

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Enantyum 50 mg/2ml Solution for injection/infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 2 ml contains: dexketoprofen 50 mg (as dexketoprofen trometamol). Each ml of solution for injection contains dexketoprofen 25 mg (as dexketoprofen trometamol).

Excipients with known effects:

Each ampoule of 2 ml contains 200 mg ethanol (96 per cent) and 8.0 mg sodium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear and colourless solution.

pH (7.0-8.0)

Osmolarity (270-328 mOsmol/l)

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of acute pain of moderate to severe intensity, when oral administration is not appropriate such as post-operative pain, renal colic and low back pain.

4.2 Posology and method of administration

Posology

Adults

The recommended dose is 50 mg every 8 – 12 hours. If necessary, the administration can be repeated 6 hours apart. The total daily dose should not exceed 150 mg.

Enantyum solution for injection/infusion is intended for short term use and the treatment must be limited to the acute symptomatic period (no more than two days). Patients should be switched to an oral analgesic treatment when possible.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

In case of moderate to severe postoperative pain, Enantyum solution for injection/infusion can be used in combination with opioid analgesics, if indicated, at the same recommended doses in adults (see section 5.1).

Elderly

No dosage adjustment is generally necessary in elderly patients. However because of the physiological decline in renal function in elderly patients a lower dose is recommended in case of mild renal function impairment: 50 mg total daily dose (see section 4.4).

Hepatic impairment

The dosage should be reduced to 50 mg total daily dose in patients with mild to moderate (Child-Pugh score 5 - 9) hepatic impairment and hepatic function should be closely monitored (see section 4.4). Enantyum solution for injection/infusion should not be used in patients with severe hepatic dysfunction (Child-Pugh score 10 - 15) (see section 4.3).

Renal impairment

The dosage should be reduced to 50 mg total daily dose in patients with mildly impaired renal function (creatinine clearance 60 - 89 ml / min) (see section 4.4). Enantyum solution for injection/infusion should not be used in patients with moderate to severe renal dysfunction (creatinine clearance ≤ 59 ml / min) (see section 4.3).

Pediatric population

Enantyum has not been studied in children and adolescent. Therefore, safety and efficacy in children and adolescents have not been established and the product should not be used in children and adolescent.

Method of administration

Enantyum solution for injection/infusion can be administered either by intramuscular or by intravenous route:

- Intramuscular use: the content of one ampoule (2 ml) of Enantyum solution for injection/infusion should be administered by slow injection deep into the muscle.
- Intravenous use:
 - Intravenous infusion: the diluted solution, prepared as described in section 6.6, should be administered as a slow intravenous infusion, lasting 10 to 30 min. The solution must be always protected from natural daylight.
 - Intravenous bolus: if necessary, the content of one ampoule (2 ml) of Enantyum solution for injection/infusion can be administered in a slow intravenous bolus over no less than 15 seconds.

Instructions on handling the product:

When Enantyum solution for injection/infusion is administered intramuscularly or as intravenous bolus, the solution should be injected immediately after its removal from the coloured ampoule (see also sections 6.2 and 6.6).

For administration as intravenous infusion, the solution should be diluted aseptically and protected from natural daylight (see also section 6.3 and 6.6). For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Enantyum solution for injection/infusion must not be administered in the following cases:

- patients with hypersensitivity to the active substance, to any other NSAID, or to any of the excipients listed in section 6.1.
- patients in whom substances with a similar action (e.g. acetylsalicylic acid and other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema.
- known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates
- patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

- patients with active peptic ulcer/gastrointestinal haemorrhage or any history of gastrointestinal bleeding, ulceration or perforation.
- patients with chronic dyspepsia.
- patients who have other active bleeding or bleeding disorders.
- patients with Crohn's disease or ulcerative colitis.
- patients with severe heart failure.
- patients with moderate to severe renal dysfunction (creatinine clearance ≤ 59 ml/min).
- patients with severely impaired hepatic function (Child-Pugh score 10 - 15).
- patients with haemorrhagic diathesis and other coagulation disorders.
- patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- during the third trimester of pregnancy and lactation period (see section 4.6).

Enantyum solution for injection/infusion is contraindicated for neuraxial (intrathecal or epidural) administration due to its ethanol content.

4.4 Special warnings and precautions for use

Administer with caution in patients with a history of allergic conditions.

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

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

Gastrointestinal safety

Gastrointestinal 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 gastrointestinal events. When gastrointestinal bleeding or ulceration occurs in patients receiving Enantyum, the treatment should be withdrawn.

The risk of gastrointestinal 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.

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). These patients should commence treatment on the lowest dose available

As with all NSAIDs, any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with dexamethopfen. Patients with gastrointestinal symptoms or history of gastrointestinal disease should be monitored for digestive disturbances, especially gastrointestinal bleeding.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial 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 acetylsalicylic acid (see section 4.5).

Renal Safety

Caution should be exercised in patients with impairment of renal functions. In these patients, the use of NSAIDs may result in deterioration of renal function, fluid retention and oedema. Caution is also required in patients receiving diuretic therapy or those who could develop hypovolaemia as there is an increased risk of nephrotoxicity.

Adequate fluid intake should be ensured during treatment to prevent dehydration and possibly associated increased renal toxicity.

As with all NSAIDs, it can increase plasma urea nitrogen and creatinine. As with other inhibitors of prostaglandin synthesis, it can be associated with adverse effects on the renal system, which can lead to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure.

Elderly patients are more likely to be suffering from impaired renal function (see section 4.2).

Liver Safety

Caution should be exercised in patients with impairment of hepatic functions. As with other NSAIDs, it can cause transient small increases in some liver parameters, and also significant increases in SGOT and SGPT. In case of a relevant increase in such parameters, therapy must be discontinued.

Elderly patients are more likely to be suffering from impaired hepatic function (see section 4.2).

Cardiovascular and cerebrovascular safety

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate heart failure. Special caution should be exercised in patients with a history of cardiac disease, in particular those with previous episodes of heart failure as there is an increased risk of triggering heart failure, since fluid retention and oedema have been reported in association with NSAIDs therapy.

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). There are insufficient data to exclude such a risk for dexketoprofen.

Consequently, patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with dexketoprofen 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).

All non-selective NSAIDs can inhibit platelet aggregation and prolong bleeding time via inhibition of prostaglandin synthesis. The concomitant use of dexketoprofen and prophylactic doses of low molecular weight heparin in the postoperative period has been assessed in controlled clinical trials and no effect on coagulation parameters was observed. Nevertheless, patients who are receiving therapy that interferes with haemostasis, such as warfarin or other coumarins or heparins should be carefully monitored if dexketoprofen is administered (see Section 4.5).

Elderly patients are more likely to be suffering from impaired cardiovascular function (see section 4.2).

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. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Enantyum solution for injection/ infusion should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Other information

Particular caution is required in patients with:

- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- dehydration
- directly after major surgery

If the physician considers long-term dexketoprofen therapy to be necessary, hepatic and renal function and the blood count should be regularly checked.

Severe acute hypersensitivity reactions (anaphylactic shock, for example) have been observed on very rare occasions. Treatment must be discontinued at the first signs of severe hypersensitivity reactions following intake of Enantyum. Depending on the symptoms, any medically required procedures must be initiated by specialist healthcare professionals.

Patients with asthma combined with chronic rhinitis, chronic sinusitis, and/or nasal polyposis have a higher risk of allergy to acetylsalicylic acid and/or NSAIDs than the rest of the population. Administration of this medicinal product can cause asthma attacks or bronchospasm, particularly in subjects allergic to acetylsalicylic acid or NSAIDs (see section 4.3).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Enantyum in case of varicella.

Enantyum solution for injection/infusion should be administered with caution to patients suffering from haematopoietic disorders, systemic lupus erythematosus or mixed connective tissue disease.

As other NSAIDs, dexketoprofen can mask the symptoms of infectious diseases. In isolated cases an aggravation of soft tissue infections has been described in temporal connection with the use of NSAIDs. Therefore the patient is advised to consult a physician immediately if signs of a bacterial infection occur or worsen during therapy.

Each ampoule of Enantyum solution for injection/infusion contains 12.35 vol% ethanol (alcohol), i.e. up to 200 mg per dose equivalent to 5 ml beer or 2.08 ml wine per dose.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant and breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

This medicinal product contains less than 1 mmol sodium (23mg) per dose, i.e. essentially “sodium-free”.

Paediatric population

The safe use in children and adolescents has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions apply to non-steroidal antiinflammatory drugs (NSAIDs) in general:

Inadvisable combinations:

- Other NSAIDs (including cyclooxygenase-2 selective inhibitors) and high doses of salicylates (≥ 3 g/day):

administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect.

- Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4), due to the high plasma protein binding of dexketoprofen and the inhibition of platelet function and damage to the gastroduodenal mucosa. If the combination cannot be avoided, close clinical observation and monitoring of laboratory values should be carried out.
- Heparins: increased risk of haemorrhage (due to the inhibition of platelet function and damage to the gastroduodenal mucosa). If the combination cannot be avoided, close clinical observation and monitoring of laboratory values should be carried out.
- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Lithium (described with several NSAIDs): NSAIDs increase blood lithium levels, which may reach toxic values (decreased renal excretion of lithium). This parameter therefore requires monitoring during the initiation, adjustment and withdrawal of treatment with dexketoprofen.
- Methotrexate, used at high doses of 15 mg/week or more: increased haematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory agents in general.
- Hydantoines and sulphonamides: the toxic effects of these substances may be increased.

Combinations requiring precautions:

- Diuretics, ACE inhibitors, antibacterial aminoglycosides and angiotensin II receptor antagonists: Dexketoprofen may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e. g. dehydrated patients or elderly patients with compromised renal function), the coadministration of agents that inhibit cyclo-oxygenase and ACE inhibitors, angiotensin II receptor antagonists or antibacterial aminoglycosides may result in further deterioration of renal function, which is usually reversible. In case of combined prescription of dexketoprofen and a diuretic, it is essential to ensure that the patient is adequately hydrated and to monitor renal function at the start of the treatment (see section 4.4 Special warnings and special precautions for use).
- Methotrexate, used at low doses, less than 15 mg/week: increased haematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory agents in general. Weekly monitoring of blood count during the first weeks of the combination. Increased surveillance in the presence of even mildly impaired renal function, as well as in the elderly.
- Pentoxifylline: increased risk of bleeding. Intensify clinical monitoring and check bleeding time more often.
- Zidovudine: risk of increased red cell line toxicity via action on reticulocytes, with severe anaemia occurring one week after the NSAID is started. Check complete blood count and reticulocyte count one to two weeks after starting treatment with the NSAID.
- Sulfonylureas: NSAIDs can increase the hypoglycaemic effect of sulfonylureas by displacement from plasma protein binding sites.

Combinations needing to be taken into account:

- Beta-blockers: treatment with a NSAID may decrease their antihypertensive effect via inhibition of prostaglandin synthesis.
- Cyclosporin and tacrolimus: nephrotoxicity may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combination therapy, renal function has to be measured.
- Thrombolytics: increased risk of bleeding.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
- Probenecid: plasma concentrations of dexketoprofen may be increased; this interaction can be due to an inhibitory mechanism at the site of renal tubular secretion and of glucuronoconjugation and requires adjustment of the dose of dexketoprofen.
- Cardiac glycosides: NSAIDs may increase plasma glycoside concentration.
- Mifepristone: There is a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.
- Quinolone Antibiotics: Animal data indicate that high doses of quinolones in combination with NSAIDs can

increase the risk of developing convulsions.

- Tenofovir: concomitant use with NSAID can increase plasma urea nitrogen and creatinine, renal function should be monitored in order to control a potential synergic influence on renal function.
- Deferasirox: concomitant use with NSAIDs can increase the risk of gastrointestinal toxicity. Close clinical monitoring is required when deferasirox is combined with these substances.
- Pemetrexed: concomitant use with NSAIDs may decrease pemetrexed elimination, therefore caution should be made when administering higher doses of NSAIDs. In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs doses should be avoided for 2 days before and 2 days following pemetrexed administration.

4.6 Fertility, pregnancy and lactation

Enantyum solution for injection/infusion is contraindicated during third trimester of pregnancy and lactation (see section 4.3).

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. Nevertheless, animal studies with dexketoprofen haven't shown reproductive toxicity (see section 5.3). During the first and second trimester of pregnancy, dexketoprofen should not be given unless clearly necessary. If dexketoprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Breastfeeding

It is not known whether dexketoprofen is excreted in human milk. . Enantyum is contraindicated during breast-feeding (see section 4.3).

Fertility

As with other NSAIDs, the use of Enantyum 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 dexketoprofen should be considered.

4.7 Effects on ability to drive and use machines

Enantyum solution for injection/infusion may cause undesirable effects such as dizziness, visual disturbances or drowsiness. The ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in these cases.

4.8 Undesirable effects

The adverse events reported as at least possibly related with dexketoprofen in clinical trials, as well as the adverse reaction reported after the marketing of Enantyum 50mg/2ml solution for injection/infusion are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/100)	Very rare (<1/10000)
Blood and lymphatic system disorders		Anaemia		Neutropenia, thrombocytopenia
Immune system disorders			Laryngeal oedema	Anaphylactic reaction, including anaphylactic shock
Metabolism and nutrition disorders			Hyperglyceaemia, hypoglyceaemia, hypertriglyceridaemia, anorexia	
Psychiatric disorders		Insomnia		
Nervous system disorders		Headache, dizziness, somnolence	Paraesthesia, syncope	
Eye disorders		Blurred vision		
Ear and labyrinth disorders			Tinnitus	
Cardiac disorders			Extrasystole, tachycardia	
Vascular disorders		Hypotension, flushing	Hypertension, thrombophlebitis superficial	
Respiratory, thoracic and mediastinal disorders			Bradypnoea	Bronchospasm, dyspnoea
Gastrointestinal disorders	Nausea, vomiting	Abdominal pain,dyspepsia, diarrhoea, constipation, haematemesis, dry mouth	Peptic ulcer, peptic ulcer haemorrhage or peptic ulcer perforation (see section 4.4)	Pancreatitis
Hepatobiliary disorders			Hepatocellular injury	
Skin and subcutaneous tissue disorders		Dermatitis, pruritus, rash, sweating increased	Urticaria, acne	Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, facial oedema, photosensitivity

				reaction
Musculoskeletal and connective tissue disorders			Muscle stiffness, joint stiffness, muscle cramp, back pain	
Renal and urinary disorders			Acute renal failure, polyuria, renal pain, ketonuria, proteinuria	Nephritis or nephrotic syndrome
Reproductive system and breast disorders			Menstrual disorder, prostatic disorder	
General disorders and administration site conditions	Injection site pain, injection site reaction, including inflammation, bruising or haemorrhage	Pyrexia, fatigue, pain, feeling cold	Rigors, peripheral oedema	
Investigations			Liver function test abnormal	

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal 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.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

As with other NSAIDs the following undesirable effects may appear: aseptic meningitis, which might predominantly occur in patients with systemic lupus erythematosus or mixed connective tissue disease; and haematological reactions (purpura, aplastic and haemolytic anaemia, rarely agranulocytosis and medullar hypoplasia).

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare).

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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The symptomatology following overdose is not known. Similar medicinal products have produced gastrointestinal (vomiting, anorexia, abdominal pain) and neurological (somnolence, vertigo, disorientation, headache) disorders. In case of accidental or excessive intake or administration, immediately institute symptomatic therapy. Dexketoprofen trometamol may be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: propionic acid derivatives

ATC code: M01AE17

Dexketoprofen trometamol is the tromethamine salt of S-(+)-2-(3-benzoylphenyl)propionic acid, an analgesic, antiinflammatory and antipyretic medicinal product, which belongs to the non-steroidal anti-inflammatory group of drugs (M01AE).

Mechanism of action

The mechanism of action of non-steroidal antiinflammatory medicinal products is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway.

Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG₂ and PGH₂, which produce prostaglandins PGE₁, PGE₂, PGF₂ α and PGD₂ and also prostacyclin PGI₂ and tromboxanes (TxA₂ and TxB₂). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as kinins, causing an indirect action which would be additional to the direct action.

Pharmacodynamic effects

Dexketoprofen has been demonstrated to be an inhibitor of COX - 1 and COX -2 activities in experimental animals and humans.

Clinical efficacy and safety

Clinical studies performed on several pain models demonstrated effective analgesic activity of dexketoprofen.

The analgesic efficacy of intramuscular and intravenous dexketoprofen in the management of moderate to severe pain was investigated in several surgical pain models (orthopaedic and gynaecologic/abdominal surgery) as well as in musculo-skeletal pain (acute low back pain model) and renal colic.

In the studies performed, the onset of analgesic effect was rapid, and within the first 45 minutes the peak analgesic effect occurred. Duration of analgesic effect after the administration of 50 mg of dexketoprofen is usually 8 hours.

Clinical studies in postoperative pain management have demonstrated that Enantyum solution for injection/infusion when used in combination with opioids significantly reduced opioid consumption. In the post-operative pain studies where patients received morphine by a patient controlled analgesia device, patients treated with dexketoprofen required significantly less morphine (between 30 – 45% less) than patients in the placebo group.

5.2 Pharmacokinetic properties

Absorption

After intramuscular administration of dexketoprofen trometamol to humans, the peak concentrations are reached at 20 minutes (range 10 to 45 min). For 25 to 50 mg single doses the area under the curve has been shown to be dose proportional after both intramuscular and intravenous administration.

Distribution

As with other medicinal products with a high plasma protein binding (99%), the volume of distribution has a mean value below 0.25 l/kg. The distribution half-life was approximately 0.35 hours and the elimination half-life ranged

between 1 – 2.7 hours.

In multiple-dose pharmacokinetic studies, it was observed that C_{max} and AUC after the last intramuscular or intravenous administration were not different from that obtained following a single dose, indicating that no drug accumulation occurs.

Biotransformation and elimination

After administration of dexketoprofen trometamol only the S-(+) enantiomer is obtained in urine, demonstrating that no conversion to the R-(-) enantiomer occurs in humans

The main elimination route for dexketoprofen is glucuronide conjugation followed by renal excretion.

Elderly

In healthy elderly subjects (65 years and older), exposure was significantly higher than in young volunteers after single and repeated oral doses (up to 55%) whereas there was no statistically significant difference in peak concentrations and time to reach peak concentration. The mean elimination half-life was prolonged after single and repeated doses (up to 48%), and the apparent total clearance was reduced.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and immunopharmacology. The chronic toxicity studies carried out in mice and monkeys gave a No Observed Adverse Effect Level (NOAEL) at doses 2 fold higher than maximum recommended human dose. In monkey, at higher doses, the main adverse effect observed were blood in faeces, decreased body weight gain and, at the highest dose, erosive gastrointestinal lesions. These effects appeared at doses determining a drug exposure 14-18 fold higher than that at the maximum recommended human dose.

There are not studies on the carcinogenic potential in animals.

As it has been recognised for the whole pharmacological class of NSAIDs, dexketoprofen may cause changes of embryo-foetal survival in animal models, both indirectly, through the gastrointestinal toxicity on the pregnant mothers, and directly upon the development of the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96 per cent)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Enantyum solution for injection/infusion must not be mixed in a small volume (e.g. in a syringe) with solutions of dopamine, promethazine, pentazocine, pethidine or hydroxyzine, as this will result in a precipitation of the solution.

The diluted solutions for infusion obtained as stated in Section 6.6 must not be mixed with promethazine or pentazocine.

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

4 years.

After dilution according to directions given in Section 6.6., the diluted solution, provided it is adequately protected from natural daylight, has been shown to be chemically stable for 24 hours, when stored at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect it from the light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass coloured ampoules containing 2 ml of solution for injection/infusion.

Packs containing: 1, 5, 6, 10, 20, 50 or 100 ampoules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Enantyum solution for injection/infusion has shown to be compatible when mixed in small volumes (e.g. in a syringe) with injectable solutions of heparin, lidocaine, morphine and theophylline.

For administration as intravenous infusion the content of one ampoule (2 ml) of Enantyum solution for injection/infusion should be diluted in a volume of 30 to 100 ml of normal saline, glucose or Ringer lactate solution. The solution should be diluted aseptically and protected from natural daylight (see also section 6.3). The diluted solution is a clear solution.

Enantyum solution for injection/infusion, diluted in a volume of 100 ml of normal saline or glucose solution has shown to be compatible with the following medicinal products: dopamine, heparin, hydroxyzine, lidocaine, morphine, pethidine and theophylline.

No sorption of the active ingredient has been found when diluted solutions of Enantyum solution for injection/infusion have been stored in plastic bags or administration devices made of Ethyl Vinyl Acetate (EVA), Cellulose Propionate (CP), Low Density PolyEthylene (LDPE) and PolyVinyl Chloride (PVC).

Enantyum solution for injection/infusion is for single use only and any unused solution should be discarded. Prior to administration, the solution should be inspected visually to make sure it is clear and colourless: it should not be used if particulate matter is observed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratorios Menarini S.A.
Alfonso XII, 587-08918
Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER

PA0901/001/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2004
Date of last renewal: 08 July 2007

10 DATE OF REVISION OF THE TEXT

April 2018