PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CIFRAN 250 Film-coated tablets

CIFRAN 500 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIFRAN 250 Tablets

Each film coated tablet contains:

Ciprofloxacin hydrochloride equivalent to ciprofloxacin 250 mg

CIFRAN 500 Tablets

Each film coated tablet contains:

Ciprofloxacin hydrochloride equivalent to ciprofloxacin 500 mg

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CIFRAN 250 Tablets*:* White, round, film-coated tablets debossed with `250' on one side and plain on the other side, with intact coating.

CIFRAN 500 Tablets*:* White caplet shaped, film-coated tablets debossed with `500' on one side and plain on the other side, with intact coating.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIFRAN is indicated for the treatment of severe and/or complicated infections caused by ciprofloxacin-sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated.

CIFRAN is not indicated/approved for the initiation of treatment (first line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to ciprofloxacin, unless treatment with other appropriate antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated or not tolerated.

CIFRAN is indicated for the treatment of the following bacterial infections where these infections are compliant with the indication context:

Severe and/or complicated lower respiratory tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa*, Haemophilus influenzae and Haemophilus para-influenzae*.

Severe and/or complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa*, Staphylococcus epidermidis* and *Streptococcus faecalis*.

Severe and/or complicated skin and soft tissue infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa*, Staphylococcus aureus, Staphylococcus epidermidis and Streptococcus pyogenes.*

Severe and/or complicated gastro-intestinal infections: Infective diarrhoea caused by *E. coli*, *Campylobacter jejuni*, *Shigella flexneri* and *Shigella sonnei*.

Severe and/or complicated bone infections: Osteomyelitis due to susceptible gram-negative organisms.

Prophylaxis of invasive infections due to *Neisseria meningitidis* in patients over 18 years of age.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to **CIFRAN**. Therapy with **CIFRAN**

may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

*In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly.

4.2 Posology and method of administration

Posology

Dosage and Duration of Treatment:

The dosage range is 250 - 750 mg twice daily.

The duration of treatment to contain and eradicate infection depends upon the type and severity of the infection, immunological status,clinical response and bacteriological findings.

Use the lowest effective dose for the shortest time to contain and eradicate the infection.

For severe and complicated infections more prolonged therapy may be required.

In streptococcal infections the treatment must last at least 10 days because of the risk of late complications.

For infections of the kidneys, urinary tract and abdominal cavity the treatment period is up to 7 days.

In all other infections the treatment period is 7-14 days.

Severe and /or complicated infections of the lower respiratory tract: 750 mg twice daily.

In cystic fibrosis patients the dose is 750 mg twice daily. The low body mass of these patients should, however, be taken into consideration when determining dosage (7,5 to 15 mg/kg/day).

Severe and /or complicated infectious diarrhoea: 500 mg twice daily.

Severe and /or complicated infections of the urinary tract: 500 mg twice daily.

Severe and /or complicated infections of the skin: 750 mg twice daily.

Severe and /or complicated bone infections: 750 mg twice daily. Treatment may be required for 4-6 weeks or longer.

Prophylaxis of invasive infections due to Neisseria meningitides: 500mg single dose tablet.

In cases of a mild/moderate/acute and uncomplicated infection, where all other appropriate antimicrobials approved for a similar indication have failed, are contraindicated, or are not well tolerated, the following dosage instruction are advised:

Infections of the lower respiratory tract: 250 mg twice daily

Infections of the urinary tract: 250 mg twice daily

Infections of the skin: 500 mg twice daily

Infectious diarrhoea: 500 mg twice daily

Bone infections: 500 mg twice daily

If the patient is unable to take **CIFRAN** film-coated tablets, because of the severity of the illness or for other reasons (e.g. patients on parenteral nutrition), therapy should be commenced with intravenous ciprofloxacin. After intravenous administration treatment may be continued orally.

Special populations

Geriatric patients (> 65 years)

Elderly patients should receive a dose as low as possible; this will depend on the severity of the illness and on the creatinine clearance.

Patients with renal and hepatic impairment

Patients with renal impairment

- Patients with creatinine clearance between 30 and 60 mL/min/1, 73m² (moderate renal impairment) or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/dL), the maximum daily dose should be 1 000 mg for oral administration.

- Patients with creatinine clearance less than 30 mL/min/1,73m² (severe renal impairment) or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/dL) the maximum daily dose should be 500 mg for oral administration.

Patients with renal impairment on haemodialysis

- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² (moderate renal impairment) or serum concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/dL), the maximum daily dose should be 1 000 mg for oral administration (all formulations).

- For patients with creatinine clearance less than 30 mL/min/1,73m² (severe renal impairment) or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/dL), the maximum daily dose should be 500 mg for oral administration (all formulations).

Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD)

- The maximum daily oral dose of **CIFRAN** should be 500 mg (1 x 500 mg **CIFRAN** film coated tablet or 2 x 250 mg **CIFRAN** film-coated tablets).

Patients with hepatic impairment

- In patients with hepatic impairment, no dose adjustment is required.

Patients with renal and hepatic impairment

- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² (moderate renal impairment) or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and1,9 mg/dL), the maximum daily dose should be 1 000 mg for oral administration (all formulations).

Method of administration

Oral use.

CIFRAN tablets should be swallowed whole with plenty of liquid and may be taken with or without meals.

A reduction in absorption of ciprofloxacin can be expected if taken with dairy products or with mineral fortified drinks. The film-coated tablets should not be taken concurrently with dairy products or with mineral-fortified drinks alone (e.g. milk, yoghurt, and calcium fortified orange juice). However, dietary calcium as part of a meal does not significantly affect **CIFRAN** absorption (see section 4.5).

4.3 Contraindications

- **CIFRAN** is contraindicated in patients who have shown hypersensitivity to ciprofloxacin, any other quinolones, or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).

- History of tendon disorders.
- Concomitant administration of **CIFRAN** and tizanidine (see section 4.5).
- Concomitant use of ciprofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to prolonged QTcF interval known to be associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with concomitant use at time intervals shorter than QT intervals usually associated with dysrhythmias.
- A history of tendon, muscle, joint, nerve, central nervous system, epilepsy or psychotic disorders especially those related to previous quinolone/fluoroquinolone use where alternative, appropriate antibiotic choices are available for treatment.
- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available.
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in the elderly.
- Patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer alternative appropriate antibiotic choices are available, has failed or is not well tolerated.

CIFRAN is contraindicated in children under 18 years and in growing adolescents.There is evidence of damage to the cartilage of weight bearing joints in immature animals.

4.4 Special warnings and precautions for use

CIFRAN should be used with caution in patients with a history of convulsive disorders.
Crystalluria related to the use of ciprofloxacin has been observed. Patients receiving **CIFRAN** should be well hydrated and excessive alkalinity of the urine should be avoided.
Side effects that may be potentially life-threatening are pancytopenia and marrow suppression (see section 4.8).
Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels (see section 4.5).

Tendinitis may occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids and in patients with a kidney or lung transplant. Close monitoring of these patients is therefore necessary if **CIFRAN** is prescribed. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with **CIFRAN** must be discontinued immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Tendinitis and/or tendon rupture may still occur for several months after completion of treatment. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Streptococcus pneumoniae infections

CIFRAN should not be used for treatment of pneumococcal infections due to limited efficacy against *Streptococcus pneumoniae.*

Severe infections and/or infections due to Gram-positive or anaerobic bacteria:

CIFRAN should not be used in staphylococcal infections and infections involving anaerobic bacteria.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with **CIFRAN** (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, **CIFRAN** should be discontinued immediately, and an alternative treatment should be considered. if the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of **CIFRAN**, treatment with **CIFRAN** must not be restarted in this patient at any time.

Blood glucose:

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Gastrointestinal System

***Pseudomembranous colitis*:**

Pseudomembranous colitis which may be fatal if not treated should be considered if severe and persistent diarrhoea develops during or after treatment with **CIFRAN**. In such cases **CIFRAN** must be discontinued and appropriate antimicrobial and supportive therapy initiated. Medicines that inhibit peristalsis are contra-indicated.

Cardiac disorders:

CIFRAN has been associated with QT prolongation (see section see section 4.3 and section 4.8).

Concomitant use of **CIFRAN** with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrhythmias e.g. class IA or III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics, (**see section 4.5**) or congenital QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infection, or bradycardia.

A pre-treatment ECG and frequent follow up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated.

Women tend to have a longer baseline QTc interval compared with men and may be more sensitive to medicines prolonging the QTC interval, such as **CIFRAN**.

Elderly patients may be more susceptible to effects of **CIFRAN** on the QT interval.

There is some evidence of an increased risk of aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, fluoroquinolones such as **CIFRAN** should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm

and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).See section 4.3.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department of a hospital.

There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed.

Fluoroquinolones should not be prescribed to patients with mitral valve and or aortic valve regurgitation. (see section 4.3)

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3 Contraindications).

Renal function should be assessed before initiation of treatment and monitored during treatment with fluoroquinolones and ACE inhibitors/angiotensin receptor blockers.

Children and adolescents:

CIFRAN is contraindicated in children less than 18 years. In children arthropathy is reported to occur commonly. See boxed warning under section 4.3.

Central nervous system:

CIFRAN is known to trigger seizures or lower the seizure threshold.

CIFRAN should be used with caution in patients with epilepsy or a history of CNS disorders(e.g. lowered convulsion threshold, previous history of convulsions, reduced cerebral blood flow, altered brain structure or stroke, see boxed **WARNING**). If seizures occur **CIFRAN** should be discontinued.

CIFRAN should only be used where alternative appropriate therapies have failed, are contraindicated or not tolerated, since these patients are endangered due to possible central nervous system side effects. Cases of status epilepticus have been reported (see section 4.3 and section 4.8).

Psychiatric side effects

Psychiatric reactions may occur even after first administration of **CIFRAN**. In rare cases, depression or psychosis can progress to suicidal ideation/thoughts culminating in attempted suicide or completed suicide, **see section 4.3 and section 4.8**). In the occurrence of such cases, **CIFRAN** should be discontinued.

Peripheral & polyneuropathy:

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones alone or in combination including **CIFRAN**.

CIFRAN should be discontinued and a medical practitioner be consulted in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.

The recovery process of neuropathy may be prolonged (weeks or months) and full recovery to the pretreatment status may not occur.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency:

Haemolytic reactions have been reported with ciprofloxacin in patients with G6PD deficiency. **CIFRAN** 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.

Photosensitivity:

Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking **CIFRAN** should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.

Therapy should be discontinued if photosensitisation (i.e. sunburn-like skin reactions) occurs (see section 4.8).

Musculoskeletal System:

The use of **CIFRAN** in patients with myasthenia gravis is contraindicated if alternative appropriate antibiotic choices are available **(see section 4.3**). **CIFRAN** may exacerbate the symptoms of myasthenia gravis.

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with **CIFRAN**, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of **CIFRAN** therapy (see section 4.3).

The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.

In single cases during the administration of **CIFRAN**, achillotendinitis was observed. Cases of partial or complete rupture of the Achilles tendon have been reported predominantly in the elderly on prior systemic treatment with glucocorticoids (**see section 4.3**). Therefore, at any signs of an achillotendinitis (e.g. painful swelling) the administration of **CIFRAN** should be discontinued and a medical practitioner be consulted.

CIFRAN should not be used in patients with a history of tendon disorders, especially those related to previous exposure to quinolone or fluoroquinolone use (see **section 4.3**).

CIFRAN should only be used in these patients if appropriate alternative antibiotic choices are not available, have failed, are contraindicated, or not tolerated.

Resistance:

Long-term or repeated administration of **CIFRAN** can lead to superinfections with resistant bacteria or yeast-like fungi.

Clostridium Difficile-Associated Diarrhoea:

Clostridium difficile (C.difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including **CIFRAN**, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile,* and institute surgical evaluation as clinically indicated.

Hypersensitivity:

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reactions occur, **CIFRAN** should be discontinued and an adequate medical treatment is required.

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 **CIFRAN** and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with **CIFRAN** 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).

Impaired renal function:

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

Concomitant use with ACE inhibitors/Angiotensin-receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin-receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/angiotensin-receptor blockers.

Hepatobiliary system:

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with **CIFRAN**. 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.

Vision disorders:

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

Interaction with laboratory tests

Ciprofloxacin may interfere with the Mycobacterium tuberculosis culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking **CIFRAN**.

Influence on laboratory parameters/urinary sediment

CIFRAN may cause a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, or a temporary increase in urea, creatinine or bilirubin in the serum. Hyperglycaemia, hypoglycaemia, crystalluria or haematuria may occur.

4.5 Interaction with other medicines and other forms of interaction

Medicines known to prolong QT interval:

Some fluoroquinolones, including ciprofloxacin as contained in **CIFRAN**, have the potential to prolong the QT interval and is contraindicated in patients also receiving Class IA anti-arrhythmic medicines (such as quinidine and procainamide) or Class III anti-arrhythmics (such as amiodarone and sotalol). In addition, caution should be exercised when **CIFRAN** is used with other medicines known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants). See section 4.4.

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-Angiotensin receptor inhibitors:

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

A case series of 16 reports of acute kidney injury (AKI) associated with enalapril and ciprofloxacin as co-suspect or interacting medicines was identified in VigiBase, the WHO global database of individual case safety reports. Analysis of 11 cases indicated that in most patients although clinical conditions and a number of medicines were likely to have increased their risk of AKI, including ACE inhibitor-related AKI, the event did not occur until after a ciprofloxacin prescription lending weight to ciprofloxacin being the cause or a combined action of ciprofloxacin and enalapril. Furthermore, the interaction between ACE inhibitors and fluoroquinolones to precipitate acute kidney injury is a class effect for all ACE inhibitors and not just enalapril, and also a class effect of all the fluroquinolones not just with ciprofloxacin. The publication signal April 2017 from Uppsala Monitoring Centre also indicated that with a nested control study in older men, there was a greater than additive risk to develop acute kidney injury with the concomitant use of fluoroquinolones and renin angiotensin receptor blockers. Thus, concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

Theophylline:

Concurrent administration of **CIFRAN** with theophylline- containing medicines may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate (see Cytochrome P450 in section 4.4).

Chelation complex formation:

The simultaneous administration of **CIFRAN** and multivalent cation-containing medicines and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids and highly buffered medicines (e.g. anti-retrovirals) containing magnesium, aluminium or calcium reduce the absorption of **CIFRAN**. **CIFRAN** tablets should be administered 1-2 hours before, or at least 4 hours after taking these preparations. This restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

NSAID

Concomitant administration of the nonsteroidal anti-inflammatory medicines (e.g. fenbuten) with quinolones such as **CIFRAN** increases the risk of central nervous system stimulation and convulsive seizures.

Ciclosporin:

Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed.

Warfarin:

The simultaneous administration of **CIFRAN** and warfarin may intensify the action of warfarin.

Oral antidiabetic agents

Hypoglycaemia has been reported when **CIFRAN** and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), were co-administered (see section 4.8).

Concurrent administration of **CIFRAN** and glibenclamide containing medicines can intensify the action of glibenclamide leading to hypoglycaemia.

Probenecid:

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and **CIFRAN** increases the ciprofloxacin serum concentrations.

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

Methotrexate:

Renal tubular transport of methotrexate may be inhibited by concomitant administration of **CIFRAN**, potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate-associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant **CIFRAN** therapy is indicated.

Phenytoin:

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving **CIFRAN** and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related side effects when **CIFRAN** is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of **CIFRAN** with phenytoin.

Tizanidine:

Tizanidine must not be administered together with **CIFRAN** (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 (see section 4.4).

Clozapine:

Following concomitant administration of 250 mg **CIFRAN** with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 9 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with **CIFRAN** are advised (see section 4.4).

Ropinirole:

Concomitant use of ropinirole with ciprofloxacin as in **CIFRAN**, a moderate inhibitor of the CYP450 1A2 isoenzyme, 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 **CIFRAN** (see section 4.4).

Omeprazole:

Concomitant administration of **CIFRAN** and omeprazole containing medicinal products will result in a slight reduction of C_{max} and AUC of ciprofloxacin.

Agomelatine:

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see section 4.4).

Zolpidem:

Co-administration with **CIFRAN** may increase blood levels of zolpidem; concurrent use is not recommended.

Other xanthine derivatives:

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

Vitamin K antagonists:

Simultaneous administration of **CIFRAN** 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 normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of **CIFRAN** with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon, or fluindione).

Duloxetine:

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

Lidocaine:

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, as contained in **CIFRAN**, a moderate inhibitor of CYP450 1A2 isozyme, reduces

clearance of intravenous lidocaine by 22 %. Although lidocaine treatment was well tolerated, a possible interaction with **CIFRAN** associated with side-effects may occur upon concomitant administration.

Sildenafil:

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

Food and Dairy Products

The concurrent administration of dairy products or mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice) and **CIFRAN** should be avoided because the absorption of **CIFRAN** is reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

4.6 Pregnancy, breastfeeding and fertility

Use of **CIFRAN** during pregnancy and lactation is contraindicated (see section 4.3).

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciplofloxacin. 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 medicine could cause damage to articular cartilage in the human immature organism / foetus.

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, **CIFRAN** should not be used during breastfeeding. Mothers on **CIFRAN** should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

Even when **CIFRAN** is taken as prescribed, it can affect the speed of reaction to such an extent that the ability to drive or to operate machinery is impaired. This applies particularly in combination with alcohol.

4.8 Undesirable effects

The following side effects have been observed:

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Less frequent	Mycotic superinfections; Candida and other fungal infections; Antibiotic associated colitis (with possible fatal outcome)
Blood and lymphatic system disorders	Less frequent	Eosinophilia, leucocytopenia, granulocytopenia, anaemia, neutropenia, thrombocytopenia, leucocytosis, thrombocytaemia, haemolytic anaemia, agranulocytosis, pancytopenia, bone marrow suppression (see section 4.4).
Immune system disorders	Less frequent	Allergic reaction, allergic oedema/angioedema, anaphylactic reaction, anaphylactic shock, serum sickness-like reaction.
Metabolism and nutrition disorders	Less frequent	Decreased appetite, hypoglycaemia, hyperglycaemia.
Psychiatric disorders	Less frequent	Psychomotor hyperactivity / agitation, confusion and disorientation, anxiety reaction, abnormal dreams, depression and psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide), hallucinations.
	Frequency unknown	Mania, hypomania
Nervous system disorders	Less frequent	Dizziness, headache, sleep disorders, taste disorders, paraesthesia, dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo, migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial hypertension, pseudotumor cerebri.

	Frequency unknown	Peripheral neuropathy and polyneuropathy (see section 4.4), Guillain-Barre syndrome.
Eye disorders	Less frequent	Visual disturbances (e.g. diplopia), visual colour distortions.
Ear and labyrinth disorders	Less frequent	Tinnitus, hearing loss, impaired hearing
Cardiac disorders	Less frequent	Tachycardia
	Frequency unknown	Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4); aortic aneurysm and dissection. Mitral valve and/or aortic valve regurgitation*
*Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation was diagnosed.		
Vascular disorders	Less frequent	Vasodilation, hypotension, syncope, vasculitis.
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea (including asthmatic condition).
Gastrointestinal disorders	Frequent	Nausea, diarrhoea
	Less frequent	Vomiting, gastro-intestinal and abdominal pain, flatulence, dyspepsia, antibiotic associated colitis (see section 4.4), pancreatitis.
Hepatobiliary disorders	Less frequent	Increase in transaminases, increased bilirubin, hepatitis, hepatic impairment, cholestatic icterus, hepatic necrosis

		very seldom progressing to life-threatening hepatic failure (see section 4.4).
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria, photosensitivity reactions (see section 4.4), petechiae, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), erythema multiforme, toxic epidermal necrolysis (potentially life-threatening).
	Frequency unknown	Acute generalized exanthematous pustulosis (AGEP), DRESS.
Musculoskeletal, connective tissue and bode disorders	Less frequent	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), exacerbation of symptoms of myasthenia gravis (see section 4.4).
Renal and urinary disorders	Less frequent	Renal impairment, renal failure, haematuria, crystalluria (see section 4.4), tubulointerstitial nephritis.
General disorders and administration site conditions	Frequent	Injection site reaction
	Less frequent	Asthenia, fever, oedema, sweating (hyperhidrosis).
Investigations	Less frequent	Increase in blood alkaline phosphatase, increased amylase.
	Frequency unknown:	International normalized ratio increased (in patients treated with Vitamin K antagonists).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects may be exaggerated or exacerbated (see section 4.8).

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg or Ca-containing antacids which reduce the absorption of ciprofloxacin. Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Ciprofloxacin is a fluoroquinolone antibiotic. Fluoroquinolones bring about their bactericidal action by inhibiting the bacterial DNA gyrase enzyme. DNA gyrase is responsible for continuous introduction of negative supercoils into DNA. This is an ATP dependent reaction that requires both strands of the DNA to be cut to permit passage of a segment of DNA through the break; the break is then resealed. Fluoroquinolones decrease the introduction of negative supercoils into DNA and cause rapid cessation of DNA synthesis by interfering with the propagation of DNA replication.

The following organisms are usually resistant: Enterococcus faecium, Ureaplasma urealyticum, Nocardia asteroides.

5.2 Pharmacokinetic properties

Absorption

Ciprofloxacin is well absorbed when given orally with a bioavailability of 70 %. The mean peak plasma concentrations achieved after oral administration of 250 mg, 500 mg and 750 mg of ciprofloxacin are 1,2 µg/mL, 2,4 µg/mL and 4,3 µg/mL respectively, achieved within 1-2 hours of administration. Absorption is delayed when ciprofloxacin is given with a meal.

Distribution

Plasma protein binding ranges from 20 to 40 %. Ciprofloxacin is widely distributed throughout the body viz. lung, skin, fat, muscle, cartilage, bone and genital tissues including the prostate. It is present in active form in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile and prostatic secretions

Biotransformation

Ciprofloxacin is partly metabolised in the liver. About 50 % of an oral dose is recovered unchanged in the urine and 15 % as active metabolites viz. oxociprofloxacin. The rest undergoes biliary excretion and transluminal secretion across the intestinal mucosa

Elimination

The plasma elimination half-life is about 3,5 – 4,5 hours. The half-life may be prolonged in severe renal insufficiency and in the elderly.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

colloidal anhydrous silica,

magnesium stearate,

maize starch,

microcrystalline cellulose,

Sodium starch glycollate (Type A)

purified talc,

and film coating: Opadry OY-S58910 white consisting of hydroxymethylcellulose, titanium dioxide C177891 and polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C, protected from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

All strengths:

Tablets are packed in a blister strip comprising of PVC film coated with PVdC and an aluminium foil backing.

Cartons contain 10 tablets each.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

a Sun Pharma company

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER:

CIFRAN 250 Film-coated tablets: 33/20.1.1/0365

CIFRAN 500 Film-coated tablets: 33/20.1.1/0366

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 1999

10. DATE OF REVISION OF THE TEXT

TBA

Botswana Only :	S2
CIFRAN 250 Tablets: Reg. No: BOT 0400701	

CIFRAN 500 Tablets: Reg. No BOT 0400702
Namibia Only: NS2 CIFRAN 250 Tablets: 04/20.1.1/0602 CIFRAN 500 Tablets: 04/20.1.1/0603