SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revafen 50 mg/2 ml I.M./I.V. Ampoule Containing Solution for Injection and Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance: Each 2 ml ampoule contains 73.8 mg dexketoprofen trometamol equivalent to 50 mg dexketoprofen.

Excipients: Each 2 ml ampoule contains;
Ethanol (96%) 200mg
Sodium Chloride 8mg
Sodium Hydroxide for pH adjustment
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection and infusion
Clear and colorless solution pH (6.5-8.5)
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 /administrationfrequency and duration

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

REVAFEN 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, REVAFEN can be used in combination with opioid analgesics,if indicated, at the same recommended doses in adults (see section 5.1).

Method of administration:
REVAFEN can be administered either by intramuscular or by intravenous route.

I.M. administration:
The content of one ampoule (2 ml) of REVAFEN has to be administered by slow injection deep into the muscle.

I.V. administration:
I.V. 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.
I.V.bolus:If necessary, the content of one ampoule (2 ml) of REVAFEN can be administered in a slow intravenous bolus over no less than 15 seconds.

Instructions on handling the product:
When REVAFEN is administered intramuscularly or as intravenous bolus, the solution has to 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 must be diluted aseptically and protected from natural daylight (see also section 6.3 and 6.6).

Additional information for special populations:

Renal failure:
The dosage has to be reduced to 50 mg total daily dose in patients with mildly impaired renal function (creatinine clearance 50-80 ml / min) (see section 4.4). REVAFEN should not be used in patients with moderate to severe renal dysfunction (creatinine clearance lower than 50 ml / min) (see section 4.3).

Hepatic failure:
The dosage has t 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). REVAFEN should not be used in patients with severe hepatic dysfunction (Child-Pugh score 10 - 15) (see section 4.3).

Pediatric population:

REVAFEN has not been studied in children and adolescents. Therefore the safety and efficacy in children and adolescents have not been established and the product should not be used in patients younger than 18 years.

Geriatric population:
The elderly are at increased risk for the serious consequences of adverse reactions. If it is considered necessary to use NSAIDs, the lowest effective dose should be used as soon as possible. The patient should be monitored regularly for bleeding during NSAID therapy. Due to the physiologic regression of renal function in elderly patients, a lower dose (total daily dose of 50 mg) is recommended if the kidney function is slightly impaired (see section 4.4).

4.3. Contraindications

REVAFEN must not be administered in the following cases:

- Patients with hypersensitivity to the dexketoprofen, to any other NSAID, or to any of the excipients.
- Patients with the history ofhypersensivity reaction ibuprofen, acetylsalicylic acid and other NSAIDs (e.g. asthma, non-infective rhinitis, angioedema or urticaria)
- Patients with active peptic ulcer/bleeding or repeating peptic ulcer/bleeding (proven ulcers or bleeding event occurring at two or more and different times) or patients with a history of chronic dyspepsia.
- Patients with gastrointestinal bleeding or any other active bleeding or bleeding disorders.
- Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Patients with Crohn's disease or ulcerative colitis.
- Patients with a history of bronchial asthma.
- Patients with severe heart failure.
- Patients with moderate or severe renal dysfunction (creatinine clearance ≤50 ml/min).
- Patients with severely impaired hepatic function (Child-Pugh score 10 - 15).
- Patients with haemorrhagic diathesis and other coagulation disorders.
- During the third trimester of pregnancy andlactation period (see section 4.6).

REVAFEN is contraindicated for neuraxial (intrathecal or epidural) administration due to its ethanol content.

4.4. Special warnings and special precautions for use

The safety and efficacy in children and adolescents have not been established.

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

The use of REVAFEN 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 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 REVAFEN, 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 older people.

The older people:The older people 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.

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).

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 dexketoprofentrometamol. Patients with gastrointestinal symptoms or history of gastrointestinal disease should be monitored for digestive disturbances, especially gastrointestinal bleeding.

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).

All non-selective NSAIDs can inhibit platelet aggregation and prolong bleeding time via inhibition of prostaglandin synthesis. The concomitant use of dexketoprofentrometamol 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 dexketoprofentrometamol is administered (see Section 4.5).

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 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 dexketoprofentrometamol.

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

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue diseases, the risk of aseptic meningitis may be increased (see Section 4.8).

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 Section 4.8). 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. REVAFEN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

As in all NSAIDs, dexketoprofentrometamol may increase plasma urea nitrogen and creatinine.

Cardiovascular, Renal and Hepatic Disorder:

Administration of NSAIDs causes a dose-dependent decrease in prostaglandin formation and initiates renal failure. Patients who are at the highest risk of this reaction are impaired renal function, those with heart disease, those with liver dysfunction, diuretic users and elderly individuals. Renal function should be monitored in these patients (see Section 4.3).

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.

Older patients are more likely to be suffering from impaired renal, cardiovascular and hepatic functions (see section 4.2).

REVAFEN 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 REVAFEN contains 200 mg of ethanol equivalent to 5 ml beer or 2.08 ml wine per dose. Harmful for people suffering from alcoholism.

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

This medicinal product contains less than 1 mmol per dose (23 mg) of sodium. This should be considered for patients with a controlled sodium diet.

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:

- The use of two or more NSAIDs (including acetylsalicylic acid) should be avoided as this may increase the risk of adverse effects (see Section 4.4).
- 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 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 orelderly 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).
- 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.
- Pentoxyfylline: 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 can exacerbate heart failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.
- Mifepristone: Because of a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone, NSAIDs should not be used for 8-12 days after mifepristone administration.
- Quinolone: Animal data indicate that high doses of quinolones in combination with NSAIDs can increase the risk of developing convulsions.

Additional information for special populations:

Pediatric population:

REVAFEN has not been studied in children and adolescents. Therefore the safety and efficacy in children and adolescents have not been established and the product should not be used in patients younger than 18 years.

4.6 Pregnancy and lactation

General advice

Pregnancy Category C

Women with child-bearing potential / Contraception

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 aprostaglandin 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 dexketoprofentrometamol haven't shown reproductive toxicity (see section 5.3).Women with childbearing potential should apply appropriate birth control.

Pregnancy

REVAFEN is contraindicated in the third trimester of pregnancy.

During the first and second trimester of pregnancy, dexketoprofentrometamol should not be given unless clearly necessary. If dexketoprofentrometamol 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 ductusarteriosus 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.

Lactation

REVAFEN is contraindicated during lactation.

It is not known whether or not Dexketoprofen is excreted in breast milk, although few studies have been performed so far, .NSAIDs can be seen in very low concentrations in breast milk.

Fertility

As with other NSAIDs, the use of dexketoprofentrometamol 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 dexketoprofentrometamol should be considered. During the first and second trimester of pregnancy, dexketoprofentrometamol should not be given unless clearly necessary.

4.7 Effects on ability to drive and use machines

After taking the NSAIDs, undesirable effects such as dizziness, drowsiness, fatigue and visual impairment are possible. Affected patients should not drive or use machines.

4.8 Undesirable effects

The adverse events reported as at least possibly related with dexketoprofen trometamol in clinical trials, as well as the adverse reaction reported after the marketing of parenteral dexketoprofen 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				Anaphylactic reaction, 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
Hepatobiliarydisorders			Hepatitis	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			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 (laboratory tests)			Liver function test abnormal	

Gastrointestinal: 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. Pancreatitis has rarely been reported.

Hypersensitivity: Hypersensitivity reactions have been reported after treatment with NSAIDs. These include: (a) non-specific allergic reactions and anaphylaxis; (b) respiratory reactions involving asthma, severe asthma, bronchospasm or dyspnea; or (c) various types of rashes, itching, urticaria, purpura, angioedema and more rarely, exfoliative and bullous dermatoses. (including epidermal necrolysis and erythema multiforme).

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 haemolyticanaemia, rarely agranulocytosis and medullar hypoplasia).

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

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).

Other adverse reactions reported with lower frequency include:

Kidney: Nephrotoxicity in various forms including interstitial nephrite, nephrotic syndrome and renal failure.

Liver: Abnormal liver function, hepatitis and jaundice.

Neurological and special sensations: Reports of aseptic meningitis such as visual disturbances, optic neuritis, headache, paresthesia, neck stiffness, headache, nausea, vomiting, fever or disorientation. (see section 4.4), depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise-fatigue, fatigue and dizziness.

Hematologic: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia and hemolytic anemia.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare) have been reported. Sensitivity to light.

4.9 Overdose

Dexketoprofentrometmol overdose symptoms are unknown. The following are the symptoms observed in general with NSAIDs:

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhea, disorientation, excitation, coma, dizziness, giddiness, tinnitus, fainting, and sometimes convulsions. Acute renal failure and liver damage are likely to occur in significant intoxication cases.

b) Therapeutic measures

Symptomatic treatment should be performed urgently according to the patient's clinical condition in case of accidental or excessive intake.

Good urine output should be ensured.

Kidney and liver functions should be closely monitored.

Patients should be kept under observation for at least four hours after taking potentially toxic amounts of medication.

Common or long-term convulsions should be treated with intravenous diazepam.

Depending on the patient's clinical condition, other measures may be considered. Dexketoprofentrometamol can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical group: Propionic acid derivative

ATC code: M01AE17

Dexketoprofentrometamol the tromethamine salt of S - (+) - 2- (3-benzoylphenyl) propionic acid is an analgesic, antiinflammatory and antipyretic drug included in the non-steroidal antiinflammatory drug (NSAID) group.

The mechanism of action of dexketoprofentrometamol is related to inhibition of prostaglandin synthesis by inhibition of cyclooxygenase pathway.

In particular, the conversion of arachidonic acid to PGE1, PGE2, PGF2α and PGD2 prostaglandins as well as cyclic endoperoxides producing PGI2 prostacyclin and thromboxanes (TxA2 and TxB2) is inhibited to PGG2 and PGH2. In addition, inhibition of the synthesis of prostaglandins could affect other inflammation mediators suchas kinins, causing an indirect action which would be additional to the direct action.

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

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

The analgesic efficacy of intramuscular and intravenous dexketoprofentrometamol 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, the analgesic effect started rapidly and reached its highest level within the first 45 minutes. The analgesic effect time after ingestion of 50 mg dexketoprofen is usually 8 hours.
Clinical studies of postoperative pain have demonstrated that REVAFEN 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 IM is given by Dexketoprofentrometamol, the peak concentration is reached in 20 minutes (between 10 and 45 minutes). For a single dose of 25 to 50 mg, the area under the curve (AUC) has been shown to be proportional to the dose after both IM and IV use.

In multi-dose pharmacokinetic studies, the $C_{max}$and AUC values after the last IM or IV injection were not different from those obtained after taking a single dose. This shows that there is no accumulation of drugs in the body.

Distribution:

As for other drugs that bind highly to plasma proteins (99%), the mean value of the dispersion volume is less than 0.25 L / kg. The distribution half-life is approximately 0.35 hours.

Biotransformation:

Obtaining only the S - (+) enantiomer in urine after administration of dexketoprofentrometamol indicates that the S - (+) enantiomer in humans does not turn into the R - (-) enantiomer.

Elimination:

The elimination half-life is between 1-2.7 hours. Dexketoprofen's major elimination pathway is renal excretion following glucuronide conjugation.

Linearity / Nonlinear state:

Dexketoprofentrometamol shows linear pharmacokinetics with a dose-dependent increase during systemic exposure following intramuscular or intravenous administration.

Characteristics of patients

Elderly:

The duration of drug stay in healthy elderly individuals (65 years and over) in single and repeated oral doses is significantly higher than in young volunteers (up to 55%). However, there is no statistically significant difference in peak concentrations and time to reach peak concentrations. After single and repeated doses, the mean elimination half-life is extended (up to 48%) and the total clearance decreases.

5.3 Preclinical safety data

Preclinical data based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and immunopharmacology revealed no special hazard for humans in addition to those already mentioned in other sections of the SPC. The chronic toxicity studies carried out in mice and monkeys gave a No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day. The main adverse effect observed at high doses was gastrointestinal erosions and ulcers in a dose related manner.

As it has been recognised for the whole pharmacological class of NSAIDs, dexketoprofentrometamol 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

5.1 List of excipients

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

6.2 Incompatibilities

REVAFEN, 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

24 months

Diluted solution stored according to the instructions given in section 6.6 and stored sufficiently protected from daylight has been shown to be chemically stable at 25 ° C for 24 hours.

Microbiological aspects of the product should be used immediately after dilution.

6.4 Special precautions for storage

Store at room temperature below 25 ° C, protect from light. Store the ampoules in their original carton boxes.

6.5 Nature and contents of container

2 ml amber type I glass ampoules in carton box,
6 pcs in one pack.

6.6 Instructions for use and handling and disposal

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

For administration as intravenous infusion the content of one ampoule (2 ml) of REVAFEN 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.

REVAFEN, 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 REVAFEN 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).

REVAFEN 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.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

2016-102

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17.02.2016
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

17.02.2016