FASIGYN®

Tinidazole

Reference Market: Belgium

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FASIGYN 500 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is tinidazole. Each tablet contains 500 mg tinidazole.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.
White, round, convex and film coated tablets, with the inscription "FAS 500" engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FASIGYN (tinidazole) 500 mg tablets is indicated in adults, adolescents and children aged > 12 years in the oral treatment of the following infections:

a) Anaerobic infections:
Infections when anaerobes (such as *Bacteroides fragilis*, other species of *Bacteroides*, *Fusobacteria* spp. or *Peptococcus* spp., *Peptostreptococcus* spp., *Clostridium* spp., *Eubacterium* spp. and *Veillonella* spp) have been isolated or are suspected of being the responsible pathogens for infections such as: sepsis, chronic sinusitis, pneumonia, empyema, pulmonary abscess, osteomyelitis due to *Bacteroides*, septic abortion, peritonitis, postoperative abdominal infections, phlegmons, postoperative parietal infections.

b) Vaginitis due to *Gardnerella vaginalis.*

c) Genitourinary tract infections due to *Trichomonas vaginalis* in both male and female patients.
When infection with *Trichomonas vaginalis* is confirmed or even suspected, simultaneous treatment of the consort is recommended.

d) Intestinal and liver infections due to *Entamoeba histolytica* and intestinal infections due to *Giardia lamblia*.

4.2 Posology and method of administration

Posology

1. Urogenital trichomoniasis

Recommended dosage in urogenital trichomoniasis in both male and female patients is a single 2 g dose of tinidazole, i.e. 4 tablets of FASIGYN in one dose.

2. Amebiasis

a) *Acute amebic dysentery*
Recommended dosage to treat acute amebic dysentery is 4 tablets of FASIGYN o.d. for 2-3 days. In those cases in which a three-day, 2 g-a-day treatment would prove to be inadequate, total duration of treatment may be extended to six days.

b) *Amebic liver abscess*
Total dosage of tinidazole to treat amebic liver abscess varies from 4.5 to 12 g, depending on the virulence of pathogen. Mostly, a single daily dose of 3-4 tablets of FASIGYN will be administered for three days. If needed, treatment can be pursued for up to 6 days. For amebic liver abscess, the aspiration of pus may be required in addition to therapy with FASIGYN.

3. Giardiasis

Recommended dosage in intestinal infections due to *Giardia lamblia* is 4 tablets of FASIGYN in a single dose. Stools of patients with *Giardia* involvement should be examined 7-10 days after conclusion of therapy so as to detect presence of *Giardia lamblia*.

4. Vaginitis due to *Gardnerella vaginalis*

Cases of vaginitis due to *Gardnerella vaginalis* have been successfully treated with a single oral dose of 2 g of tinidazole, i.e. 4 tablets of FASIGYN. However, better cure rates were attained with the use of 2 g daily doses for two days (i.e. a total of 4 g).

5. Anaerobic infections

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 judgement must determine the duration of therapy, particularly when eradication of infection from certain sites may be difficult.

Table 1 - Summary of posology for each indication for the **adults**

Indications	*No. of tablets (in a single dose with a meal)*	*Duration of Therapy*
Urogenital trichomoniasis (male and female):	4 tablets of 500 mg	1 day
Acute amebic dysentery	4 tablets of 500 mg	2-3 days (up to 6 days as needed)
Amebic liver abscess	3-4 tablets of 500 mg	3-6 days
Giardiasis	4 tablets of 500 mg	1 day
Vaginitis due to non specific *Gardnerella*	4 tablets of 500 mg	1-2 days
Anaerobic infections	4 tablets of 500 mg on the first day followed by 2 tablets of 500 mg for 4 to 5 days	5-6 days

Paediatric population
The maximum adult dosage should not be exceeded in children.
Clinical data are not available to allow dosage recommendations for children below the age of 12 years in the treatment or the prevention of anaerobic infections in that age-group.

Table 2 - Summary of posology for each indication for **children ≥ 12 years**

Indications	*mg/kg/day (in a single dose with a meal)*	*Duration of Therapy*
Urogenital trichomoniasis	50 - 75 mg/kg	1 day (repeat once as needed)
Acute amebic dysentery	50 - 60 mg/kg	3 days
Amebic liver abscess	50 - 60 mg/kg	5 days
Giardiasis	50-75 mg/kg	1 day (repeat once as needed)

Hepatic Impairment Patients
There are no clinical or pharmacokinetic data of tinidazole in patients with hepatic impairment. Since a significant amount of the tinidazole dose is known to be eliminated by hepatic metabolism, tinidazole should be administered cautiously in patients with hepatic impairment, especially when receiving the drug for longer periods of time (> 5 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 that elimination.

Method of administration
It is recommended that Fasigyn be taken during or after a meal.
Fasigyn should not be taken with alcohol (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance tinidazole, other 5-nitroimidazole derivatives, or any of the excipients listed in section 6.1.
- Pregnancy and lactation: tinidazole is contraindicated during the first trimester of pregnancy and in nursing mothers (see section 4.6).
- As with other drugs of similar structure, FASIGYN 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 toxicologic studies.

- FASIGYN is also contraindicated in patients with organic neurological disorders.

4.4 Special warnings and precautions for use

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). The use of tinidazole for longer treatment than usually required should be carefully considered.

Neurological disturbances such as dizziness, vertigo, incoordination, ataxia, peripheral neuropathy and rarely convulsions can occur. If any abnormal neurological signs develop during therapy, the drug should be discontinued immediately.

Concomitant use of alcoholic beverages should be avoided during and for at least 3 days following completion of tinidazole therapy (see section 4.5).

Sodium
This medicine contains less than 1 mmol sodium (23 mg), that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
Concomitant use of alcoholic beverages should be avoided during therapy and at least for three days after the end of treatment, because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia).

Anticoagulants
FASIGYN, like the other 5-nitroimidazole derivatives, may potentiate the effects of oral coumarin anticoagulants (warfarin, acenocoumarol, dicumarol, anisindione, phenindione, phenprocoumon). Prothrombin times should be closely monitored and adjustments to the dose of the anticoagulant should be made as necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of tinidazole in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3).

Tinidazole crosses the placental barrier. Since the effects of compounds of this class on foetal development are unknown, tinidazole is contra-indicated 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 (see section 5.3). The teratogenic potential of tinidazole was evaluated in a large population-based data set.Of 22,843 cases with congenital anomaly, only 10 (0.04%) had mothers treated with tinidazole during pregnancy, and of 38,151 controls (without congenital anomaly), 16 (0.04%) had mothers treated with tinidazole during pregnancy. Most mothers had been treated mainly in the second trimester.

Breastfeeding

Tinidazole is excreted in human milk to such an extent that effects on breastfed newborns/infants are likely.

Tinidazole is contraindicated during breastfeeding (see section 4.3). Tinidazole may be present in breast milk for more than 72 hours after administration. Women should not breastfeed during and for at least three days after having discontinued taking FASIGYN. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tinidazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

Clinical data on male and female fertility are not available. Animal studies show impaired fertility in males and females following dosing with tinidazole (see section 5.3).

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

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

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by MedDRA system organ class 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 (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**	**Frequency Not known *(Cannot be Estimated from the Available Data)***
Blood and lymphatic system disorders				Leukopenia
Immune system disorders				Anaphylactic shock, 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, tongue discolouration
Skin and subcutaneaous tissue disorders	Dermatitis allergic, pruritus		Severe skin reactions (such as erythema multiforme, Stevens-Johnson syndrome and epidermal necrolysis)	Angioedema, urticaria
Renal and urinary disorders				Chromaturia
General disorders and administration site conditions				Pyrexia, fatigue
Investigations				Laboratory tests changes

Candidal overgrowth in the vagina may occur with treatment with 5-nitro-imidazole derivatives, including tinidazole.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation 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 according to their local country requirements.

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

Pharmacotherapeutic group:
Other Antibacterials (Imidazole derivatives); ATC code: J01XD02
Agents against amoebiasis and other protozoal diseases (Nitroimidazole derivatives), ATC code: P01AB02

FASIGYN (tinidazole) is a synthetic derivative of the substituted imidazole compounds. It is used in the treatment of infections due to *Trichomonas vaginalis*, *Entamoeba histolytica*, *Giardia lamblia*, and sensitive obligate anaerobic bacteria, such as *Bacteroides fragilis*, *Bacteroides melaninogenicus*, *Bacteroides* spp., *Fusobacteria* spp., *Peptococcus* spp., *Peptostreptococcus* spp., *Clostridium* spp., *Eubacteria* spp. and *Veillonella* spp. Tinidazole is also active *in vitro* against *Gardnerella vaginalis*, but is not active against *Candida albicans*.

The chemical name of FASIGYN (tinidazole) is 1-(2-(ethylsulfonyl)ethyl)-2- methyl-5-nitroimidazole. It is a pale yellow, crystalline substance that is relatively insoluble in water and soluble in organic solvents such as methanol and chloroform.

Mechanism of action
The mode of action of FASIGYN (tinidazole) against anaerobic bacteria involves penetration of the drug into the cell of the microorganisms and subsequent alteration of DNA strands or inhibition of their synthesis.

5.2 Pharmacokinetic properties

Absorption
FASIGYN (tinidazole) is rapidly and completely absorbed after a single 2-g oral dose. Peak serum levels usually occur within one to two hours after administration and decline slowly. The substance is still detectable in the serum after 72 hours. Serum levels after a single oral 2 g dose of FASIGYN are 41 ± 5 mcg/ml at 1 hour, 46 ± 4 mcg/ml at 4 hours and 19 ± 2 mcg/ml at 24 hours. Co-administration of FASIGYN (tinidazole) with a high-fat meal results in no change in AUC, but slight reduction in C_{max} (~15 %) and prolongation of T_{max} from 1.6 to 3.0 h.

The pharmacokinetics of tinidazole following intravenous administration are linear over the dose range of 400 to 1600 mg.

Distribution
FASIGYN (tinidazole) is well distributed into body tissues in clinically effective concentrations and effectively passes the blood brain barrier. The apparent volume of distribution is about 0.63-0.65 L/kg (~50 L). About 12 % of plasma tinidazole is bound to plasma proteins.

Biotransformation:
Tinidazole is primarily eliminated by hepatic metabolism (>40 %). In vitro studies using human liver microsomes indicate that tinidazole is metabolized primarily by CYP3A4 with minor metabolism by CYP2B6. Following intravenous administration, tinidazole is the major component in the plasma, and only minor traces of the 2-hydroxymethyl metabolite are detected.

Elimination
Some 20-25 % of administered tinidazole is recovered in the urine unchanged with another 12 % recovered as metabolites. Up to 5 % of the administered dose is excreted in the feces. The tinidazole half-life is 12.7 hours ± 0.5 hours

Hepatic Impairment patients
The pharmacokinetics of tinidazole in patients with hepatic impairment has not been studied. Since a significant amount of the tinidazole dose is known to be eliminated by hepatic metabolism, it is necessary to exercise caution in the selection of appropriate dosage in these patients, especially when receiving the drug for longer periods of time (> 5 days) (see section 4.2).

Renal impairment
The pharmacokinetics of tinidazole are not markedly changed in patients with moderate to severe renal failure (see section 4.2).

5.3 Preclinical safety data

Repeated dose toxicity
A repeated-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 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-fold the highest human dose based upon plasma AUC comparisons).

Mutagenicity/carcinogenicity
Tinidazole showed some evidence of mutagenic potential. In an in vitro mutagenicity assay, tinidazole was found mutagenic in some bacterial strains both with and without the metabolic activation system. 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.

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.

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 6.3-fold 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 (2.5-fold 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.

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 no-observed-adverse-effect level (NOAEL) for testicular and spermatogenic effects were 100 mg/kg/day (approximately 0.5-fold 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Alginic acid
Maize starch
Magnesium stearate
Sodium lauryl sulfate

Film coating
Hydroxypropyl methylcellulose 2910
Propylene glycol
Titanium dioxide (E171)

6.2 Incompatibilities

None known.

6.3 Shelf life

Do not use Fasigyn after the expiry date which is stated on the carton/Blister after EXP:.
The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Keep this medicine out of the reach and sight of children.

Do not store above 25° C and protect from light.

6.5 Nature and contents of container

Blisters of 4 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. FURTHER INFORMATION

Marketing Authorisation Holder:

Pfizer S.A., Boulevard de la Plaine, 17, 1050 Brussels, Belgium

Manufactured, Packaged and Released by: :

FAREVA AMBOISE

Zone Industrielle, 29 route des Industries, 37530 Pocé Sur Cisse, France

8. DATE OF REVISION OF THE TEXT

October 2020

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers

Union of Arabic Pharmacists