IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0915/008/001
Case No: 2086658

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Helsinn Birex Therapeutics Ltd

Damastown, **Mulhuddart**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Biravid 200 mg Film-Coated tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/07/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Biravid 200 mg Film-Coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet Contains 200mg ofloxacin

Excipients: Each tablet contains 108.9mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets {short term: tablets}

White, round, film-coated tablets 11 mm in diameter, scored on both sides. One side of the tablet debossed ‘FXN’ on one side of the break-line and ‘200’ on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ofloxacin is a synthetic 4-fluoroquinolone antibacterial agent. It is effective in vitro against a wide range of Gram-negative and Gram-positive organisms. It is indicated for the treatment of the following infections when caused by sensitive organisms:

Respiratory tract: Acute, chronic or recurrent respiratory tract infections (bronchitis) caused by *Haemophilus influenzae* or other Gram-negative or multi-resistant pathogens, as well as by *Staphylococcus aureus*. In respiratory tract infection ofloxacin is not recommended as first-line therapy for the treatment of pneumococcal pneumonia. *Streptococcus pneumoniae* is the most frequent pathogen responsible for community acquired pneumonia.

Urinary Tract: Acute and chronic lower urinary tract infections; acute and chronic upper urinary tract infections (pyelonephritis). Uncomplicated non-gonococcal gonorrhoea, non-gonococcal urethritis and cervicitis

Biravid tablets are also indicated for infection prophylaxis in neutropenic patients.

Skin and soft tissue infection.

4.2 Posology and method of administration

General dosage recommendations: Biravid tablets should be swallowed with liquid; they should not be taken within two hours of magnesium/aluminium containing antacids, sucralfate or iron preparations since reduction of absorption of ofloxacin can occur. They may be taken on an empty stomach or with meals.

The dose of ofloxacin is determined by the type and severity of the infection. The dosage range for adults is 200mg to 800mg daily. Up to 400mg may be given as a single dose, preferably in the morning.
Daily doses of more than 400mg must be divided into two separate doses and be given at approximately equal intervals.

Respiratory tract infection: 400mg daily is the recommended dose for the treatment of infections caused by sensitive organisms.

Ofloxacin is not recommended as first-line treatment for pneumococcal pneumonia but in circumstances where a physician considers is appropriate to use ofloxacin in patients with pneumococcal pneumonia, a dose of 800mg daily should be used. In these cases, the drug should be given as two divided doses daily.

Lower respiratory tract infection: 400mg daily increasing, if necessary, to 400mg twice daily.
Lower urinary tract infection: 200-400mg daily.
Upper urinary tract infection: 200-400mg daily increasing, if necessary, to 400mg twice a day.

Uncomplicated urethral and cervical gonorrhoea: A single dose of 400mg.
Non-gonococcal urethritis and cervicitis: 400mg daily in single or divided doses.
Infection prophylaxis in neutropenia: 400-800mg daily for up to 2 months as required.
Skin and soft tissue infections: Oral 400mg twice a day.

Impaired renal function: The dosage of Biravid should be adjusted according to the degree of renal impairment.

With a creatinine clearance of 20-50 ml/minute (serum creatinine 1.5-5.0mg/dl) a dose of 200mg should be administered initially followed by 100-200 mg every 24 hours. If creatinine clearance is less than 20ml/minute (serum creatinine greater than 5mg/dl) a dose of 200mg should be given initially and then reduced to 100mg and administered every 48 hours.

In patients undergoing haemodialysis or peritoneal dialysis, 100mg should be given every 24 hours.

4.3 Contraindications

Ofloxacin must not be used in patients with known hypersensivity to ofloxacin or other similar quinolone drugs and any of the excipients.

In children or adolescent in the growth phase, during pregnancy, in women at risk of pregnancy or during lactation because, judging from animal experiments, a risk of damage to the growth-plate cartilage in the growing organism cannot be entirely excluded.

It should not be used in patients with a history of quinolone-induced tendon disorders or in patients with epilepsy.

In patients with pre-existing CNS lesions involving a lowered convulsions threshold.

4.4 Special warnings and precautions for use

o *Clostridium difficile*- associated disease
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with ofloxacin, may be symptomatic of pseudo-membranous colitis.
If pseudo-membranous colitis is suspected, ofloxacin must be stopped immediately.
Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products inhibiting the peristalsis are contraindicated in this clinical situation.

o Patients predisposed to seizures
As with other quinolones, ofloxacin should be used with extreme caution in patients predisposed to seizures.

- Tendinitis

Tendinitis, rarely observed with quinolones, may occasionally lead to rupture involving Achilles tendon in particular. Elderly patients are more prone to tendinitis. The risk of tendon rupture may be increased by coadministration of corticosteroids.
If tendinitis is suspected, or at the first signs of pain or inflammation, treatment with ofloxacin must be halted immediately. Appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

- Patients with renal impairment

Since ofloxacin is mainly excreted by the kidneys, the dose of ofloxacin should be adjusted in patients with renal impairment. (see section 4.2 Posology and method of administration).

- Prevention of photosensitization

Because of the risk of photosensitization, exposure to strong sunlight and UV radiation should be avoided during treatment with ofloxacin.

- Secondary Infection

As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patients conditions is essential. If secondary infection occurs, appropriate measures should be taken.

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Caution is recommended if the drug is to be used in psychotic patients or in patients with a history of psychiatric disease.

Use with great caution in patients with pre-existing central nervous system disorders.

Patients with pre-existing significant renal or hepatic disorders should be carefully monitored to detect any deterioration in function. A reduction in dosage may be required.

4.5 Interaction with other medicinal products and other forms of interaction

- Antacids

Antacids containing aluminium (including sucralfate) and magnesium hydroxides, aluminium phosphate, zinc, iron are liable to reduce the absorption of ofloxacin tablets. Ofloxacin should be administered approximately 2 hours apart from antacids.

- Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of ofloxacin were found with theopohylline in a clinical study. However, a pronounced lowering of the cereberal seizure threshold may occur when quinolones are given concurrently with theopohylline, non-steroidal anti-inflammatory drugs, or other drugs, which lower the seizure threshold.

- Vitamin K antagonists

Coagulation tests should be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives.

- Probenecid, cimetidine, furosemide or methotrexate

Particularly in case of high dose therapy, mutual impairment of excretion and an increase in serum levels must be considered when quinolones are administered together with other drugs that also undergo renal tubular secretion. Sudden reduction in blood pressure may occur when Biravid is administered with hypotensive agents. In such cases, or if the drug is given concomitantly with barbiturate anaesthetics, cardiovascular function should be monitored.

Concurrent administration with anticoagulant therapy may require adjustment of the dose of the latter as prolonged of bleeding time has been reported. In a study with phencourmarin no interactions were noted.
Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administration concurrently; patients treated with this combination should be closely monitored.
Concomitant use with some phenylpropionic acid derived non-steroidal anti-inflammatory drugs may lead to toxicity possibly because of renal effects.
Ofloxacin may inhibit the growth of *mycobacterium tuberculosis*, and therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.
Determination of opiates or porphyrins in urine may give false-positive results during treatment with ofloxacin.

4.6 Pregnancy and lactation

Ofloxacin must not be prescribed in pregnancy or in women at risk of pregnancy. Because ofloxacin is excreted in human breast milk, either breast-feeding or treatment of the mother must be stopped because of the risk to the child. (see 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

Some adverse reactions (e.g. dizziness/vertigo, drowsiness, visual disturbance) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating a special machine).

4.8 Undesirable effects

The information given below is based on data from clinical studies and on extensive post marketing experience.

The following frequency rating has been used:
Very common: more than 10%
Common: 1% to 10%
Uncommon: 0.1% to 1%
Rare: 0.01% to 0.1%
Very rare: less than 0.01%
Isolated cases

<u>Anaphylactic/oid reactions, mucocutaneous reactions</u>
Uncommon: Symptoms such as pruritus, rash, burning eyes, tickling cough, nasal catarrh.
Rare: Anaphylactic/oid reactions such as urticaria, angio-edema, dyspnoea/bronchospasm, hot flushes, sweating, pustular eruption.
Very rare: Anaphylactic/oid shock, erythema multiforme, toxic epidermal necrolysis, photosensitisation, fixed drug eruption, vascular purpura, vasculitis which can lead in exceptional cases to skin necrolisis.
Isolated cases: Steven-Johnson syndrome; severe dyspnoea.

<u>Gastrointestinal, metabolism</u>
Uncommon: Abdominal pain, diarrhoea, nausea and vomiting.
Rare: Anorexia, enterocolitis which may, in isolated cases be haemorrhagic.
Very rare: *Pseudomembranous colitis.*
Isolated cases: Hypoglycaemia in diabetics treated with hypoglycaemic agents.

<u>Neurological</u>
Uncommon: Agitation, dizziness/vertigo, headache, sleep disorders/insomnia.
Rare: Psychotic reactions (with e.g. hallucination), anxiety, confusion, nightmares, depression, drowsiness/somnolence, peripheral sensory disturbance such as paresthesia, taste and smell disorders, visual disorders.
Very rare: Auditory disturbances like tinnitus and loss of hearing, seizures, extra-pyramidal symptoms or other disorders of muscular co-ordination, hypoesthesia.

Isolated cases: Psycotic reactions with self-endangering behaviour including suicidal ideation or acts.

Cardiovascular
Rare: Hypotension, tachycardia.
During the infusion of ofloxacin, tachycardia and a decrease in blood pressure may occur.
Such a decrease in blood pressure may, in very rare cases, be severe. In the event of a conspicuous drop in blood pressure, the infusion must be halted immediately.

Musculo-skeletal
Rare: Tendinitis.
Very rare: Arthralgia, myalgia.
Tendon rupture (e.g. Achilles tendon); as with other fluoroquinolones this undesirable effect may occur within 48 hours of starting treatment and may be bilateral.
Isolated cases: Rhabdomyolysis and/or myopathy.
Muscle weakness which may be of special importance in patients with myasthenia gravis.

Liver
Rare: Increase in enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin.
Very rare: Cholestatic jaundice.
Isolated cases: Hepatitis, which may be severe.

Kidney
Rare: Increase in serum creatinine.
Very rare: Acute renal failure.
Isolated cases: Acute interstitial nephritis.

Blood
Very rare: Anaemia, haemolytic anaemia, leukopenia, eosinophilia, thrombocytopenia.
Isolated cases: Agranulocytosis, pancytopenia, bone marrow depression.

Others
Uncommon: Development of resistant micro-organisms and fungal overgrowth.
Isolated cases: Allergic pneumonitis, attacks of porphyria in patients with porphyria.

4.9 Overdose

The most important signs to be expected following acute overdose are CNS symptoms such as confusion, dizziness, impairment of consciousness and seizures as well as gastrointestinal reactions such as nausea and mucosal erosions. Treatment of overdosage should therefore be symptomatic, with routine measures such as gastric lavage carried out as soon as possible. Elimination of ofloxacin may be increased by forced diuresis. No specific antidote exists.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutics group: Fluoroquinolone antibiotic, ATC code: J01 MA01
Ofloxacin is a quinolone-carbolic acid derivative with a wide range of antibacterial activity against both gram negative and gram positive organisms. It inhibits bacterial DNA replication by blocking DNA topo-isomerases, in particular DNA gyrase.

Therapeutic doses of ofloxacin are devoid of pharmacological effects on the voluntary or autonomic nervous system.

5.2 Pharmacokinetic properties

Ofloxacin is an oxyquinolone anti-infective that is well absorbed, widely distributed, slightly metabolised in liver to inactive metabolites and excreted in urinary tract with T½ of 6-8 hours.

5.3 Preclinical safety data

Toxicological studies have shown that administration of oxoquinolone antibacterial agents at doses higher than the therapeutic range can produce erosion of the cartilage in weight-bearing joints in immature animals of some species. No such lesions have been shown to occur in man to date. This product should not be prescribed for children.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Lactose Monohydrate
Pregelatinised Starch
Hypromellose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film Coat:
Hypromellose
Titanium Dioxide (E171)
Lactose Monohydrate
Macrogol 3000
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/aluminium blister packs of 10, 14, 20 and 50 tablets.

PVC/PVdC/aluminium blister medical sample pack of 3 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Helsinn Birex Therapeutics Ltd,
Damastown,
Mulhuddart,
Dublin 15,
Ireland.

8 MARKETING AUTHORISATION NUMBER

PA0915/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 October 2004
Date of last authorisation: 29 October 2009

10 DATE OF REVISION OF THE TEXT

July 2010