APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

CIPROBAY® XR 500 (Tablets)

COMPOSITION:

CIPROBAY XR 500 tablet contains ciprofloxacin hydrochloride monohydrate and ciprofloxacin betaine, equivalent to 500 mg ciprofloxacin.

PHARMACOLOGICAL CLASSIFICATION:

A. 20.1.1. Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Ciprofloxacin is a synthetic, 4-quinolone derivative with *in vitro* bactericidal activity against the following Gram-negative and Gram-positive organisms. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

Acinetobacter
Aeromonas
Brucella
Campylobacter jejuni
Citrobacter freundii
Citrobacter species
Corynebacterium
E. coli
Edwardsiella
Enterobacter cloacae
Enterobacter species
Haemophilus influenzae
Haemophilus para-influenzae
Hafnia
Klebsiella species
Listeria
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Pasteurella
Plesiomonas

Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella enteritidis
Serratia marcescens
Shigella flexneri
Shigella sonnei
Staphyloccocus aureus
Staphylococcus epidermidis
Streptococcus faecalis
Streptococcus pyogenes
Streptococcus species
Vibrio
Viridans streptococci
Yersinia

The following organisms show varying degrees of *in vitro* sensitivity to ciprofloxacin:
Alcaligenes, Enterococcus faecalis, Flavobacterium, Gardnerella, Legionella, Mycobacterium fortuitum, Mycobacterium tuberculosis, Mycoplasma hominis, Streptococcus agalactiae, Chlamydia.

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 500 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 500** 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 500 mg modified release tablets, ciprofloxacin is almost completely absorbed. The area under the plasma-concentration time curve (AUC) following a single dose is 7.24 mg•h/L (geo mean). Maximum plasma concentrations of 1.42 mg/L (geo mean) are attained between 1 and 4 hours after dosing.
At steady state the relative bioavailability amounts to approximately 97 % (90 % C.I: 89 – 107 %).
Exposure to drug in terms of AUC at steady state is approximately 7.77 mg*h/L (geo mean). Within 1 to 2.5 hours after ingestion of a 500 mg dose, peak concentrations of approximately 1.54 mg/L (geo mean) are reached during once-daily treatment with the modified release tablet. The terminal half life is approximately 5 hours. The steady state trough ciprofloxacin plasma concentration at the end of the dosing interval ($C_{24,ss}$) is (0.033 mg/L, geo. mean).
No accumulation of the drug is observed at steady state.

Representative single dose and steady state urinary concentrations of ciprofloxacin (mg/l) after once-daily administration of a 0.5 g modified release tablet are presented in the table below (mean range).

Time post dose (Mid point of the urine collection time interval, collection interval)				
	2h (0-4h)	6h (4-8h)	10h (8-12h)	18h (12-24h)
	Concentration in mg/l mean (range)			
Single dose	338(70-896)	137(26-289)	57(7.5-174)	27(12-55)
Steady state	368(73-968)	166(30-298)	53(15-143)	30(7.7-71)

The pharmacokinetics of **Ciprobay XR 500** 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 500** tablet. In studies comparing the 500 mg modified release regimen (**Ciprobay XR 500**) and the 250 mg bd regimen, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. 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.

INDICATIONS:

Ciprobay XR 500 is indicated solely for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*.

CONTRA-INDICATIONS:

Safety during pregnancy and lactation has not been established.

Ciprobay XR 500 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 500 is contra-indicated in patients who have shown hypersensitivity to ciprofloxacin or any other quinolones.

WARNINGS:

Ciprobay XR 500 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 500** should be well hydrated and excessive alkalinity of the urine should be avoided.

DOSAGE AND DIRECTIONS FOR USE:

Ciprobay XR 500 tablets should not be crushed or divided for intake and should be swallowed whole with plenty of liquid with or without meals.

Dosage and Duration of Treatment
500mg once daily for 3 days

Impaired Renal or Liver Function:
In patients with reduced renal function, the half-life of ciprofloxacin is prolonged and the dosage needs to be adjusted. For patients with changing renal function or patients with renal impairment and hepatic insufficiency, monitoring of drug serum levels provides the most reliable basis for dose adjustment.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The following side-effects have been observed:
-**Effects on the gastrointestinal tract**:
Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, flatulence, anorexia, oral moniliasis. 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 (pseudomembranous colitis), requiring immediate treatment. In such cases ciprofloxacin must be discontinued and appropriate therapy initiated (e.g.vancomycin, orally, 4 x 250mg/day). Drugs that inhibit peristalsis are contraindicated.
-**Effects on the nervous system**:
Dizziness, headache, tiredness, nervousness, agitation, trembling. Infrequently : insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure, anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions (even progressing to self endangering behaviour). In some instances, these reactions occurred already after the first administration of ciprofloxacin. In these cases ciprofloxacin has to be discontinued and the doctor should be informed immediately.
-**Reactions on sensory organs**:
Impaired taste and smell, visual disturbances (e.g. diplopia, colour vision), tinnitus, transitory impairment of hearing, especially at high frequencies.
-Hypersensitivity reactions:
Skin reactions, e.g. rashes, pruritus, drug fever, serum sickness like reactions. Infrequently: punctate skin haemorrhages (petechiae), blister formation with accompanying haemorrhages (haemorrhagic bullae) and small nodules (papules) with crust formation showing vascular involvement (vasculitis). Erythema nodosum, erythema exsudativum multiformе (minor), Stevens-Johnson Syndrome, Lyell Syndrome. interstitial nephritis, hepatitis, hepatic necrosis very seldom progressing to life-threatening hepatic failure. Anaphylactic / anaphylactoid reactions (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), in some instances

after the first administration. In these cases ciprofloxacin has to be discontinued and medical treatment (e.g. treatment for shock) is required.

-**Effects on the cardiovascular system**:

Tachycardia, hot flushes, migraine, fainting.

-**Other side effects**:

Joint pain, joint swelling. Very rarely: general feeling of weakness, muscular pains (which may be of special importance in patients with myaesthenia gravis), tendosynovitis, photosensitivity, transient impairment in kidney function including transient kidney failure. In single cases during the administration of ciprofloxacin, 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. Therefore, at any signs of an achillotendinitis (e.g. painful swelling) the administration of ciprofloxacin should be discontinued and a physician be consulted. Long-term or repeated administration of ciprofloxacin can lead to superinfections with resistant bacteria or yeast-like fungi.

-Effects on the blood and blood constituents:

Eosinophilia, leucocytopenia, granulocytopenia, anaemia, thrombocytopenia. Very rarely leucocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values.

-**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.

Interactions:

Concurrent administration of ciprofloxacin 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 500 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.

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 ciprofloxacin and warfarin may intensify the action of warfarin.

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

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and **CIPROBAY XR 500** increases the ciprofloxacin serum concentrations.

Metoclopramide accelerates the absorption of ciprofloxacin, resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of **CIPROBAY XR 500**.

Concomitant administration of ciprofloxacin and omeprazole results in a reduction of Cmax and AUC of ciprofloxacin.

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 500 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 3 tablets or
- PA/Alu/PP foil blisters containing 3 tablets or
- PP/Alu foil blisters containing 3 tablets.

STORAGE INSTRUCTIONS:
Store below 25ºC in a dry place. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
CIPROBAY XR 500 : 37/20.1.1/0250

NAME AND BUSINESS ADDRESS OF THE APPLICANT:
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