IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0549/015/004
Case No: 2038354

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

Ethypharm SA

17-21 rue St. Mattieu, **78550 Houdan**, **France**

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

Ethirfin 120 Milligram Tablet Prolonged Release

The particulars of which are set out in Part I and Part II of 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 **26/06/2007** until **08/01/2011**.

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

ETHIRFIN 120 mg, prolonged-release capsules hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard, prolonged-release capsule contains morphine sulphate 120 mg.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Capsule with pink opaque cap and white opaque body with '120' printed in black on the body, containing off-white to yellowish spherical microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe chronic stable pain.

This medicinal product is not suitable for initiating treatment, therefore the use should be limited to patients already controlled by immediate release morphine or by prolonged release morphine intended for twice daily administration.

4.2 Posology and method of administration

Adults
The dosage depends on the severity of the pain, the patient’s age and previous history of analgesic requirements. Patients should have their dose requirement of immediate release morphine or prolonged release morphine calculated then change to ETHIRFIN capsule once daily.

Adjustment of the dosage
An adjustment of the dosage is justified when previously prescribed doses (the last prescribed level) prove insufficient.

Frequency of evaluation
When a dosage level proves to be ineffective, it should not be maintained for more than 24 to 48 hours. The patient should therefore be assessed at short intervals until the pain is controlled. In practice, at the start of treatment, daily evaluation is recommended.

Increase of the doses
If the patient’s pain is not controlled, the doses of morphine should be increased by about 30 to 50%. In this dose adjustment process, there is no upper limit as long as undesirable effects can be controlled.

Decrease of the doses
When required, decreases of doses should be made gradually in order to avoid withdrawal syndrome.

Correspondence between different routes of administration
The dosage varies with the route of administration.

In comparison with the oral route, the intravenous dosage should be reduced by two thirds and the subcutaneous dosage by half.
When switching over from one route of administration to another, these coefficients must be taken into consideration in order to maintain the same quantity of bioavailable morphine.
Similarly, in patients previously treated with immediate release oral morphine, the daily dosage of morphine will remain unchanged.

Treatment of breakthrough pain
In case of breakthrough pain, a short-acting morphine may be administered in addition to the prolonged-release morphine maintenance treatment.

Children
The use of ETHIRFIN capsules in children has not been evaluated and is not recommended.

Special patient population
A reduction in dosage may be advisable in elderly and in patients with significantly impaired renal or hepatic functions (see section 4.4). The treatment should be started at a lower dosage and the doses and frequency of administration adapted subsequently, as for any patient, to the clinical condition.

Method of administration
Oral use.
Capsules should be administered at 24-hourly intervals.

The capsules may be swallowed whole. The capsules and contents should not be crushed or chewed. If the capsules cannot be swallowed, their contents can be administered directly in semi-solid food such as a fruit or vegetable purée, jam or yoghurt, or through gastric or gastrostomy tubes with a diameter of at least 16 FG (French gauge) with an open distal end or lateral pores. 30 to 50 ml water is sufficient to flush the tube.

4.3 Contraindications

Decompensate respiratory failure,
acute abdominal syndrome of unknown origin,
severe hepatic insufficiency,
uncontrolled convulsive disorders,
concomitant use of morphine agonist/antagonist (see section 4.5),
concomitant intake of alcohol,
breast-feeding if long term treatment after birth is necessary (see section 4.6),

hypersensitivity to morphine or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings

Sustained-released forms of morphine are not emergency treatments of pain. This formulation is not appropriate for treating peri-operative pain.

It should be emphasised that patients, once titrated to an effective dose of a certain opioid drug, should not be changed to other prolonged-release morphine or other narcotic analgesic preparations without retitration and clinical assessment. Otherwise a continuing analgesic action is not ensured.

An increase in the doses for pain management, even if there are high, does not generally reflect a development of tolerance.

Insistent and repeated demands impose frequent re-evaluation of the patient’s condition. In most cases, they reflect a genuine need for analgesics, and should not be mistaken for addictive behaviour.

When the cause of pain is treated simultaneously: the doses should be adjusted according to the results of the treatment administered.

Sudden discontinuation of prolonged treatment induces a withdrawal syndrome, characterised by the following symptoms: anxiety, irritability, shivering, mydriasis, hot flushes, sudation, lacrimation, rhinorrhoea, nausea, vomiting, abdominal cramps, diarrhoea, joint pain. The occurrence of this withdrawal syndrome can be prevented by reducing the doses gradually.

Morphine is a narcotic, which may be used for purposes for which it is not intended (misuse): in this context, chronic use may lead to physical and mental dependence and tolerance.

Morphine can nevertheless be prescribed in patients with a history of drug addiction if morphine is considered absolutely necessary for the treatment of pain.

The concomitant intake of alcohol during therapy with ETHIRFIN must be avoided, since alcohol accelerates the release of morphine which may lead to increased blood levels of morphine.

Special precautions for use

Morphine should be used with precaution in the following cases:

Disorders of consciousness, convulsive disorders, biliary tract disorders, pancreatitis, prostatic hypertrophy,

Respiratory insufficiency:
Respiration rate should be closely monitored. Drowsiness may be a warning of decompensation.
It is important to reduce the doses of morphine when other analgesic treatments are prescribed simultaneously, as such combinations enhanced the risk of sudden occurrence of respiratory failure.

Elderly:
Because of the particular sensitivity of elderly subjects to the central adverse effects (confusion) or gastrointestinal effects, and of the physiological reduction of their renal function, caution should be exercised.
Concomitant administration of other medicinal products, and particularly of tricyclic antidepressants, further increases the likelihood of undesirable effects such as confusion and constipation.
Urethro-prostatic disease, which is frequent in this population, enhances the risk of urine retention.
These considerations should nevertheless not restrict the use of morphine in elderly patients provided these precautions are complied with.

Impaired hepatic function:
Morphine should be administered under close medical supervision.

Impaired renal function:
As morphine is eliminated by the kidneys in the form of an active metabolite, reduction of dosage may be advisable (see section 4.2).
Chronic constipation and intestinal mechanical disorders:
Opioids inhibit the peristaltism of the longitudinal fibres of smooth muscles; therefore it is essential to ensure that no occlusive syndrome, in particular ileus exists before initiating the treatment.
Constipation is a common problem during treatment with opioids. A prophylactic treatment should be prescribed concomitantly with morphine.

Intracranial hypertension and head injury:
In the presence of increased intracranial pressure, morphine should be used with caution since it may induce a further rise. In patients with head injury morphine may obscure the diagnosis or the clinical course.
In these patients, morphine should be used only if the benefit of the treatment clearly outweighs the risk.

Athletes:

Morphine may produce a positive reaction to anti-doping tests.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The fact that a lot of medicinal products or substances may add their sedative effects and lead to a decrease of vigilance should be taken into account. These medicinal products are morphinic derivatives (analgesics, cough medicines, opiate dependence treatments), neuroleptics, barbiturics, benzodiazepines, other treatments of anxiety than benzodiazepines (e.g. meprobamate), sedative antidepressants (amitriptyline, doxepine, mianserine, mirtazapine, trimipramide), sedative H1 antihistaminics, central antihypertensive drugs, baclofene and thalidomide.
Monoamine oxidase inhibitors have been reported to react with narcotic analgesics, producing CNS excitation or depression with hyper- or hypotensive crises.

Contraindication of concomitant use (see section 4.3)

+ Morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine): reduction of the analgesic or cough effect by competitive blocking of the receptors, with a risk of occurrence of a withdrawal syndrome.

+ Alcohol intake:
The concomitant intake of alcohol during therapy with ETHIRFIN must be avoided, since alcohol accelerates the release of morphine which may lead to increased blood levels of morphine.
Alcohol increases the sedative effect of morphine and morphine-like analgesics.
Consumption of alcoholic drinks and medicinal products containing alcohol is contraindicated.
The impairment of vigilance may make it dangerous to drive vehicles and operate machines.

Concomitant use not recommended

+ Naltrexone:
risk of reduction of the analgesic effect. The doses of the morphinic derivative should be increased if needed.

Precaution including dose adjustment

+ Rifampicine:
Risk of decrease of the plasma concentrations of morphine and its active metabolite and thus efficacy. Clinical effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicine.

Concomitant use which needs to be taken into consideration

+ Other morphinic-agonist analgesics (alfentanil, codeine, dextromoramide, dextropropoxyphene, dihydrocodeine, fentanyl, oxycodone, pethidine, phenoperidine, remifentanil, sufentanil, tramadol).
+ Morphine-like cough treatments (dextrometorphane, noscapine, pholcodine, codeine, ethylmorphine).
+ Barbiturics.
+ Benzodiazepines and benzodiazepine-like treatments.
Increased risk of respiratory depression, that could be fatal in case of overdose

4.6 Pregnancy and lactation

Pregnancy
Animal studies indicate teratogenic effects (see section 5.3).
In humans, data on a large number of exposed pregnancies indicate no undesirable effect of morphine sulphate.
High doses administered at the end of pregnancy, even for brief periods of treatment, can cause respiratory depression in the newborn.

Chronic consumption of morphine by the mother during the last three months of pregnancy, regardless of the dose, can produce a withdrawal syndrome in the newborn characterised by irritability, vomiting, convulsions and increased lethality.

In the event of occasional consumption of high doses, chronic treatment or addiction at the end of pregnancy, neonatal monitoring is recommended in order to prevent the risks of respiratory depression or withdrawal symptoms in the newborn. Administration of an opioid antagonist should be considered if necessary.

Therefore, it is advised not to use morphine during pregnancy, except when no alternative pain treatments are available, taking into account the benefit for the mother and the potential risk for the foetus.

Lactation
Morphine is excreted in breast milk and reaches a higher concentration as in the plasma of the mother. Therefore, therapeutic relevant concentrations can be reached.

- A single administration appears without risk for the newborn,
- if repeated administrations for several days are needed, breastfeeding should be temporarily suspended,
- if long-term treatment after birth is necessary, breastfeeding is contra-indicated (see section 4.3).

4.7 Effects on ability to drive and use machines

ETHIRFIN has major influence on the ability to drive and use machines. This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers. Patients stabilized on a specific dosage will not necessarily be restricted. Therefore, patients should consult their physician to know whether driving or use of machines is permitted.

4.8 Undesirable effects

At usual doses, the most common undesirable effects of morphine are nausea, vomiting, constipation and drowsiness. If necessary, the capsules can easily be combined with an anti-emetic. Constipation can be treated with a suitable laxative.

Cardiovascular system disorders:
Uncommon (>1/1000, <1/100): clinical relevant changes of blood pressure.
Rare (>1/10000, <1/1000): facial flushing, palpitations, severe decrease in blood pressure, bradycardia, tachycardia.

Central and peripheral nervous system disorders:
Very common (>1/10): depending from dose sedation and respiratory depression.
Common (>1/100, <1/10): headache, dizziness.
Rare (> 1/10000, <1/1000): raised intracranial pressure.
Very rare (<1/10000) including isolated reports: tremor, muscular fasciculations, epileptiform convulsions.
Especially under high dosage hyperalgesia and allodynia which will not respond to a higher dose of morphine.

Psychiatric disorders:
Very common (>1/10): mood alterations.
Common(>1/100, <1/10): Psychic side-effects may occur following administration of morphine which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), sleep disturbance, changes in activity (usually suppression, occasionally excitation) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders, hallucinations, nightmares, particularly in the elderly).

Vision disorders:
Common(>1/100, <1/10): miosis.
Very rare (<1/10000) including isolated reports: blurred vision.

Respiratory system disorders:
Rare (> 1/10000, <1/1000): bronchospasm.
Very rare (<1/10000) including isolated reports: dyspnoea.

Gastrointestinal disorders:
Very common: nausea, dry mouth.
Common (>1/100, <1/10): vomiting, constipation, dyspepsia, loss of appetite.
Rare (> 1/10000, <1/1000): pancreatitis.
Very rare (<1/10000) including isolated reports: abdominal pain.

Skin and appendages disorders:
Common (>1/100, <1/10): sweating, hypersensitivity reactions, e.g. urticaria, pruritus.
Very rare (<1/10000) including isolated reports: dermal reactions (e.g. exanthema, peripheral edema).

Musculo-Skeletal system disorders:
Very rare (<1/10000) including isolated reports: muscle cramps.

Liver and biliary system disorders:
Rare (> 1/10000, <1/1000): biliary colic.
Very rare (<1/10000) including isolated reports: increased activity of hepatic enzymes.

Urinary system disorders:
Common (>1/100, <1/10): micturition disorders (difficulty in passing urine and urinary retention).
Rare (> 1/10000, <1/1000): renal colic.

Body as a whole:
Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.
The effect of morphine has led to its abuse, and dependence may develop with regular, inappropriate use.

4.9 Overdose

Signs of morphine intoxication and overdose are drowsiness, severe miosis (pinpoint pupils), respiratory depression, hypothermia and hypotension. Circulatory collapse and coma may occur in more severe cases.

Treatment of morphine overdose:
Primary attention should be given to establishing free airways and initiating assisted or controlled ventilation.

Gastric emptying may be necessary in order to remove unabsorbed drug, particularly when a modified-release formulation has been taken.

In the event of massive overdose, administration of naloxone 0.4-0.8 mg intravenously is recommended. The administration should be repeated at 2-3 minute intervals, as necessary, or a naloxone infusion of 2mg in 500ml (0.004 mg/ml) in sodium chloride solution 9 mg/ml (0.9%) or in glucose solution 5% should be administered.

The infusion should be given at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the effects of naloxone are relatively short-lived, the patient must be carefully monitored until spontaneous respiration has been reliably restored. Significant plasmatic concentrations of morphine may continue for up to 24 hours after administration and morphine overdose management should be adapted accordingly.

For less severe overdose, administration of naloxone 0.2mg intravenously will be followed by increments of 0.1mg every 2 minutes, if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected,

to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate acute withdrawal syndrome.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids; natural opium alkaloids.
ATC code: N02AA01

Morphine acts as an agonist on opioid receptors in the CNS, particularly mu and to a lesser extent kappa receptors.

Action on the central nervous system:
Morphine exerts a dose-dependant analgesic action. It can affect psychomotor behaviour and induce, depending on the dose and the patient condition, sedation or excitation.
At and above therapeutic dose levels, morphine has a depressant effect on the respiratory and coughing centres. The respiratory depressant effects of morphine subside with chronic administration. Morphine has variable emetic properties due to its triple action on the vomiting centre, possibly on the cochleovestibular centre and on gastric emptying (see below).
Finally, morphine causes miosis of central origin.

Action on smooth muscle:
Morphine reduces the tone and peristaltism of the longitudinal fibres and increases the tone of the circular fibres, thus causing spasm of the sphincters (pylorus, ileocaecal valve, anal sphincter, sphincter of Oddi, bladder sphincter).

5.2 Pharmacokinetic properties

Absorption
Morphine is well absorbed from capsules and, in general, peak plasma concentrations are achieved about 5 hours following administration. A study on the influence of food showed that this factor does not have a clinically significant influence on the pharmacokinetic profile of ETHIRFIN.
ETHIRFIN can therefore be given with or without meals. When given orally, morphine displays significant first-pass metabolism, resulting in lower bioavailability as compared with an equivalent intravenous or intramuscular dose.

Distribution
30% of the drug is bound to plasma proteins.

Metabolism
Morphine is mainly metabolised through glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide, which then undergo renal excretion. These metabolites are also partially excreted in bile and may be subject to hydrolysis and subsequent reabsorption.

Elimination
The glucuronide metabolites are eliminated essentially by the urinary route, by both glomerular filtration and tubular secretion. The amount eliminated in the faeces is small (<10%).

Linearity
The pharmacokinetics of morphine are linear across a very wide dose range.

Because of the great inter-patient variations in morphine pharmacokinetics and in patients' analgesic requirements, the daily dosage must be individually titrated to achieve appropriate pain management.

5.3 Preclinical safety data

In animal studies morphine showed a teratogenic potential and neurobehavioural deficiencies in the developing

organism, while data in humans do not show evidence of malformations or fetotoxic effects of morphine.

Experimental studies have shown that morphine sulphate induces chromosome damage in animals in somatic and germ cells and in human somatic cells. A genotoxic potential for humans cannot be eliminated.

There are no other preclinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Sugar spheres (containing sucrose and maize starch)
Hypromellose
Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1
Triethyl citrate
Talc
Hydrophobic colloidal silica

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Brilliant blue FCF (E 133)
Allura Red AC (E 129)

Black ink:
Shellac
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister (PVC/aluminium), packed in cardboard boxes.
Pack sizes: 7, 8, 10, 14, 16, 20, 28, 30, 50, 60, 90, 100, 120 or 200 capsules.

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

ETHYPHARM
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8 MARKETING AUTHORISATION NUMBER

PA 549/15/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 January 2006

10 DATE OF REVISION OF THE TEXT

February 2007