FASIGYN® Tablets
(Tinidazole)

1. NAME OF THE MEDICINAL PRODUCT

FASIGYN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: tinidazole.

Film coated tablets containing 500 mg of tinidazole.

3. PHARMACEUTICAL FORM

Film coated tablets.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Prophylaxis:

a) Prevention of post-operative infections caused by anaerobic bacteria, especially those associated with colonic, gastrointestinal and gynecological surgery.

Treatment of the following infections:

b) Anaerobic infections such as:

- *Intraperitoneal infections*: peritonitis, abscess
- *Gynecological infections*: endometritis, endomyometritis, tubo-ovarian abscess
- *Bacterial septicemia*
- *Post-operative wound infections*
- *Skin and soft tissue infections*
- *Upper and lower respiratory tract infections*: pneumonia, empyema, lung abscess

c) Non-specific vaginitis

d) Acute ulcerative gingivitis

e) Urogenital trichomoniasis in both male and female patients

f) Giardiasis

g) Intestinal amebiasis

h) Amebic involvement of the liver

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Prophylaxis

a) Prevention of post-operative infections

Use in Adults:

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

Use in Children less than 12 years:

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

Treatment

b) Anaerobic infections

Use in Adults:

Oral: An initial dose of 2 g the first day followed by 1 g daily, given as a single dose or as 500 mg twice daily.

Treatment for 5 to 6 days will generally be adequate, but clinical judgment 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.

Use in Children less than 12 years:

There is no data available to permit dosage recommendations for treatment of anaerobic infections in children below the age of 12 years.

c) Non-specific vaginitis

Use in Adults:

Non-specific vaginitis has been successfully treated with a single oral dose of 2 g. Higher cure rates have been achieved with 2 g single daily doses for two consecutive days (total dosage 4 g).

d) Acute ulcerative gingivitis

Use in Adults:

A single oral dose of 2 g.

e) Urogenital trichomoniasis

When infection with *Trichomonas vaginalis* is confirmed, simultaneous treatment of the consort is recommended.

Use in Adults:

Preferred Regimen:

A single oral dose of 2 g.

Alternative Regimen:

One 150 mg tablet orally three times daily for 5 days, or one 150 mg tablet orally twice daily for 7 days.

Use in Children:

A single dose of 50 to 75 mg/kg of body weight. It may be necessary to repeat this dose once in some cases.

f) Giardiasis

Use in Adults:

A single oral dose of 2 g or, alternatively, one 150 mg tablet administered twice daily for 7 days.

Use in Children:

A single dose of 50 to 75 mg/kg of body weight. It may be necessary to repeat this dose once in some cases.

g) Intestinal amebiasis

Use in Adults:

A single oral daily dose of 2 g for 2 to 3 days or, alternatively, 600 mg administered orally twice daily for 5 days. Occasionally, when a three-day single daily dose is ineffective, treatment may be continued for up to six days. When a five-day, twice daily course is ineffective, treatment may be continued for up to 10 days.

Use in Children:

A single dose of 50 to 60 mg/kg of body weight per day for three successive days.

h) Amebic involvement of the liver

For amebic involvement of the liver, the aspiration of pus may be required in addition to therapy with FASIGYN®.

Use in Adults:

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

Initiate treatment with 1.5 to 2 g orally as a single daily dose for 3 days. Occasionally, when a three-day course is ineffective, treatment may be continued for up to 6 days.

As an alternative regimen, 600 mg orally twice daily may be given for 5 days. Occasionally, when the five-day course is ineffective, treatment may be continued for up to 10 days.

Use in Children:

A single oral 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 FASIGYN® is easily removed by haemodialysis, patients may require additional doses of FASIGYN® to compensate.[1,7]

Oral Administration:

It is recommended that oral FASIGYN® be taken during or after a meal.

4.3. CONTRAINDICATIONS

Use of tinidazole is contraindicated during the first trimester of pregnancy, in nursing mothers (see section **4.6.** – **Fertility, pregnancy and lactation**), in patients with organic neurological disorders and in patients with known hypersensitivity to tinidazole, other 5-nitroimidazole derivatives, or any of the components of this product. As with other drugs of similar structure, tinidazole is also contraindicated in patients having, or with a history of blood dyscrasias, although no persistent hematologic abnormalities have been noted in clinical or animal studies.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with related compounds, alcoholic beverages should be avoided during and for a least 72 hours following completion of tinidazole[2] therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia).

Drugs of similar chemical structure, including tinidazole, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy and rarely, convulsions. If any abnormal neurological signs develop during tinidazole therapy, the drug 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) (see section **5.3.** – **Preclinical safety data**). The use of tinidazole for longer treatment than usually required should be carefully considered.[16]

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 (see section **4.4. - Special warnings and precautions for use**).

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.[2,7]

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy:

Animal studies have shown reproductive toxicity (see section **5.3. – Preclinical safety data**).[19] Tinidazole crosses the placental barrier. Since the effects of compounds of this class on fetal development are unknown, tinidazole is contraindicated in the first trimester of pregnancy.[19]

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 fetus (see section **5.3. – Preclinical safety data**).[19]

Lactation:

Tinidazole is distributed into breast milk. Tinidazole may be present in breast milk for more than 72 hours after administration. Women should not nurse during and for at least three days after having discontinued taking tinidazole.[7]

Fertility:
Male and female fertility may be impacted based on animal studies that have shown adverse effects on male and female fertility (see section **5.3. – Preclinical safety data**).[19]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of tinidazole on the ability to drive or use machinery has not been studied. There is no evidence to suggest that tinidazole may affect these abilities.

4.8. UNDESIRABLE EFFECTS

All ADRs listed in the CDS are presented by MedDRA SOC. Within each frequency category, the ADRs are presented in the order of clinical importance.

Adverse Reactions Table[17]

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
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		Thrombophlebitis‡ Flushing
Gastrointestinal Disorders	Vomiting Diarrhoea Nausea Abdominal pain	Glossitis Stomatitis 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

CIOMS III categories[18]: Common ≥1/100 to < 1/10 (≥1% and <10%), Not known: frequency cannot be estimated from available data.

‡ Thrombophlebitis has occasionally been observed at the infusion site with the intravenous dosage form.

4.9. OVERDOSE

Signs and Symptoms of Overdose

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

Treatment of Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Tinidazole is a 5-nitroimidazole derivative of the substituted imidazole compounds and possesses antimicrobial activity against anaerobic bacteria and protozoa. The mode of action of tinidazole against anaerobic bacteria and protozoa is believed to involve the penetration of the drug into the cell of the microorganism and subsequent damage of DNA strands or inhibition of their synthesis.

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

Tinidazole is active against *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.

5.2. PHARMACOKINETIC PROPERTIES

Absorption: Tinidazole is rapidly and completely absorbed following oral administration. When compared with oral dosing, systemic absorption from vaginal dosage forms is minimal at 10%.[7,8]

In studies with healthy volunteers receiving 2 g tinidazole orally, peak serum levels of 40-51 mcg/ml were achieved within two hours and decreased to between 11-19 mcg/ml at 24 hours.

Healthy volunteers who received 800 mg and 1.6 g tinidazole intravenously over 10-15 minutes achieved peak plasma concentrations that ranged from 14 to 21 mcg/ml for the 800 mg dose and averaged 32 mcg/ml for the 1.6 g dose. At 24 hours post-infusion, plasma levels of tinidazole decreased to 4-5 mcg/ml and 8.6 mcg/ml, respectively, justifying once daily dosing.

Plasma levels decline slowly and tinidazole can be detected in plasma at concentrations of 0.5 mcg/ml at 72 hours post-infusion and up to 1 mcg/ml at 72 hours following oral administration. The plasma elimination half-life for tinidazole is between 12-14 hours.

Distribution: 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 liters.[13] About 12% of plasma tinidazole is bound to plasma proteins.

Elimination: 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 feces.[7]

Studies in patients with renal failure (creatinine clearance <22 ml/min) indicate that there is no statistically significant change in tinidazole pharmacokinetic parameters in these patients (see section **4.2.** – **Posology and method of administration**).

5.3. PRECLINICAL SAFETY DATA

Repeat-dose toxicity

A repeat-dose toxicology study has been performed in beagle dogs using oral dosing of tinidazole at 100 mg/kg/day, 300 mg/kg/day, and 1000 mg/kg/day for 28-days. On Day 18 of the study, the highest dose was lowered to 600 mg/kg/day due to severe clinical signs. The two compound-related effects observed in the dogs treated with tinidazole were increased atrophy of the thymus in both sexes at the middle and high doses, and atrophy of the prostate at all doses in the males. A no-observed-adverse-effect level (NOAEL) of 100 mg/kg/day for females was determined. There was no NOAEL identified for males because of minimal atrophy of the prostate at 100 mg/kg/day (approximately 0.9 times the highest human dose based upon plasma AUC comparisons).[19]

Mutagenicity/carcinogenicity

Tinidazole showed some evidence of mutagenic potential.[19] 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 utilizing 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.[9-12]

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 tumors in female rats.[19]

Reproductive toxicity

Tinidazole did not cause malformations in mice or rats. An embryo-fetal developmental toxicity study in pregnant mice indicated no embryo-fetal toxicity at the highest dose level of 2,500 mg/kg (approximately 6 times the highest human therapeutic dose based upon body surface area conversions). In an embryo-fetal developmental toxicity study in pregnant rats, reduced embryo-fetal viability was noted at 500 and 2000 mg/kg/day and growth retardation (reduced fetal weight and increased skeletal variations) was noted at 500 mg/kg/day (approximately 2 times the highest human therapeutic dose based upon body surface area conversions). In a developmental toxicity study in pregnant rats dosed from GD 1-21 in which dams were allowed to deliver and rear their offspring, a higher incidence of fetal mortality was noted at 600 mg/kg; the NOAEL for developmental toxicity was 300 mg/kg.[19]

In a male fertility study in rats treated with tinidazole, male fertility was reduced 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 dose levels. 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 conversions). In another fertility study, reduced fertility was noted in male rats at 300 mg/kg/day and in female rats at 150 and 300 mg/kg/day following 20 days of dosing administration.[19]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

- Tinidazole
- F.D.C Yellow No.6 Aluminum lake
- Corn Starch USP
- Alginic Acid
- Microcrystalline Cellulose M-102
- Magnesium Stearate
- Sodium Lauryl Sulphate
- Hydroxyl Propyl Methyl Cellulose M 102
- Polyethylene glycol 8000
- Titanium di-oxide
- F.D.C Yellow No.6 Alum. lake

- Mineral oil (Heavy)

6.2. INCOMPATIBILITIES

Information not available

6.3. SHELF LIFE

36 Months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in a dry place, avoid exposure to heat and light.

6.5. NATURE AND CONTENTS OF CONTAINER

FASIGYN® (tinidazole) 500 mg is available as 4 × 10's tablets in PVC/Aluminium foil blister cards.

Fasigyn®/LPD/PK-02
According to CDS V 7.0 Dated: 30 May 2019; Supersedes CDS V 6.0 Dated: 11 July 2013

Marketed by:
Pfizer Pakistan Limited
B-2, Site, Karachi

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

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