APPROVED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

COLIPRID 250 mg TABLETS (Tablet)

COLIPRID 500 mg TABLETS (Tablet)

COLIPRID 750 mg TABLETS (Tablet)

COMPOSITION:

COLIPRID 250 mg TABLETS: Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin.

COLIPRID 500 mg TABLETS: Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin.

COLIPRID 750 mg: Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin.

The other ingredients are cellulose, microcrystalline; sodium starch glycolate; povidone; silica, colloidal anhydrous and magnesium stearate and opadry white.

Opadry white contains hypromellose, macrogol and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Ciprofloxacin is a synthetic fluroquinolone antibiotic. It is bactericidal and acts by inhibiting the A subunit of DNA-gyrase which is essential in the reproduction of bacterial DNA.

Micro-organisms resistant to ciprofloxacin:

Enterococcus faecium; Norcardia asteroides; Ureapiasma urealyticum; Peptostreptococcus

species; Peptococcus species*;* Bacteroides*; Treponem a pallidum; Staphylococcus aureus (methicillin-resistant), Stenotrophomonas maltophilia, Actinomycas, Listeria monocytogenes and Mycoplasma genitalium.*

Pharmacokinetics

After oral administration, ciprofloxacin plasma levels are dose-related and peak

at 0,5 - 2 hours. The absolute bioavailability is approximately 70 %. Protein binding is 40 %. Forty to fifty percent is excreted in urine as unchanged ciprofloxacin. Approximately 15% of a single dose is eliminated as metabolites.

Elimination is primarily renal and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 ml/minute. The elimination half-life of unchanged ciprofloxacin is 3 - 5 hours. The elimination kinetics are linear.

INDICATIONS:

COLIPRID TABLETS is indicated for the treatment of the following infections, when caused by susceptible organisms:

Lower respiratory tract infections caused by:

Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.

Urinary tract infections caused by:

Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Providencia rettgeri, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus epidermidis, Streptococcus faecalis.

Skin and soft tissue infections caused by:

Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes.

Gastro-intestinal infections:

Infective diarrhoea caused by *Campylobacter jejuni, Escherichia cofi, Shigella flexneri* and

Shigelia sonnei.

Bone Infections:

Osteomyelitis due to sensitive Gram-negative organisms.

Gonorrhoea: (except that is due to *N. gonorrhoeae*)

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

CONTRA-INDICATIONS:

COLIPRID TABLETS is contra-indicated in patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or any of the inactive ingredients of **COLIPRID TABLETS**.

Pregnancy and lactation:

COLIPRID TABLETS is contra-indicated in children under the age of 18 years and in growing adolescents.

Experimental evidence indicates lesions of the cartilage of weight-bearing joints in immature members of certain animal species.

WARNINGS AND SPECIAL PRECAUTIONS:

COLIPRID TABLETS should be used in caution with patients with a history of convulsive disorders.

Crystalluria related to the use of **COLIPRID TABLETS** has been observed. Patients receiving **COLIPRID TABLETS** should be well hydrated and excessive alkalinity of the urine should be avoided.

Side-effects that may be potentially life-threatening are pancytopenia and bone marrow depression (see **"SIDE-EFFECTS"**).

Streptococcus pneumonia infections

COLIPRID TABLETS should not be used for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumonia.*

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

For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, **COLIPRID TABLETS** should be used in combination with an appropriate antibacterial agent.

Genital tract infections

Genital tract infections may be caused by fluoroquinolone-resistant *Nesseria gonorrhoeae* isolates. In genital tract infections thought to be due to *N. Gonorrhoeae,* **COLIPRID TABLETS** should not be used.

Cardiac disorders

COLIPRID TABLETS is associated with cases of QT prolongation. In general, elderly patients may be more susceptible to **COLIPRID TABLETS**-associated effects on the QT interval. Precaution should be taken when using **COLIPRID TABLETS** with concomitant medicinal products that can result in prolongation of the QT interval (e.g. class IA or III antidysrhythmics) or in patients with risk factors for torsades de pointes (e.g. known QT prolongation, uncorrected hypokalaemia).

Hypersensitivity

In some instances, hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately. Anaphylactic/anaphylactoid reactions can progress to life threatening shock, even after the first administration. In these cases **COLIPRID TABLETS** has to be discontinued, medical treatment (e.g. treatment for shock) is required.

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, **COLIPRID TABLETS** must be discontinued and appropriate therapy initiated. Medicines that inhibit peristalsis are contraindicated.

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

Musculoskeletal system

At any sign of tendonitis (e.g. painful swelling) the administration of **COLIPRID TABLETS** should be discontinued, physical exercise should be avoided, and a medical practitioner consulted. Tendon rupture (predominantly Achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids and in patients with kidney or lung transplant. Close monitoring of these patients is necessary if they are prescribed **COLIPRID TABLETS**. The risk is still present weeks after completion of treatment.

Nervous system

In patients with epilepsy 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), **COLIPRID TABLETS** should only be used where the benefits of treatment exceed the risks, since these patients are vulnerable because of possible central-nervous side effects.

In some instances the CNS reactions already occurred after the first administration of **COLIPRID TABLETS**. In these cases **COLIPRID TABLETS** must be discontinued and the medical practitioner informed immediately. Depression or psychosis can progress to result in self endangering behaviour.

Skin and appendages

COLIPRID TABLETS has been shown to produce photosensitivity reactions. Patients taking **COLIPRID TABLETS** should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e. sunburn-like skin reactions) occurs.

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicines which are metabolised via the same enzymatic pathway (e.g. theophylline, methylxanthines, caffeine, duloxetine, clozapine) are administered concomitantly with **COLIPRID TABLETS**. Increased plasma concentrations associated with medicine specific side effects may be observed due to inhibition of their metabolic clearance by **COLIPRID TABLETS** (See **"INTERACTIONS"**).

Patients receiving **COLIPRID TABLETS** should be well hydrated and excessive alkalinity of the

urine should be avoided.

Long-term or repeated administration of **COLIPRID TABLETS** can lead to superinfections with resistant bacteria or fungi.

Ability to Drive and Use Machines

The ability to drive a motor vehicle or operate machinery may be impaired by **COLIPRID TABLETS**, particularly when used in combination with alcohol.

INTERACTIONS:

Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels.

There is a high risk of tendonitis (see **"SIDE-EFFECTS"**).

Concurrent administration of **COLIPRID TABLETS** 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 toxicity. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

COLIPRID TABLETS should be administered 1 - 2 hours before, or at least 4 hours after taking iron preparations, 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 medicines (NSAIDSs), with quinolones such as **COLIPRID TABLETS** may increase the risk of central nervous system stimulation and seizures.

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

The simultaneous administration of **COLIPRID TABLETS** and warfarin may lead to warfarin toxicity; therefore the INR should be closely monitored.

Concurrent administration of **COLIPRID TABLETS** and glibenclamide can potentiate the action of

glibenclamide, leading to hypoglycaemia.

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

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

Concurrent administration of **COLIPRID TABLETS** with ropinirole may lead to elevated plasma concentrations of ropinirole. Monitoring for ropinirole-related side effects and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with **COLIPRID TABLETS**.

Concurrent administration of **COLIPRID TABLETS** with lidocaine (lignocaine) may lead to elevated plasma concentrations of lidocaine and increase in side effects related to lidocaine also occurs.

Concurrent administration of **COLIPRID TABLETS** with clozapine may lead to elevated serum concentrations of clozapine and N-desmethylclozapine. Careful monitoring of clozapine associated adverse effects and appropriate adjustment of clozapine dosage during and shortly after co-administration with **COLIPRID TABLETS** is advised.

Concurrent administration of **COLIPRID TABLETS** with sildenafil may lead to elevated serum concentrations of sildenafil. Therefore, sildenafil should be used with caution when co-administered with **COLIPRID TABLETS**.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (See **"CONTRA-INDICATIONS"**).

On the basis of animal studies, it has been reported that ciprofloxacin, as in **COLIPRID TABLETS** may cause damage to articular cartilage in the fetus. It has also been reported to cause teratogenic effects in animals. Therefore, **COLIPRID TABLETS** should not be given to pregnant women.

Lactation: Ciprofloxacin is excreted in breastmilk. **COLIPRID TABLETS** should not be used during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

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

administered concomitantly.

COLIPRID TABLETS should be swallowed whole with plenty of liquid and may be taken with or without meals.

Dosage and Duration of Treatment:

The dosage range is 250 - 750 mg twice daily. The duration of treatment depends upon the severity of the infection, clinical response and bacteriological cultures. For acute uncomplicated cystitis in women, the treatment period is 3 days. Generally, treatment should be continued for at least 3 days after the signs and symptoms of the infection have disappeared. For acute infections the usual treatment period is 5 - 10 days with **COLIPRID TABLETS**. For severe and complicated infections more prolonged therapy may be required. In streptococcal infections the treatment must last at least 10 days.

Infections of the lower respiratory tract:

Mild to moderate: 250 - 500 mg twice daily.

Severe or complicated: 750 mg twice daily.

In cystic fibrosis patients: 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).

Infections of the urinary tract:

Acute uncomplicated cystitis: 250 mg twice daily.

Mild to moderate: 250 mg twice daily.

Severe or complicated: 500 mg twice daily.

Infections of the skin:

Mild to moderate: 500 mg twice daily.

Severe or complicated: 750 mg twice daily.

Infectious diarrhoea: 500 mg twice daily.

Bone Infections:

Mild to moderate: 500 mg twice daily.

Severe or complicated: 750 mg twice daily.

Treatment may be required for 4 - 6 weeks or longer.

Gonorrhoea: A single dose of 250 mg.

Elderly patients should be treated with the lowest possible dose.

Impaired Renal or Liver Function:

In patients with reduced renal function, the half-life of ciprofloxacin may be prolonged. The dosage needs to be adjusted as shown below.

For patients with renal impaired and hepatic insufficiency, monitoring of medicine serum levels provides the most reliable basis for dose adjustment.

Dose adjustment of ciprofloxacin for patients with renal or hepatic impairment:

2.1 Kidney insufficiency:

2.2 Cl_{cr}> 31 mL/min/1,73m^2 Max 800 mg/day intravenously.

2.3 Cl_{cr}< 30 mL/min/1,73m^2 Max 400 mg/day intravenously.

2.4 Impaired renal function

As in 1.2 above; after dialysis and haemodialysis on dialysis days.

2.5 **Renal impairment and CAPD (chronic ambulatory peritoneal dialysis):**

2.6 Oral administration of either **COLIPRID TABLETS** as 500 mg tablets or 2 x 250 mg tablets or **COLIPRID TABLETS** suspension equivalent to 500 mg **COLIPRID TABLETS** is indicated.

For CAPD patients with peritonitis, the recommended daily oral dose is 500 mg four times a day.

2.7 **Hepatic impairment**: No dose adjustment.

2.8 **Hepatic and renal impairment**: As in 1.1 and 1.2 above.

SIDE-EFFECTS:

Side-effects

Gastrointestinal disorders

Frequent: Impaired taste and smell, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain and flatulence. The development of severe and persistent diarrhoea may indicate pseudomembranous colitis, requiring immediate treatment. In such cases **COLIPRID TABLETS** must be discontinued and appropriate therapy initiated.

Less frequent: pancreatitis

Eye disorders

Less frequent: Visual disturbances (e.g. diplopia, colour vision).

Ear and labyrinth disorders

Less frequent: Tinnitus, transient impairment of hearing, vertigo, hearing loss.

Blood and the lymphatic system disorders

The following side effects have been reported but the frequencies are unknown: Eosinophilia, leucocytopaenia, granulocytopaenia, anaemia, thrombocytopenia, leucocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values, pancytopenia, bone marrow depression.

Skin and subcutaneous tissue disorders

The following side effects have been reported but the frequencies are unknown: Rashes, pruritus, urticaria and photosensitivity (blisters, sensation of skin burning), erythema nodosum and erythema exsudativum multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, punctate skin haemorrhages (petechiae), haemorrhagic bullae and papules with signs of vascular involvement (vasculitis).

Nervous system disorders

Less frequent: Headache, migraine, dizziness, tiredness, nervousness and trembling, hypoaesthesia, paraesthesia, dysaesthesia, hyperaesthesia, ~~l~~insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure, seizures, peripheral neuropathy and polyneuropathy.

Psychiatric disorders

Less frequent: Agitation, anxiety states, confusion, disorientation, hallucinations, psychotic reactions (even progressing to self-endangering behaviour), depression, nightmares.

Musculoskeletal, connective tissue and bone disorders

The following side effects have been reported but the frequencies are unknown: Joint pain, joint swelling, general feeling of weakness (arthralgia), and myalgia (which may be of special importance in patients with myasthenia gravis) and tendosynovitis, cases of tendon rupture and achillotendonitis, increased muscle tone and cramping.

Cardiac disorders

Less frequent: Tachycardia, flushes, QT prolongation, ventricular dysrhythmia, Torsades de Pointes.

Vascular Disorders

Less frequent: syncope, hypotension, vasodilatation and vasculitis,

Renal and urinary disorders

The following side effects have been reported but the frequencies are unknown.

Crystalluria, interstitial nephritis, transient renal impairment including transient renal failure, and haematuria.

Immune system disorders

The following side effects have been reported but the frequencies are unknown:

Anaphylactic/anaphylactoid reactions can occur (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), serum sickness-like reaction, in some instances after the first administration. In these cases **COLIPRID TABLETS** has to be discontinued and appropriate medical treatment instituted.

Investigations

The following side effects have been reported but the frequencies are unknown: Abnormal prothrombin level, increased amylase, Increased blood alkaline phosphatase, hyperglycaemia.

Hepatobiliary Disorders

Hepatic necrosis, very seldom progressing to hepatic failure, hepatic impairment, jaundice, hepatitis, increase in transaminases and bilirubin.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of acute, excessive oral over-dosage, reversible renal toxicity has been reported. Apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of oral **COLIPRID TABLETS**. Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive.

IDENTIFICATION:

COLIPRID TABLETS 250 mg:

White to off-white, round shaped, film coated tablets, with a score line on one side and debossed with ‘F’ and ‘23’ with a score line in between on the other side.

COLIPRID TABLETS 500 mg:

White to off-white, capsule shaped, film coated tablets, with a score line on one side and debossed

with 'F 22' on the other side.

COLIPRID TABLETS 750 mg:

White to off-white, capsule shaped, film-coated tablets debossed with 'C' on one side and '93' on the other side.

PRESENTATION:

COLIPRID TABLETS 250 mg TABLETS:

Blister pack:

Tablets are packed in blisters that are comprised of silver aluminium foil and clear PVC/PVdC.

Pack size: 6's- Each blister strip contains 6 tablets. 1 blister strip containing 6 tablets is packed in a cardboard carton.

Pack size: 10's- Each blister strip contains 10 tablets. 1 blister strip containing 10 tablets is packed in a cardboard carton.

HDPE container pack:

Pack size: 10's

Tablets are packed in a white, opaque, wide mouth round 40 ml HDPE container with a white opaque 33 mm PP closure with induction sealing wad. No desiccant is included in the container. The HDPE container is packed in a cardboard carton.

Pack size: 100's

Tablets are packed in a milky-white, round 80 ml HDPE container with a white opaque 43 mm PP closure with induction sealing wad. No desiccant is included in the container. The HDPE container is packed in a cardboard carton.

COLIPRID TABLETS 500 mg TABLETS:

Blister pack:

Tablets are packed in blisters that are comprised of silver aluminium foil and clear PVC/PVdC.

Pack size: 10's- Each blister strip contains 10 tablets. 1 blister strip containing 10 tablets is packed in a cardboard carton.

HDPE container pack:

Pack size: 100's

Tablets are packed in a milky-white, opaque, wide mouth round 140 ml HDPE container with a white opaque 43 mm PP closure with induction sealing wad.

No desiccant is included in the container. The HDPE container is packed in a cardboard carton.

COLIPRID TABLETS 750 mg TABLETS:

Blister pack:

Tablets are packed in blisters that are comprised of silver aluminium foil and clear PVC/PVdC.

Pack size: 10's- Each blister strip contains 10 tablets. 1 blister strip containing 10 tablets is packed in a cardboard carton.

HDPE container pack:

Pack size: 100's

Tablets are packed in a milky-white, opaque, wide mouth round 200 ml HDPE container with a white opaque 45 mm PP closure with induction sealing wad.

No desiccant is included in the container. The HDPE container is packed in a cardboard carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep bottle tightly closed.

Keep blisters in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

COLIPRID 250 mg TABLETS (Tablet): 45/20.1.1/0201

COLIPRID 500 mg TABLETS (Tablet): 45/20.1.1/0202

COLIPRID 750 mg TABLETS (Tablet): 45/20.1.1/0203

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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