## 1. NAME OF THE MEDICINAL PRODUCT

SPECTRUM 250 mg film-coated tablets
SPECTRUM 500 mg film-coated tablets
SPECTRUM 750 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| Ingredients | SPECTRUM 250 mg | SPECTRUM 500 mg | SPECTRUM 750 mg |
|---|---|---|---|
| **Active ingredients** | | | |
| Ciprofloxacin hydrochloride<br>Equivalent amount of Ciprofloxacin (INN) | 291.08 mg<br>250.00 | 582.138 mg<br>500.00 mg | 873.239 mg<br>750.000 mg |
| **Excipients:** | | | |
| Croscarmellose sodium | 12.50 mg | 25.00 mg | 37.50 mg |
| Cellulose microcrystalline | 17.92 mg | 35.84 mg | 53.76 mg |
| Povidone (PVP K-30) | 7.50 mg | 15.00 mg | 22.50 mg |
| Magnesium Stearate | 3.50 mg | 7.00 mg | 10.50 mg |
| Silica Colloidal Anhydrous | 2.50 mg | 5.00 mg | 7.50 mg |
| **Film-coating :** | | | |
| Hypromellose E15 | 5.61 mg | 11.22 mg | 16.83 mg |
| Titanium dioxide (E171) | 2.42 mg | 4.84 mg | 7.26 mg |
| Talc | 1.216 mg | 2.61 mg | 3.63 mg |
| Propylene glycol | 1.21 mg | 2.42 mg | 3.63 mg |
| Propylene glycol 6000 | 0.55 mg | 1.10 mg | 1.646 mg |
| # Alcool isopropylique | ------ | ------ | ------ |
| # Eau purifiée | ------ | ------ | ------ |

*# Does not appear in the finished product*

For one film-coated tablet

Excipients with known effects: not applicable.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SPECTRUM film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on bacterial resistance to ciprofloxacin before initiating therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

In Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

- pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Genital tract infections
  - gonococcal uretritis and cervicitis due to sensitive strains of Neisseria gonorrhoeae
  - epididymo-orchitis including infections due to sensitive strains Neisseria gonorrhoeae
  - pelvic inflammatory disease including cases due to susceptible Neisseria gonorrhoeae
- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- Prophylaxis of invasive infections due to Neisseria meningitidis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

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

In 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**

The dosage depends on the indication, severity, and site of infection, the susceptibility of the causative bacteria to ciprofloxacin, the patient's renal function, and the weight of the child and adolescent.
The duration of treatment depends on the severity of the disease and clinical and bacteriological evolution.
The treatment of infections caused by certain bacteria (e.g., *Pseudomonas aeruginosa, Acinetobacter, or staphylococci*) may require higher doses of ciprofloxacin, as well as the concomitant administration of other appropriate antibacterial agents.
The treatment of certain infections (e.g., upper gynecological infections, intra-abdominal infections, infections in neutropenic patients, and osteoarticular infections) may require the concomitant administration of other appropriate antibacterial agents depending on the specific microorganism involved.

*In Adults*

| Indications | Daily dose in mg | Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin) |
|---|---|---|
| Infections of the lower respiratory tract | 500 mg twice daily to 750 mg twice daily | 7 to 14 days |

| | | | |
|---|---|---|---|
| Infections of the upper respiratory tract | Acute exacerbation of chronic sinusitis | 500 mg twice daily to 750 mg 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 | 750 mg twice daily | 28 days up to 3 months |
| Urinary tract infections (see section 4.4) (voir Mises en garde spéciales et précautions d'emploi) | Uncomplicated cystitis | 250 mg twice daily to 500 mg twice daily | 3 days |
| | | In pre-menopausal women, 500 mg single dose may be used | |
| | Complicated cystitis, Uncomplicated pyelonephritis | 500 mg twice daily | 7 days |
| | Complicated pyelonephritis | 500 mg 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 | 500 mg twice daily to 750 mg twice daily | 2 to 4 weeks (acute) to 4 to 6 weeks (chronic) |
| Genital tract infections | Gonococcal uretritis and cervicitis | 500 mg as a single dose | 1 day (single dose) |
| | Epididymo-orchitis and pelvic inflammatory diseases | 500 mg twice daily to 750 mg twice daily | At least 14 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 | 500 mg twice daily | 1 day |
| | Diarrhoea caused by *Shigella dysenteriae* type 1 | 500 mg twice daily | 5 days |
| | Diarrhoea caused by *Vibrio cholerae* | 500 mg twice daily | 3 days |
| | Typhoid fever | 500 mg twice daily | 7 days |
| | Intra-abdominal infections due to Gram-negative bacteria | 500 mg twice daily to 750 mg twice daily | 5 to 14 days |
| Infections of the skin and soft tissue | | 500 mg twice daily to 750 mg twice daily | 7 to 14 days |
| Bone and joint infections | | 500 mg twice daily to 750 mg twice daily | max. of 3 months |
| Neutropenic patients with fever that is suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance. | | 500 mg twice daily to 750 mg twice daily | Therapy should be continued over the entire period of neutropenia |
| Prophylaxis of invasive infections due to *Neisseria meningitidis* | | 500 mg 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. Drug administration should begin as soon as possible after suspected or confirmed exposure. | | 500 mg twice daily | 60 days from the confirmation of *Bacillus anthracis* exposure |

*Pediatric population*

| Indications | Daily dose in mg | Total duration of |
|---|---|---|

| | | |
|---|---|---|
| | | **treatment (potentially including initial parenteral treatment with ciprofloxacin)** |
| Cystic fibrosis | 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. | 10 to 14 days |
| Complicated urinary tract infections and pyelonephritis | 10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. | 10 to 21 days |
| Inhalation anthrax post- exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure. | 10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose. | 60 days from the confirmation of *Bacillus anthracis* exposure |
| Other severe infections | 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. | According to the type of infections |

*Elderly patients*

In elderly patients, the dose administered will depend on the severity of the infection and 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 | 250-500 mg every 12 h |
| < 30 | > 169 | 250-500 mg every 24 h |
| Patients on haemodialysis | > 169 | 250-500 mg every 24h (after dialysis) |
| Patients on peritoneal dialysis | > 169 | 250-500 mg 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**

The tablets should be swallowed with a drink, without being chewed. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets 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 case of severe impairment or if the patient is unable to swallow the tablets (e.g. patients fed by tube), it is recommended to start treatment with intravenous administration of ciprofloxacin until a relay by oral route is possible.

### 4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients listed in the section 2.
- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

### 4.4 Special warnings and precautions for use

**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-administered 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 uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates.

Ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, 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 improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

**Urinary tract infections**

The resistance of Escherichia coli to fluoroquinolones (the pathogen most frequently responsible for urinary tract infections) varies within the European Union. Prescribers should take into consideration the local prevalence of Escherichia coli resistance to fluoroquinolones.

A single dose of ciprofloxacin, which can be used in the treatment of uncomplicated cystitis in premenopausal women, is expected to be less effective than longer-term treatment. This is all the more important to take into account as the rate of resistance of Escherichia coli to quinolones is increasing.

**Intra-abdominal infections**

Data on the effectiveness of ciprofloxacin in the treatment of post-operative intra-abdominal infections are limited.

**Travellers' diarrhoea**

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

**Osteoarticular infections**

Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

**Anthrax disease**

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.

**Pediatric 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.

In immature animals, ciprofloxacin may cause arthropathy in weight-bearing joints. Safety data from a randomized, double-blind study regarding the use of ciprofloxacin in children (ciprofloxacin: n = 335, mean age = 6.3 years; comparators: n = 349, mean age = 6. 2 years; range = 1 to 17 years) demonstrated an incidence of arthropathies suspected of being related to taking the drug (detected on the basis of clinical signs and symptoms linked to the joints) on D +42 of 7, 2% and 4.6 under ciprofloxacin and comparators. After 1 year of follow-up, the incidence of treatment-related arthropathy was 9.0% and 5.7%, respectively. The increase over time in cases of arthropathy suspected of being related to taking the drug was not statistically significant between the different groups. Given the possible occurrence of adverse events on the joints and/or surrounding tissues, treatment should only be initiated after careful assessment of the benefit/risk ratio (see section 4.8).

*Broncho-pulmonary infections in cystic fibrosis*

Children and adolescents aged 5 to 17 years were included in the clinical trials. Experience in children aged 1 to 5 years is more limited.

*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 examinations.

Clinical trials have included children and adolescents aged 1-17 years.

*Other specific severe infections*

Other severe infections, in accordance with official recommendations, or after careful assessment of the benefit/risk ratio when other treatments cannot be used, or after failure of conventional treatment and when the bacteriological results justify it.
The use of ciprofloxacin in these specific severe infections, other than those mentioned above, has not been evaluated in clinical trials and clinical experience in this area is limited. Therefore, caution is advised when treating patients with these types of 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 reaction occurs, ciprofloxacin should be discontinued 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 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 the slightest sign of tendonitis (e.g. painful swelling or inflammation), treatment with ciprofloxacin should be discontinued. The affected limb must be put to rest.

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

**Aortic aneurysm and aortic dissection**

Epidemiological studies report an increased risk of aortic aneurysm and aortic dissection after taking fluoroquinolones, particularly in the elderly.
Therefore, fluoroquinolones should only be used after careful benefit/risk assessment and consideration of other treatment options in patients with a family history of aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or other risk factors or conditions predisposing to aortic aneurysm and aortic dissection (e.g., Marfan syndrome, Ehlers-Danlos vascular syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, known atherosclerosis).
In the event of sudden abdominal, chest or back pain, patients should be advised to contact an emergency medical service immediately.

**Vision problems**

An ophthalmologist should be consulted immediately if vision decreases or any other eye disorder develops.

**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 rays 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, isolated or associated) have been reported in patients treated with ciprofloxacin. In order to prevent progression towards irreversible damage, taking ciprofloxacin must be interrupted as soon as symptoms of neuropathy appear, in particular: pain, burning, tingling, numbness and/or muscle weakness (see section 4.8)

**Cardiac disorders**

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for the QT prolongation 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 in Elderly patients, section 4.5, section 4.8, section 4.9).

**Hypoglycemia**

As with other quinolones, hypoglycemia has been reported most commonly in diabetic patients, primarily in the elderly population. In all diabetic patients, it is recommended to monitor blood sugar levels regularly (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 4.8v). 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**

Cases of crystalluria linked to the use of ciprofloxacin have been reported (See section 4.8) Patients treated with ciprofloxacin must be adequately hydrated and any excessive alkalinity of urine must be avoided.

**Renal failure**

Ciprofloxacin is excreted mainly unchanged via the kidneys. A dosage adjustment is therefore necessary in patients with renal insufficiency, as described in (section 4.2), in order to avoid an increase in adverse effects 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 bacteria resistant to ciprofloxacin in the event of long-term treatment, treatment of nosocomial infections and/or infections due to *Staphylococcus and Pseudomonas*.

**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,). Co-administration of ciprofloxacin and tizanidine is contra-indicated. consequently if these these substances are taked concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations of products (e.g. of theophylline) may be necessary (see section 4.5)

Ciprofloxacin inhibits CYP1A2 and may therefore increase the serum concentration of concomitantly administered substances metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, if these substances are used concomitantly with ciprofloxacin, clinical signs of possible overdose should be closely monitored and serum concentrations of the products (e.g. theophylline) may need to be determined (see section 4.5). Concomitant administration of ciprofloxacin and tizanidine is contraindicated.

**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 treated with drugs known to prolong the QT interval (e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics). (see section 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), 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) Which results in a decrease in Tmaxof ciprofloxacin. 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 maximal concentration and The area under the curve 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 (Cmax increase: 7-fold, range: 4 to 21-fold; area under the curve 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 of these two medicines is not recommended (see section 4.4)

*Theophylline*

Concurrent administration of ciprofloxacin and theophylline can cause an increase in serum theophylline concentration and undesirable effects. Due to theophylline 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)

*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 and 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 the Area under the curve and the maximat concentration 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 Cmax 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*

The maximal concentration and the area under the curve of sildenafil were lined 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 trials, fluvoxamine, a potent inhibitor of CYP450 isoenzyme 1A2, was shown to markedly inhibit agomelatine metabolism, resulting in 60-fold increased agomelatine exposure. Although no clinical data are available regarding a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 isoenzyme 1A2, similar effects can be expected when administered concomitantly (*See section4.4*, "Cytochrome P450").

*Zolpidem*

Concomitant administration of ciprofloxacin may result in increased blood concentrations of zolpidem: concurrent use is not recommended.

**4.6 Fertility, pregnancy and breastfeeding**

**Pregnancy**

The available data on the administration of ciprofloxacin to pregnant women do not indicate any malformation or fetal/neonatal toxicity of ciprofloxacin. Animal studies do not reveal any direct or indirect toxic effects on reproduction. In the prenatal phase and in young animals, effects on immature cartilage have been observed during exposure to quinolones. The occurrence of joint damage caused by the drug on the cartilage of the immature human body/fetus cannot therefore be excluded (*See* section 5.3).

As a precautionary measure, it is preferable to avoid the use of ciprofloxacin 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.

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

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

### 4.8 Undesirable effects

The most commonly reported adverse drug reactions are nausea and diarrhoea.
Adverse reactions reported during clinical trials and post-marketing of SPECTRUM film-caoted tablet (oral, intravenous and sequential treatment) are listed below by frequency. The frequency analysis considers both oral and intravenous data for ciprofloxacin.

| 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 superinfections | | | |
| **Blood and Lymphatic System Disorders** | | Eosinophilia | Leukopenia<br>Anaemia<br>Neutropenia<br>Leukocytosis<br>Thrombocytopenia<br>Thrombocytaemia | Anaemia Haemolytic<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 Disorders** | | Decreased appetite | Hyperglycaemia<br>Hypoglycaemia (see section 4.4) | | |
| **Psychiatric Disorders** | | Psychomotor hyperactivity / agitation | Confusion and disorientation<br>Anxiety reaction<br>Abnormal dreams<br>Depression (which may lead to suicidal ideations/ thoughts or suicide attempts or suicide) (see section 4.4)<br>Hallucinations | Psychotic reactions (which may lead to suicidal ideations/ thoughts or suicide attempts or suicide) (see section 4.4) | |
| **Nervous System Disorders** | | Headache<br>Dizziness<br>Sleep disorders<br>Dysgueusie | Paresthesia and dysesthesia<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) |
| **Eye Disorders** | | | Visual disturbances (e.g. diplopia) | Visual colour distortions | |

| | | | | | |
|---|---|---|---|---|---|
| **Ear and Labyrinth Disorders** | | | Tinnitus<br>Hearing loss / Hearing impaired | | |
| **Cardiac Disorders** | | | Tachycardia | | Ventricular arrhythmia, and torsades de pointes (reported mainly in patients with risk factors for QT interval), QT interval prolongation (see sections 4.4 & 4.9) |
| **Vascular Disorders** | | | Vasodilatation<br>Hypotension<br>Syncope | Vasculitis | |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | Dyspnoea (including asthmatic condition) | | |
| **Gastro-intestinal Disorders** | Nausea<br>Diarrhoea | Vomiting<br>Gastrointestinal and abdominal pains<br>Dyspepsia<br>Flatulence | Antibiotic-associated colitis (potentially fatal in very rare cases) (See 4.4) | Pancreatitis | |
| **Hepatobiliary Disorders** | | Increase in transaminase<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** | | Skin rash<br>Pruritus<br>Urticaria | Photosensitivity reactions (see section 4.4) | Petechiae<br>Erythema multiforme<br>Erythema nodosum<br>Stevens-Johnson syndrome (potentially life- threatening)<br>SynLyell drome (potentially life-threatening) | Acute Generalised Exanthematous Pustulosis (AGEP)<br>Drug hypersensitivity syndrome (DRESS syndrome) |
| **Musculo-skeletal and Connective Tissue Disorders** | | Musculoskeletal 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 (mainly the Achilles tendon) (see section 4.4)<br>Exacerbation of myasthenia symptoms (see section 4.4) | |
| **Renal and Urinary Disorders** | | Renal impairment | Renal failure<br>Haematuria<br>Crystalluria (see section 4.4)<br>Tubulointerstitial nephritis | | |
| **General Disorders and Administration Site conditions** | | Asthenia<br>Fever | Oedema<br>Sweating (hyperhidrosis) | | |
| **Investigations** | | Increase in blood alkaline | Increased amylase | | Increased INR (International |

| | | | | | |
|---|---|---|---|---|---|
| | | phosphatase | | | normalised ratio) (in patients treated with Vitamin K antagonists) |

**Pediatric population:**

The incidence of arthropathies (arthralgia, arthritis) mentioned above refers to data collected in adult studies. In children, arthropathies are frequently reported (see section 4.4).

**Reporting suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continuous monitoring of the benefit/risk ratio of the drug.

### 4.9 Overdose

Following an overdose of 12 g, mild symptoms of toxicity have been described. Acute renal failure has been reported following an acute overdose of 16 g.

Symptoms of overdose include dizziness, tremor, headache, asthenia, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic failure, as well as crystalluria and hematuria. Reversible renal toxicity has been described.

In addition to standard emergency measures, e.g. gastric lavage followed by administration of medicinal charcoal, it is recommended to monitor renal function, including urinary pH, and to acidify, if necessary, to prevent further crystalluria. Patients must benefit from correct hydration. Antacids containing calcium or magnesium can theoretically reduce the absorption of ciprofloxacin in the event of an overdose.

Hemodialysis or peritoneal dialysis only eliminates ciprofloxacin in small quantities (< 10%).

In the event of an overdose, symptomatic treatment should be instituted. ECG monitoring should be performed due to possible prolongation of the QT interval.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02.**

**Mechanism of action**

Ciprofloxacin is an antibiotic belonging to the fluoroquinolone group. Its bactericidal activity results from the inhibition of topoisomerase type II (DNA gyrase) and topoisomerase IV, necessary for the replication, transcription, repair and recombination of bacterial DNA.

**PK/PD relationship**

**Pharmacokinetic/pharmacodynamic ratio**

Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) 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.

**Resistance mechanism**

*In vitro resistance can develop through successive mutations leading to modifications of the target sites of ciprofloxacin on DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones is variable. Single mutations do not necessarily result in clinical resistance, but multiple mutations generally result in clinical resistance to several or all active substances in that therapeutic class.*

*Resistance mechanisms through membrane impermeability and/or active efflux can have variable effects on bacterial sensitivity to fluoroquinolones depending on their physicochemical properties and depending on the affinity of the transport systems for the different antibiotics of this therapeutic class. All in-vitro resistance mechanisms are frequently observed in clinical isolates. Resistance to other families of antibiotics through mechanisms such as those affecting*

*membrane permeability (common with Pseudomonas aeruginosa) and efflux mechanisms can alter the sensitivity of bacteria to ciprofloxacin.*
*Plasmid resistance encoded by the qnr genes was observed.*

**Antibacterial activity spectrum**

The critical concentrations separate sensitive strains from strains of intermediate sensitivity, and the latter from resistant ones:

*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 influenzaeand Moraxella catarrhalis* | S ≤ 0.5 mg/l | R > 0.5 mg/l |
| *Neisseria gonorrhoeae* | 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. The critical concentrations defined for ciprofloxacin correspond to treatment using high doses.

* Non-species critical concentrations were determined primarily based on PK/PD data and are independent of the MIC distribution of specific species. They only apply to species for which no species-specific critical concentration has been defined and not to those for which a sensitivity test is not recommended.
The prevalence of acquired resistance may vary geographically and with time for selected species 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.

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

| **COMMONLY SUSCEPTIBLE SPECIES** |
|---|
| Aerobic Gram-positive micro-organisms<br>*Bacillus anthracis* (1) |
| Aerobic Gram-negative micro-organisms<br>*Aeromonas* spp. *Brucella* spp. *Citrobacter koseri Francisella tularensis Haemophilus ducreyi* |
| Haemophilus influenzae* Legionella spp.<br>Moraxella catarrhalis* Neisseria meningitidis<br>Pasteurella spp.<br>Salmonella spp.* Shigella spp.* ADRCFCFDCVibrio spp. Yersinia pestis |
| Anaerobic micro-organisms<br>Mobiluncus |
| Other micro-organisms Chlamydia trachomatis ($) Chlamydia pneumoniae ($) Mycoplasma hominis ($) Mycoplasma pneumoniae ($) |
| **SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM** |
| Aerobic Gram-positive micro-organisms Enterococcus faecalis ($) Staphylococcus spp. *(2) |
| Aerobic Gram-negative micro-organisms |

| |
|---|
| Acinetobacter baumannii+ Burkholderia cepacia+* Campylobacter spp.+*<br>Citrobacter freundii* Enterobacter aerogenes Enterobacter cloacae* Escherichia coli* Klebsiella oxytoca Klebsiella pneumoniae* Morganella morganii* Neisseria gonorrhoeae* Proteus mirabilis* Proteus vulgaris* Providencia spp. Pseudomonas aeruginosa* Pseudomonas fluorescens Serratia marcescens* |
| Anaerobic micro-organisms Peptostreptococcus spp. Propionibacterium acnes |
| **INHERENTLY RESISTANT ORGANISMS** |
| Aerobic Gram-positive micro-organisms<br>Actinomyces Enteroccus faecium Listeria monocytogenes |
| Aerobic Gram-negative micro-organisms |
| *Stenotrophomonas maltophilia* |
| Anaerobic micro-organisms<br>*Excepted as listed above* |
| Other micro-organisms *Mycoplasma genitalium Ureaplasma urealitycum* |
| * Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications<br>+ Resistance rate ≥ 50% in one or more EU countries<br>($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily 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.<br>(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. |

~~**Dual blockade of the renin-angiotensin-aldosterone system (RAAS)**~~

~~Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.~~
~~ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of endorgan damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.~~
~~These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.~~
~~ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.~~
~~ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both.~~
~~The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.~~

~~**Hydrochlorothiazide**~~
~~Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume,~~

~~increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss and decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.~~

~~After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours; the antihypertensive effect persists for up to 24 hours.~~

**5.2 Pharmacokinetic properties**

**Absorption**

After oral administration of single doses of 250 mg, 500 mg and 750 mg of ciprofloxacin tablets, ciprofloxacin is rapidly and extensively absorbed, mainly in the small intestine, and its maximum serum concentration is reached within 1 to 2 hours. after taking.

After administration of single doses of 100-750 mg, the maximum serum concentrations (Cmax) obtained are dose-dependent and range between 0.56 and 3.7 mg/l. Serum concentrations are proportional to the administered dose up to a dose of 1000 mg.

Absolute bioavailability is approximately 70-80%.

After administration of an oral dose of 500 mg every 12 hours, the area under the serum concentration-time curve (AUC) obtained is equivalent to that observed after a one-hour intravenous infusion of 400 mg of ciprofloxacin every 12 hours.

**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 concentrations are elevated in many tissues, such as the lungs (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses and inflammatory lesions (cantharidin vesicular fluid), or the urogenital tract (urine, prostate, endometrium) where total concentrations exceed those reached in plasma.

**Biotransformation**

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is a moderate inhibitor of CYP450 1A2 isoenzymes.

**Elimination**

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

| Excretion of ciprofloxacin (% of dose) | | |
|---|---|---|
| | **Oral Administration** | |
| | **Urine** | **Faeces** |
| Ciprofloxacin | 44.7 | 25.0 |
| Metabolites (M1-M4) | 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 12 h.

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.

In children:

The pharmacokinetic data in children are limited.

A study in children showed that Cmax and AUC were independent of age (beyond the age of one year). No significant increase in Cmax and AUC was observed after repeated administration (10 mg/kg three times daily).

In 10 children with severe sepsis Cmax 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 included in the same range as those reported in adults at therapeutic doses. Based on population pharmacokinetic analysis of children with various infections, the average predictive half-life in children is approximately 4-5 hours and the bioavailability of the oral suspension is 50-80%.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional single dose, repeated dose toxicology, carcinogenicity or reproductive toxicity studies.

Like other quinolones, ciprofloxacin is phototoxic in animals at exposure levels relevant to clinical practice. Photomutagenesis/photocarcinogenesis data show weak photomutagenic or phototumorigenic effects of ciprofloxacin in in-vitro studies and in animal experiments. These effects are comparable to those 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.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Croscarmellose sodium, Cellulose microcrystalline, Povidone (PVP K-30), Magnesium Stearate, Silica Colloidal Anhydrous, hypromellose, titanium dioxide (E171), Talc, Propylene glycol, PEG 6000,

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Blisters of PVC/ALU.
SPECTRUM 250 & 500 mg: packs of 10, 16 & 20.
SPECTRUM 750 mg: pack of 10.

*Not all pack sizes may be marketed.*

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADRESS

- Marketing Authorization holder:

***COOPER PHARMA***
41, Rue Mohamed DIOURI, 20110 Casablanca
Morocco

- Manufacturing, Control, Packaging site & batch release site:

***COOPER PHARMA***
Route 107, Km 2.5 Douar Oulad Sidi Abbou
Tit Mellil Casablanca
Morocco

## 8. MARKETING AUTHORISATION NUMBER

SPECTRUM 250 mg B/10: 20/4365/DGC&PHS/2018.
SPECTRUM 500 mg B/10: 20/4366/DGC&PHS/2018.
SPECTRUM 750 mg B/10: 20/4366/DGC&PHS/2018

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 06 June 2018.
Date of renewal of authorization: not applicable

## 10. DATE OF REVISION OF THE TEXT

Avril 2019.

## PRESCRIPTION AND DELIVERY CONDITIONS

Table A (list I)