APPROVED PACKAGE INSERT

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM: **CIPROBAY® XR 1000** (Tablets)

COMPOSITION:

CIPROBAY XR 1000 tablet contains ciprofloxacin hydrochloride monohydrate and ciprofloxacin betain, equivalent to 1000 mg ciprofloxacin.

CIPROBAY XR tablets contain the following inactive ingredients; Crospovidone, Magnesium stearate, Silica colloidal (anhydrous), Succinic acid, Hypromellose 15cP, Polyethylene glycol, Titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A. 20.1.1. Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Ciprofloxacin is a synthetic, 4-quinolone derivative. Ciprofloxacin inhibits DNA gyrase in a way that arrests the bacterial metabolism, since vital information can no longer be read from the bacterial chromosome.

Resistance to ciprofloxacin develops slowly and in stages (multiple-step type).

The following are usually resistant:

Enterococcus faecium, Ureaplasma urealyticum, Nocardia asteroides.

With a few exceptions anaerobes are moderately sensitive (e.g. *Peptococcus, Peptostreptococcus*) to resistant (e.g. *Bacteriodes, Treponema pallidum*).

Pharmacokinetics:

Ciprobay XR 1000 tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35 % of the dose is contained within an immediate-release component, while the remaining 65 % is contained in a slow-release matrix. Ciprobay XR 1000 tablets are designed to release all of the dose prior to the tablet reaching the distal region of the small intestine.

Following oral administration of the 1000 mg modified release tablets, ciprofloxacin is rapidly and almost completely absorbed.

The pharmacokinetics of Ciprobay XR 1000 tablets are not altered by the co-administration with food.

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the Ciprobay XR 1000 tablet.

The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 % to 2 % of the dose is recovered from the bile in the form of metabolites. Approximately 20 % to 35 % of an oral dose of immediate-release ciprofloxacin is recovered from the faeces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Pharmacokinetic parameters obtained at steady state with the 500 mg twice daily and 1000 mg once-daily dose regimens are shown in the table below. Maximum plasma concentrations are attained between 1 and 4 hours after dosing. Cmax values obtained with Ciprobay XR 1000 were higher than seen with the corresponding twice daily regimen, but AUC values for the once-daily and twice daily regimens were equivalent.

Ciprofloxacin Pharmacokinetics (Mean + SD) Following Ciprobay 500 and Ciprobay XR 1000 Administration:

	C_{max} (mg/L)	AUC_{0-24h} (mg*h/L)	$T_{1/2}$ (hr)	T_{max} (hr)§
Ciprobay XR 1000 od	3,11±1,08	16,83±5,65	6,31±0,72	2,0(1-4)
Ciprobay 500 bd	2,06±0,41	17,04±4,79	5,66±0,89	2,0(0,5-3,5)

§ median (range)

INDICATIONS:

Ciprobay XR 1000 is indicated for the treatment of:

- ***Complicated Urinary Tract Infections*** *caused by* Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis.
- **Acute Uncomplicated Pyelonephritis** caused by *Escherichia coli*.

CONTRA-INDICATIONS:

Safety during pregnancy and lactation has not been established.

Ciprobay XR 1000 is contra-indicated in children under 18 years and in growing adolescents, except where the benefits of treatment exceed the risks. Experimental evidence indicates that, species variable reversible lesions of the cartilage of weight bearing joints has been seen in immature members of certain animal species.

Ciprobay XR 1000 is contra-indicated in patients who have shown hypersensitivity to ciprofloxacin or any other quinolones.

Impaired Renal or Liver Function:

Where creatinine clearance is equal to or less than 30 ml/min/1,73m^2 or where the serum creatinine concentration is equal to or greater than 2,0 mg/100 ml or in patients on haemodialysis or CAPD, the administration of Ciprobay XR 1000 is not recommended in this patient population.

WARNINGS:

Ciprobay XR 1000 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 Ciprobay XR 1000 should be well hydrated and excessive alkalinity of the urine should be avoided.

Interactions:

Concurrent administration of CIPROBAY XR 1000 with theophylline 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.

Ciprobay XR 1000 tablets should be administered 1 - 2 hours before, or at least 4 hours after taking iron preparations, highly buffered drugs (e.g. anti-retrovirals), antacids containing magnesium, aluminium, calcium or sucralfate as interference with absorption may occur. This restriction does not apply to antacids belonging to the class of H_2 receptor blockers. The concurrent administration of dairy products or mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice) and ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however does not significantly affect absorption.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with quinolones has been reported to increase the risk of central nervous system stimulation and convulsive seizures.

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

The simultaneous administration of Ciprobay XR 1000 and warfarin may intensify the action of warfarin.

In particular cases, concurrent administration of Ciprobay XR 1000 and glibenclamide can intensify the action of glibenclamide (hypoglycaemia).

Metoclopramide accelerates the absorption of ciprofloxacin, resulting in a shorter time to reach maximum plasma concentrations.

Concomitant administration of Ciprobay XR 1000 and omeprazole results in a slight reduction of Cmax and AUC of ciprofloxacin.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of Ciprobay XR 1000 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 Ciprobay XR 1000 therapy is indicated.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant Ciprobay XR 1000.

PREGNANCY AND LACTATION:

Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Ciprobay XR 1000 tablets should not be crushed or divided for intake and should be swallowed whole with plenty of liquid with or without meals.

Unless otherwise prescribed, the following guideline doses are recommended:

Ciprobay XR 1000 tablets: in complicated urinary tract infections or acute uncomplicated pyelonephritis: 1000 mg once daily for 7-14 days.

Ciprobay XR 1000 can be taken on an empty stomach. The concurrent administration of dairy products or mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice) and ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however does not significantly affect absorption

Elderly patients should receive a dose as low as possible depending on the severity of their illness and on the creatinine clearance.

If the patient is unable to take tablets, because of the severity of the illness or for other reasons (e.g. patients on enteral nutrition), it is recommended to commence the therapy with an intravenous form of ciprofloxacin. After intravenous administration the treatment can be continued orally.

Impaired Renal or Liver Function:

Where creatinine clearance is equal to or less than 30 ml/min/1,73m^2 or where the serum creatinine concentration is equal to or greater than 2,0 mg/100 ml or in patients on haemodialysis or CAPD, the administration of Ciprobay XR 1000 is not recommended in this patient population.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The most common Adverse Reactions based on all clinical studies with ciprofloxacin (oral, parenteral).

BODY SYSTEM

Incidence of frequency ≥1 % < 10 % Adverse Drug Reactions (common)

Digestive system: nausea, diarrhoea.

Skin and appendages: rash.

Incidence of frequency ≥ 0,1 % < 1 % (uncommon)

Body as a whole: abdominal pain, moniliasis, asthenia (general feeling of weakness, tiredness).

Cardiovascular system: (thrombo)-phlebitis.

Digestive system: SGOT increased, SGPT increased, vomiting, dyspepsia, abnormal liver function test, alkaline phosphatase increased, anorexia, flatulence, bilirubinemia.

Hemic and lymphatic system: eosinophilia, leukopenia.

Metabolic and nutritional disorder: creatinin increased, BUN (urea) increased.

Musculo Skeletal system: arthralgia (joint pain).

Nervous system: headache, dizziness, insomnia, agitation, confusion.

Skin and appendages: pruritus, maculopapular rash, urticaria.

Special senses: taste perversion.

Incidence of frequency ≥ 0,01 % < 0,1 % (rare)

Body as a whole: pain, pain in extremities, back pain, chest pain.

Cardiovascular system: tachycardia, migraine, syncope (fainting) vasodilatation (hot flushes), hypotension.

Digestive system: moniliasis (oral), jaundice, cholestatic jaundice, pseudomembranous colitis.

Hemic and lymphatic system: anemia, leucopenia (granulocytopenia), leucocytosis, altered prothrombin values, thrombocytopenia, thrombocytemia (thrombocytosis).

Hypersensitivity: allergic reaction, drug fever, anaphylactoid (anaphylactic) reaction.

Metabolic disorders: edema (peripheral, vascular, face), hyperglycemia.

Musculo-Skeletal system: myalgia (muscular pain), joint disorder (joint swelling).

Nervous system: hallucination, sweating, paresthesia (peripheral paralgesia), anxiety, abnormal dreams. (nightmares), depression, tremor (trembling), convulsion, hyperesthesia.

Respiratory system: dyspnea, larynx edema.

Skin and appendages: photosensitivity reaction.

Special senses: tinnitus, transitory deafness (especially at high frequencies), abnormal vision (visual disturbances), diplopia, chromatopsia, taste loss (impaired taste).

Urogenital system: acute kidney failure, kidney function abnormal, vaginal moniliasis, hematuria, crystalluria, nephritis interstitial.

Incidence of frequency < 0,01 % (very rare)

Cardiovascular system: vasculitis (petechiae, haemorrhagic bullae, papules, crust formation).

Digestive system: moniliasis (gastrointestinal), hepatitis.

Hemic and lymphatic system: hemolytic anemia.

Hypersensitivity: shock (anaphylactic; life threatening), pruritic rash.

Metabolic and nutritional disorder: amylase increased, lipase increased.

Nervous system: grand mal convulsion, abnormal (unsteady) gait.

Skin and appendages: petechia, erythema multiforme (minor), erythema nodosum.

Musculo-skeletal system: myasthenia.

The most common Adverse Reactions based on post marketing reports.

Incidence of frequency < 0,01 % (very rare)

Digestive system: liver necrosis (very rarely progressing to life threatening hepatic failure), life threatening pseudomembranous colitis with possible fatal outcome, pancreatitis.

Hemic and lymphatic system: petechia (punctate skin hemorrhages), agranulocytosis, pancytopenia (life-threatening), marrow depression (life-threatening).

Musculo-Skeletal system: Tendinitis (predominantly achillo tendinitis); partial or complete tendon rupture (predominantly achilles tendon), exacerbation of symptoms of myasthenia gravis.

Nervous system: psychosis, intracranial hypertension, ataxia, hyperesthesia, hypertonia, twitching.

Skin and appendages: Stevens-JohnsonSyndrome, epidermal necrolysis (Lyell-Syndrome), fixed eruption

Hypersensitivity: Serum sickness like reaction.

Special senses: parosmia (impaired smell) Anosmia (usually reversible on discontinuation)

Gastrointestinal System:

In the event of severe and persistent diarrhoea during or after treatment a doctor must be consulted, since this symptom can hide a serious intestinal disease (life threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment. In such cases Ciprobay XR 1000 must be discontinued and appropriate therapy initiated (eg vancomycin, orally 4 x 250 mg/day). Drugs that inhibit peristalsis such as loperamide should not be used.

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Nervous System:

In epileptics and in patients who have suffered from previous CNS- disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects.

In some instances the CNS reactions occurred after the first administration of Ciprobay XR 1000 already. In rare cases depression or psychosis can progress to self endangering behaviour. In these cases Ciprobay XR 1000 has to be discontinued and the doctor should be informed immediately.

Hypersensitivity:

In some instances, the hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately. Anaphylactic/anaphylactoid reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases Ciprobay XR 1000 has to be discontinued, medical treatment (e.g. treatment for shock) is required

Musculo-Skeletal System:

At any sign of tendinitis (e. g. painfull swelling) the administration of Ciprobay XR 1000 should be discontinued, physical exercises be avoided, and a physician be consulted. Tendon rupture (predominantly achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids.

Skin and Appendages:

Ciprobay XR 1000 has been shown to produce photosensitivity reactions. Patients taking Ciprobay XR 1000 should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitation (i. e. sunburn-like skin reactions) occur.

Influence on laboratory parameters / urinary sediment:

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage, temporary increase in urea, creatinine or bilirubin in the serum; in individual cases: hyperglycaemia, crystalluria or haematuria.

Other information:

Even when the medicine 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

Nearly white to slightly yellowish coated oblong tablet with C 1000 QD imprinted on the upper side and BAYER on the lower side

PRESENTATION:

- White opaque PE plastic bottles with a PP screw-cap closure containing 7 tablets or
- PA/Alu/PP foil blisters containing 7 tablets or
- PP/Alu foil blisters containing 7 tablets

STORAGE INSTRUCTIONS:

Store at or below 25ºC in a dry place. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

38/20.1.1/0024

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Bayer (Pty) Ltd

Registration No. 1968/011192/07

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