ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fluoxine T 500/600 breakable tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg ciprofloxacin hydrochloride and 600 mg tinidazole.
For full list of excipient, see section 60.1.

3. PHARMACEUTICAL FORM

White coloured, film-coated, capsule-shaped tablets, plain on one side and with a breakline on the other side. The tablets can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Concerning ciprofloxacin

FLUOXINE T contains a combination of antibiotics, ciprofloxacin, belonging to the family of quinolones, and tinidazole, belonging to the family of nitro-imidazole derivatives. FLUOXINE T is indicated in infections caused by germs that are sensitive to the active ingredients and for which ciprofloxacin- or tinidazole-based mono-therapies are not effective, such as:

- Chronic pouchitis and/or pouchitis resistant to the other treatment.
- Pelvic inflammatory disease.

4.2 Posology and method of administration

Posology
Andult

- Chronic pouchitis or those resistant to other treatment: 1 tablet of Fluoxine T, twice a day for 4 weeks (1,000 mg og ciprofloxacine +1,200 mg of tinidazole per day for 4 weeks).
- Upper genital infections: 1 tablet of Fluoxine T twice a day for 7 days (500 mg of ciprofloxacin + 600 mg of tinidazole twice a day for 7 days).

Method of administration
Fluoxine T tablet is administered during or after a meal, preferentially. The tablets should be swallowed whole, whit no chewing. Fluoxine T should not be taken with dairy products (milk, yoghurt) or fruit juices that are enriched with minerals (calcium enriched orange juice) (see section 4.5).
Concerning ciprofloxacin

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility of to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescent the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Patients with renal and hepatic impairment
Recommended starting and maintenance doses for patients with impaired renal functions:

Creatinine Clearance [mL/min/1.73m²]	Serum creatinine [µmol/L]	Oral dose [mg]
> 60	< 124	Serum usual dosage
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Fluoxine T tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified-juice (e.g. calcium-fortified orange juice) (see section 4.5).

4.3 Contraindications

Concerning ciprofloxacin

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients listed in section 6.1.
- Concimitant adminstration of cirpofloxacin and tizandine (see section 4.5).

Concerning tinidazole

- As with other drug of similar structure, tinidazole is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent hoaematological 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

Concerning ciprofloxacin

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administrered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Gonococcal urethris, cervicitis, epididymo-orchitis and pelvis inflammatory diseases may be caused by fluoroquinolone-resistant *Nesseiria gonorrhoeae* isolates. Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretris or cervicitis only if ciprofloxacin-resistant *Nesseiria gonorrhoeae* can be excluded.
For epididymo-orchitis and pelvic inflammatory disases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvment is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections
Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infection – varies across the European Union. Proscribers are advised to take into accound the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.
The single dose of ciprofloxacin that may be used in uncomplicated cystis in pre-menopausal woman is expected to be associated with lower efficacy than the longer treatment duration. This is amm the more to be taken into accound as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacine should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of bones and joints
Ciprofloxacin should be used in combination with the other antimicrobial aagents depending on the results of the microbiological documentation.
Inhalational anthrax
Use in humans is based on *In vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Paediatric population
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin n = 335; mean age = 6.3 years; comparators n = 349; mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day + 42 of 7.2 % and 4.6 %. Respectively, an incident of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use. The use of ciprofloxacin for specific sevrere infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reactions occurs, ciprofloxacin should be discontinuated and an adequate medical treatment is required.

Musculoskeletal system
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the tratment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central nervous system
Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported? Ciprofloxacin should be used with caution in patients with CNS disorers which may be predisposed to seizures. If seizures occur ciprofloxacin should ne discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culmunating in attempted suicide or completed suicide. In the occurence of such cases, ciprofloxacin should be discontinuated.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory distrurbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciproflocxacin should be discontinuated in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Congenital long QT syndrom.
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarythmics, tricycle antidepressants, macrolides, antipsychotic).
- Uncorrected electrolyte imblance (e.g. hypokalaemia, hypomagnesaemia).
- Cardiac disease (e.g. heart failure, myocardial infraction, bradycardia).

Elderly patients and woman may be more sensitive to QTc-prolonging medication. Therefore , caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.

(See section 4.2 Elderly patients, section 4.8, section 4.9).

Hyperglycemia

As with other quinolones, hypoglycemia has been reported most often in diabetic patients, predominantely in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Gastrointestinal system
The occurence of severe and persistant diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-assiciated colitis (life-threatening with possible fatal outcomes), requiring immediate treatment (see section 4.8). in such cases, ciprofloxacin should immediately be discontinuated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function
Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system
Cases of hepatic necrosis and life-theratening heaptic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, prurius, or tender abdomen), the treatment should be discontinuated.

Glucose-6-phosphate dehydrogenase defiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurence of haemolysis should be monitored.

Resistance
During of following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitanlty administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizandine, duloxeti
ne). Co-administration of ciprofloxacin and tizandine is contra-indicated. Therefore, patients taking these substances concommitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentration (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacine with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in vitro* activity of ciprofloxacin against against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients from patients currently taking ciprofloxacin.

Concerning tinidazole
As with related compounds, alcoholic beverages should be avoided during tinidazole 600 mg tablets therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, comiting, tachycardia). Alcohol should be avoidded until 72 hours after discontinuing tinidazole 600 mg tablets.

Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with tinidazole 600 mg tablets, abnormal neurological signs develop, therapy should be discontinuated.

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 biological effects. Mutagenicity results with tinidazole for longer treatment (positive and negative) (see section 5.3). The use of tinidazole for longer treatmet than usually required should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction

Concerning ciprofloxacin

Effects of other products on ciprofloxacin:
Drugs known to prolong QT interval
Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class I and III anti-arythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation complex formation
The simultaneous administration of ciprofloxacine (oral) and multivalent cation-containing drugs and miniral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), suvralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and dairy product
Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy product or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid
Probenecid inteferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentration.

Metoclopramide
Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole
Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Effects of ciprofloxacin on other medicinal products:
Tizandine
Tizandine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizandine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6-24 to fold) when given concomitantly with ciprofloxacin. Increased serum tizandine concentration is associated with a potential hypotensive and sedative effect.

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline
Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentration should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxyfylline (oxpentifylline), raised serum concentration of these xanthine derivatives were reported.

Phenytoin
Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such as that monitoring of drug levels is recommended.

Cyclosporin
A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentration in these patients.

Vitamin K antagonists
Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patients so that the contribution of ciprofloxacin to the increase in the INR (International Normalised Ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluinidione).

Duloxetine
In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effect can be expected upon concomitant administration (see section 4.4).

Ropinirole
It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22 %. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with the side effects may occur upon concomitant administration.

Clozapine
Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentration of clozapine and N-desmethylclozapine were increased by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section4.4).

Sildenafil
C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Concerning tinidazole
Alcohol
Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided (see section 4.4).

Anticoagulant

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 anticoagulant should be made as necessary.

4.6 Fertility, pregnancy and lactation

Concerning ciprofloxacin

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant woman indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism/foetus (see section 5.3). As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnacy.

Breast-feeding
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

Concerning tinidazole
Pregnancy
Fertility studies in rats receiving 100 mg and 300 mg tinidazole/kg had no effect on fertility, adult and pup weight, gestation, viability or lactation. There was a slight, not significant, increase in resorption rate at the 300 mg/kg dose.
Tinidazole crosses the placental barrier. Since the effect 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 tinidazole 600 mg tablets is harmfull 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 discontinuated taking tinidazole 600 mg tablets.

4.7 Effects on ability to drive and use machines

Concerning ciprofloxacine

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

Concerning tinidazole
No special precautions should be necessary. However, drugs of similar chemical structure, including tinidazole 600 mg tablets, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If any abnormal neurological signs develop during tinidazol 600 mg tablet therapy, the drug should be discontinuated.

4.8 Undesirable effects

Concerning ciprofloxacin

Classification of expected frequencies
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 (cannot be estimated from the available data).

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin sorted by categories of frequencies are listed below. The frequency analysis takes into accound data from both oral and intravenous administration of ciprofloxacin.

Infections and infestations

Uncommon:	mycotic super-infections.
Rare:	antibiotic associated colitid (very rarely possible fatal outcome) (see section 4.4).

Blood and lymphatic system disorders

Uncommon:	eosinophilia.
Rare:	leukopenia, anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytaemia.
Very rare:	haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-thretening).

Immune system disorders

Rare:	allergic reaction, allergic oedema/angioedema
Very rare:	anaphylactic reaction, anaphylactic shoch (life-threatening) (see section 4.4), serum-sickness-like reaction.

Metabolism and nutrition disorders

Uncommon:	decreased appetite.
Rare:	hyperglycaemia, hypoglycaemia (see section 4.4).

Psychiatric disorders

Uncommon:	psychomotor hyperactivity/agitation.
Rare:	confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicideà (see sections 4.4), hallucinations.
Very rare:	psychotic reactions (potentially culminating in suicidal ideations.thoughts or suicide attempts and completed suicide) (see section 4.4).

Nervous system disorders

Uncommon:	headache, dizziness, sleep disorders, taste disorders.
Rare:	par- and dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus) (see section 4.4), vertigo.
Very rare:	migraine, disturbed coordination, Gait disturbance, olfactory nervedisorders, intracranial hypertension and pseudotumor cerebri.
Frequency not known:	peripheral neuropathy and polyneuropathy (see section 4.4).

Eye disorders

Rare:	visual disturbances (e.g. diplopia).
Very rare:	visual colour distortion.

Ear and labyrinth disorders

Rare:	tinnitus, hearing loss/hearing impaires.

Cardiac disorders

Rare:	tachycardia.
Frequence not known:	ventricular arrythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see sections 4.4 and 4.9).

Vascular disorders

Rare:	vasodilation, hypotension, syncope.
Very rare:	vasculitis.

Respiratory, thoracic and mediastinal disorders

Rare:	dyspnoea (including asthmatic condition).

Gastro-intestinal disorders

Common:	nausea, diarrhoea.
Uncommon:	vomiting, gastro-intestinal and abdominal pains, dyspepsia, flatulence.
Very rare:	pancreatis.

Hepatobiliary disorders

Uncommon:	increase trasaminases, increased bilirubin.
Rare:	hepatic impairment, cholestatic icterus, hepatitis.

Skin and subcutaneous tissues disorders

Uncommon:	rash, pruritus, urticaria.
Rare:	photosensitivity reactions (see sections 4.4).
Very rare:	petechiae, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal ncrolysis (potentially life-threatening).
Frequency not known:	acute generalised exanthematous pustolosis (AGEP).

Musculo-skeletal and connective tissue disorders

Uncommon:	musculo-skeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia.
Rare:	myalia, arthritis, increased muscle tone and cramping.
Very rare:	muscular weakness, tendinitis, tendon ruptur (predominantly achilles tendon) (see section 4.4.), exacerbation of symptoms of myasthenia gravis (see section 4.4).

Renal and urinary disorders

Uncommon:	renal impairment.
Rare:	renal failure, haematuria, crystalluria (see section 4.4), tubulointerstitial nephritis.

General disorders and administration site conditions

Uncommon:	asthenia, fever.
Very rare:	oedema, sweating (hyperhidrosis).

Investigation

Uncommon:	increase in blood alkaline phosphatase.
Rare:	increased amylase.
Frequency not known:	international normalised ratio increased (in patients treated with vitamine K antagonists).

Paediatric population

The incidence of arthropathy, mentioned above, is referring to data collectioned in studies with adults. In children, arthropathy is reported to occur commonly (see section4.4).

Concerning tinidazole

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

Automatic nervous system: flushing.

Body as a whole:	fever, tiredness.
Central and peripheral nervous system:	ataxia, convulsion (rarely), dizziness, headache, hypoesthesia, parathesia, peripheral neuropathy, sensory disturbances, vertigo.
Gastrointestinal:	abdominal pain, anorexia, diarrhoea, durry tongue, glossitis, nausea, stomatis, vomiting.
Haematopoietic:	transient leukopenia.
Skin/appendages:	hypersensitivity reactions, occasionally sever may occur in rare cases in the form of the skin rash, pruritus, urticaria, and angineurotic oedema.
Special senses:	metallic taste.
Urinary system:	dark urine.

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.

4.9 Overdose

Concerning ciprofloxacin

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucination, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal functiun, including urinary pH and acidity, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antiacids may theoratically reduce the absorption of ciprofloxacin in overdoses.

On a small quantity of ciprofloxacin (< 10 %) is eliminated by haemodialysis or peritoneal dialysis.

In the event of overdose, symptomatic treatment should be implemented ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Concerning tinidazole

In acute animal studies with mice and rats, the LD_{50} for mice was > 3600 mg/kg and > 2300 mg/kg for oral and intraperitoneal administration respectively. For rats, the LD_{50} was > 2000 mg/kg for both oral and intraperitoneal administration.

Signs and symptoms of overdosage: there are no reported overdoses in humans with tinidazole 600 mg tablets.

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 dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Combinations of antibacterials, ciprofloxacin and tinidazole; ATC code J01RA11

Mechanism of action
As a fluoroquinolone antibacterial agent, the bacterial action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Pharmacokinetic/pharmacodynamic: relationship relationship
Efficacy mainly depends on the relation betweeen the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance
In vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA-gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations genrally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity
Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains.

EUCAST Recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteriaceae	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas spp.	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter spp.	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrheae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species related breakpoints*	S ≤ 0.5 mg/L	R > 1 mg/L
[1]*Staphylococcus* spp. – breakpoints for ciprofloxin relate to high dose therapy. * Non-species-related breakpoints have been determined mainly on basis of PK/PD data and are independent of MIC distribution of specific species. They are for use only for species that have not been given a species-species breakpoint and not for those species where susceptibility testing is not recommended.		

The prevalence of acquired resistance may vary geographically and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Grouping of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species) (see section 4.4).

COMMONLY SUSCEPTIBLE SPECIES	SPECIES FOR WHICH AQUIRED RESISTANCE MAY BE A PROBLEM	INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)	Anaerobic Gram-positive micro-organisms *Enterococcus faecalis* (*) *Staphylococcus* spp.*(2)	Aerobic Gram-positive micro-organisms *Actinomyces* *Enterroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Aeronomas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Hoaemophilius ducreyi* *Hoaemophulius influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersenia pestis*	Aerobic Gram-negative micro-organisms *Acinetobacter baumanii*+ *Burkholderia cepacia*+* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter clacae** *Escherichia coli* *Klebsella oxytoca* *Klebsella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**	Aerobic Gram-negative micro-organisms *Stenotrophonomas maltophilia*
Anaerobic micro-organism *Mobiluncus*	Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*	Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Chlamydia trachomatis (*) *Chlamydia pneumoniae* (*) *Mycoplasma hominis* (*) *Mycoplasma pneumoniae* (*)		Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ Resistance rate $\geq$ 50 % in one or more EU countries

(*) Natural intermediate susceptibility in the absence of acquired mechanism of resistance

(1) Studies have been conducted in expiremental animal infections due to inhalations of *Bacillus anthracis* spores: these studies reveal that antibiotics starting early after exposition avoid the occurence of the disease if the treatment is made up to the decrease of the number of spores in the organisms under the infective dose. The recommended use in human subjects is based primarly on *in vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose. 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.

(2) Methicillin-resistant *S. Aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50 % among all staphylococcal species and is usually higher in nosocomial isolates.

Concerning tinidazole

Tinidazole is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves *Trichonomas vaginalis*, *Entomoeba histolytica* and *Giardia lambia*.

The mode of action of tinidazole 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 sunthesis.

Tinidazole 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 ling between *H. pylori* and gastric carcinoma.

Clinical evidence has shown that the combination of tinidazol 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 ulcers and reduces the risk of ulcer recurrence.

5.2 Pharmacokinetic properties

Concerning ciprofloxacin

Absorption
Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 100 mg.
The absolute bioavailability is approximately 70-80 %.
A 500 mg oral dose given every 12 h has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 h.

Distribution
Protein binding of ciprofloxacin is low (20-30 %). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation
Low concentrations of four metabolites have reported, which were identified as: desethyleneciprofloxacin (M1), sulphociprofloxacin (M2) oxociprofloxacin (M3) and formylciprofloxacin (M4). The metabolites display *in vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP450 1A2 iso-enzymes.

Elimination
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with a normal renal function is approximatelu 4-7 hours.

Excretion of ciprofloxacin (% dose)		
	Oral administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1 % of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients
The pharmacokinetic data in paediatric patients are limited.

In a study in children, C_{max} and AUC were not age-dependant (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10mg/kg three times daily) was observed.

In children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg.h/L (range 11.8-32.0 mg.h/L) and 16.5 mg.h/L (range 11.0-23.8 mg.h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approximately 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80 %.

Concerning tinidazole

Tinidazole is rapidely and completely absorbed following oral administration. In studies with healthy volunteers receiving 2 g tinidazole orally, peak serum levels of 40-51 microorganisms/mL were achieved within two hours and decreased to between 11-19 microorganisms/mL at 24 hours. Healthy volunteers who received 800 mg and 1.6 g tinidazole IV over 10 – 15 minutes achieved peak plasma concentrations that ranged from from 14 to 21 mg/mL for the 800 mh dose and avereged 32 mg/mL for the 1.6 dose. At 24 hours postinfusion, plasma levels of tinidazole decreased to 4-5 mg/mL and 8.6 mg/mL respectively, justifying once daily dosing. Plasma levels decline slowly and tinidazole can be detected in plasma at concentration of up to 1 microorganism/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 L. 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 < 22 mL/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

Concerning ciprofloxacin

Non-clinical data reveal no special hazard for humans based on conventional studies or single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or photomorigenic effect of ciprofloxacin *in vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joint in immature animals. The extent of the cartilage damage varies according to age, species and dose, the doamage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dogs) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

Concerning tinidazole

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 assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The active substances are ciprofloxacin (as ciprofloxacine chlorhydrate) and tinidazole.
The other ingredients are: microcrystalline cellulose, maize starch, purified water, talc, magnesium stearate, anhydrous colloidal silica, sodium starch glycolate, crospovidone, opadry II white (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25 °C in a dry place in the absence of light.

6.5 Nature and contents of container

Box of 10 tablets in blister (PVC/Aluminium).

6.6 Special precautions for disposal

No special requirement

7. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

8. MARKETING AUTHORISATION HOLDER

Exphar s.a.
Av. Franklin Roosevelt, 104
1330 Rixensart
BELGIUM

Phone: 32+2+344.48.70
Fax: 32+2+346.03.14

9. MANUFACTURER

Gracure Pharmaceuticals Ltd.,
E-1105, Industrial Area, Phase-III,Bhiwadi, Dist. Alwar (Raj.)
INDIA

Phone: 91+11+25920748
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10. DATE OF REVISION OF THE TEXT

08/2014