Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Morsadex 50 mg/2 ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains dexketoprofen trometamol corresponding to 25 mg of dexketoprofen.
One ampoule (2 ml) contains dexketoprofen trometamol corresponding to 50 mg of dexketoprofen.

Excipients with known effect
Each ampoule contains 200 mg ethanol (96 %) and 8.0 mg sodium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless solution, free from visible particles.
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.

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

Paediatric population
Morsadex has not been studied in children and adolescents. Therefore the safety and efficacy of Morsadex in children and adolescents have not been established and the medicine should not be used in children and adolescents.

Elderly
No dosage adjustment is generally necessary in older 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 dysfunction

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). Morsadex should not be used in patients with severe hepatic dysfunction (*Child-Pugh* score 10-15) (see section 4.3).

Renal dysfunction
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). Morsadex should not be used in patients with moderate to severe renal dysfunction (creatinine clearance ≤59 ml / min) (see section 4.3).

Method of administration
Morsadex can be administered either by intramuscular or by intravenous route:
- Intramuscular use: the content of one ampoule (2 ml) of Morsadex 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 Morsadex can be administered in a slow intravenous bolus over no less than 15 seconds.

Instructions on handling the product
When Morsadex is administered intramuscularly or as intravenous bolus, the solution should be injected immediately after its removal from the 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

Morsadex must not be administered in the following cases:
- patients with hypersensitivity to the active substance 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 angioedema;
- known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates;
- patients with 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).

Morsadex 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 Morsadex 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 Morsadex, 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 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 dexketoprofen trometamol. 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 medicines 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 aspirin) (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.
Older 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.
Older 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 congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. 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.

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 trometamol.

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 trometamol 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 trometamol 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 trometamol is administered (see section 4.5).

Older 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. Morsadex 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 Morsadex. 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 Morsadex in case of varicella.

Morsadex 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.

Dexketoprofen trometamol, like other NSAIDs may reduce female fertility, so it is not recommended for women planning to become pregnant. In women who have difficulties with conception or undergoing investigation of infertility, should be considered discontinuation of dexketoprofen trometamol. Dexketoprofen should not be used in the first and second trimester of pregnancy, unless it is absolutely necessary.
Paediatric population
The safe use in children and adolescents has not been established.

Excipients
Each ampoule of Morsadex contains 200 mg of ethanol 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 (23 mg) per dose, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions apply to non-steroidal anti-inflammatory drugs (NSAIDs) in general.

Inadvisable combinations:
- Other NSAIDs, including 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 anti-inflammatory 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).
- Methotrexate, used at low doses, less than 15 mg/week: increased haematological toxicity of methotrexate via a decrease in its renal clearance by anti-inflammatory 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 may increase plasma glycoside concentration.
- 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 Antibiotics: Animal data indicate that high doses of quinolones in combination with NSAIDs can increase the risk of developing convulsions.

4.6 Fertility, pregnancy and lactation

Morsadex 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. From the 20th week of pregnancy onward, dexketoprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. During the first and second trimester of pregnancy, dexketoprofen trometamol should not be given unless clearly necessary. If dexketoprofen trometamol 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. Antenatal monitoring for oligohydramnios should be considered after exposure to dexketoprofen for several days from gestational week 20 onward. Dexketoprofen should be discontinued if oligohydramnios is found.

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

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

Breast-feeding

It is not known whether dexketoprofen is excreted in human milk.

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

4.7 Effects on ability to drive and use machines

Morsadex has minor or moderate influence on the ability to drive and use machines due to the possibility of dizziness or drowsiness.

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 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			Hyperglycaemia, 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			Hepatitis, jaundice	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			Menstrual disorder, prostatic disorder	

breast disorders				
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	

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) 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, Website: www.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 according to the patient's clinical condition.
Dexketoprofen trometamol may be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, propionic acid derivatives ATC code: M01AE17

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

Mechanism of action
The mechanism of action of non-steroidal anti-inflammatory 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, PGF2α 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 trometamol.

The analgesic efficacy of intramuscular and intravenous dexketoprofen trometamol 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 Morsadex 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

Absorbtion
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 medicine accumulation occurs.
Biotransformation and eliminiation
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

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 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, dexketoprofen trometamol 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

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

Water for injections

6.2 Incompatibilities

Morsadex 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

5 years.

Chemical and physical in-use stability has been demonstrated in 0.9 % sodium chloride, 5 % glucose and Ringer lactate solution for 18 hours at 25 °C and at 2-8 °C, provided it is adequately protected from natural daylight.
From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light. Do not freeze.

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

6.5 Nature and contents of container

Type I amber glass ampoules of 2 ml.

Pack size: 1, 5, 6, 25 or 100 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Morsadex 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 Morsadex should be diluted in a volume of 30-100 ml of 0.9 % sodium chloride, 5 % 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.

Morsadex diluted in a volume of 100 ml of 0.9 % sodium chloride or 5 % 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 Morsadex for 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).

Morsadex 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

AS Kalceks
Krustpils iela 71E
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA2165/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th December 2017
Date of last renewal: 27th November 2022

10 DATE OF REVISION OF THE TEXT

November 2022