**SUMMARY OF PRODUCT CHARACTERISTICS**

**1. NAME OF THE MEDICINAL PRODUCT**

TINAZOL® tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

The active substance is tinidazole. Each film-coated tablet contains 500 mg of tinidazole BP.

Excipients with known effect : this drug contains sodium methylparahydroxybenzoate and sodium propylparahydroxybenzoate, see section 4.4.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablets.

White, round, biconvex & film-coated tablets, with imprints « TINAZOL 500 » on one side.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Tinidazole 500 mg tablets is indicated in adults, adolescents and children over 12 years old for oral treatment of the following infections:

1. Infections caused by anaerobic bacteria

Infections in which anaerobic bacteria (such as *Bacteroides fragilis*, others *Bacteroides* and *Fusobacteria spp* or *Peptococcus* spp., *Peptostreptoccus* spp., *Clostridium* spp., *Eubacterium* spp. and *Veillonella* spp) have been confirmed or are suspected to be the pathogen responsible for infection such as: septicaemia, chronic sinusitis, pneumonia, empyema, lug abscesses, *Bacteroides* osteomyelitis, septic abortion, peritonitis, post-operative abdominal infections, phelgmons and post-operative parietal infections.

1. Vaginitis caused by *Gardnerella vaginalis*
2. Infections of genito-urinary tract caused by *Trichomonas vaginalis* in botch female and male patients. When infection with *Trichomonas vaginalis* has been confirmed or is suspected, similtaneous treatment of the consort is recommended.
3. Intestinal and liver infections caused by *Entamoeba histolytica* and *Giardia lamblia* intestinal infections.

**4.2 Posology and method of administration**

**Posology**

1. Urogenital Trichomoniasis

Recommended dose for urogenital trichomoniasis in both men and women is a single dose of 2 g of tinidazole, i.e a single dose of 4 tablets of TINAZOL.

1. Amoebiasis
2. *Acute Amoebic Dysentery*

The recommended dosage for the treatment of acute amoebic dysentery is 4 tablets of TINAZOL as a single daily dose for two to three days. In the occasional instance when a three days treatment, with a 2 g daily dose, is ineffective, treatment may be continued for six days.

1. *Amoebic Liver Abscess*

In amoebic liver abscess treatment, total dose of tinidazole varies according to the virulence of the pathogenic agent between 4.5 to 12 g. In most cases, 3 to 4 tablets of TINAZOL in a single daily dose is given during 3 days. If necessary, the treatment may be continued for up to six days.

Initiate treatment with 1.5 to 2g as a single oral daily dose for three days.

In amoebic liver abscess the aspiration of pus may be required in addition to therapy with TINAZOL.

1. Giardiasis

In intestinal tract infections caused by *Giardia lamblia*, recommended dose is 4 tablets of TINAZOL in a single administration. Patient’s stool with giardiasis should be checked for *Giardia lamblia* 7 to 10 days after treatment.

1. *Gardnerella vaginalis* vaginitis

*Gardnerella vaginalis* vaginitis have been successfully treated with a single oral dose of 2 g of tinidazole, i.e. 4 tablets of TINAZOL. Higher cure rates have been achieved with a 2 g daily dose on 2 consecutive days (total dose of 4 g).

1. Anaerobic infections

An initial dose of 2 g the first day followed by 1 g daily in a single administration (or as 500 mg twice daily). Treatment for 5 to 6 days is usually adequate. Duration of the treatment should depend on the clinical assessment of the patient’s condition, particularly when eradication of some infection foci is proving difficult.

Table 1 Dosage summary for each indication in **adults**:

|  |  |  |
| --- | --- | --- |
| *Indications* | *Quantity of tablets*  *(in one intake during a meal)* | *Duration of treatment* |
| Urinary-genital Trichomoniasis  (In men and women) | 4 tablets of 500 mg | 1 day |
| Acute Amoebic Dysentery | 4 tablets of 500 mg | 2 to 3 days  (may be continued for up to 6 days if necessary) |
| Amoebic Liver Abscess | 3 to 4 tablets of 500 mg | 3 to 6 days |
| Giardiasis | 4 tablets of 500 mg | 1 day |
| Non-specificvaginitis due to *Gardnerella* | 4 tablets of 500 mg | 1 to 2 days |
| Anaerobic bacterial infections | 4 tablets of 500 mg the first day  followed by 2 tablets of 500 mg the next 4 to 5 days | 5 to 6 days |

*Paediatric population*

The maximum posology in adults should not be exceeded in children.

There is no clinical data available to allow dosage recommendations of tinidazole for children below the age of 12 in the treatment or the prophylaxis of anaerobic infections.

Table 2 Dosage summary for each indication in **children over 12 years old**:

|  |  |  |
| --- | --- | --- |
| *Indications* | *mg/ kg/ day*  *(in one intake during a meal)* | *Duration of treatment* |
| Urinary-genital Trichomoniasis | 50 to 75 mg/kg | 1 (repeat one time if necessary) |
| Acute Amoebic Dysentery | 50 to 60 mg/kg | 3 days |
| Amoebic Liver Abscess | Amoebic Liver Abscess | 5 days |
| Giardiasis | 50 to 75 mg/kg | 1 day (repeat once if necessary) |

Patients with hepatic failure

There is no clinical or pharmacokinetic data on tinidazole use in patients with hepatic impairment. It is known that a significant amount of tinidazole dose is eliminated by the hepatic metabolism. Therefore, caution is recommended when treating patients with hepatic impairment, especially when the drug is administrated for a longer period of time (> 5 days).

Patients with renal impairment

Dosage adjustements 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.

**Method of administration**

It is recommended to take TINAZOL during or after a meal.

Concomitant intake of alcoholic beverages should be avoided (see section 4.5).

**4.3 Contraindications**

* Hypersensitivity to the active substance, tinidazole, or other 5-nitroimidazole derivatives, or to any of the excipients listed in section 6.1.
* Pregnancy and breastfeeding : tinidazole is contraindicated during the first trimester of pregnancy.and in breastfeeding women (see section 4.6).
* As with other drugs of similar structure, TINAZOL is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal toxicology studies.
* TINAZOL should be avoided in patients with organic neurological disorders.

**4.4 Special warnings and precautions for use**

Carcinogenicity has been seen in mice and rats chronically treated with metronidazole, another 5-nitroimidazole derivatives. Althoug carcinogenecity data are not available for tinidazole, the two molecules are structurally similar and therefore likely to induce the same biological effects. Mutagenicity results with tinidazole were mixed (positive and negative) (see section 5.3). The use of tinidazole for a longer period of treatment than generally recommended should be carefully considered.

Neurological disturbances such as dizziness, vertigo, incoordination, ataxia, peripheral neuropathy and, rarely convulsions may occur. If suspicious neurological symptoms occur during tinidazole treatment, the treatment should be discontinued.

Concomitant use of alcoholic beverages should be avoided during tinidazole treatment and at least until three days after discontinuing tinidazole (see section 4.5).

This drug contains sodium methylparahydroxybenzoate and sodium propylparahydroxybenzoate that may cause allergic reactions (including delayed reactions).

**4.5 Interaction with other medicinal products and other forms of interaction**

Alcohol:

Alcoholic beverages should be avoided during tinidazole treatment and at least until three days after discontinuing tinidazole as a disulfiram-like reaction may occur (flushing, abdominal cramps, vomiting, tachycardia)).

Anticoagulants:

TINAZOL, as other 5-nitroimidazole derivatives may potentiate the effects of coumarin-type oral anticoagulants (warfarine, acenocoumarol, dicoumarol, anisindione, phenindione, phenprocoumon). Prothrombin times should be closely monitored and adjustments to the dose of the anticoagulants should be adjusted as necessary.

**4.6 Fertility, pregnancy and breastfeeding**

**Pregnancy:**

Data on the use of tinidazole in pregnant women are limited.

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

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.

There is no evidence that tinidazole is harmful during the latter stages of pregnancy, but it should be used in the second and the third trimesters only in cases where it is absolutely necessary, when the benefits of the therapy outweigh possible risks in both mother and fetus (see section 5.3).

Teratogenic potential of tinidazole was assessed on the basis of a large population-based data set. Of 22.843 cases with congenital anomalies, only 10 (0,04%) had a mother treated with tinidazole during pregnancy, and of 38.151 control cases (without anomalies), 16 (0,04%) had a mother treated with tinidazole during pregnancy. The majority of the mothers had been treated mainly in the second semester.

**Breastfeeding:**

Tinidazole is excreted in breast milk in an amount that may have an effect on nursing infants.

Tinidazole is contraindicated during breastfeeding (see section 4.3). 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. A decision should be made whether to discontinue breastfeeding or to discontinue/ avoid treatment with tinidazole; depending of the benefit of breastfeeding versus the benefit of treating the mother.

**Fertility:**

There are no human data available on the effect of tinidazole on fertility. Animal studies have shown that tinidazole has adverse effects on male and female fertility (see section 5.3).

**4.7 Effects on ability to drive and use machines**

The effect of tinidazole on the ability to drive or operate heavy machineny has not been studied.

However, there is no evidence that tinidazole can affect these faculties.

**4.8 Undesirable effects**

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

The table below lists undesirable effects indentified in clinical trials and post-maketing surveillance according to MedDRA system organ class classification and frequency.

Within each frequency category, the adverse drug reactions 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,  ˂ 1/10)** | **uncommon (≥ 1/1 000 ;  ˂ 1/100)** | **Rare (≥ 1/10 000 ; ˂ 1/1 000)** | **Not known (the frequency cannot be estimated from the available data)** |
| Blood and the lymphatic system disorders |  |  |  | Leukopenia |
| Immune system disorders |  |  |  | Anaphylactic shock, drug hypersensivity |
| Metabolism and nutrition disorders | Decreased apetite |  |  |  |
| Nervous sytem disorders | Headache |  |  | Convulsions, peripheral neuropathy, hypoaesthesia,sensory disturbances, ataxia, dizziness, dysgeusia |
| Ear and labyrinth disorders | Vertigo |  |  |  |
| Vascular disorders |  |  |  | Flushing |
| Gastro-intestinal disorders | Vomiting,  diarrhoea, nausea, abdominal pains |  |  | Glossitis, stomatitus, tongue discoloration |
| Skin and subcutaneous tissue disorders | Allergic dermatitis, pruritis |  | Severe skin reactions (such as erythema multiforme, Stevens-Johnson syndrome and epidermal necrolysis) | Angiœdema, urticaria |
| Renal and urinary disorders |  |  |  | Chromaturia |
| General disorders and administration site conditions |  |  |  | Pyrexia, fatigue |
| Investigations |  |  |  | Changes in biological tests |

During treatment with 5-nitro-imidazole derivatives, as tinidazole, surinfection by *Candida albicans* can happen.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

**4.9 Overdose**

Signs and symptoms of overdosage:

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

Treatment of overdosage:

There is no specific antidote for treatment of overdosage with tinidazole. Symptomatic and supportive treatment should be given, a gastric lavage may be useful.

Tinidazole is easily dialysable.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antibacterial for systemic use, ATC code: J01XD02.

Agents against amoebiasis and other protozoal diseases ( Nitroimidazole derivtaes), ATC code: P01AB02.

Tinidazole is a derivative of the substitued imidazole group of compounds. Tinidazole has been shown to be effective against *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*, and against anaerobic bacteria such as *Bacteroides fragilis*, *Bacteroides melaninogenicus,* *Bacteroides spp*., *Fusobacterium spp*., *Peptococcus spp*., *Peptostreptococcus spp*, *Clostridium spp*., *Eubacterium spp*., and *Veillonella spp*.

Tinidazole is also active in vitro against *Gardnerella vaginalis* but it is inactive against *Candida albicans*.

Tinidazole chemical name is: 1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole.

Tinidazole is a pale yellow crystalline solid that is insoluble in water, but soluble in organic solvents such as methanol and chloroform.

Mechanism of action:

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

**5.2 Pharmacokinetic properties**

Absorption

Tinidazole is rapidly and completely absorbed following oral administration of a single oral dose of 2g of tinidazole. Peak serum levels were obtained 1 to 2 hour(s) post-administration. Then plasma levels of tinidazole decreased slowly and tinidazole remains detectable in serum at 72 hours after oral administration.

The peak serum levels following oral administration of a single dose of 2 mg of tinidazole were: 41 ± 5 µg/ml

at 1 hour, 46 ± 4 µg/ml at 4 hours and 19 ± 2 µg/ml at 24 hours.

Administration of tinidazole with a high-fat meal does not alter the AUC, but there was a small reduction in the Cmax (~ 15%) and a prolongation of Tmax from 1.6 to 3.0 hours. After intravenous administration, the pharmacokinetics of tinidazole are linear in the dose range of 400 to 1600 mg.

Distribution

Tinidazole is well distributed into tissues at clinically effective concentrations and effectively crosses the blood-brain barrier. The apparent volume of distribution is approximately 0.63-0.65 l/kg (~ 50 l). About 12% of plasma tinidazole is bound to plasma proteins.

Biotransformation

Most of the administered dose of tinidazole is eliminated by hepatic metabolism (> 40%). In vitro studies using human liver microsomes have shown that tinidazole metabolism is primarily mediated by CYP3A4 with minor metabolism by CYP2B6. After intravenous administration, tinidazole is the major substance in plasma and only minor traces of the 2-hydroxymethyl metabolite are detected.

Elimination

20-25% of the administered dose of tinidazole is excreted by the kidneys as unchanged tinidazole, and about 12% as metabolites. Up to 5% of the administered dose is excreted in the feces. The plasmatic half-life of tinidazole is approximately 12.7 ± 0.5 hours.

Patients with liver impairment:

The pharmacokinetics of tinidazole have not been studied in patients with hepatic impairment. It is known that a significant amount of the tinidazole dose is eliminated by hepatic metabolism. Therefore, caution is recommended when treating patients with hepatic impairment, especially when the drug is administered for a longer period of time (>5 days) (see section 4.2).

Patients with renal impairment:

Moderate to severe renal failure does not significantly change tinidazole pharmacokinetics (see section 4.2).

**5.3 Preclinical safety data**

Repeat dose toxicity:

A repeat-dose toxicology study was conducted in Beagle dogs with tinidazole oral dose at 100 mg/kg/day, 300 mg/kg/day and 1000 mg/kg/day during 28 days. On day 18 of the study, the highest dose was reduced to 600 mg/kg/day due to severe clinical signs. The two component-related effects observed in tinidazole-treated dogs were: increased thymus athrophy in both sexes at intermediate and high doses and prostate atrophy at all doses in males. A Non Observed Adverse Effect Level (NOAEL) of 100 mg/kg/day was determined in females. No NOAEL was identified for males due to minimal prostate atrophy at 100 mg/kg/day (approximately 0.9 times the highest human dose based on plasma AUC comparisons).

Mutagenicity/ carcinogenicity:

Tinidazole has shown some evidence of mutagenic potential. In an in vitro mutagenicity assay, tinidazole was mutagenic in some bacterial strains, even ones without metabolic activation systems. Tinidazole was negative for mutagenicity in mammalian cell cultures using Chinese hamster V79 lung cells (HGPRT assay system) and was negative for the genotoxicity assay of sister chromatid exchange in Chinese hamster ovary (CHO) cells Tinidazole was positive for genotoxicity in vivo in the mouse micronucleus test. No carcinogenicity studies of tinidazole in rats, mice or hamsters have been reported. However, metronidazole (another 5-nitroimidazole derivatives), has been shown to be carcinogenic in mice and rats, but not in hamsters. In several studies, metronidazole showed evidence of pulmonary, hepatic and lymphatic oncogenesis in mice and mammary and liver tumours in rats.

Reproductive toxicity

Tinidazole did not cause malformations in mice or rats. An embryo-fetal developmental toxicity study in pregnant mice showed no embryo-fetal toxicity at the highest dose of 2500 mg/kg (approximately 6.3 times the highest human therapeutic dose based on body surface area conversions). In an embryo-fetal developmental toxicity study in pregnant rats, decreased embryo-fetal viability was observed at 500 and 2000 mg/kg/day and growth retardation (decreased fetal weight and increased skeletal variations) was observed at 500 mg/kg/day (2.5 times the body dose). In a developmental toxicity study in pregnant rats given tinidazole from day 1 to day 21 of gestation and allowed to deliver and rear their offspring, a higher incidence of fetal mortality was observed at doses of 600 mg/kg; the NOAEL for developmental toxicity was established at 300 mg/kg.

In a male fertility study in rats treated with tinidazole, fertility was reduced at 600 mg/kg/day. Degeneration of seminiferous tubules in the testes and corresponding effects on measures of spermatogenesis were seen at 300 and 600 mg/kg/day. The No Observable Toxic Effect Level (NOAEL) for effects on the testes and spermatogenesis was determined to be 100 mg/kg/day (approximately 0.5 times the highest therapeutic dose in humans based on body surface area conversions). In another fertility study, a decrease in fertility was observed in male rats at 300 mg/kg/day and in females at 150 and 300 mg/kg/day after 20 days of treatment.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

For one coated tablet:

*maize starch, microcristalline cellulose, sodium methylparahydroxybenzoate (E219), sodium propylparahydroxybenzoate (E217), talc, magnesium stearate, colloidal anhydrous silica, hypromellose, titanium dioxide (E171), polyethylene glycol 6000.*

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Store in the original package, protect from heat, light and moisture

Store below 30°C.

Keep out the reach and sight of children.

**6.5 Nature and contents of container**

Box of 4 film-coated tablets packaged in PVC-Aluminium blister.

**6.6 Special precautions for disposal and other handling**

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

**7. CATEGORY OF DISTRIBUTION**

Medicinal product not subject to medical prescription  Prescription only medicine

**8. MARKETING AUTHORISATION HOLDER**

EXPHAR s.a.

Zoning Industriel de Nivelles Sud, zone II

Avenue Thomas Edison 105

1402 Thines (Belgium).

Phone 0032 (0)67 68 84 05

Fax 0032 (0)67 68 84 19

**9. MANUFACTURER**

GRACURE Pharmaceuticals Ltd.,

Unit: E-1105, Industrial Area, Phase-III,

Bhiwadi, Dist. Alwar (Raj.)

Phone 91.11.25.92.07.48

Fax 91.11.25.92.07.47

**10. DATE OF REVISION OF THE TEXT**

September 2020.