SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Tinirem 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tinidazole 500 mg.

Excipient(s) with known effect:
This product contains 0.09 mg sunset yellow FCF E110.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, round film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the following infections:

- Eradication of *Helicobacter pylori* associated with duodenal ulcers, in the presence of antibiotic and acid suppressant therapy. See Posology and Method of Administration section.
- 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.
- Non-specific vaginitis.
- Acute ulcerative gingivitis.
- Urogenital trichomoniasis in both male and female patients.
- Giardiasis.
- Intestinal amoebiasis.
- Amoebic involvement of the liver.
- 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

Posology

- *Eradication of H.pylori associated with duodenal ulcers:*
  Adults: the usual dose of Tinirem 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.

- *Intestinal amoebiasis:*
  Adults: A single oral daily dose of 2g for 2 or 3 days.
  Children: A single oral daily dose of 50 to 60mg per kg body-weight on each of three 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 Tinirem.
  Initiate treatment with 1.5 to 2g as a single oral daily may be given for three days. Occasionally when a three day course is ineffective, treatment may be continued for up to six days.
  Children: A single oral daily dose of 50 to 60mg per kg body-weight on each of 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.

- *Giardiasis:*
  Adults: A single dose of 2g.
  Children: A single oral dose of 50 to 75mg per kg body-weigh. It may be necessary to repeat this dose

- *Urogenital trichomoniasis*:
  (when infection with *Trichomonas vaginalis* is confirmed, simultaneous treatment of the consort is recommended)
  Adults: A single oral dose of 2g. Children: A single oral dose of 50 to 75mg per kg body-weight. It may be necessary to repeat this dose

- *Acute necrotising ulcerative gingivitis (Vincent's infection):*
  Adults: A single oral dose of 2g.

- *Bacterial vaginosis (non-specific vaginits):*
  Adults: A single 2g dose is usually given, although higher cure rates have been achieved with a 2g dose on 2 successive days (total dose 4g).

- *Prevention of postoperative anaerobic infections:*
  Adults: 2g is given by mouth 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.

- *Anaerobic bacterial infections:*
  Adults: An initial dose of 2g the first day followed by 1g daily as a single dose or as a 500mg twice daily. Treatment for 5 or 6 days will generally be adequate.
  Children: < 12 years – there is no data available.

Method of Administration
Oral administration during or after a meal.

4.3 Contraindications

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 Tinirem therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing Tinirem.
Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with Tinirem 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 forms of interaction

When given in conjunction with alcohol, Tinirem may provoke a disulfiram-like reaction in some individuals and should be avoided, (see section 4.4).
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 Fertility, pregnancy and lactation

Fertility
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.

Pregnancy
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 Tinirem 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.

Lactation
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 Tinirem.

4.7 Effects on ability to drive and use machines

No special precautions are necessary. However, Tinirem has been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy and rarely convulsions. If any abnormal neurological signs develop during Tinirem 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

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

In acute animal studies with mice and rats, the LD_{50} for mice was >3600mg/kg and >2300mg/kg for oral and intraperitoneal administration respectively. For rats, the LD_{50} was >2000mg/kg for both oral and intraperitoneal administration.
Signs and symptoms of overdosage: There are no reported overdoses in humans with Tinirem.
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: Antibacterials for systemic use, other antibacterials, ATC code: J01XD02

Tinidazole 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 Tinirem 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.

Tinidazole is active against *Helicobacter pylori*, *Gardnerella vaginalis*, and most anaerobic bacteria including *Bacteroides Fragilis*, *Bacteroides melanoginus*, 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.

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 Posology and method of administration).

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

Core
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Colloidal silicon dioxide
Povidone
Glycerol
Talc

Coating

Hypromellose
Polyethylene glycol 400
Titanium dioxide E171
Quinoline yellow E104
Sunset yellow E110

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 Years

6.4 Special precautions for storage

Store below 25 ºC. Protect from light and moisture.

6.5 Nature and contents of container

PCV/Aluminium blisters. Pack-sizes of 4, 12, 40 and 400 tablets.
PP containers with PE closure. Pack-sizes of 100, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

04715/06761/REN/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 31-10-2019

10. DATE OF REVISION OF THE TEXT

18/07/2023