IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0549/009/001
Case No: 2034767

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

ETHYPHARM KETOPROFEN SR 100 mg prolonged-release hard capsules

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 **20/04/2007** until **14/04/2009**.

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

Ethypharm Ketoprofen SR 100 mg prolonged-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains ketoprofen 100mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

Capsule, hard with opaque white cap and body, containing off-white spherical microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of:
- chronic inflammatory rheumatism, such as rheumatoid arthritis and ankylosing spondylitis,
- osteoarthritis.

4.2 Posology and method of administration

Oral use.

Adults and adolescents over the age of 15 years:
The usual daily dose is 200mg, however 100mg may be sufficient in some patients.

No data have been provided in children in these indications, so this product should only be used in adults and adolescents over the age of 15.

A dose of 100mg is particularly recommended in elderly patients, in patients with chronic congestive heart failure and in patients with renal impairment (creatinine clearance 30-50 ml/min) or with hepatic impairment (see section 4.4 “Special warnings and special precautions for use”).

The capsule should be swallowed whole with food once daily, with a large glass of water.

4.3 Contraindications

- hypersensitivity to ketoprofen or to any of the excipients,
- last trimester of pregnancy (see section 4.6 “Pregnancy and lactation”),
- a history of asthma induced by administration of ketoprofen or similar acting substances, such as other non-steroidal anti-inflammatory agents (NSAIDs) or acetylsalicylic acid,
- history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy

- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding),
- severe hepatic failure,
- severe renal failure,
- severe heart failure
- gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The use of Ethypharm ketoprofen SR with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Patients with asthma associated with chronic rhinitis, chronic sinusitis and/or nasal polyposis are more likely to exhibit allergic reactions after taking acetylsalicylic acid and/or non-steroidal anti-inflammatory agents than the general population. Administration of this product may induce an attack of asthma (see section 4.3 “Contraindications”).

Gastrointestinal effects

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose asprin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in intial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as asprin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Ethypharm ketoprofen SR, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohns disease) as these conditions may be exacerbated (see section 4.8 - undesirable effects).

Cardiovascular and cerbrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemioligical data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be assoicated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for ketoprofen.

Patients wtih uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ketoprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Urine output and renal function should be closely monitored in patients with renal or hepatic impairment, in patients on diuretic treatment, following major surgery which involved hypovolaemia, and particularly in the elderly.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2) In the elderly, as half-life of NSAIDs is longer, doses should be reduced (see section 4.2 “Posology and method of administration”).

During long-term treatment, monitoring of blood count and hepatic and renal function is recommended.

Skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, stevens-johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occuring in the majority of cases within the first treatment. Ethypharm Ketoprofen SR should be discontinued at the first appearence of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients with a previous history of photosensitivity or phototoxicity reactions should be carefully monitored.

Ketoprofen, as any other NSAID, may mask symptoms of an underlying infectious disease.

The use of ketoprofen as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ketoprofen should be considered.

Ethypharm Ketoprofen SR is a slow release formulation, therefore this treatment is not suitable when a quick onset of efficacy at the beginning of the treatment is required.

4.5 Interaction with other medicinal products and other forms of interaction

Certain substances or therapeutic classes have a potential to contribute to the occurrence of hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), heparins (of low molecular weight or non-fractionated), cyclosporin and tacrolimus, and trimethoprim.
The occurrence of hyperkalaemia may depend upon the existence of a combination of factors.
This risk is increased by combined administration of the above-named substances.

Concomitant administration of ketoprofen with the following products calls for strict monitoring of the patient’s clinical condition and laboratory values.

Combinations to be avoided:

- **Other NSAIDs (including salicylates at high doses):** increased risk of gastrointestinal ulcer and haemorrhage (due to additive synergic effects).

- **Oral anticoagulants:** increased risk of a haemorrhagic effect of the oral anticoagulant (due to inhibition of platelet function and damage to the gastroduodenal mucosa by NSAIDs).
If the combination can not be avoided, close clinical observation and monitoring of laboratory values are required.

- **Heparins:** (by the parenteral route): increased risk of haemorrhage (due to inhibition of platelet function and damage to the gastroduodenal mucosa by NSAIDs).
If the combination can not be avoided, it calls for close clinical observation (and monitoring of laboratory values for non fractionated heparins).

- **Lithium:** (reported with diclofenac, ketoprofen, indomethacin, phenylbutazone, piroxicam): elevation of the blood lithium levels, which may attain toxic levels (via reduced renal excretion of lithium).
If necessary, blood lithium levels should be closely monitored and the dosage of lithium adjusted during the combined treatment and after withdrawal of the NSAID.

- **Methotrexate (at doses above 15 mg/week):** Increased haematotoxicity of methotrexate (due to a reduction of renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding sites by NSAIDs).
Methotrexate should not be administered less than 12 hours before the start or after the end of a ketoprofen treatment.

- **Ticlopidine:** increased risk of haemorrhage (due to synergy of the inhibitory effects on platelet aggregation).
If the combination can not be avoided, close clinical observation and monitoring of laboratory values (including bleeding time) are required.

Combinations to be administered with precaution:

- **Diuretics, angiotensin converting enzyme inhibitors:** acute renal failure in dehydrated patients (reduced glomerular filtration due to decreased renal prostaglandin synthesis).
Additionally, the antihypertensive effect is reduced.
The patient should be hydrated and renal function monitored at the start of treatment.
- Corticosteroids increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Anti-coagulants: NSAIDSs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4)
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4)

- **Methotrexate at low doses (less than 15 mg/week):** increased haematotoxicity of methotrexate (due to a reduction of renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding sites).
Weekly monitoring of blood count is recommended during the first weeks of combined treatment.
Closer observation is necessary in the event of any (even mild) impairment of renal function and in elderly subjects.

- **Pentoxifylline:** increased risk of haemorrhage.
Clinical observation should be increased and bleeding time monitored more frequently.

- **Zidovudine:** risk of increased toxic effects on red blood cells (effect on the reticulocytes), with onset of severe anaemia eight days after the start of the NSAID treatment.
Full blood count and reticulocyte count are recommended eight to 15 days after the start of the NSAID treatment.

Combinations to be given due consideration:

- **Beta-blockers:** (by extrapolation from reported interaction with indomethacin): reduced antihypertensive effect (inhibition of vasodilator prostaglandins by NSAIDs).

- **Cyclosporin, tacrolimus:** risk of additive nephrotoxic effects, particularly in elderly subjects.

- **Intrauterine contraceptive device:** there is a controversial possibility of decreased efficacy of the intrauterine contraceptive device.

- **Thrombolytics:** increased risk of haemorrhage.

4.6 Pregnancy and lactation

Pregnancy:
No particular malformation effects have been reported in humans. However clinical experience of use in pregnancy is limited.

During the last trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (pulmonary hypertension with premature closure of the ductus arteriosus),
- renal dysfunction which may progress to renal failure with oligoamnios ;
- expose the mother and child, at the end of pregnancy, to possible prolongation of bleeding time ;
- inhibit uterine contractions and delay/prolong delivery.

Consequently, NSAIDs should be administered only if necessary during the first two trimesters of pregnancy. With the exception of very restricted obstetrical uses which require specialised monitoring, prescription of NSAIDs is contraindicated in the last trimester of pregnancy.

Lactation:
Since NSAIDs are excreted in breast milk, their use should be avoided during breast-feeding as a precautionary measure.

4.7 Effects on ability to drive and use machines

Patients should be warned that there is a possibility of dizziness, drowsiness and blurred vision.

4.8 Undesirable effects

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.
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The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease (see section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

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System organ class	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.01-0.1%)	Very rare/isolated reports (less 0.01%)
Blood and the lymphatic system disorders				Leukopenia, anaemia, thrombocytopenia, pancytopenia, agranulocytosis
Psychiatric disorders		Mood disorder		
Nervous system disorders		Headache, dizziness, drowsiness, somnolence		
Eye disorders				Blurred vision
Ear and labyrinth disorders		tinnitus		
Cardiac disorders			Congestive heart failure, hypertension	
Respiratory, thoracic and mediastinal disorders				Possible asthmatic attacks, particularly in patients with known allergy to acetylsalicylic acid and other NSAIDs
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, constipation, abdominal pain, gastrointestinal discomfort, gastralgia		Peptic ulcer, gastrointestinal bleeding, intestinal perforation	
Hepatobiliary disorders			Elevation of transaminases levels, hepatitis	
Skin and subcutaneous tissue disorders		Eruption, rash, pruritis	exacerbated chronic urticaria, alopecia	Bullous eruption (Steven Johnson, Lyell syndrome), Angioedema, erythema multiform, photosensitivity
Renal and urinary disorders			Abnormal renal function tests, acute renal failure, interstitial nephritis, nephrotic syndrome	Oedema (especially in patients with hypertension)
General disorders and administration site conditions				Anaphylactic shock

4.9 Overdose

In adults and adolescents, the main signs of overdose are headache, dizziness, drowsiness, nausea, vomiting, diarrhoea and abdominal pain. In serious intoxication, hypotension and respiratory depression and gastrointestinal haemorrhage have been observed.

The patient should be transferred immediately to a specialised hospital unit where symptomatic treatment should be instituted. Owing to the slow release characteristics of the product, ketoprofen will continue to be absorbed 16 hours after ingestion.
Evacuation of gastric content or administration of activated charcoal may be performed in order to reduce the absorption of ketoprofen.

There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivates: ATC Code: M01AE03

Ketoprofen is a non-steroidal anti-inflammatory agent of the propionic group, derived from arylcarboxylic acid.

It has the following properties:

- analgesic activity,
- antipyretic activity,
- anti-inflammatory activity,
- inhibition of platelet functions.

All these properties result from the reduction of prostaglandin synthesis by inhibition of the cyclo-oxygenase pathway.

5.2 Pharmacokinetic properties

Ethypharm Ketoprofen SR is a pH-independent prolonged-release form of ketoprofen intended for a once-a-day therapeutic dosage regimen.
The ketoprofen microgranules are dispersed gradually in the intestinal tract.

Absorption
After oral administration, ketoprofen is almost completely absorbed from the intestinal tract but undergoes first-pass metabolism.
A maximum plasma concentration of about 2.7 µg/ml is attained about 6 hours after administration of a dose of 200 mg; significant levels are found at the 24th hour. The product does not accumulate after repeated administration in the course of treatment.
The degree of absorption is not influenced by concomitant food intake.

Distribution
Ethypharm Ketoprofen SR capsule procures continuous, regular impregnation with ketoprofen.
Ketoprofen is 99% bound to plasma proteins.
Ketoprofen diffuses into synovial fluid, where levels higher than the serum concentrations are found more than 4 hours after oral administration.
It crosses the placental barrier.

Metabolism
Two processes are involved in the biotransformation of ketoprofen: one very minor (hydroxylation), and the other largely predominant (conjugation with glucuronic acid).

Less than 1% of the dose of ketoprofen administered is recovered in unchanged form in the urine, whereas the glucuronide metabolite accounts for about 65 to 75%.

Excretion
The drug is excreted as metabolites essentially by the urinary route. The rate of excretion is rapid, since 50% of the dose administered is eliminated in the first 6 hours, regardless of the route of administration. The prolonged-release form does not alter the renal excretion processes.
The half-life for the terminal elimination phase is about 7 hours.
In the 5 days after oral administration, 75 to 90% of the dose is excreted by the kidneys and 1 to 8% in the faeces.

Populations at risk
The elimination of ketoprofen is decreased in the elderly and the half-life is prolonged.
The half-life in patients with renal insufficiency increases with the severity of the impairment (see section 4.2 “Posology and method of administration”).

5.3 Preclinical safety data

In subchronic and chronic experiments, ketoprofen resulted in the formation of lesions and ulceration in the gastrointestinal tract and renal lesions in several animal species.

In several *in vitro* and *in vivo* mutagenicity tests ketoprofen had no significant positive effects. Long-term experiments in rats and mice showed no evidence of a carcinogenic potential of ketoprofen.

Experiments in various animal species showed no evidence of a teratogenic effect of ketoprofen.

From 6 mg/kg/day, ketoprofen resulted in an impairment of implantation and fertility in female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose,
Maize starch,
Eudragit NE30D (Polyacrylate Dispersion 30 %),
Eudragit RS30D (Poly [ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride] 1:2:0.1 (dispersion 30 %)),
Eudragit RL30D (Poly [ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride] 1:2:0.2 (dispersion 30 %)),
Triethyl citrate,
Colloidal anhydrous silica,
Talc

Capsule shell: titanium dioxide (E 171), gelatin.
Printing ink: shellac, potassium hydroxide, black iron oxide (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Prolonged-release capsule, hard in PVC/Aluminium blisters, pack of 10, 14, 15, 28, 30, 100.
Prolonged-release capsule, hard in Polypropylene container: 30, 100 capsules.
Not all pack sizes and container 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 SA
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F-78550 Houdan
FRANCE

8 MARKETING AUTHORISATION NUMBER

PA 549/9/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 February 2002
Date of last renewal: 16 April 2004

10 DATE OF REVISION OF THE TEXT

April 2007