warnings and precautions for use

As with related compounds, alcoholic beverages should be avoided during Fasigyn therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing Tinidazole.

Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with Fasigyn abnormal neurological signs develop, therapy should be discontinued.

Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although carcinogenicity data is not available for tinidazole, the two drugs are structurally related and therefore there is a potential for similar biologic effects. Mutagenicity results with tinidazole were mixed (positive and negative). The use of tinidazole for longer treatment than usually required should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided.

Anticoagulants: Drugs of similar chemical structure have been shown to potentiate the effects of oral anticoagulants. Prothrombin time should be closely monitored and adjustments to the dose of the anticoagulants should be made as necessary.

4.6 Pregnancy and lactation

Pregnancy

Animal studies have shown reproductive toxicity. Tinidazole crosses the placental barrier. Since the effects of compounds of this class on foetal development are unknown, tinidazole is contraindicated in the first trimester of pregnancy.

There is no evidence that tinidazole is harmful during the latter stages of pregnancy, but it should be used in the second and third trimesters only in cases where it is absolutely necessary, when the benefits of therapy outweigh possible risks to both mother and foetus.

Breast-feeding

Tinidazole is excreted in breast milk. Tinidazole may continue to appear in breast milk for more than 72 hours after administration. Women should not nurse until at least 3 days after having discontinued taking Tinidazole

Fertility

There are no human data on the effect of tinidazole on fertility. Male and female fertility may be impacted based on animal studies that have shown adverse effects on male and female fertility

4.7 Effects on ability to drive and use machines

No special precautions should be necessary. However, drugs of similar chemical structure, including Fasigyn, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If any abnormal neurological signs develop during Fasigyn therapy, the drug should be discontinued.

4.8 Undesirable effects

Reported side effects have generally been infrequent, mild and self-limiting.

The reported undesirable effects are listed below according to MedDRA system organ class classification and frequency. Within each frequency category, the ADRs are presented in the order of clinical importance. Frequency categories are expressed as: 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 (the frequency cannot be estimated from the available data).

System Organ Class	*Common*	*Not known*
Blood and the lymphatic system disorders		Leukopenia
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 Stomatitus 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

4.9 Overdose

Signs and symptoms of overdosage: There are no reported overdoses in humans with Tinidazole

Treatment for overdosage: There is no specific antidote for treatment of overdosage with tinidazole. Treatment is symptomatic and supportive. Gastric lavage may be useful. Tinidazole is easily dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for systemic use

ATC code: J 01XD02

Fasigyn is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves *Trichomonas vaginalis, Entamoeba histolytica* and *Giardia lamblia.*

The mode of action of Fasigyn against anaerobic bacteria and protozoa involves penetration of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.

Fasigyn is active against *Helicobacter pylori*, *Gardnerella vaginalis* and most anaerobic bacteria including *Bacteroides fragilis*, *Bacteroides melaninogenicus*, Bacteroides spp., Clostridium spp., Eubacterium spp., Fusobacterium spp., Peptococcus spp., Peptostreptococcus spp. and Veillonella spp.

Helicobacter pylori (H.pylori) is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with this agent. *H.pylori* is also implicated as a major contributing factor in the development of gastritis and ulcer recurrence in such patients. Evidence suggests a causative link between *H.pylori* and gastric carcinoma.

Clinical evidence has shown that the combination of Fasigyn with omeprazole and clarithromycin eradicates 91-96% of *H.pylori* isolates.

Various different *H.pylori* eradication regimens have shown that eradication of *H.pylori* heals duodenal ulcers and reduces the risk of ulcer recurrence.

5.2 Pharmacokinetic properties

Tinidazole is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2g tinidazole orally, peak serum levels of 40-51 micrograms/ml were achieved within two hours and decreased to between 11-19 micrograms/ml at 24 hours. Healthy volunteers who received 800mg and 1.6g tinidazole IV over 10-15 minutes achieved peak plasma concentrations that ranged from 14 to 21mcg/ml for the 800mg dose and averaged 32mcg/ml for the 1.6g dose. At 24 hours postinfusion, plasma levels of tinidazole decreased to 4-5mcg/ml and 8.6mcg/ml respectively, justifying once daily dosing. Plasma levels decline slowly and tinidazole can be detected in plasma at concentrations of up to 1 microgram/ml at 72 hours after oral administration. The plasma elimination half-life for tinidazole is between 12-14 hours.

Tinidazole is widely distributed in all body tissues and also crosses the blood brain barrier, obtaining clinically effective concentrations in all tissues. The apparent volume of distribution is about 50 litres. About 12% of plasma tinidazole is bound to plasma protein.

Tinidazole is excreted by the liver and kidneys. Studies in healthy patients have shown that over 5 days, 60-65% of an administered dose is excreted by the kidneys with 20-25% of the administered dose excreted as unchanged tinidazole. Up to 5% of the administered dose is excreted in the faeces.

Studies in patients with renal failure (creatinine clearance <22ml/min) indicate that there is no statistically significant change in tinidazole pharmacokinetic parameters in these patients.

5.3 Preclinical safety data

Repeat-dose toxicity

In a repeat-dose toxicity study in beagle dogs, oral administration of tinidazole increased atrophy of the thymus in both sexes at 300 and 600 mg/kg/day, and atrophy of the prostate in males at all doses of 100, 300 and 600 mg/kg/day. The initial highest dose of 1000 mg/kg/day was lowered to 600 mg/kg/day due to severe clinical signs. The no-observed-adverse-effect level for females was 100 mg/kg/day (approximately 0.9 times the highest human dose based upon plasma AUC).

Genotoxicity/carcinogenicity

Tinidazole showed some evidence of mutagenic potential. In an in vitro mutagenicity assay, tinidazole was mutagenic in the TA 100, S. typhimurium tester strain both with and without metabolic activation. Tinidazole was negative for mutagenicity in a mammalian cell culture system utilising Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

Tinidazole carcinogenicity studies in rats, mice or hamsters have not been reported. However, metronidazole, a chemically-related nitroimidazole, has been reported to be carcinogenic in mice and rats but not hamsters. In several studies metronidazole showed evidence of pulmonary, hepatic, and lymphatic tumorigenesis in mice and mammary and hepatic tumours in female rats.

Reproductive and developmental toxicity

Tinidazole did not cause malformations in mice or rats. In rats, oral administration of tinidazole reduced embryo-foetal viability and growth retardation (reduced foetal weight and increased skeletal variations) from 500 mg/kg/day (approximately 2 times the highest human therapeutic dose based upon body surface area). In a rat developmental toxicity study, a higher incidence of foetal mortality was noted following oral administration of 600 mg/kg (approximately 3 times the highest human therapeutic dose based upon body surface area). Embryo-foetal toxicity was not observed in mice at the highest dose level of 2,500 mg/kg (approximately 6 times the highest human therapeutic dose based upon body surface area).

In a male rat fertility study, oral administration of tinidazole reduced fertility at 600 mg/kg/day. Degeneration of the seminiferous tubules in the testes with corresponding effects on spermatogenic measures were noted at 300 and 600 mg/kg/day. The NOAEL for testicular and spermatogenic effects was 100 mg/kg/day (approximately 0.5 times the highest human therapeutic dose based upon body surface area). In another study, oral

administration of tinidazole reduced fertility in male rats at 300 mg/kg/day and in female rats at 150 and 300 mg/kg/day.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose

Maize starch

Povidone (K-30)

Purified water

Colloidal anhydrous silica

Magnesium Stearate

Sodium starch glycolate

Purified Talc

Instacoat Aqua III white

Tartrazine Lake ISI

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light & moisture.

6.5 Nature and contents of container

10×10 tablets in Alu / PVC blister packed in a carton.

6.6 Special precautions for disposal and other handling

No special instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Name	**Brawn Laboratories Limited.**
Location (address)	13, N.I.T. Industrial Area, FARIDABAD-121 001, (HARYANA)

Country	INDIA
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E-mail	regulatory2@brawnlabs.in
Website	www.brawnlabs.in

8. Marketing authorization number(s)

0019/NMR/LD

9. Date of first authorization/renewal of the authorization

Not Applicable

10. Date of revision of the text

Not Applicable