**National Agency for Food & Drug Administration & Control**

**(NAFDAC)**

# Registration & Regulatory Affairs (R & R)

# Directorate

# SUMMARY OF PRODUCT CHARACTERISTICS

# (SmPC) TEMPLATE

## 1. NAME OF THE MEDICINAL PRODUCT

Galcipro-TN Caplet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated caplet contains 500mg ciprofloxacin (as hydrochloride) and 600mg Tinidazole.
For a full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Oblong, nearly white to off-white caplets marked with "CPX TN" on one side and scored on the reverse side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indication

Galcipro-TN film-coated caplets are indicated for the treatment of a wide variety of infections caused by susceptible gram positive and gram negative organisms along with anaerobes and protozoa (see sections 4.4 and 5.1).
These include: urinary tract infections, skin and skin structure infections, bone and joint infections. It is also used in the treatment of anthrax infections, acute sinusitis, uncomplicated cervical and urethral gonorrhea, thyphoid fever, and gastro-intestinal tract infections. Galcipro-TN is also used for for the treatment of complicated intra-abdominal infections caused by E. coli, Pseudononas aeruginosa, P. mirabilis, K. pneumoniae, and Bacteroides fraginalis.

Special attention should be paid to available information on resistance to ciprofloxacin + Tinidazole before commencing therapy.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

**Adults**

- Exacerbations of chronic obstructive pulmonary disease
- Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- Pneumonia including aspiration pneumonia
- Empyema
- Lung abscess

• Chronic suppurative otitis media
• Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
• Urinary tract infections
• Genital tract and Gynaecological infections
- Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
- Epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to susceptible *Neisseria gonorrhoeae*
- Endometritis, endomyometritis, tube-ovarian abscess.

• Infections of the gastro-intestinal tract (e.g. diarrhoeas of mixed bacterial and protozoal origin and Intestinal amoebiasis)
• Eradication of *Helicobacter pylori* associated with duodenal ulcers, in the presence of antibiotic and acid suppressant therapy (see section 4.2).
• Intra-abdominal infections
• Infections of the skin and soft tissue caused by Gram-negative bacteria
• Anaerobic infections such as:

- Intraperitoneal infections: peritonitis, abscess.
- ENT infections like sinusitis, chronic suppurative otitis media, cholesteatoma and mastoiditis.
- Infections of the bones and joints
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)
- Bacterial septicaemia.
- Post-operative wound infections.
- Non-specific vaginitis.
- Acute ulcerative gingivitis.
- Urogenital trichomoniasis in both male and female patients.
- Giardiasis.
- Amoebic involvement of the liver.
- Surgical prophylaxis and surgical wound infections: The prevention of post-operative infections caused by anaerobic bacteria, especially those associated with colonic, gastro-intestinal and gynaecological surgery.
- Dermatological infections like cellucitis, breast and other cutaneous abscesses, gangrene, diabetic and decubitus ulcers.
- Orofacial and dental infections.

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

**Children and adolescents**
- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.
Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

## 4.2 Posology and method of administration

**Posology**
Route: Oral administration during or after a meal.

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin/Tinidazole of the causative organism(s), the renal function of the patient and, in children and adolescents 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 certiain bacteria (e.g. *Psuedomonas aeruginosa, Acinetobacter* or *Staphylococci*) may require higher doses and co-administration with other appropriate antibacterial agents.
***Adults***

| **Indications** | | **Daily dose in mg** | **Total duration of treatment** |
|---|---|---|---|
| Infections of the lower respiratory tract | | 500mg/600mg twice daily to 750mg/900mg twice daily | 7 to 14 days |
| Infections of the upper respiratory tract | Acute exacerbation of chronic sinusitis | 500mg/600mg twice daily to 750mg/900mg twice daily | 7 to 14 days |

| | | | |
|---|---|---|---|
| | Chronic suppurative otitis media | 500 mg twice daily to 750 mg twice daily | 7 to 14 days |
| | Malignant external otitis | 750mg/900mg twice daily | 28 days up to 3 months |
| Urinary tract infections (see section 4.4) | Uncomplicated cystitis | 250mg/300mg twice daily to 500mg/600mg twice daily | 3 days |
| | | In pre-menopausal women, 500mg/600mg single dose may be used | |
| | Complicated cystitis, Uncomplicated pyelonephritis | 500mg/600mg twice daily | 7 days |
| | Complicated pyelonephritis | 500mg/600mg twice daily to 750 mg twice daily | at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses) |
| | Prostatitis | 500mg/600mg twice daily to 750mg/900mg twice daily | 2 to 4 weeks (acute) to 4 to 6 weeks (chronic) |
| Genital tract infections | Gonococcal uretritis and cervicitis | 500mg/600mg as a single dose | 1 day (single dose) |
| | Epididymo-orchitis and pelvic inflammatory diseases | 500mg/600mg twice daily to 750mg/900mg twice daily | at least 14 days |
| | Gonorrhoea | 500mg/600mg daily | 3 days |
| Infections of the gastro-intestinal tract and intra-abdominal infections | Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea | 500mg/600mg twice daily | 1 day |
| | Infectious diarrhoea or Diarrhoea caused by *Shigella dysenteriae* type 1 | 500mg/600mg twice daily | 5 to 7 days |
| | Diarrhoea caused by *Vibrio cholerae* | 500mg/600mg twice daily | 3 days |
| | Typhoid fever | 500mg/600mg twice daily | 7 to 10 days |
| | Intra-abdominal infections due to Gram-negative bacteria | 500mg/600mg twice daily to 750mg/900mg twice daily | 5 to 14 days |
| | Intestinal amoebiasis | 1,000mg/1,200mg as a single dose | 2 to 3 days (continued for up to 6 days if ineffective) |
| Infections of the skin and soft tissue | | 500mg/600mg twice daily to 750mg/900mg twice daily | 7 to 14 days |
| Bone and joint infections | | 500mg/600mg twice daily to 750mg/900mg twice daily | 4 to 6 weeks. Max. of 3 months |
| Neutropenic patients with fever suspected to be due to a bacterial infection.<br>Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance. | | 500mg/600mg twice daily to 750mg/900mg twice daily | Therapy should be continued over the entire period of neutropenia |
| Prophylaxis of invasive infections due to *Neisseria meningitides, and meningococcal meningitis* | | 500mg/600mg as a single dose | 1 day (single dose) |

| | | |
|---|---|---|
| Prophylaxis of meningococcal meningitis | 500mg/600mg as a single dose | 1 day (single dose) |
| Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate.<br>Drug administration should begin as soon as possible after suspected or confirmed exposure. | 500mg/600mg twice daily | 60 days from the confirmation of *Bacillus anthracis* exposure |
| Chancroid | 500mg/600mg twice daily | 5 days |
| Treatment of Anaerobic Infections | 500mg/600mg twice daily | 5 to 10 days |
| Non-specific vaginitis | 1,000mg/1,200mg as a single dose | For 2 consecutive days |
| Acute ulcerative gingivitis | | 5 to 7 days |
| Urogenital Trichomoniasis | 1,000mg/1,200mg as a single dose | 1 day |

***Paediatric population***
Galcipro-TN is not recommended for those below the age of 18 years.

***Elderly patients***
Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

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

| **Creatinine Clearance [mL/min/1.73 $m^2$]** | **Serum Creatinine [µmol/L]** | **Oral Dose [mg]** |
|---|---|---|
| > 60 | < 124 | See Usual Dosage. |
| 30-60 | 124 to 168 | 250-500mg/300-600mg every 12 h |
| < 30 | > 169 | 250-500mg/300-600mg every 24 h |
| Patients on haemodialysis | > 169 | 250-500mg/300-600mg every 24 h (after dialysis) |
| Patients on peritoneal dialysis | > 169 | 250-500mg/300-600mg every 24 h |

In patients with impaired liver function no dose adjustment is required.
Dosing in children with impaired renal and/or hepatic function has not been studied.

**Method of administration**
Caplets are to be swallowed unchewed with fluid. It is recommended that the caplets be taken during or after a meal. Patients should be advised to drink plenty of fluid. The caplets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).
In severe cases or if the patient is unable to take caplets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin/Tinidazole until a switch to oral administration is possible.

## 4.3 Contraindications
- Galcipro-TN is contraindicated in patients with a known hypersensitivity to ciprofloxacin (or other quinolones), tinidazole (or other 5-nitroimidazole derivatives) or to any of the excipients listed in section 6.1.

- As with other drugs of similar structure, tinidazole one of the components of Galcipro-TN 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.
- Contraindicated in pregnancy especially during the first trimester and in nursing mothers during the neonatal period (see section 4.6).
- Avoid concomitant administration of ciprofloxacin and tizanidine (see section 4.5).
- Galcipro-TN is also contra-indicated in children under 18 years and in growing adolescents, except where the benefits of treatment exceed the risks. Experimental evidence indicates that species-variable reversible lesions of the cartilage of weight-bearing joints (arthropathy), has been seen in immature members of certain animal species.
- It should be used with caution in patients with a history of convulsive disorders. Doses should be reduced in patients with liver disease.

## 4.4 Special warnings and precautions for use

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

Paediatric population
Galcipro-TN contains Ciprofloxacin. 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 incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase 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 (see section 4.8).
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 treatment 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.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated (see section 4.8).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

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 disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued. Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued 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 syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations. (See section 4.2 Elderly patients, section 4.5, section 4.8, section 4.9).

Hypoglycemia

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

Gastrointestinal System

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated 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-threatening hepatic 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, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency

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 occurrence of haemolysis should be monitored.

Resistance

During or 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 a 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 concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5). Co-administration of ciprofloxacin and tizanidine is contra-indicated.

Methotrexate

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

Interaction with tests

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

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

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 IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).
- **Chelation Complex Formation:** The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate 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 Products:** Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products 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 interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.
- **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:

- **Tizanidine:** Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration ($C_{max}$ increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated 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 concentrations 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 pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.
- **Phenytoin:** Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such 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 concentrations 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 patient so that the contribution of ciprofloxacin to the increase in 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 fluindione).
- **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 effects 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, results in an increase of $C_{max}$ and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).
- **Lidocaine:** It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.
- **Clozapine:** Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations 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 section 4.4).
- **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.
- **Agomelatine:** In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-

fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see 'Cytochrome P450' in section 4.4).
- **Zolpidem:** Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

Effects of other products on Tinidazole:
- **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. Dosage of oral anticoagulants may need to be adjusted during tinidazole therapy and up to 8 days after discontinuation.
- **Cholestyramine** may decrease oral bioavailability; separate dosing of cholestyramine and tinidazole is recommended.
- **Ethyl alcohol**, **ethanol**-containing preparations, **propylene glycol**: It is recommended that these substances not be used concurrently with tinidazole, or for 3 days following tinidazole therapy; abdominal cramps, nausea, vomiting, headache, or flushing may occur.
- Intravenous **phenytoin** or intravenous **fosphenytoin**: Concomitant administration with tinidazole increases half-life and decreases clearance of phenytoin.
- **Oxytetracycline** may antagonize the therapeutic effect of tinidazole.
- **Lithium** concentrations may increase when tinidazole therapy is introduced; serum lithium and serum creatinine levels should be monitored several days after beginning tinidazole in order to detect possible lithium intoxication.
- **Fluorouracil**: Tinidazole may decrease the clearance of fluorouracil (resulting in increased side effects; if co-administration cannot be avoided monitor for fluorouracil-associated toxicity.
- **Disulfiram**in: It is recommended that tinidazole not be used concurrently with, or for 2 weeks following disulfiramin in alcoholic patients; such use may result in confusion and psychotic reactions because of combined toxicity.
- Cytochrome p450 inhibitors such as **cimetidine** or **ketoconazole** taken concurrently with tinidazole may prolong half-life and decrease plasma clearance of tinidazole
- Cytochrome p450 inducers such as : Fosphenytoin, Phenobarbital, Phenytoin and **rifampin** taken concurrently with tinidazole may increase elimination and decrease plasma concentration of tinidazole.
- **Cyclosporine**, **tacrolimus**: Tinidazole may increase levels of these drugs; monitor for signs of calcineurin-inhibitor associated toxicities.

## 4.6 Pregnancy and lactation

**Pregnancy:**
The data that are available on administration of ciprofloxacin to pregnant women 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).

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 tinidazole 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.
As a precautionary measure, it is preferable to avoid the use of Galcipro-TN during pregnancy.

**Breast-feeding:**
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.
Tinidazole is excreted in breast milk. Tinidazole may continue to appear in breast milk for more than 72 hours after administration.
It is advisable not to administer Galcipro-TN during breast-feeding.

### 4.7 Effects on ability to drive and use machines
Due to its neurological effects, ciprofloxacin may affect reaction time. Tinidazole and drugs of similar chemical structure have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. Thus, the ability to drive or to operate machinery may be impaired.
If any abnormal neurological signs develop during Galcipro-TN therapy, the drug should be discontinued.

### 4.8 Undesirable effects
Reported side effects have generally been infrequent, mild and self-limiting.
The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.
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** ≥ 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 | **Frequency not known** (cannot be estimated from the available data) |
|---|---|---|---|---|---|
| **Infections and Infestations** | | Mycotic super-infections | | | |
| **Blood and Lymphatic System Disorders** | | Eosinophilia | Leukopenia<br>Anaemia<br>Neutropenia<br>Leukocytosis<br>Thrombocytopenia<br>Thrombocytaemia | Haemolytic anaemia<br>Agranulocytosis<br>Pancytopenia (life-threatening)<br>Bone marrow depression (life-threatening) | |
| **Immune System Disorders** | | | Allergic reaction<br>Allergic oedema / angiooedema | Anaphylactic reaction<br>Anaphylactic shock (life-threatening) (see section 4.4)<br>Serum sickness-like reaction | |
| **Metabolism and Nutrition** | | Decreased appetite | Hyperglycaemia<br>Hypoglycaemia (see | | |

| | | | | | |
|---|---|---|---|---|---|
| **Disorders** | | | section 4.4) | | |
| **Psychiatric Disorders** | | Psychomotor hyperactivity / agitation | Confusion and disorientation<br>Anxiety reaction<br>Abnormal dreams<br>Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4)<br>Hallucinations | Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4) | Mania, incl. hypomania |
| **Nervous System Disorders** | | Headache<br>Dizziness<br>Sleep disorders<br>Taste disorders | Par- and Dysaesthesia<br>Hypoaesthesia<br>Tremor<br>Seizures (including status epilepticus see section 4.4)<br>Vertigo | Migraine<br>Disturbed coordination<br>Gait disturbance<br>Olfactory nerve disorders<br>Intracranial hypertension and pseudotumor cerebri) | Peripheral neuropathy and polyneuropathy (see section 4.4)<br>Convulsions peripheral<br>Paraesthesia<br>Hypoaesthesia<br>Sensory disturbances<br>Ataxia<br>Dysgeusia |
| **Eye Disorders** | | | Visual disturbances (e.g. diplopia) | Visual colour distortions | |
| **Ear and Labyrinth Disorders** | | Vertigo | Tinnitus<br>Hearing loss / Hearing impaired | | |
| **Cardiac Disorders** | | | Tachycardia | | Ventricular arrhythmia 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** | | | Vasodilatation<br>Hypotension<br>Syncope | Vasculitis | Flushing |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | Dyspnoea (including asthmatic condition) | | |
| **Gastrointestinal** | Nausea | Vomiting | Antibiotic associated | Pancreatitis | Glossitis |

| | | | | | |
|---|---|---|---|---|---|
| **Disorders** | Diarrhoea | Gastrointestinal and abdominal pains<br>Dyspepsia<br>Flatulence | colitis (very rarely with possible fatal outcome) (see section 4.4) | | Stomatitus<br>Tongue discolouration |
| **Hepatobiliary Disorders** | | Increase in transaminases<br>Increased bilirubin | Hepatic impairment<br>Cholestatic icterus<br>Hepatitis | Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4) | |
| **Skin and Subcutaneous Tissue Disorders** | | Rash<br>allergic<br>Pruritus<br>Urticaria<br>Dermatitis | Photosensitivity reactions (see section 4.4) | Petechiae<br>Erythema multiforme<br>Erythema nodosum<br>Stevens-Johnson syndrome (potentially life-threatening)<br>Toxic epidermal necrolysis (potentially life-threatening) | Acute Generalised Exanthematous Pustulosis (AGEP)<br>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<br>Angioedema |
| **Musculo-skeletal and Connective Tissue Disorders** | | Musculo-skeletal pain (e.g. extremity pain, back pain, chest pain)<br>Arthralgia | Myalgia<br>Arthritis<br>Increased muscle tone and cramping | Muscular weakness<br>Tendinitis<br>Tendon rupture (predominantly Achilles tendon) (see section 4.4)<br>Exacerbation of symptoms of myasthenia gravis (see section 4.4) | |
| **Renal and Urinary Disorders** | | Renal impairment | Renal failure<br>Haematuria<br>Crystalluria (see section 4.4)<br>Tubulointerstitial nephritis | | Chromaturia |
| **General Disorders and Administration Site Conditions** | | Asthenia<br>Fever | Oedema<br>Sweating (hyperhidrosis) | | Pyrexia<br>Fatigue |
| **Investigations** | | Increase in blood alkaline phosphatase | Increased amylase | | International normalised ratio increased (in patients treated with Vitamin K antagonists) |

Paediatric population
The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

## 4.9 Overdose

**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.
Signs and Symptoms of overdosage
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.
Treatment of Overdosage:
Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses
Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis but Tinidazole is easily dialysable.
In the event of overdose, symptomatic and supportive treatment should be implemented. Gastric lavage may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

**Tinidazole:**
Hepatotoxicity: Tinidazole is typically given for a few days only, but serum enzyme elevations have been reported with its use, and serum enzyme elevations during therapy is listed as a possible adverse event in the product label. Tinidazole is also capable of causing anaphylactic and allergic reactions including urticaria, angioedema and bronchospasm, reactions which can be associated with minor serum enzyme elevations. Tinidazole, despite considerable use worldwide, has not been linked convincingly to instances of clinically apparent liver injury with jaundice.

**Toxicity**
Tinidazole
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.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Ciprofloxacin**
Ciprofloxacin is a fluorinated 4-quinolone antimicrobial agent with a similar antibacterial spectrum with norfloxacin but greater activity.

Mechanism of Action
Ciprofloxacin has been shown to be bactericidal with the MIC (minimum inhibitory concentration) close to the MBC. The bactericidal action of ciprofloxacin results from the inhibition of A subunit of the bacterial enzyme type II topoisomerase (DNA-gyrase) and topoisomerase IV, which catalyses the supercoiling necessary to pack DNA into bacterial cells for bacterial DNA replication, transcription, repair and recombination.
Its inhibition leads to irreversible chromosome damage and cell death. A secondary action on cell membranes may also contribute to their bactericidal action.

Efficacy mainly depends on the relation between 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

Resistance can be induced as can cross-resistance between the 4-quinolones, although it has been considered unlikely that such resistance would diminish any clinical effect since the increased MICs are still within achievable concentrations in vitro. The antibacterial activity of ciprofloxacin is reduced in acid media.

*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 generally 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

As antibacterial concentrations of ciprofloxacin are obtained in serum and body tissues as well as in the urine following oral administration, ciprofloxacin has been suggested for use in the treatment of a wide range of infections caused by susceptible organisms. MICs for susceptible Gram-negative aerobic organisms range from 0.004 to 2µg per mL and for Gram-positive organisms from 0.12 to 4µg per mL. Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

Susceptible Gram-negative organisms include: *Escherichia coli, Citrobacter, Enterobacter, Klebsiella, Proteus, Salmonella, Shigella,* and *Yersinia* spp. *Pseudomonas aeruginosa* is susceptible as are other *Pseudomonas* spp., but to a lesser degree. *Haemophilus, Neisseria*, and *Acinetobacter* spp. are sensitive as are *Campylobacter, Providencia, Serratia*, and *Legionella* spp. Others include *Chlamydia trachomatis, Gardnerella vaginalis, Mycoplasma hominis,* and some *Mycobacterium* spp.

Gram-positive organisms are less sensitive although Staphylococci, Streptococci, and *Listeria* spp. can be inhibited. The anaerobic organisms *Bacteroides* and *Clostridium* spp. may be susceptible or they may not. Methicillin-resistant staphylococci are reported to be sensitive. *Streptococcus pneumoniae* resistant to other antibiotics have also been inhibited by ciprofloxacin.

**Tinidazole**

Tinidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and anaerobic protozoa; it also has a radiosensitising effect on hypoxic tumour cells.

Mechanism of Action

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 synthesis. Tinidazole's mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of tinidazole has been reduced.

Spectrum
Tinidazole is active against several protozoa including *Balantidium coli, Blastocystis hominis, Entamoeba histolytica, Giardia intestinalis (Giardia lamblia)*, and *Trichomonas vaginalis*. Most obligate anaerobic bacteria including*, Bacteroides* and *Clostridium* spp., are sensitive in-vitro to tinidazole. It is bactericidal. Minimum inhibitory concentrations for susceptible anaerobic bacteria generally range from 0.1 to 0.8uμg per mL. It also has activity against the facultative anaerobes *Gardnerella vaginalis* and *Campylobacter* spp. and against some spirochaetes. Resistance to tinidazole appears to be rare; cross-resistance to other nitroimidazoles such as metronidazole has been demonstrated.

## 5.2 Pharmacokinetic properties

### Ciprofloxacin

ABSORPTION
Following oral administration of single doses of 250mg, 500mg, and750 mg of ciprofloxacin tablets, ciprofloxacin is rapidly and well absorbed after oral administration mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later. A 500mg oral dose produces a mean peak plasma concentration of about 2.5μg per mL after 1 to 2 hours. Food does not impair oral absorption, but may delay the time to peak serum concentrations.

Single doses of 100-750mg produced dose-dependent maximum serum concentrations ($C_{max}$) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours 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 hours.

DISTRIBUTION
The volume of distribution of ciprofloxacin is high (approximately 300L), this is well above the extravascular volume indicating extensive tissue penetration in therapeutic concentrations. Ciprofloxacin is present in in the active form and reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), skin, fat, muscle, cartilage, bone, sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.
It is also present in the saliva, nasal, and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile secretions, prostatic secretions, cerebrospinal fluid and the aqueous humour. The concentrations of the drug in urine, kidney, lung and prostate tissue, stool, bile, macrophages, and neutrophils are higher than serum levels. Ciprofloxacin concentrations in the cerebrospinal fluid and prostatic fluid are lower than in the serum. Plasma protein binding is low; figures vary but range from 20 to 40%. Ciprofloxacin crosses the placenta and is distributed into the amniotic fluid in humans. It is also excreted in breast milk, concentrations were higher than concomitant serum concentrations for up to 12 hours after a dose.

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.

METABOLISM
Ciprofloxacin is partly metabolised in the liver. About 50% of an oral dose is recovered unchanged in the urine and 15% as metabolites viz. oxociprofloxacin. The rest undergoes biliary excretion and transluminal secretion across the intestinal mucosa. Preliminary studies of drug metabolism in man indicate that there are four metabolites of ciprofloxacin which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4), all are microbiologically

active. The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound. It undergoes minimal first pass metabolism.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

EXCRETION
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. About 30 to 50% of an oral dose of ciprofloxacin is excreted in the urine within 24 hours as unchanged drug and biologically active metabolites. Peak urinary concentrations ranging from about 300 to 500ug per mL have been achieved after a 500mg oral dose. Renal clearance is approximately 300mL per minute. Dose adjustments in patients with renal insufficiency are thus required. Significant amounts of an oral dose appear in the faeces (faecal elimination is about 25% of oral dose). The serum elimination half-life of unchanged ciprofloxacin in subjects with normal renal function is approximately 4-7 hours though it may be prolonged in renal insufficiency and in the elderly. The elimination kinetics are linear; after repeated dosing at 12 hourly intervals and once steady state has been reached, no accumulation occurs.
Ciprofloxacin is not effectively removed by peritoneal or haemodialysis.
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-dependent (above one year of age). No notable increase in $C_{max}$ and AUC upon multiple dosing (10 mg/kg three times daily) was observed.
In 10 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 approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

**Tinidazole**

ABSORBTION
The pharmacokinetics of tinidazole resembles those of metronidazole although the half-life is longer. Tinidazole is rapidly and completely absorbed after oral administration and, typically, a peak plasma concentration of about 40ug per mL is achieved 2 hours after after a single 2g dose, falling to 10ug per mL at 24 hours and 2.5ug per mL a 48 hours; concentrations above 8ug per mL are maintained by daily maintenance doses of 1g. Comparable concentrations are achieved with equivalent intravenous doses. The plasma elimination half-life of tinidazole is 12 to 14 hours.

DISTRIBUTION
Tinidazole is widely distributed into body tissues in clinically effective concentrations and effectively crosses the blood brain barrier. Concentrations similar to those in plasma have been achieved in bile, breast milk, cerebrospinal fluid, saliva, and a variety of body tissues; it crosses the placenta readily. The apparent volume of distribution is about 50 litres. About 12%, is reported to be bound to plasma proteins.

METABOLISM
Results from the pharmacokinetic and metabolic studies of labelled tinidazole showed that Ethyl 2-5(5-hydroxy-2-methyl-4-nitro-1-imidazolyl)-ethyl sulphone, a product of the hepatic biotransformation of tinidazole involving hydroxylation and nitro-group migration, was the major metabolite in urine; 2-

hydroxymethyltinidazole was a minor metabolite. Unnchanged drug and the major urinary metabolite were present in faeces. In plasma, the minor metabolite was also present but not the major metabolite.

EXCRETION
Tinidazole is excreted by the liver and kidneys. Unchanged drug and metabolites are excreted in the urine and, to a lesser extent, in the faeces. 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.
In patients with moderate to severe renal impairment (creatinine clearance <22ml/min), the pharmacokinetic characteristics are not markedly changed in comparison with those in normal volunteers. Thus modification of the dosage in patients with impaired renal function is not necessary (see section 4.2).

## 5.3 Preclinical safety data

**Ciprofloxacin**
Non-clinical data reveal no special hazards for humans based on conventional studies of 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 phototumorigenic 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 joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) 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.

**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 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
Tablet Core:
Ciprofloxacin +Tinidazole DC Granules, Magnesium Stearate
Film Coating:
Instacoat White

## 6.2 Incompatibilities
Not applicable.

## 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Product should be stored below 30°C and protected from light.

### 6.5 Nature and contents of container

Transparent colourless PVC/Aluminium blister
Pack sizes of 10 or 100 film-coated caplets.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7 APPLICANT/MANUFACTURER

SKG-Pharma Limited
7/9 Sapara Street,
Ikeja, Lagos State, Nigeria.
Tel: +234(1)44544640
Email: skgpharma@yahoo.com