



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

CPMP/1988/00

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) SUMMARY
INFORMATION ON THE OPINION PURSUANT**

TO ARTICLE 10 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED, FOR

KÉTOPROFÈNE ETHYPHARM LP¹

International Nonproprietary Name (INN): **ketoprofen**

BACKGROUND INFORMATION

In July 1999 Laboratoires Ethypharm SA submitted applications for Mutual Recognition of the Marketing Authorisation granted by the Competent Authority in France, acting as Reference Member State, for Kétoprofène Ethypharm LP 100 mg and 200 mg prolonged-release capsules, referring to essential similarity to two already authorised medicinal products in the EU.

Kétoprofène Ethypharm LP is a hard capsule filled with prolonged-release microgranules containing either 100 mg or 200 mg of the active substance ketoprofen, which is a non-steroidal anti-inflammatory drug (NSAID) marketed within the European Union for about 25 years under different tradenames.

Kétoprofène Ethypharm LP prolonged-release capsules are indicated in adults and adolescents over 15 years for symptomatic treatment of chronic inflammatory rheumatisms, such as rheumatoid arthritis and ankylosing spondylitis and osteoarthritis. Kétoprofène Ethypharm LP prolonged-release capsules are to be administered once a day.

The Mutual Recognition procedure started on 01 September 1999. The Concerned Member States were Austria, Belgium, Denmark, Finland, Germany Greece, Ireland, Italy, Luxembourg, Netherlands, Sweden and the United Kingdom. In the course of the Mutual Recognition procedure the Concerned Member State, Sweden considered that the authorisation of Kétoprofène Ethypharm LP may present a risk to public health and referred the matter to the CPMP on 30 November 1999 under article 10 of Directive 75/319/EEC as amended.

The public health risk raised by Sweden, and to be addressed by the applicant, was to document the safe use of ketoprofen in patients with severe heart failure. In addition, further issues to be addressed were justification of:

- maintenance of the last trimester of pregnancy as a contra-indication
- the reference product used in the bioequivalence study.
- the change of the method of manufacture of the test-product

The CPMP adopted accordingly a list of questions on 16 December 1999.

The Marketing Authorisation Holder provided written responses on 23 March 2000.

The CPMP having considered the written responses received from the Applicant, the Rapporteur/Co-Rapporteur's assessment reports and the comments from CPMP members was of the opinion that the public health risk issue raised by Sweden should not prevent the granting of a marketing authorisation provided that adequate amendments to the Summaries of Product Characteristics (SPC) are made, as

¹ Kétoprofène Ethypharm LP is the tradename in the Reference Member State. Other tradenames in the Concerned Member States are: Ethypharm Ketoprofen SR, Ketofen Retard, Ketoprofen Retard Scand Pharm, Arket XL

7 Westferry Circus, Canary Wharf, London E14 4HB, UK

Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13

E-mail: mail@emea.europa.eu <http://www.emea.eu.int>

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stated in the following overall summary of the scientific evaluation and the amended SPC attached (200 mg strength as a relevant example).

The CPMP adopted a positive opinion on 29 June 2000 recommending the granting of the Marketing Authorisation for Kétoprofène Ethypharm LP 100 mg and 200 mg prolonged-release hard capsules with amendments to the Summaries of Product Characteristics (SPC) of the Reference Member State.

On the basis of the Opinion adopted by the CPMP the European Commission issued a Decision on 27 December 2000.

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF KETOPROFENE ETHYPHARM LP

Ketoprofen is a non-steroidal anti-inflammatory substance (NSAID) which has been marketed within the European Union for about 25 years under different tradenames. Kétoprofène Ethypharm LP prolonged-release capsules are considered to be essentially similar to two already authorised medicinal products in the EU. Kétoprofène Ethypharm LP prolonged-release capsules are indicated in adults and adolescents over 15 years for symptomatic treatment of chronic inflammatory rheumatisms, such as rheumatoid arthritis and ankylosing spondylitis and osteoarthritis.

The main issue for arbitration was to document the safe use of ketoprofen in patients with severe heart failure. Further issues raised were justification of:

- maintenance of the last trimester of pregnancy as a contra-indication
- the reference product used in the bioequivalence study.
- the change of the method of manufacture of the test-product

Based on the assessment of the documentation submitted by the applicant, the following conclusions can be drawn:

Quality issues:

- The change of the manufacturing method between the test product and the industrial batches has been documented in an acceptable way. It is shown that regardless of the change from a five step coating into a two step coating process the performance and the specifications of the batches remain unchanged.

Clinical issues:

- The applicant has sufficiently demonstrated the identity of the reference products. The minor differences in capsule shell do not have an impact on the kinetics of release of ketoprofen and therefore do not influence clinical performance. In addition, a bioequivalence study performed by the applicant shows that the reference products are bioequivalent.
- Based on the published data available it cannot be demonstrated that the use of ketoprofen in patients with severe uncontrolled heart failure is safe. Although there are few or no alternatives to NSAIDs when anti-inflammatory effect is required in patients with the life threatening situation of severe uncontrolled heart failure, administration of NSAIDs may aggravate the situation. Thus, ketoprofen should be contraindicated in such patients.
- In addition, a warning should be added concerning treatment of patients with heart failure, to identify the risk of possible worsening of the condition and recommendation of monitoring of the patients.
- The reports provided by the applicant regarding the use of the product during the last trimester of pregnancy clearly demonstrate the associated risks. Therefore, 'last trimester of pregnancy should be maintained as a contra-indication.

GROUND FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- based on the published data available it cannot be demonstrated that the use of ketoprofen in patients with severe uncontrolled heart failure is safe. Therefore 'Severe uncontrolled heart failure' should be added in section 4.3 (Contra-indications)
- to strengthen the warning the sentence: "In patients with heart failure, worsening of the condition may occur due to sodium and fluid retention, particularly in the elderly. In these patients, close monitoring of cardiac and renal function is required. See also section 4.3 "Contra-indications". " should be added in section 4.4 (Special warnings and precautions for use)
- the following warning: "In the elderly, as half-life of NSAIDs are longer, doses should be reduced." should be added in section 4.4 (Special warnings and precautions for use)
- congestive heart failure should be added under section 4.8 (Undesirable effects)

the CPMP has recommended the amendment of the Summaries of Product Characteristics as set out in Annex III of the opinion.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

(200 mg as a relevant example)

1. NAME OF THE MEDICINAL PRODUCT

{Tradename of the product; See Annex II } 200 mg prolonged-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains ketoprofen 200 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release capsule, hard

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 200 mg, however 100 mg 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 100 mg 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 recurrent gastric or duodenal ulcer,
- active gastric or duodenal ulcer,
- severe hepatic failure,
- severe renal failure,
- severe uncontrolled heart failure
- gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding.

4.4 Special warnings and special precautions for use

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 haemorrhage or ulcers/perforations can occur at any time in the course of treatment and are not necessarily preceded by premonitory signs or restricted to patients with a history of such manifestations. The risk is relatively higher in elderly or fragile subjects, in those with low body weight, in patients with a platelet function disorder and in patients on anticoagulant or platelet aggregation inhibiting treatment (see section 4.5 “Interaction with other medicinal product and other form of interaction”).

In the event of gastrointestinal haemorrhage or ulcer, treatment should be discontinued immediately.

Ketoprofen should be administered with caution and under close observation in patients with a history of gastrointestinal disorders (e.g. ulcerative colitis, Crohn’s disease).

In patients with heart failure, worsening of the condition may occur due to sodium and fluid retention, particularly in the elderly. In these patients, close monitoring of cardiac and renal function is required. See also section 4.3 “Contra-indications”.

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.

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.

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.

{Tradename of the product} 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.
- **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

- Common gastrointestinal effects included: nausea, vomiting, diarrhoea, constipation, abdominal pain, gastrointestinal discomfort and gastralgia.
Other serious undesirable effects are peptic ulcer, gastrointestinal bleeding and intestinal perforation. Bleedings occur more frequently as the dose increases.
- Rare cases of renal system effects included: abnormal renal function tests, acute renal failure, interstitial nephritis, nephrotic syndrome. Rarely, especially in patients with hypertension, oedema can occur.
- Hepatic system: elevation of transaminase levels and rare cases of hepatitis may be observed.

- Cardiovascular system: congestive heart failure, hypertension
- Occasional cases of headaches, dizziness, drowsiness, somnolence, mood disorders and tinnitus may be observed.
- Hypersensitivity reactions:
 - rare cases of angioedema and anaphylactic shock,
 - eruption, rash, pruritis, exacerbated chronic urticaria,
 - possible asthmatic attacks, particularly in patients with known allergy to acetylsalicylic acid and other NSAIDs.
- Skin reactions: photosensitivity, alopecia, exceptionally bullous eruptions (Stevens-Johnson and Lyell syndrome) and erythema multiform.
- Some modifications in haematological parameters have been observed: moderate reduction in haemoglobin levels and a few cases of non serious leukopenia, anaemia, thrombocytopenia, pancytopenia and agranulocytosis.

Vision disorders: visual disturbances such as blurred vision.

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 derivatives: 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

{Tradename of the product} capsule 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

{Tradename of the product} 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 (Ammonio Methacrylate Copolymer Type B),
Eudragit RL30D (Ammonio Methacrylate Copolymer Type A),
triethyl citrate,
colloidal anhydrous silica,
talc

Capsule shell: titanium dioxide (E 171), gelatin, black iron oxide (E 172).
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

10 prolonged-release capsules in blister packs (PVC/Aluminium)
14 prolonged-release capsules in blister packs (PVC/Aluminium)
15 prolonged-release capsules in blister packs (PVC/Aluminium)
28 prolonged-release capsules in blister packs (PVC/Aluminium)
30 prolonged-release capsules in blister packs (PVC/Aluminium)
100 prolonged-release capsules in blister packs (PVC/Aluminium)

6.6 Instructions for use, handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

{Name and address of the Marketing Authorisation Holder; See Annex II}

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

**LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL
PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT/MARKETING AUTHORISATION
HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES**

ANNEX II

<u>Member State</u>	<u>Marketing Authorisation Holder/Applicant</u>	<u>Tradename</u>	<u>Strengths</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>	<u>Packaging</u>	<u>Package size</u>
Austria (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan - France	Ethypharm Ketoprofen SR	100 mg 200 mg	Prolonged-release capsules, hard	Oral use	PVC/Alu blister pack	14, 15, 28, 30 capsules
Belgium (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Kétoprophène Ethypharm LP	100 mg 200 mg	Prolonged release capsules, hard	Oral use	PVC/Alu Blister pack	14, 15, 28, 30 capsules
Denmark (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Ethypharm Ketoprofen SR	100 mg 200 mg	Prolonged release capsules, hard	Oral use	PVC/Alu Blister pack	14, 15, 28, 30 capsules
Finland (Concerned MS)	Merck Generics UK Ltd 12 Station Close, Potters Bar, Hertfordshire EN6 1TL - England	Ketofen Retard	100 mg 200 mg	Prolonged release capsules, hard	Oral use	PVC/Alu blister pack polyethylene closure	10, 30, 100 capsules
France (Reference MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Kétoprophène Ethypharm LP	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu blister pack	14, 15, 28, 30 capsules
Greece (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Ethypharm Ketoprofen SR	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu blister pack	14, 15, 28, 30 capsules
Ireland (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Ethypharm Ketoprofen SR	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu blister pack	14, 15, 28, 30 capsules
Italy (Concerned MS)	Ethypharm SR 17/21, rue Saint-Matthieu 78550 Houdan – France	Ethypharm Ketoprofen SR	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu blister pack	14, 15, 28, 30 capsules
Luxembourg (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Kétoprophène Ethypharm LP	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu Blister pack	14, 15, 28, 30- capsules
Netherlands (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Ethypharm Ketoprofen SR	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu Blister pack	14, 15, 28, 30 capsules
Sweden (Concerned MS)	Scand Pharm, Generics AB, Box 23033 (Ynglingagatan 14,5) 10435 Stockholm – Sweden	Ketoprofen Retard Scand Pharm	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu blister pack polypropylene container with polyethylene closure	100 capsules 30, 100 capsules
United Kingdom (Concerned MS)	Ethypharm SA 17/21, rue Saint-Matthieu 78550 Houdan – France	Arket XL	100 mg 200 mg	Prolonged release Capsules, hard	Oral use	PVC/Alu blister pack	14, 15, 28, 30 capsules