

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT AND INTERNATIONAL NONPROPRIETARY NAME (INN)

TINAZOL film-coated tablets 500 mg

Tinidazole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of tinidazole as an active substance.

3. PHARMACEUTICAL FORM

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 (see section 4.2).

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 TINAZOL is 500mg twice daily co-administered with omeprazole 20mg twice daily and clarithromycin 250mg twice daily for 7 days.

Clinical studies using this 7day regimen have shown similar H. pylori eradication rates when omeprazole 20mg once daily was used.

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 TINAZOL.

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 tablets whole with a glass of water during or after a meal.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 (see section 4.6).

4.4. Special warnings and precautions for use

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

Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with **TINAZOL** 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) (see section 5.3). The use of tinidazole for longer treatment than usually required should be carefully considered.

4.5. Interaction with other medicinal products and other form 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 time should be closely monitored and adjustments to the dose of the anticoagulants should be made as necessary.

4.6. Pregnancy and lactation

Pregnancy:

Fertility studies in rats receiving 100mg and 300mg tinidazole/kg had no effect on fertility, adult and pup weights, gestation, viability or lactation. There was a slight, not significant, increase in resorption rate at the 300mg/kg dose.

Tinidazole crosses the placental barrier. Since the effects of compounds of this class on foetal development are unknown, the use of tinidazole during the first trimester is contraindicated. There is no evidence that **TINAZOL** is harmful during the latter stages of pregnancy, but its use during the

second and third trimesters requires that the potential benefits be weighed against possible hazards to mother or 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 TINAZOL.

4.7. Effects on ability to drive and use machines

No special precautions should be necessary. However, drugs of similar chemical structure, including TINAZOL, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoesthesia) and rarely convulsions. If any abnormal neurological signs develop during TINAZOL 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (the frequency cannot be estimated from the available data).

<i>System Organ Class</i>	<i>Common</i>	<i>Not known</i>
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 Hypoesthesia 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9. Overdose

In acute animal studies with mice and rats, the LD50 for mice was >3600mg/kg and >2300mg/kg for oral and intraperitoneal administration respectively. For rats, the LD50 was >2000mg/kg for both oral and intraperitoneal administration.

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: J01XD02

TINAZOL 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 **TINAZOL** 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.

TINAZOL 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 **TINAZOL** 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, (see section 4.2).

5.3. Preclinical safety data

Tinidazole has been shown to be mutagenic in some bacterial strains tested in vitro (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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- lactose monohydrate,
- pregelatinized starch,
- povidone,
- sodium starch glycolate,
- magnesium stearate

FILM: Opadry II white, purified water

6.2. Incompatibilities

No major incompatibilities have been noted.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

TINAZOL film-coated tablets store below 30°C in original packaging, out of reach of children! There are no special requirements for storage.

6.5. Nature and contents of container

Carton box with 4 tablets of 500 mg tinidazole in blister pack (1 blister x 4 tablets).

Carton box with 14 tablets of 500 mg tinidazole in blister pack (1 blister x 14 tablets).

6.6. Special precautions for disposal of unused medicine products

The procedure of unused drugs and waste materials derived from these drugs is carried out according to the regulations for the handling and disposal of pharmaceutical waste.

7. MARKETING AUTHORIZATION HOLDER

ZADA Pharmaceuticals Ltd.

Donji Bistarac without number

75300 Lukavac

Bosnia and Herzegovina

8. MARKETING AUTHORIZATION NUMBER(s)

TINAZOL, film-coated tablets, 4 x 500 mg in a box: 04-07.3-2-6614/16

TINAZOL, film-coated tablets, 14 x 500 mg in a box: 04-07.3-2-6615/16

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION

TINAZOL, film-coated tablets, 4 x 500 mg: 21.12.2016

TINAZOL, film-coated tablets, 14 x 500 mg: 21.12.2016

10. DATA OF LAST/PARTIAL REVISION OF THE TEXT: 08.2016.