SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BIOTECH CIPROFLOXACIN 250 Film coated tablets

BIOTECH CIPROFLOXACIN 500 Film coated tablets

BIOTECH CIPROFLOXACIN 750 Film coated tablets

2. QUALITATIVE AND QUANTITATIVE

BIOTECH CIPROFLOXACIN 250: Each film coated tablet contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin.

BIOTECH CIPROFLOXACIN 500: Each film coated tablet contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin.

BIOTECH CIPROFLOXACIN 750: Each film coated tablet contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin.

For full list of excipients, see section 6.1

Sugar free.

3. PHARMACEUTICAL FORM

Film coated tablets.

BIOTECH CIPROFLOXACIN 250: White coloured, biconvex, circular film coated tablet, embossed NJB on one side and 250 on other side.

BIOTECH CIPROFLOXACIN 500: White coloured, biconvex, capsule shaped film coated tablet, embossed NJB on one side and 500 on other side.

BIOTECH CIPROFLOXACIN 750: White coloured, biconvex, capsule shaped film coated tablet, embossed NJB on one side and 750 on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOTECH CIPROFLOXACIN 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.

BIOTECH CIPROFLOXACIN 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.

BIOTECH CIPROFLOXACIN 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:

Enterobacter cloacae, Escherichia coli, Haemophilus influenza, Haemophilus para-influenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.

Severe and/or complicated 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.

Severe and/or complicated 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 epidermidis, Streptococcus pyogenes.

Severe and/or complicated gastrointestinal infections:

Infective diarrhoea caused by *Campylobacter jejuni, Escherichia coli, 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.

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

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 BIOTECH CIPROFLOXACIN. Therapy with BIOTECH CIPROFLOXACIN 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.

4.2 Posology and method of administration

Posology

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 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.

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

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 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 infectious diarrhoea:

500 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*: 500 mg 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.

Missed dose

If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remains before the next dose, the missed dose should not be taken, and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Special populations

Geriatric patients (> 65 years)

Elderly patients should be treated with the lowest possible dose; this will depend on the severity of the illness and on the creatinine clearance (see section 4.2 for dose adjustment).

Patients with renal and hepatic impairment

Patients with renal impairment

- Patients with creatinine clearance between 30 and 60 mL/min/1,73 m² (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/1,73 m² (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 less than 30 mL/min/1,73 m² (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 on dialysis days after dialysis.

- For patients with creatinine clearance less than 30 mL/min/1,73 m² (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 on dialysis days after dialysis.

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

- The maximum daily oral dose of BIOTECH CIPROFLOXACIN should be 500 mg (1 x 500 mg BIOTECH CIPROFLOXACIN film coated tablet or 2 x 250 mg BIOTECH CIPROFLOXACIN 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/1,73 m² (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.
- For patients with creatinine clearance less than 30 mL/min/1,73 m² (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.

Method of administration

BIOTECH CIPROFLOXACIN tablets can be taken independent of mealtimes. If BIOTECH CIPROFLOXACIN is taken on an empty stomach, the active substance is absorbed more rapidly.

A reduction in absorption of BIOTECH 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 BIOTECH CIPROFLOXACIN absorption (see section 4.5).

BIOTECH CIPROFLOXACIN tablets should be swallowed whole with plenty of liquid.

4.3 Contraindications

BIOTECH CIPROFLOXACIN is contraindicated in:

- Patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Concomitant use of BIOTECH 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.
- Patients with confirmed mitral valve and /aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated.
- Concomitant use of fluoroquinolones as contained in BIOTECH CIPROFLOXACIN with ACE inhibitors/ angiotensin receptor blockers in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in the elderly.
- Concomitant use of BIOTECH CIPROFLOXACIN and tizanidine (see section 4.5).

BIOTECH CIPROFLOXACIN is contraindicated in children under the age of 18 years. There is evidence of damage

to the cartilage of weight-bearing joints in immature animal.

4.4 Special warnings and precautions for use

Crystalluria related to the use of BIOTECH CIPROFLOXACIN has been observed. Patients receiving BIOTECH CIPROFLOXACIN 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 depression. (See section 4.8).

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

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 BIOTECH CIPROFLOXACIN is prescribed. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with BIOTECH CIPROFLOXACIN 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.

The use of BIOTECH CIPROFLOXACIN should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with BIOTECH CIPROFLOXACIN should only be initiated in the absence of alternative treatment options and after careful benefit/ risk assessment (see also section 4.3).

Streptococcal infections (including *Streptococcus pneumoniae*):

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

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

For the treatment of severe infections, BIOTECH CIPROFLOXACIN should be used in combination with another appropriate antibacterial medicine.

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

Cardiac disorders

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

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 BIOTECH CIPROFLOXACIN.

Elderly patients may be more susceptible to effects of BIOTECH CIPROFLOXACIN on the QT interval (see section 4.5, 4.8, 4.9).

Concomitant use of BIOTECH CIPROFLOXACIN 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 Ill antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics), (see section 4.5) or congenital long QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia.

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

whether concomitant use is contraindicated.

There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, BIOTECH CIPROFLOXACIN should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissections, or in the presence of other risk factors or conditions predisposing aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known arthrosclerosis) (see section 4.3).

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

Concomitant use with ACE inhibitors/ Angiotensin-receptor blockers

Concomitant use of fluoroquinolones such as BIOTECH CIPROFLOXACIN and ACE inhibitors/ renin-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/ renin-angiotensin receptor blockers whether used separately or concomitantly.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving ciprofloxacin, as contained in BIOTECH CIPROFLOXACIN.

BIOTECH CIPROFLOXACIN should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/ or weakness in order to prevent the development of an irreversible condition (see section 4.8).

The recovery process of neuropathy may be prolonged (weeks or months) and full recovery to the pre-treatment

status may not occur.

Psychiatric reactions

Psychiatric reactions may occur as soon as after the first administration of BIOTECH CIPROFLOXACIN. Less frequently, depression and psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide (see sections 4.3 and 4.8). If depression, psychotic reactions, suicide-related thoughts or behaviour occur, treatment with BIOTECH CIPROFLOXACIN should be stopped (see section 4.8).

Urinary tract infections

The local prevalence of resistance in *Escherichia coli* (the most common pathogen involved in urinary tract infections) to fluoroquinolones should be taken into account when initiating treatment with BIOTECH CIPROFLOXACIN.

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

Complicated urinary tract infections and pyelonephritis

The treatment of urinary tract infections with BIOTECH CIPROFLOXACIN should be considered when other treatments cannot be used and should be based on the results of the microbiological documentation.

Intra-abdominal infections

Limited data exists regarding the efficacy of BIOTECH CIPROFLOXACIN in the treatment of post-operative intra-abdominal infections.

Travellers' diarrhoea

Information on resistance to ciprofloxacin in relevant pathogens in the countries visited should be taken into consideration when considering treatment with BIOTECH CIPROFLOXACIN.

Infections of the bones and joints

BIOTECH CIPROFLOXACIN should be used in combination with other antimicrobial medicines depending on the results of the microbiological documentation.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylactic and anaphylactoid reactions can occur (e.g., facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), in some instances after the first administration and may be life-threatening. If such reaction occurs, BIOTECH CIPROFLOXACIN has to be discontinued and appropriate medical treatment instituted.

Prolonged, disabling and potentially irreversible serious adverse medicine reactions

Less frequent cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse medicine reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones such as BIOTECH CIPROFLOXACIN irrespective of their age and pre-existing risk factors. BIOTECH CIPROFLOXACIN should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to the Achilles tendon), sometimes bilateral, may occur during treatment with BIOTECH CIPROFLOXACIN, it may occur within 48 hours after initiating treatment. Inflammation and tendon rupture may occur up to several months after BIOTECH CIPROFLOXACIN treatment

has been discontinued (see section 4.3). The risk of tendinitis and tendon rupture may be increased in elderly patients, during strenuous physical activity, in patients with renal impairment, patients with solid organ transplants or in patients being concomitantly treated with corticosteroids (see section 4.8). Therefore, concomitant use of corticosteroids should be avoided.

At the any sign of tendinitis (e.g., painful swelling or inflammation), treatment with BIOTECH CIPROFLOXACIN should be discontinued and physical exercise be avoided. Care should be taken to keep the affected limb at rest, any inappropriate physical exercise should be avoided, a medical practitioner should be consulted. Corticosteroids should not be used if signs of tendinopathy occur.

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

Patients with myasthenia gravis

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

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

There is some evidence of increased risk of aortic aneurysm and/or dissection, particularly in elderly population.

There is some evidence, although inconclusive, of a possible association between fluoroquinolone such as BIOTECH CIPROFLOXACIN use and mitral valve and/ or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram should be performed before oral BIOTECH CIPROFLOXACIN are prescribed. BIOTECH CIPROFLOXACIN should not be prescribed to patients with mitral valve and/ or aortic valve regurgitation (see section 4.3).

Vision disorders

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

Photosensitivity

BIOTECH CIPROFLOXACIN has been shown to produce photosensitivity reactions. Extended periods of exposure to sunlight and UV irradiation should be avoided during treatment with BIOTECH CIPROFLOXACIN, as photosensitivity reactions may occur (see section 4.8). Therapy should be discontinued if photosensitisation (i.e., sunburn-like skin reactions) occurs (see section 4.8)

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 BIOTECH CIPROFLOXACIN (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, BIOTECH CIPROFLOXACIN 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 BIOTECH CIPROFLOXACIN, treatment with BIOTECH CIPROFLOXACIN must not be restarted in this patient at any time.

Seizures

BIOTECH CIPROFLOXACIN should be used with caution in patients with a history of convulsive disorders.

BIOTECH CIPROFLOXACIN is known to trigger seizures or lower the seizure threshold.

BIOTECH CIPROFLOXACIN 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 4.8).

If seizures occur BIOTECH CIPROFLOXACIN should be discontinued (see section 4.8).

Dysglycaemia

Disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8). This is usually more prevalent in elderly diabetic patients, receiving concomitant treatment with an oral hypoglycaemic medicine (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. Careful monitoring of blood glucose is recommended in diabetic patients.

Gastrointestinal system

Pseudomembranous colitis which may be fatal if not treated should be considered if severe and persistent diarrhoea develop during and after treatment with BIOTECH CIPROFLOXACIN. In such cases, BIOTECH CIPROFLOXACIN should immediately be discontinued, and appropriate antimicrobial and supportive therapy should be initiated. Anti-peristaltic medicines are contraindicated in this situation.

Impaired renal function

Elimination of BIOTECH CIPROFLOXACIN is primarily renal; dosage adjustment may be required in patients with impaired renal function (see section 4.2) to avoid an increase in adverse reactions due to the accumulation of ciprofloxacin.

Hepatobiliary system

There have been reports of hepatic necrosis and life-threatening hepatic failure with BIOTECH CIPROFLOXACIN treatment (see section 4.8). If any signs and symptoms of hepatic disease occurs (such as anorexia, jaundice, dark urine, pruritus or tender abdomen), treatment should be discontinued. There may be a temporary increase in

transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage (see section 4.8).

Glucose-6-phosphate dehydrogenase deficiency

In patients with glucose-6-phosphate dehydrogenase deficiency, haemolytic reactions have been reported with the use of BIOTECH CIPROFLOXACIN. The potential occurrence of haemolysis should be monitored.

Resistance

During or following a course of treatment with BIOTECH CIPROFLOXACIN bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

In the treatment of infections caused by *Pseudomonas aeruginosa,* an aminoglycoside must be administered concomitantly (See section 4.1 and 4.2).

Long-term or repeated administration of BIOTECH CIPROFLOXACIN can lead to super infections with resistant bacteria or fungi.

Cytochrome P450

BIOTECH CIPROFLOXACIN inhibits CYP1A2 and may thus cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g., theophylline, methylxanthines, caffeine, clozapine, olanzapine, ropinirole, duloxetine, agomelatine). Therefore, patients taking these medicines concomitantly with BIOTECH CIPROFLOXACIN should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g., of theophylline) may be necessary (see section 4.5). Concomitant administration of BIOTECH CIPROFLOXACIN and tizanidine is contraindicated (see section 4.3).

Methotrexate

The concomitant use of BIOTECH CIPROFLOXACIN and methotrexate is not recommended (see section 4.5).

Interaction with tests

As a result of the *in vitro* activity of BIOTECH CIPROFLOXACIN against *mycobacterium tuberculosis*, it may give a false negative result in bacteriological tests on specimens from patients currently on BIOTECH CIPROFLOXACIN treatment.

Influence on laboratory parameters/urinary sediment

BIOTECH CIPROFLOXACIN 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.

Paediatric population

BIOTECH CIPROFLOXACIN is contraindicated in children less than 18 years. In children arthropathy is reported to occur commonly (see section 4.3 and 5.2).

Other specific severe infections

The use of BIOTECH CIPROFLOXACIN for specific severe infections, other than those mentioned above, has not been evaluated and limited data is available. Caution is thus advised when treating patients with other severe infections with BIOTECH CIPROFLOXACIN.

When treating other severe infections, it should be done in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify the use of BIOTECH CIPROFLOXACIN.

4.5 Interaction with other medicines and other forms of interaction

Fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers

Concomitant use of fluoroquinolones as contained in BIOTECH CIPROFLOXACIN and ACE inhibitors/ renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3). Vulnerable patients (e.g., elderly, patients with impaired renal function, patients taking diuretics, NSAIDs and dehydrated patients) have an additional risk of nephrotoxicity.

Effects of other products on BIOTECH CIPROFLOXACIN

Medicines known to prolong QT interval

BIOTECH CIPROFLOXACIN should not be used in patients receiving medicines known to prolong QT interval e.g., Class IA and III anti-dysrhythmics, tricyclic antidepressants, macrolides, antipsychotics (see section 4.3 and 4.4).

Chelation complex formation

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

Food and dairy products

Dietary calcium as part of a meal does not significantly affect the absorption of BIOTECH CIPROFLOXACIN. However, the absorption of BIOTECH CIPROFLOXACIN may be reduced by the concurrent administration of dairy products or mineral-fortified drinks (e.g., milk, yoghurt, calcium-fortified orange juice). Concurrent administration should thus be avoided.

Probenecid

Probenecid interferes with renal secretion of BIOTECH CIPROFLOXACIN. Co-administration of probenecid and BIOTECH CIPROFLOXACIN increases the BIOTECH CIPROFLOXACIN serum concentrations.

Metoclopramide

Metoclopramide accelerates the absorption of BIOTECH CIPROFLOXACIN, resulting in shorter time to reach maximum plasma concentrations. No effect was observed on the bioavailability of BIOTECH CIPROFLOXACIN.

Omeprazole

A slight reduction in C_{max} and AUC of BIOTECH CIPROFLOXACIN were observed with the concomitant use of omeprazole.

Effects of BIOTECH CIPROFLOXACIN on other medicines

Tizanidine

The concomitant administration of BIOTECH CIPROFLOXACIN and tizanidine is contraindicated (see section 4.3). A clinical study in healthy subjects showed an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC10-fold, range: 6 to 24-fold) with co-administration. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of BIOTECH CIPROFLOXACIN, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of BIOTECH 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 toxicity and theophylline-induced side effects, that may be life threatening or fatal. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored, and theophylline dosage adjustments made as appropriate (see section 4.4).

Other xanthine derivatives

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

Phenytoin

Concomitant use of BIOTECH CIPROFLOXACIN and phenytoin may lead to increased or reduced phenytoin serum levels. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related side effects when BIOTECH CIPROFLOXACIN is discontinued in patients receiving both medicines it is recommended to monitor phenytoin therapy, including phenytoin serum-concentration measurements, during and shortly after co-administration of BIOTECH CIPROFLOXACIN with phenytoin.

Ciclosporin

Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists

The concomitant administration of BIOTECH CIPROFLOXACIN and vitamin K antagonists may augment its

anticoagulant effects. The contribution of BIOTECH CIPROFLOXACIN to the increase in INR (international normalised ratio) is difficult to assess, due to the fact that the risk may vary according to the underlying infection, age and general condition of the patient. The INR should be monitored frequently during, and shortly after, concomitant administration of BIOTECH CIPROFLOXACIN with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon or fluindione).

The simultaneous administration of BIOTECH CIPROFLOXACIN and warfarin may lead to warfarin toxicity; therefore, the INR should be closely monitored.

Duloxetine

Studies demonstrated an interaction between duloxetine and strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, with a possible increase of C_{max} and AUC of duloxetine. Although no clinical data are available on a possible interaction with BIOTECH CIPROFLOXACIN, this may suggest a possible similar interaction with BIOTECH CIPROFLOXACIN.

Ropinirole

The concomitant use of ropinirole and BIOTECH CIPROFLOXACIN may result in an increase in C_{max} and AUC of ropinirole by 60 % and 84 %, respectively. Ropinirole-related side effects should be monitored and dose adjusted as appropriate during and shortly after co-administration with BIOTECH CIPROFLOXACIN (see section 4.4).

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicines with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22 %.

Although lidocaine treatment was well tolerated, a possible interaction with BIOTECH CIPROFLOXACIN associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with BIOTECH CIPROFLOXACIN are advised (see section 4.4).

Sildenafil

Caution is advised when prescribing BIOTECH CIPROFLOXACIN concomitantly with sildenafil as C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin.

Agomelatine

It was demonstrated in studies 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 BIOTECH CIPROFLOXACIN, as a moderate inhibitor of CYP450 1A2, similar effects may be expected upon concomitant administration (see 'Cytochrome P450' in section 4.4).

Zolpidem

Concomitant use of BIOTECH CIPROFLOXACIN and zolpidem may increase blood levels of zolpidem therefore concurrent use is not recommended.

NSAID

Concomitant administration of the non-steroidal anti-inflammatory medicines, such as fenbufen with quinolones such as BIOTECH CIPROFLOXACIN may increase the risk of central nervous system stimulation and seizures.

Glibenclamide

Concurrent administration of BIOTECH CIPROFLOXACIN and glibenclamide can potentiate the action of glibenclamide, leading to hypoglycaemia.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

Pregnancy

On the basis of animal studies, it has been reported that ciprofloxacin, as in BIOTECH CIPROFLOXACIN may cause damage to articular cartilage in the foetus. Therefore, BIOTECH CIPROFLOXACIN should not be given to pregnant women.

Breastfeeding

BIOTECH CIPROFLOXACIN is excreted in breastmilk. Due to the potential risk of articular damage, BIOTECH CIPROFLOXACIN should not be used during breastfeeding.

4.7 Effect on the ability to drive and use machines

The ability to drive a motor vehicle or operate machinery may be impaired by BIOTECH CIPROFLOXACIN. Due to its neurological effects, ciprofloxacin may affect reaction time. This applies particularly in combination with alcohol.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) are nausea and diarrhoea.

Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations		Mycotic superinfections, antibiotic associated colitis (with possible fatal outcome).	
Blood and lymphatic system disorders		Eosinophilia, leukopenia, granulocytopenia, anaemia, thrombocytopenia, thrombocythemia, leukocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values, neutropenia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening).	
Immune system disorders		Allergic reaction, allergic oedema/ angioedema, anaphylactic reaction, anaphylactic shock (life threatening) (see section 4.4), serum sickness-like reaction.	
Endocrine disorders			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
Metabolism and nutrition disorders		Decreased appetite and food intake, hyperglycaemia, hypoglycaemia (see	Hypoglycaemic coma (see section 4.4).

	section 4.4).	
Psychiatric disorders*	Nervousness, psychomotor hyperactivity/ agitation, confusion and disorientation, anxiety reaction, abnormal dreams, hallucinations, psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide), depression (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4).	Mania, including hypomania.
Nervous system disorders*	Insomnia, peripheral paralgesia, unsteady gait, convulsions, increase in intracranial pressure and pseudotumor cerebri, impaired taste and smell, dizziness, headache, tiredness, trembling, migraine, olfactory nerve disorders, disturbed coordination, sleep disorders, vertigo, par- and dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus) (see section 4.4).	Peripheral neuropathy and polyneuropathy (section 4.4).

Eye disorders*		Visual disturbances (e.g. diplopia, colour vision), visual colour distortions.	
Ear and labyrinth disorders*		Tinnitus, transient impairment of hearing – especially at high frequencies, hearing loss.	
Cardiac disorders**		Tachycardia.	Ventricular dysrhythmia and Torsades de Pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9.
Vascular disorders**		Vasodilation, hypotension, vasculitis, syncope, flushing.	
Respiratory, thoracic and mediastinal disorders		Dyspnoea (including asthmatic condition).	
Gastrointestinal disorders	Nausea, diarrhoea.	Vomiting, dyspepsia, gastrointestinal and abdominal pain, flatulence, pancreatitis, antibiotic associated colitis (very seldom with possible	

	fatal outcome) (see section 4.4).	
Hepato-biliary disorders	Increase in transaminases, increased bilirubin, cholestatic icterus (especially in patients with liver damage, temporary increase in urea, creatinine or hyperbilirubinemia), hepatitis, hepatic impairment, hepatic necrosis, very seldom progressing to life-threatening hepatic failure, has been reported. (See section 4.4).	
Skin and subcutaneous tissue disorders	Rashes, urticaria, pruritis, photosensitivity (blisters, sensation of skin burning) (see section 4.4), erythema nodosum, erythema exsudativum multiforme, punctate skin haemorrhages (petechiae), Stevens-Johnson syndrome (potentially life-threatening), Lyell's syndrome (toxic epidermal necrolysis) (potentially life-threatening).	Acute Generalised Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
Musculoskeletal, connective tissue disorders*	Joint pain, joint swelling, musculoskeletal pain (e.g., extremity pain, back pain, chest pain),	

	arthralgia, myalgia, arthritis, increased muscle tone and cramping, muscular weakness, tendinitis, tendon rupture (predominantly Achilles tendon) (see section 4.4), exacerbation of myasthenia gravis (see section 4.4).	
Renal and urinary disorders	Tubulointerstitial nephritis, transient renal impairment including transient renal failure, haematuria and crystalluria (see section 4.4).	
General disorders and administration site conditions*	Asthenia, fever, oedema, sweating (hyperhidrosis).	
Investigations	Increase in blood alkaline phosphatase, Increased amylase.	International normalised ration increased (in patients treated with vitamin K antagonists).

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see Section 4.4).

Post-marketing Experience:

Metabolism and nutrition disorders	Hyperglycaemia, hypoglycaemic coma
Nervous system disorders	Peripheral neuropathy and polyneuropathy, Guillain-Barre syndrome
Cardiac disorders	QT prolongation, ventricular dysrhythmia, Torsades de Pointes*, aortic aneurysm and dissection
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis (AGEP)
Investigations	Increased International Normalised Ratio (INR) (in patients treated with Vitamin K antagonist)

*These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

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.

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/ risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

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

Apart from routine emergency measures, e.g., ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidity, if required, to prevent crystalluria. Patients should be kept well hydrated. Magnesium- or calcium-containing antacids may theoretically reduce the absorption of oral BIOTECH CIPROFLOXACIN.

Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

In the event of an overdose, treatment is symptomatic and supportive. ECG monitoring should be undertaken, as there may be a possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Fluoroquinolones.

ATC code: J01MA02

Mechanism of action

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

5.2 Pharmacokinetic properties

Absorption

After oral administration, ciprofloxacin plasma levels are dose-related and peak at 0,5 - 2 hours. The absolute bioavailability is approximately 70 %.

Distribution

Protein binding is 40 %. Forty to fifty percent is excreted in urine as unchanged ciprofloxacin.

Elimination

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/min.

The elimination half-life of unchanged ciprofloxacin is 3 - 5 hours. The elimination kinetics is linear.

Paediatric population:

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6,1 mg/L (range 4,6-8,3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7,2 mg/L (range 4,7-11,8 mg/L) for children between 1 and 5 years of age. The AUC values were 17,4 mg*h/L (range 11,8-32,0 mg*h/L) and 16,5 mg*h/L (range 11,0-23,8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4 - 5 hours and the bioavailability of the oral suspension ranges from 50 to 80 %.

Micro-organisms resistant to ciprofloxacin

Enterococcus faecium; Norcardia asteroides; Ureaplasma urealyticum; Peptostreptococcus species; *Peptococcus* species; Bacteroides; *Treponema pallidum.*

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Colloidal silicon dioxide

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch.

Film-coating:

Opadry Y-1-7000 White consisting of hypromellose 2910

Polyethylene glycol 400

Titanium dioxide

Polyethylene glycol 4000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

BIOTECH CIPROFLOXACIN 250: 36 months

BIOTECH CIPROFLOXACIN 500: 24 months

BIOTECH CIPROFLOXACIN 750: 24 months

6.4 Special precautions for storage

Store in a cool dry place at or below 25 °C.

6.5 Nature and contents of container

BIOTECH CIPROFLOXACIN 250 and 500 are available in either of the following presentations:

- White HDPE containers containing 50 or 100 tablets
- Transparent PVC and silver aluminium blister strips containing 10 tablets per strip and 1 strip per outer carton.

BIOTECH CIPROFLOXACIN 750 is packed in white HDPE containers containing 50 or 100 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground floor, Block K West, Central Park

400 16th Road, Randjespark

Midrand

1685

8. REGISTRATION NUMBER

BIOTECH CIPROFLOXACIN 250: A40/20.1.1/0368

BIOTECH CIPROFLOXACIN 500: A40/20.1.1/0369

BIOTECH CIPROFLOXACIN 750: A40/20.1.1/0370

9. DATE OF FIRST AUTHORISATION

Date on the registration certificate: 12 June 2009

10. DATE OF REVISION OF THE TEXT

27 June 2023