Ciprofloxacin 250mg Film-Coated Tablets

Summary of Product Characteristics Updated 26-Feb-2016 | Accord Healthcare Limited

1. Name of the medicinal product

Ciprofloxacin 250mg Film-Coated Tablets

2. Qualitative and quantitative composition

Each Ciprofloxacin 250mg Tablet contains 291.1mg ciprofloxacin hydrochloride equivalent to 250mg Ciprofloxacin (INN).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated Tablets.

Ciprofloxacin 250mg tablets are white to off-white, round, biconvex film coated tablet with inscription 'AM' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin 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 resistance to ciprofloxacin before commencing therapy.

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

Adults

• Lower Respiratory tract infections due to Gram-negative bacteria

- pneumonia

- exacerbations of chronic obstructive pulmonary disease

- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

• 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 susceptible *Neisseria gonorrhoeae*

- epididymo-orchitis including cases due to susceptible *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 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

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin 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 certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

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

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)	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

Paediatric 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

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	250-500 mg every 12 h
≤30	>169	250-500 mg every 24 h
Patients on haemodialysis	>169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	>169	250-500 mg every 24 h

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

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. 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 severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Streptococcal Infections (including Streptococcus pneumoniae)

Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

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.

Genital tract infections

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

Therefore, 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 based on local prevalence data. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections

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

Travellers' diarrhoea

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

Infections of the bones and joints

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

Inhalational anthrax

Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Paediatric population

The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents. Treatment should be initiated only after a careful benefit/ risk evalulation, due to possible adverse events related to joints and/ or surrounding tissue (see section 4.8).

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).

Broncho-pulmonary infections in cystic fibrosis

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

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.

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

Other specific severe infections

Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.

The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such 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 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 (see section 4.8).

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 Geriatric 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). Co-administration of ciprofloxacin and tizanidine is contra-indicated. 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).

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 falsenegative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Vision disorders

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

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 the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, and 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, aluminum, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminum, 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 Cmax 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.

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 ('Cytochrome P450' in section 'Special warnings and precautions for use).

Zolpidem

Co-administration ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

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 Cmax 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.

4.6 Fertility, 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).

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 to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea. ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of 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 available data)
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life- threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia, Hypoglycaemia (see section 4.4)		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation	Psychotic reactions (potentially culminating in	Mania, hypomania

			Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations	suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension 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 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 section 4.4 and 4.9)
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastro-intestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases	Hepatic impairment Cholestatic icterus	Liver necrosis (very rarely progressing to life- threatening	

		Increased bilirubin	Hepatitis	hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP) DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome
Musculo-skeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

Paediatric patients

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme,

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

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

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

reported.

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon it is recommended to monitor renal 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.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone Antibacterials, Fluoroquinolones, ATC code: J 01 MA 02

Mechanism of action:

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

PK/PD relationship:

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:

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:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteriaceae	S ≤0.5 mg/L	R > 1 mg/L
Pseudomonas spp	S ≤0.5 mg/L	R > 1 mg/L
Acinetobacter spp	S ≤1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤0.5 mg/L	R > 0.5 mg/L
Neisseria 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. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific

breakpoint and not for those species where susceptibility testing 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.

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

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms
Bacillus anthracis (1)
Aerobic Gram-negative micro-organisms
Aeromonas spp.
Brucella spp.
Citrobacter koseri
Francisella tularensis
Haemophilus ducreyi
*Haemophilus influenzae**
Legionella spp.
*Moraxella catarrhalis**
Neisseria meningitidis
Pasteurella spp.
Salmonella spp.*
Shigella spp.*
Vibrio spp.
Yersinia pestis
Anaerobic micro-organisms
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.+ *
*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
Actinomyces
Enteroccus faecium
Listeria monocytogenes
Aerobic Gram-negative micro-organisms
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Excepted as listed above
Other micro-organisms
Mycoplasma genitalium
Ureaplasma urealitycum
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
+ Resistance rate ≥50% in one or more EU countries
($): 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.
(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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.

Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 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

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

Biotransformation

Low concentrations of four metabolites have 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 known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with 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.

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%.

5.3 Preclinical safety data

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.

6. Pharmaceutical particulars

6.1 List of excipients

Each tablet contains:

- croscarmellose sodium,
- microcrystalline cellulose,
- povidone,
- magnesium stearate.

The tablet film-coat consists of:

- hypromellose,
- lactose monohydrate,
- titanium dioxide E171,
- macrogol 4000,
- sodium citrate
- purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

PVC 250 µm//Al 20 µm blisters.

The Ciprofloxacin 250mg Tablets are available in pack sizes of 10, 12, 20, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special instructions for use/handling.

7. Marketing authorisation holder

ACCORD HEALTHCARE LIMITED

SAGE HOUSE

319 PINNER ROAD

HARROW

MIDDLESEX

HA1 4HG

8. Marketing authorisation number(s)

PL 20075/0048

9. Date of first authorisation/renewal of the authorisation

25 July 2003

10. Date of revision of the text

05/02/2016

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin 250mg Film-Coated Tablets
Ciprofloxacin 500mg Film-Coated Tablets
Ciprofloxacin 750mg Film-Coated Tablets
(Ciprofloxacin Hydrochloride)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What are Ciprofloxacin tablets and what are they used for

Ciprofloxacin belongs to a group of medicines known as the quinolone antibacterials, fluoroquinolones. It has high anti-bacterial activity against a wide range of organisms.
Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults:

Ciprofloxacin is used to treat the following bacterial infections:

- respiratory tract infections(e.g. certain types of pneumonia)
- long lasting or recurring ear or sinus infections
- urinary tract infections (bladder and kidneys infection)
- genital tract infections in men and women (e.g. gonorrhoea, a sexually transmitted disease)
- gastro-intestinal tract infections (e.g.severe gastro-enteritis) and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to prevent infections due to the bacteria *Neisseria meningitides* which causes meningitis(brain and spinal cord inflammation)
- anthrax inhalation exposure (infection that occurs when the spores from bacteria *Bacillus anthracis* enters the body).

Ciprofloxacin may be used in the management of patients with low white blood cell counts (neutropenia) who have a fever that is suspected to be due to a bacterial infection.
If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin.

Children and adolescents:
Ciprofloxacin should be used under specialist medical supervision, to treat the following bacterial infections for children and adolescents:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis (genetic disorder known to be an inherited disease of the secretory glands, including the glands that make mucus and sweat).
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis).
- anthrax inhalation exposure (infection that occurs when the spores from bacteria Bacillus anthracis enters the body).

Ciprofloxacin may also be used to treat other specific severe infections in children and adolescents when your doctor considers this as necessary.

2. What you need to know before you take Ciprofloxacin tablets

Do not take Ciprofloxacin if you:
- are allergic (hypersensitive) to the Ciprofloxacin, to any other quinolone drugs or to any of the other ingredients of Ciprofloxacin tablets (see section 6).
- are taking tizanidine (see Section 2: Taking other medicines).

Warnings and precautions:
Talk to your doctor, pharmacist or nurse before taking Ciprofloxacin Tablets if:

- you suffer from 'fits' or epilepsy or any other neurological conditions.
- you have ever had kidney problems because your treatment may need to be adjusted
- you have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin
- you are diabetic because you may experience a risk of hypoglycaemia with ciprofloxacin. you have myasthenia gravis (a type of muscle weakness) because symptoms can be exacerbated.
- you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anaemia with ciprofloxacin.
- If your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist immediately

Heart problems
- Caution should be taken when using this kind of medicine, if you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called 'bradycardia'), have a weak heart (heart failure), have a history of heart attack (myocardial infarction), you are female or elderly or you are taking other medicines that result in abnormal ECG changes (see section *Taking other medicines*).

For the treatment of some genital tract infections, your doctor can prescribe another antibiotic in addition to ciprofloxacin. If there is no improvement in symptoms after 3 days of treatment, please consult your doctor.

Contact your doctor **immediately**, if any of the following occurs **while taking Ciprofloxacin**. Your doctor will decide whether treatment with Ciprofloxacin needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin tablets and contact your doctor immediately.**
- If your eyesight becomes impaired or if your eyes seem to be otherwise affected, **consult an eye specialist immediately.**
- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. Inflammation and ruptures of tendons may occur even within the first 48 hours of treatment or up to several months after discontinuation of Ciprofloxacin tablets therapy. At the first sign of any pain or inflammation stop taking Ciprofloxacin tablets and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.
- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin tablets and contact your doctor immediately.
- You may experience **psychiatric reactions** the first time you take Ciprofloxacin tablets. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin tablets. In rare cases, depression or psychosis can progress to thoughts of suicide, suicide attempts, or completed suicide. If this happens, stop taking Ciprofloxacin tablets and contact your doctor immediately.
- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin tablets and contact your doctor immediately.
- **Hypoglycemia** has been reported most often in diabetic patients, predominantly in elderly population. If this happens, contact your doctor immediately.
- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin tablets, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin tablets immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.
- Tell the doctor or laboratory staff that you are taking Ciprofloxacin tablets if you have to provide a **blood or urine sample**.
- If you suffer from **kidney problems**, tell the doctor because your dose may need to be adjusted.
- Ciprofloxacin tablets may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin tablets and contact your doctor immediately.
- Ciprofloxacin tablets may cause a reduction in the number of white blood cells and your resistance to infection may be decreased. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Your skin becomes more sensitive to sunlight or ultraviolet (UV) light when taking Ciprofloxacin tablets. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Other medicines and Ciprofloxacin:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those medicines obtained without a prescription.
Ciprofloxacin can increase the level of the following substances in the blood:
- Agomelatine,
- Zolpidem

Do not take Ciprofloxacin together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin").

The following medicines are known to interact with Ciprofloxacin in your body. Taking Ciprofloxacin together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- Vitamin K antagonists (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione) or other oral anti-coagulants (to thin the blood)
- theophylline (for breathing problems)
- phenytoin (used to treat epilepsy)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)
- cyclosporin (used to treat psoriasis, dermatitis, rheumatoid arthritis and in organ transplantation)
- probenecid (used to prevent gout)
- metoclopramide (used to treat nausea and vomiting (feeling/being sick) and migraine)
- ropinirole (used to treat Parkinson's disease)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- olanzapine (an antipsychotic)
- other medicines that can alter your heart rhythm: medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), tricyclic antidepressants, some antimicrobials (that belong to the group of macrolides), some antipsychotics.

Ciprofloxacin may **increase** the levels of the following medicines in your blood:
- pentoxifylline (for circulatory disorders)
- caffeine
- duloxetine (for depression, diabetic nerve damage or incontinence)
- lidocaine (for heart conditions or anesthetic use)
- sildenafil (e.g. for erectile dysfunction)

Some medicines **reduce** the effect of Ciprofloxacin. Tell your doctor if you take or wish to take:
- antacids

- omeprazole
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer or lanthanum carbonate)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin with food and drink
Unless you take Ciprofloxacin during meals, do not eat or drink any dairy products (such as milk or yogurt) or drinks with added calcium when you take the tablets. These can affect the absorption of ciprofloxacin and so you should take your tablets either 1 to 2 hours before or at least 4 hours after you have such products.

Pregnancy and breast-feeding
It is preferable to avoid the use of Ciprofloxacin during pregnancy. Tell your doctor if you are pregnant or planning to become pregnant.

Do not take Ciprofloxacin tablets during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Ask your doctor or pharmacist for advice before taking any other medicine.

Driving and using machines
Ciprofloxacin may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to ciprofloxacin before driving a vehicle or operating machinery. If in doubt, talk to your doctor.
Important information about some of the ingredients of Ciprofloxacin tablets:
Lactose monohydrate – If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Ciprofloxacin tablets

Always take ciprofloxacin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
a) Take the tablets exactly as your doctor has told you. The tablets should **always** be taken with plenty of water, as this will help to prevent the formation of tiny crystals in your urine (crystalluria).
b) Do not chew the tablets because they do not taste nice.
c) Do try to take the tablets at around the same time every day.

You can take the tablets at meal times or between meals. Any calcium you take as a part of a meal will not seriously affect uptake. However, **do not** take ciprofloxacin tablets with dairy products such as milk or yogurt or with fortified fruit juices (eg.Calcium-fortified orange juice).

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted. The treatment usually lasts from 5 to 21 days, but may take longer for severe infections.
Your dose will be dependent on the type and severity of your infection, your age, weight and kidney function. Your doctor will choose the best dose for you.

If you take more Ciprofloxacin tablets than you should
If you take more than the prescribed dose, get medical help immediately. If possible, take your tablets or the box with you to show the doctor.
If you forget to take Ciprofloxacin tablets
If you forget to take a dose, take the normal dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose and just carry on as before. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin tablets
It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, ciprofloxacin can cause side-effects, although not everybody gets them.

You may suffer an allergic reaction, symptoms of which include rash, itching, difficulty in breathing or swelling of the face, lips, throat or tongue. If this happens to you, stop taking the tablets immediately and seek medical help.

STOP taking the tablets immediately and seek medical help if any of the following occur:

- muscle pain and/or weakness, inflammation of the joints and joint pain, increased muscle tone and cramping, inflammation of the tendons or tendon rupture, particularly affecting the large tendon at the back of the ankle (Achilles tendon). If you experience this, rest the affected limb, discontinue treatment and seek medical advice immediately. See section 2.
- Unusual feelings of pain, burning, tingling, numbness or muscle weakness in the extremities (neuropathy)-See section 2.
- infection with symptoms such as fever and serious deterioration of your general condition (there may be a dangerous drop in a type of white blood cells (agranulocytosis)
- Severe allergic reactions manifested as various skin eruptions or rashes, breathing problem (for example, the potentially fatal anaphylactic reaction, Stevens-Johnson syndrome or toxic epidermal necrolysis),
- Hypersensitivity reactions called DRESS drug reaction with eosinophilia and systemic symptoms such as Fever, severe rash, joint pain, enlarged lymph nodes and inflammation of one or more internal organs such as liver leading to abdominal pain, yellowing of the skin and whites of the eyes and/or heart, lungs and kidneys; with changes to your blood counts, particularly white blood cells called eosinophils. See section 2.
- Liver problems (eg. Jaundice –yellowing of skin and white part of eyes)- very rarely can lead to life-threatening liver failure
- mental disturbances (psychotic reactions and depression potentially leading to thoughts of suicide and suicide attempts), hallucinations (apparent perception of something not present)

- inflammation of the bowel (colitis) which causes attacks of diarrhoea, sometimes containing blood and/or mucus) linked to antibiotic use (can be fatal in very rare cases)
- blood or crystals in the urine, decreased urination (kidney failure)

These are potentially serious side effects and you will need to seek urgent medical attention.

Other side effects are as below-

Common: may affect up to 1 in 10 people

- nausea, diarrhoea
- joint pains in children

Uncommon: may affect up to 1 in 100 people

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- decreased appetite
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- hives
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)
- Feeling highly excited (mania) or feeling great optimism and overactivity (hypomania),

Rare: may affect up to 1 in 1,000 people

- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- decreased blood sugar (hypoglycaemia) (see Section 2: Warnings and precautions)
- confusion, disorientation, anxiety reactions, strange dreams
- tremors, seizures or giddiness
- eyesight problems including double vision
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Warnings and precautions)
- urinary tract inflammation
- fluid retention or excessive sweating
- increased levels of the enzyme amylase

Very rare: may affect up to 1 in 10,000 people

- a special type of reduced red blood cell count (haemolytic anaemia); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Warnings and precautions)
- allergic reaction known as serum sickness
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure and pseudotumor cerebri)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- small, pin-point bleeding under the skin (petechiae);

Not known: frequency cannot be estimated from the available data
- abnormal fast heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm (called 'prolongation of QT interval', seen on ECG, electrical activity of the heart)
- pustular rash
- influence on blood clotting (in patients treated with Vitamin K antagonists)
- periods of overactive and excited behaviour
- Feeling highly excited (mania) or feeling great optimism and overactivity (hypomania), hypersensitivity reaction called DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ciprofloxacin tablets

Do not store above 25°C. Store in the original package.
Keep out of the reach and sight of children.
Do not use your tablets after the expiry date stated on the label or carton.
Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Ciprofloxacin tablet contains?

The **Active** ingredient in your tablet is Ciprofloxacin Hydrochloride.
The **Other** ingredients are croscarmellose sodium, microcrystalline cellulose, povidone, magnesium stearate. The tablet coating is made of hypromellose, lactose monohydrate,

macrogol 4000, sodium citrate and the colouring agent titanium dioxide (E171) (*see section 2 for Important information about some of the ingredients of Ciprofloxacin tablets).*

What Ciprofloxacin tablet looks like and contents of the pack?
Ciprofloxacin 250mg tablets are White to off-white, round, biconvex film coated, marked with 'AM' on one side and plain on the other side.
Ciprofloxacin 500mg tablets are White to off-white, capsule shape, biconvex, film coated, marked with 'CI' on one side and plain on the other side.
Ciprofloxacin 750mg tablets are White to off-white, capsule shape, biconvex, film coated, marked with 'CJ' on one side and plain on the other side.

Ciprofloxacin 250mg Tablets are available in blister packs of 10, 12, 20, 50, and100 tablets.
Ciprofloxacin 500mg Tablets are available in blister packs of 10, 12, 20, and 100 tablets.
Ciprofloxacin 750mg Tablets are available in blister packs of 10, 20, 50 and 100 tablets.
(Not all pack sizes may be marketed).

Marketing Authorisation holder and Manufacturer

Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow, Middlesex ,
HA1 4HF, United Kingdom

This leaflet was last revised in 02/2016.

Advice/medical education
Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.

Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly.

Loperamide 2mg Hard Capsules (PL 29831/0381)

Summary of Product Characteristics Updated 22-Jun-2017 | Wockhardt UK Ltd

1. Name of the medicinal product

Loperamide 2mg Hard Capsules

Diarrhoea Relief Capsules

Diah-Limit

Numark Diarrhoea Relief 2mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 2mg Loperamide hydrochloride.

Excipient with known effect: lactose

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Capsules

Hard gelatin capsule – green and dark grey.

4. Clinical particulars

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea, in adults and children 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method of administration

Posology:

Acute Diarrhoea

Adults and children over 12:

Two capsules (4 mg) initially, followed by one capsule (2 mg) after each loose stool.

The usual dose is 3-4 capsules (6 mg – 8 mg) a day. The total daily dose should not exceed 6 capsules (12 mg).

Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome in adults aged 18 and over

Two capsules (4 mg) to be taken initially, followed by 1 capsule (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 capsules (12 mg).

Paediatric population

Loperamide hydrochloride is contraindicated in children less than 12 years of age.

Elderly

No dose adjustment is required for the elderly.

Renal Impairment

No dose adjustment is required for patients with renal impairment.

Hepatic Impairment

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide hydrochloride should be used with caution in such patients because of reduced first pass metabolism (see section 4.4 Special warnings and precautions for use).

Method of administration

Oral use. The capsules should be taken with liquid.

4.3 Contraindications

This medicine is contraindicated:

• in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• in children less than 12 years of age.

- in patients with acute dysentery, which is characterised by blood in stools and high fever.
- in patients with acute ulcerative colitis.
- in patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter.
- in patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.

Loperamide hydrochloride must not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. Loperamide must be discontinued promptly when ileus, constipation or abdominal distension develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide hydrochloride is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in young children and in frail and elderly patients with acute diarrhoea. Use of this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, this medicine should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of loperamide hydrochloride should be discontinued and patients should be advised to consult their doctor.

Patients with AIDS treated with this medicine for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

Although no pharmacokinetic data are available in patients with hepatic impairment, this medicine should be used with caution in such patients because of reduced first pass metabolism, as it may result in a relative overdose leading to CNS toxicity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

Cardiac events including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

Special Warnings to be included on the leaflet:

Only take Loperamide Capsules to treat acute episodes of diarrhoea associated with Irritable Bowel Syndrome if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

- If you are aged 40 or over and it is some time since your last IBS attack
- If you are aged 40 or over and your IBS symptoms are different this time
- If you have recently passed blood from the bowel
- If you suffer from severe constipation
- If you are feeling sick or vomiting
- If you have lost your appetite or lost weight
- If you have difficulty or pain passing urine
- If you have a fever
- If you have recently travelled abroad

Consult your doctor if you develop new symptoms, if your symptoms worsen, or if your symptoms have not improved over two weeks.

4.5 Interaction with other medicinal products and other forms of interaction

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine or ritonavir, which are both P-glucoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide plasma levels. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages, is unknown.

The concomitant administration of loperamide (4 mg single dose) and itraconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 3 to 4-fold increase in loperamide plasma concentrations. In the same study a CYP2C8 inhibitor, gemfibrozil, increased loperamide by approximately 2-fold. The combination of itraconazole and gemfibrozil resulted in a 4-fold increase in peak plasma levels of loperamide and a 13-fold increase in total plasma exposure. These increases were not associated with central nervous system (CNS) effects as measured by psychomotor tests (i.e., subjective drowsiness and the Digit Symbol Substitution Test).

The concomitant administration of loperamide (16 mg single dose) and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide plasma concentrations. This increase was not associated with increased pharmacodynamic effects as measured by pupillometry.

Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.

It is expected that drugs with similar pharmacological properties may potentiate loperamide's effect and that drugs that accelerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established, although from animal studies there are no indications that loperamide hydrochloride possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer this medicine in pregnancy, especially during the first trimester.

Breast-feeding

Small amounts of loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breast-feeding.

Women who are pregnant or breast feeding infants should therefore be advised to consult their doctor for appropriate treatment.

4.7 Effects on ability to drive and use machines

Loss of consciousness, depressed level of consciousness, tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with this medicine. Therefore, it is advisable to use caution when driving a car or operating machinery. See Section 4.8, Undesirable Effects.

4.8 Undesirable effects

Adults and children aged ≥12 years

The safety of loperamide hydrochloride was evaluated in 2755 adults and children aged ≥ 12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea.

The most commonly reported (i.e., ≥1% incidence) adverse drug reactions (ADRs) in clinical trials with loperamide hydrochloride in acute diarrhoea were: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%).

Table 1 displays ADRs that have been reported with the use of loperamide HCl from either clinical trial (acute diarrhoea) or post-marketing experience.

The frequency categories use the following convention: 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); and very rare (<1/10,000).

Table 1: ***Adverse Drug Reactions***

System Organ Class	**Indication**		
	Common	**Uncommon**	**Rare**
Immune System Disorders			Hypersensitivity reaction[a] Anaphylactic reaction (including Anaphylactic shock)[a] Anaphylactoid reaction[a]
Nervous System Disorders	Headache	Dizziness Somnolence[a]	Loss of consciousness[a] Stupor[a] Depressed level of consciousness[a] Hypertonia[a] Coordination abnormality[a]

Eye Disorders			Miosis[a]
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia[a]	Ileus[a] (including paralytic ileus) Megacolon[a] (including toxic megacolon[b]) Abdominal distension
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption[a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme) Angioedema[a] Urticaria[a] Pruritus[a]
Renal and Urinary Disorders			Urinary retention[a]
General Disorders and Administration Site Conditions			Fatigue[a]

a: Inclusion of this term is based on post-marketing reports for loperamide HCl. As the process for determining post marketing ADRs did not differentiate between chronic and acute indications or adults and children, the frequency is estimated from all clinical trials with loperamide HCl (acute and chronic), including trials in children ≤ 12 years (N=3683).

b: See section 4.4 Special Warnings and Special Precautions for use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms:

In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, and respiratory depression), constipation, urinary retention and ileus may occur. Children and patients with hepatic dysfunction may be more sensitive to CNS effects.

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval prolongation, torsades de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed (see section 4.4). Fatal cases have also been reported.

Management:

If symptoms of overdose occur, naloxone can be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone (1 to 3 hours), repeated treatment with naloxone might be indicated. Therefore, the patient should be monitored closely for at least 48 hours in order to detect possible CNS depression.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.

In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of anti-diarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other antidiarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

5.2 Pharmacokinetic properties

Absorption: Most ingested loperamide is absorbed from the gut, but as a result of significant first pass metabolism, systemic bioavailability is only approximately 0.3%.

Distribution: Studies on distribution in rats show a high affinity for the gut wall with a preference for binding to receptors of the longitudinal muscle layer. The plasma protein binding of loperamide is 95%, mainly to albumin. Non-clinical data have shown that loperamide is a P-glycoprotein substrate.

Metabolism: loperamide is almost completely extracted by the liver, where it is predominantly metabolized, conjugated and excreted via the bile. Oxidative N-demethylation is the main metabolic pathway for loperamide, and is mediated mainly through CYP3A4 and CYP2C8. Due to this very high first pass effect, plasma concentrations of unchanged drug remain extremely low.

Elimination: The half-life of loperamide in man is about 11 hours with a range of 9-14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses (40 mg/kg/day – 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

Non-clinical in vitro and in vivo evaluation of loperamide indicates no significant cardiac electrophysiological effects within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold). However, at extremely high concentrations associated with overdoses (see section 4.4), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch

Lactose

Povidone

Sodium Starch Glycollate

Magnesium Stearate

Gelatin Capsule Shell (Size 4):

Body

Titanium Dioxide (E171)

Black Iron Oxide (E172)

Gelatin

Cap

Patent Blue V (E131)

Titanium Dioxide (E171)

Yellow Iron Oxide (E172)

Gelatin

Printing ink

Shellac

Simeticone

Titanium dioxide (E171)

Propylene glycol (E1520)

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years from the date of manufacture.

6.4 Special precautions for storage

Store in the original container in order to protect from moisture.

6.5 Nature and contents of container

Blister strip comprising 250 micron PVC with 20 micron hard tempered aluminium foil.

6, 8, 10, 12 or 30 capsules pack

6.6 Special precautions for disposal and other handling

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Wockhardt UK Limited

Ash Road North

Wrexham

LL13 9UF

UK

8. Marketing authorisation number(s)

PL 29831/0381

9. Date of first authorisation/renewal of the authorisation

29 November 2007

10. Date of revision of the text

15/06/2017

Company Contact Details

Wockhardt UK Ltd

Address
Ash Road North, Wrexham Industrial Estate,
Wrexham, LL13 9UF

Telephone
+44 (0)1978 661 261

Fax
+44 (0)1978 660 130

6355

PACKAGE LEAFLET: INFORMATION FOR THE USER

LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg

[Loperamide Hydrochloride]

Read all of this leaflet carefully before you start taking this medicine as it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. WHAT LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg IS AND WHAT IT IS USED FOR

Loperamide Hydrochloride is one of a group of medicines called "anti-diarrhoeals" which are used to treat diarrhoea.

Loperamide Hydrochloride is used to treat sudden, short-lived (acute) attacks of diarrhoea in adults and children 4 years and over and long-lasting (chronic) diarrhoea in adults. It works by making the stools more solid and less frequent.

REMEMBER - This medicine has been prescribed for you only. Do not give it to anyone else.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg

Always inform your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

Do not use Loperamide Hydrochloride Capsules:

- If you are allergic to Loperamide or any other ingredient in this product (listed in section 6)
- In children under the age of 4
- If your doctor has told you that you have a condition where slowing of the stomach or intestine should be avoided. For example: constipation, bloated tummy (particularly in children with severe dehydration or AIDS patients), inflammation of the bowel (eg. any form of colitis).

Loperamide Hydrochloride should not be used on its own in acute dysentery, the symptoms of which may include blood in your stools and a high temperature.

If in doubt about any of the above, ask your doctor or pharmacist.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking this medicine:

- If you suffer from liver disease. You may need to be more closely supervised during treatment and the dosage may have to be altered.
- If you have AIDs and notice signs of stomach distension (swelling) whilst taking Loperamide, stop taking them and see your doctor immediately.
- If your diarrhoea lasts for more than 2 days.

Loperamide Hydrochloride only treats the symptoms of diarrhoea. When you have diarrhoea, your body loses large amounts of fluid and salts. You should therefore replace this lost fluid by taking more liquids than you normally would. This is especially important for children.

Your doctor may have also given you a special powder containing sugar and salts (known as oral rehydration therapy) to help your body replace the fluid and salts lost during diarrhoea.

If you have been told by your doctor that you have an intolerance to some sugars, you should check with your doctor before taking this medicine.

Other medicines and Loperamide Hydrochloride Capsules 2mg

Always tell your doctor or pharmacist if you are unsure about taking any other medicines as you should not take any other anti-diarrhoeal preparations whilst taking Loperamide Hydrochloride (except for oral rehydration therapy - see under Warnings and precautions above).

Please tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

Especially:

- Quinidine used in heart conditions
- Ritonavir used in the treatment of HIV and AIDs
- Desmopressin used to treat bed-wetting.

Loperamide Hydrochloride Capsules 2 mg with food and drink

Swallow the correct number of capsules whole with some liquid.

Pregnancy

If you are pregnant, think you might be pregnant or are planning to become pregnant, you should talk to your doctor who will decide if you can take Loperamide Hydrochloride.

Breast-feeding

Do not take Loperamide Hydrochloride if you are breast-feeding as small amounts of the medicine may get into your milk. You should talk to your doctor about suitable treatment.

Driving and using machines

These capsules may cause dizziness, sleepiness or tiredness. If affected you should not drive or operate machinery or take part in activities where these may put you or others at risk.

Loperamide Hydrochloride Capsules 2mg contain lactose

If you have been told by your doctor that you have an intolerance to some sugars, you should talk to your doctor before taking this medicine.

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Front Side Printing Size : 180 x 210mm

ARTWORK DETAIL LABEL

Product	**LOPERAMIDE HCl CAPSULES 2 mg**				
Buyer/Country	**Co-pharma**	Component	Pack Insert		
Dimension	**180 x 210 mm - Same size**			Pack	---------
New Item Code	**1027626**	Old Item Code	**1026885**		
Colour Shades	**Black**			No. of Colours	**One**

Change Control No.	*** **Record Number: 83462**	Artwork Version	**4.0**
Design/Style	**Front & Back Printing. To be supplied in UNFOLDED size.**		
Substrate	**60 GSM Paper.**		
Special Instructions	**Printing clarity to be clear & sharp.**		
Autocartonator Requirements	**Pack insert supply should be as per auto-cartonator. Refer auto-cartonator drawing for instructions.**		

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**

F-10-R0/PDC-001

3. HOW TO TAKE LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg

Always read the label on your medicine and follow your doctor's instructions carefully. Ask your pharmacist if you are not sure about anything.

The dose of Loperamide Hydrochloride that you will need will depend on whether your diarrhoea is a sudden, short-lived attack (acute) or a long-lasting condition (chronic).

Acute diarrhoea

Adults: take two capsules to begin with and then 1 capsule after each episode of diarrhoea for up to 5 days. Never take more than 8 capsules in any 24 hour period.

Children aged 9-12 years: take one capsule 4 times daily until diarrhoea is controlled or for up to 5 days. Never take more than this dose.

Children aged 4-8 years: Not recommended for use in children aged 4-8 years. Your doctor will prescribe a suitable alternative.

If your symptoms are not getting better within 2 days of taking your first dose of Loperamide Hydrochloride, you should see your doctor again. The reason is that your doctor may want to examine you to further check on the cause of the diarrhoea.

Chronic diarrhoea

Adults only: your doctor will tell you how much Loperamide Hydrochloride to take. The initial dose will probably be between two and four capsules per day taken in divided doses, but will depend on each individual's needs. When your doctor is satisfied that you are receiving the daily dose that best suits you, he or she will probably suggest that the frequency at which you take Loperamide Hydrochloride is twice a day. Never take more than 8 capsules in any 24 hour period.

Children: NOT recommended.

If you take more Loperamide Hydrochloride Capsules 2 mg than you should

If you, or anyone else, take too much Loperamide Hydrochloride, contact your doctor or local hospital without delay.

If you forget to take Loperamide Hydrochloride Capsules 2 mg

If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Never take two doses to make up for forgotten doses. If you are worried ask your pharmacist or doctor for advice.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious Side effects:

Allergic reactions to Loperamide Hydrochloride are very rare (less than 1 in 10,000 patients affected). An allergic reaction can be recognised, by skin rash, itching, shortness of breath or swollen face. **If any of these signs occur, stop taking Loperamide Hydrochloride and see your doctor immediately.**

Severe bloated tummy or stoppage of bowel activity or difficulty urinating (passing water) have been reported. **If this should occur, stop taking Loperamide Hydrochloride and contact your doctor.**

If you have severe stomach pain or bloating, with a swollen abdomen, fast heart beat, low blood pressure (dizziness on standing) and high fever **stop taking Loperamide Hydrochloride and contact your doctor immediately.**

If you experience loss of consciousness or a reduced level of consciousness, or uncordinated movements **stop taking Loperamide Hydrocholride and contact your doctor immediately.**

If you experience very painful skin blistering that may peel **stop taking** Loperamide and **contact your doctor or hospital immediately** as this may be a very serious skin disorder.

Common side effects (affects less than 1 in 10 patients)

- Headache
- Constipation
- Nausea
- Flatulence (wind).

Uncommon side effects (affects less than 1 in 100 patients)

- Dizziness
- Drowsiness
- Stomach pain and discomfort (including cramps)
- Vomiting
- Indigestion
- Skin rash
- Dry mouth.

Rare side effects (affects less than 1 in 1000 patients)

- Eye problems such as constriction of the pupils
- Tiredness
- Itching and hives.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE LOPERAMIDE HYDROCHLORIDE CAPSULES 2 mg

As with all medicines, Loperamide Hydrochloride should be kept in a safe place where children cannot see or reach it.

Do not store above 25°C. Store the medicine in its original container.

Do not use the medicine after the expiry date printed on the packaging. Always return any left over medicine to your pharmacist. Only keep it if your doctor tells you to.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Loperamide Hydrochloride Capsules 2 mg contains

The active substance(s) is Loperamide Hydrochloride.

What Loperamide Hydrochloride Capsules 2 mg looks like and contents of the pack

Hard gelatin capsules. A white powder encapsulated within a Size “4” Hard Gelatin Capsules with a mauve opaque body and a dark green opaque cap, printed “Loperamide 2” [Circular manner] on the cap in black. Contents of pack: 10 capsules packed in a blister and 3 such blisters packed in a carton.

Marketing Authorisation Holder and Manufacturer

Co-pharma Limited
Unit 4, Metro Centre, Tolpits Lane,
Watford, Hertfordshire, UK, WD18 9SS

This medicinal product is authorised in the Member States of the EEA under the following names: Not applicable

This leaflet was last revised in 12/2015.

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Back Side Printing Size : 180 x 210mm

ARTWORK DETAIL LABEL

Product	**LOPERAMIDE HCl CAPSULES 2 mg**				
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