SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
SOLKET “80 mg powder for oral solution”

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
A bipartite sachet contains:
Active substance: ketoprofen lysine salt 80 mg equal to 50 mg of ketoprofen
Excipients with known effects: sorbitol

For the full list of excipients, see paragraph 6.1.

3. PHARMACEUTICAL FORM
Powder for oral solution

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults: symptomatic treatment of inflammatory states associated to pain such as: rheumatoid arthritis, ankylosing spondylitis, painful arthrosis, extra-articular rheumatism, Post-traumatic flogosis, painful inflammatory diseases in dentistry, otorhinolaryngology, urology and pneumology.
Children: symptomatic and short-term treatment of inflammatory states associated to pain, even accompanied by pyrexia, such as those affecting osteoarticular system, post-surgery pain and otitis.

4.2 Posology and method of administration
Adults: one 80 mg sachet (whole dose) three times daily with meals.
The maximum daily dose is 200 mg ketoprofen, corresponding to 320 mg ketoprofen lysine salt. The risk-benefit ratio should be carefully considered before starting treatment with the 200 mg daily dose of ketoprofen, and higher doses are not recommended (see also section 4.4).

Special populations
Children aged 6 to 14 years: half a 40 mg sachet (half dose) three times daily with meals.
Solket 80 mg powder for oral solution is contraindicated in children under 6 years of age (see section 4.3)
Elderly: dosage should be carefully determined by the physician, who should consider a possible reduction in the above dosages (see section 4.4).
Patients with hepatic impairment: it is recommended that therapy be instituted at the lowest daily dosage (see section 4.4).
Patients with mild or moderate renal impairment: it is recommended to reduce the initial dose and practice maintenance therapy with the lowest effective dose. Individualized adjustments may be considered only after establishing good tolerability of the drug. Monitor diuresis volume and renal function (see section 4.4).

Solket should not be used in patients with severe hepatic and renal dysfunction (see section 4.3).
The lowest effective dose should be used for the shortest period necessary to relieve symptoms (see section 4.4).

Instructions on sachet use: opening the sachet along the line indicated "half dose" yields a 40 mg dose. Opening the sachet along the line indicated "full dose" yields an 80 mg dose. Pour the contents of a sachet or half sachet into half a glass of water and stir.

4.3 Controindications
Solket should not be administered in the following cases:
- Hypersensitivity to the active ingredient, other nonsteroidal anti-inflammatory drugs (NSAIDs) or any of the excipients listed in section 6.1.
- In patients with a history of hypersensitivity reactions such as bronchospasm, asthma attacks, acute rhinitis, nasal polyps, urticaria, angioneurotic edema, or other allergic-type reactions to ketoprofen or substances with similar mechanism of action (e.g., acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs, NSAIDs). Severe anaphylactic reactions, rarely fatal, have been observed in these patients (see section 4.8).
- Patients with prior bronchial asthma.
- Severe heart failure.
- Active peptic ulcer/hemorrhage, or history of recurrent peptic ulcer/hemorrhage (two or more distinct, proven episodes of bleeding or ulceration).
- History of gastrointestinal bleeding, ulceration or perforation, or chronic dyspepsia.

- History of gastrointestinal bleeding or perforation resulting from prior NSAID therapy.
- Leukopenia and thrombocytopenia.
- Crohn's disease or ulcerative colitis.
- Gastritis.
- Severe liver failure (cirrhosis of the liver, severe hepatitis).
- Severe renal failure.
- Hemorrhagic diathesis and other coagulation disorders, subjects with hemostatic disorders.
- During intensive diuretic therapy.
- Third trimester of pregnancy and lactation (see section 4.6).
- Children younger than 6 years of age.

4.4 Special warnings and precautions for use

Warnings

Adverse effects can be minimized by using the lowest effective dose for the shortest possible duration of treatment needed to control symptoms (see section 4.2 and the sections below on gastrointestinal and cardiovascular risks).
Concomitant use of Ketoprofen lysine salt with other NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.
In the elderly and in patients with a history of ulceration, especially if complicated by bleeding or perforation (see section 4.3), the risk of gastrointestinal bleeding, ulceration, or perforation is higher with increased doses of NSAIDs. These patients should start treatment with the lowest available dose. Concomitant use of protective agents (misoprostol or proton pump inhibitors) should be considered for these patients and also for patients taking low doses of aspirin or other medications that may increase the risk of gastrointestinal events (see below and section 4.5).
Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the early stages of treatment.
Caution should be exercised in patients taking concomitant medications that could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, or antiplatelet agents such as aspirin (see section 4.5).

Elderly: elderly patients have an increased frequency of adverse reactions to NSAIDs, especially bleeding and gastrointestinal perforations, which can be fatal (see paragraph 4.2).

Children: gastrointestinal bleeding, occasionally severe, and ulceration have been reported in some pediatric patients treated with ketoprofen lysine salt (see section 4.8); therefore, the product should be administered under close supervision of the physician, who should evaluate the necessary dosage schedule on a case-by-case basis.
Patients with current or previous gastrointestinal disease should be closely monitored for the occurrence of digestive disorders, especially gastrointestinal bleeding.
When gastrointestinal bleeding or ulceration occurs in patients taking Solket 80 mg powder for oral solution, treatment should be discontinued.

Patients with active or prior peptic ulcer disease:
NSAIDs should be administered with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8 adverse effects)
Some epidemiologic evidence suggests that ketoprofen may be associated with an elevated risk of severe gastrointestinal toxicity, compared with other NSAIDs, especially at high doses (see also sections 4.2 and 4.3).

Skin Reactions
Serious skin reactions some of them fatal, such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with NSAID use (see section 4.8). In the early stages of therapy, patients appear to be at higher risk: onset of the reaction occurs in most cases within the first month of treatment. Ketoprofen lysine salt should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

As with other nonsteroidal anti-inflammatory drugs, in the presence of infection, the anti-inflammatory, analgesic and antipyretic effects of ketoprofen lysine salt may mask symptoms of infection progression such as fever.

Precautions

Cardiovascular, renal and hepatic dysfunction:

In patients with impaired renal function, administration of ketoprofen should be done with particular caution in view of the essentially renal elimination of the drug.
At the beginning of treatment, renal function should be carefully monitored in patients with heart failure, cirrhosis, and nephrosis, in patients on diuretic therapy, or with chronic renal failure, especially the elderly. In these patients, ketoprofen administration may induce reduced renal blood flow caused by prostaglandin inhibition and result in renal decompensation. (See section 4.3 contraindications).
Caution is also required in patients on diuretic therapy or likely to be hypovolemic because the risk of nephrotoxicity is increased.
As with all NSAIDs, the drug can increase plasma urea nitrogen and creatinine.
As with other prostaglandin synthesis inhibitors, the drug may be associated with adverse events on the renal system that can lead to glomerular nephritis, renal papillary necrosis, nephrotic syndrome, and acute renal failure.

In patients with abnormalities in liver function tests or a history of liver disease, transaminase levels should be checked periodically, especially with long-term therapy.
As with other NSAIDs, the drug may cause small transient increases in some liver parameters and also significant increases in SGOT and SGPT. If there is a significant increase in these parameters, therapy should be discontinued.
Cases of jaundice and hepatitis have been reported with ketoprofen.
During long-term therapy, liver and kidney function tests should be conducted and blood counts checked.
Elderly patients are more predisposed to reduced renal, cardiovascular or hepatic function.

Cardiovascular and cerebrovascular effects
As with other NSAIDs, patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should be treated with ketoprofen lysine salt only after careful evaluation. Similar considerations should be made before starting long-term treatment in patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).
Adequate monitoring and appropriate instructions are necessary in patients with a positive history of hypertension and/or mild to moderate congestive heart failure because fluid retention and edema have been noted in association with NSAID treatment.
Clinical studies and epidemiological data suggest that the use of some NSAIDs (especially at high dosages and for long-term treatment) may be associated with an increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). There are insufficient data to rule out a similar risk for ketoprofen lysine salt.
An increased risk of atrial fibrillation associated with NSAID use has been reported.
Hyperpotassemia may occur, especially in patients with underlying diabetes, renal insufficiency, and/or concomitant treatment with hyperpotassemia-promoting agents (see section 4.5).
Under these circumstances, potassium levels should be monitored.
Masking of symptoms of underlying infections
Solket can mask symptoms of infection, which could delay the initiation of appropriate treatment and thus worsen the outcome of the infection. This has been observed in community-acquired bacterial pneumonia and bacterial complications of chickenpox. When Solket is administered for the relief of infection-related fever or pain, infection monitoring is recommended. In nonhospital settings, the patient should seek medical attention if symptoms persist or worsen.

Administer with caution in patients with allergic manifestations or prior allergy.

Respiratory disorders
Like all nonsteroidal drugs, the use of ketoprofen in patients with bronchial asthma or allergic diathesis can trigger an asthmatic crisis.
Patients with asthma associated 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 drug may cause asthmatic or bronchospasm crises, shock and other allergic phenomena especially in subjects allergic to acetylsalicylic acid or NSAIDs (see section 4.3). Due to the drug's interaction with arachidonic acid metabolism, bronchospasm crisis and possibly shock and other allergic phenomena may occur in asthmatics and predisposed subjects.

Visual disturbances
In case of visual disturbances, such as blurred vision, treatment should be discontinued.
Solket should be administered with caution in patients with hematopoietic disorders, systemic lupus erythematosus, or mixed connective tissue disorders.

Solket 80 mg powder for oral solution contains sorbitol and sodium
This medication contains 1.7 g of sorbitol per sachet. The additive effect of co-administration of medications containing sorbitol (or fructose) and daily dietary intake of sorbitol (or fructose) should be considered. Sorbitol content in oral medications may alter the bioavailability of other co-administered oral medications.
Sorbitol is a source of fructose. If your doctor has told you that you (or your child) are intolerant to certain sugars, or if you have a diagnosis of hereditary fructose intolerance, a rare genetic disorder whereby patients cannot process fructose, talk to your doctor before you (or your child) take this medication.

This medicine contains less than 1 mmol (23 mg) of sodium per sachet, meaning it is essentially "sodium-free"

4.5 Interaction with other medicinal products and other forms of interaction
Not recommended associations:

- Other NSAIDs (including selective cyclooxygenase-2 inhibitors), including high doses of salicylates (≥ 3 g/day): concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect.

- Anticoagulants (e.g., heparin and warfarin): NSAIDs may amplify the effects of anticoagulants, such as warfarin (see section 4.4) by increasing the risk of bleeding due to inhibition of platelet function and damage to the gastrointestinal mucosa (see section 4.4). If concomitant administration cannot be avoided, patient should be closely monitored.

- Platelet aggregation inhibitors (e.g., ticlopidine and clopidogrel): increased risk of bleeding due to inhibition of platelet function and gastrointestinal mucosal damage (see section 4.4).

If concomitant administration cannot be avoided, patient should be closely monitored.

- Lithium (described with several NSAIDs): NSAIDs increase plasma lithium levels (decreased renal excretion of lithium), which can reach toxic values. This parameter therefore requires monitoring, and lithium dosage should be adjusted during and following treatment with ketopreofen and other NSAIDs.

Methotrexate, used at doses higher than 15 mg/week: increased blood toxicity of methotrexate, particularly when administered at high doses (> 15 mg/week), likely related to displacement of methotrexate-binding proteins and decrease in its renal clearance due to anti-inflammatory agents in general.Allow at least 12 hours between discontinuation or initiation of ketoprofen treatment and methotrexate administration.

- Hydantoins and sulfonamides: the toxic effects of these substances may be increased.

Associations that require precaution:

- Medicines or therapeutic categories that may promote hyperpotassemia:

Some medicines or therapeutic categories may promote hyperpotassemia, e.g., potassium salts, potassium-sparing diuretics, enzyme-converter inhibitors (ACE inhibitors), angiotensin II receptor blockers, NSAIDs, heparins (low molecular weight or unfractionated), cyclosporine, tacrolimus, and trimethoprim. The occurrence of hyperpotassemia may depend on the presence of cofactors. The risk is enhanced when the above drugs are administered concomitantly.

- Tenofivir: Concomitant administration of tenofivir disoproxil fumarate and NSAIDs may increase the risk of renal failure.
- Diuretics: patients who are taking diuretics and among them, those who are particularly dehydrated are at increased risk of developing secondary renal failure due to reduced renal blood flow caused by prostaglandin inhibition. Such patients should be rehydrated before the initiation of concomitant therapy, and renal function should be closely monitored after the start of treatment (see section 4.4). NSAIDs may reduce the effect of diuretics.
- ACE inhibitors and angiotensin II antagonists: in patients with impaired renal function (e.g., dehydrated patients or elderly patients), co-administration of an ACE inhibitor or angiotensin II antagonist and agents capable of inhibiting cyclooxygenase may result in further impairment of that renal function, which includes possible acute renal failure. Therefore, the combination should be administered with caution, especially in elderly patients.

Patients should be adequately hydrated and renal function monitoring should be considered after the initiation of concomitant therapy.

- Methotrexate, used at low doses below 15 mg/week: increased blood toxicity of methotrexate due to a decrease in its renal clearance from anti-inflammatory agents in general. Perform weekly CBC monitoring during the first few weeks of the combination. Increase monitoring in the presence of even mild worsening of renal function, as well as in elderly patients.
- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Pentoxifylline: increased risk of bleeding. Increase clinical monitoring and check bleeding time more frequently.
- Zidovudine: risk of increased red cell line toxicity by action on reticulocytes, with severe anemia occurring one week after starting NSAID treatment. Check complete hemocytometric examination and reticulocyte count one to two weeks after starting NSAID treatment.
- Sulfanilureas: NSAIDs can increase the hypoglycemic effect of sulfanilureas by displacing them from plasma protein binding sites.
- Cardioactive glycosides: NSAIDs can exacerbate heart failure, reduce glomerular filtration rate, and increase levels of cardiac glycosides; however, pharmacokinetic interaction between ketorpofen and cardioactive glycosides has not been demonstrated.

Associations to consider:

- Antihypertensive Drugs (beta-blockers, ACE inhibitors, diuretics): NSAIDs can reduce the effect of antihypertensive drugs. Treatment with an NSAID may decrease their antihypertensive effect through inhibition of vasodilator prostaglandin synthesis.
- Mifepristone: The efficacy of the birth control method may theoretically be reduced due to the antiprostaglandin properties of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetylsalicylic acid). There is some evidence to suggest that concurrent administration of NSAIDs on the day of prostaglandin dose administration does not unfavorably influence the effects of mifepristone or prostaglandin on cervical maturation or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.
- Intrauterine contraceptive devices (IUDs): the effectiveness of the device may be reduced resulting in pregnancy.
- Cyclosporine, tacrolimus: concomitant treatment with NSAIDs may pose an increased risk of nephrotoxicity, especially in elderly subjects.
- Thrombolytics: increased risk of bleeding.
- Anti-aggregating agents (ticlopidine and clopidogrel) and Selective Serotonin Reuptake Inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
- Probenecid: Co-administration of probenecid may markedly reduce the plasma clearance of ketoprofen, and consequently plasma concentrations of ketoprofen may be increased; this interaction may be due to an inhibitory mechanism at the site of renal tubular secretion and glucuronoconjugation and requires adjustment of the ketoprofen dose.
- Quinolone antibiotics: animal data indicate that NSAIDs may increase the risk of seizures associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing seizures.
- Diphenylhydantoin and sulfonamides: because the protein binding of ketoprofen is high, it may be necessary to reduce the dosage of diphenylhydantoin or sulfonamides that should be administered concomitantly.
- Gemeprost: reduced efficacy of gemeprost.
- Avoid alcohol intake.

4.6 Fertility, pregnancy and lactation

Pregnancy

<u>The use of ketoprofen during the first and second trimesters of pregnancy should be avoided.</u>

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development Results of epidemiological studies suggest an increased risk of abortion and cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiac malformation increased from less than 1 percent, to about 1.5 percent. The risk was found to increase with dose and duration of therapy. In animals, administration of prostaglandin synthesis inhibitors has been shown to cause increased pre- and post-implantation loss and embryo-fetal mortality.

In addition, an increased incidence of various malformations, including cardiovascular malformations, has been reported in animals given prostaglandin synthesis inhibitors during the organogenetic period.

From 20 weeks of pregnancy onward, Solket use may cause oligohydramnios resulting from fetal renal dysfunction. This condition may be encountered shortly after the start of treatment and is usually reversible with discontinuation of

treatment. In addition, cases of ductus arteriosus constriction following treatment in the second trimester have been reported, most of which resolved after discontinuation of treatment.
Therefore during the first and second trimesters of pregnancy, Solket should not be administered unless absolutely necessary. If Solket is used by a woman who is planning a pregnancy, or during the first and second trimesters of pregnancy, the lowest possible dose should be used for the shortest possible time.
Following exposure to Solket for several days from the 20th week of gestation onward, antenatal monitoring of oligohydramnios and ductus arteriosus constriction should be considered. In case of oligohydramnios or ductus arteriosus constriction, treatment with Solket should be discontinued.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors can expose
the fetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which can progress to renal failure with oligohydramnios (see above);

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

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

Use of the drug close to delivery can cause alterations in the hemodynamics of the unborn baby's small circulation with serious consequences for breathing.Consequently, Solket is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation
Since no data are available on secretion of ketoprofen lysine salt in the breast milk, ketoprofen must not be administered during breast-feeding.

Fertility
The use of ketoprofen lysine salt, as any other drug that inhibits prostaglandin synthesis and cycloxigenase, is not recommended in women that intend to start a pregnancy.
L'uso di Ketoprofene sale di lisina, come di qualsiasi farmaco inibitore della sintesi delle prostaglandine e della cicloossigenasi è sconsigliato nelle donne che intendano iniziare una gravidanza.
The administration of NSAIDs, as well as Ketoprofen lysine salt, should be discontinued in women who have difficulty conceiving or being subjected to fertility surveys.

4.7 Effects on ability to drive and use machines
If drowsiness, dizziness, or convulsions occur as a result of ketoprofen administration, the patient should avoid driving, operating machinery, or activities requiring special vigilance.

4.8 Undesirable effects
Like all medicines, Solket 80 mg powder for oral solution can cause adverse effects, although not all people experience them.
The most commonly observed adverse events are gastrointestinal in nature.
Expected Frequency Classification:
very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), unknown (frequency cannot be defined based on available data).
The following adverse reactions have been observed with ketoprofen use in adults:

Infections and infestations
Not known: aseptic meningitis, lymphangitis

Hemolymphopoietic system disorders:
Rare: hemorrhagic anemia.
Not known: agranulocytosis, thrombocytopenia, bone marrow failure, hemolytic anemia, leukopenia, neutropenia, aplastic anemia, leukocytosis, thrombocytopenic purpura.

Immune system disorders:
Not known: anaphylactic reactions (including shock), hypersensitivity.

Metabolism and nutrition disorders.
Not known: hyperpotassemia, hyponatremia (see sections 4.4 and 4.5).

Psychiatric disorders:
Not known: depression, hallucinations, confusion, mood alteration, excitability, insomnia.
Anxiety, conduct disorder also occurred in a pediatric patient who had taken twice the dose recommended in the SmPC.

Nervous system disorders:
Uncommon: headache, dizziness, drowsiness.
Rare: paresthesias.
Very rare: dyskinesia, syncope.
Not known: convulsions, dysgeusia, tremor, hyperkinesia.

Eye disorders:
Rare: blurred vision (see paragraph 4.4).
Unknown: periorbital edema.

Ear and labyrinth disorders:
Rare: tinnitus.

Cardiac disorders:
Not known: heart failure, atrial fibrillation, palpitations, and tachycardia.

Vascular disorders:
Not known: hypertension, vasodilatation, vasculitis (including leukocytoclastic vasculitis).
Very rare: hypotension.

Respiratory, thoracic, and mediastinal disorders:
Rare: asthma.
Very rare: edema of the larynx.
Not known: bronchospasm (especially in patients with known hypersensitivity to acetylsalicylic acid and other NSAIDs), rhinitis, dyspnea, laryngospasm, acute respiratory failure (a single case, with fatal outcome, has been reported in an asthmatic and aspirin-sensitive patient). Most reactions that occurred in patients with allergies/asthma and/or known hypersensitivity to NSAIDs were severe in nature.

Gastrointestinal disorders:
The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, may occur, particularly in the elderly (see section 4.4).
Common: nausea, vomiting, dyspepsia, abdominal pain.
Uncommon: abdominal discomfort, constipation, diarrhea, flatulence, gastritis.
Rare: stomatitis, peptic ulcer, colitis.
Not known: gastralgia, exacerbation of colitis and Crohn's disease, gastrointestinal bleeding, gastrointestinal perforation (sometimes fatal, particularly in the elderly-see section 4.4), gastric ulcer, duodenal ulcer, heartburn, mouth edema, pancreatitis, hematemesis, melena, hyperchlorhydria, gastric pain, erosive gastritis, tongue edema.

Hepatobiliary disorders:
Rare: hepatitis, increased transaminase levels, increased blood bilirubin, jaundice.

Skin and subcutaneous tissue disorders:
Uncommon: rash, itching.
Not known: photosensitization, alopecia, urticaria, angioedema, bullous eruptions including Stevens-Johnson syndrome, Lyell's syndrome, and toxic epidermal necrolysis, erythema, exanthema, maculo-papular exanthema, purpura, generalized acute exanthematous pustulosis, dermatitis, contact eczema.

Renal and urinary disorders:
Very rare: hematuria
Not known: acute renal failure, tubulo-interstitial nephritis, nephritis or nephritic syndrome, nephrotic syndrome, glomerular nephritis, water/sodium retention with possible edema, acute tubular necrosis, renal papillary necrosis, oliguria, evidence of abnormal renal function, dysuria.

Systemic disorders and conditions related to site of administration:
Uncommon: edema, fatigue, peripheral edema, chills.

Very rare: asthenia, facial edema.

Diagnostic tests:
Rare: weight gain
Clinical studies and epidemiologic data suggest that the use of some NSAIDs (especially at high dosages and for long-term treatment) may be associated with a modestly increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke) (see section 4.4).

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions that occur after a drug is authorized is important, as it allows for continuous monitoring of the benefit/risk ratio of the drug. Healthcare professionals are required to report any suspected adverse reactions through the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose
Cases of overdose have been reported with doses exceeding 2.5 g of ketoprofen. In most cases, the symptoms observed were benign in nature and limited to lethargy, drowsiness, nausea, vomiting, epigastric and abdominal pain, headache, dizziness, and diarrhea. Hypotension, respiratory depression, gastrointestinal bleeding and cyanosis have been observed in severe overdose.
The patient should be transferred immediately to a specialist center to begin symptomatic treatment.
There are no specific antidotes for ketoprofen overdose.
If massive overdose is suspected, gastric lavage and institution of symptomatic and supportive treatment to compensate for dehydration, monitor urinary excretion, and correct acidosis if appropriate is recommended.
In cases of renal failure, hemodialysis may be useful for removal of the drug from the body.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic category: Anti-inflammatory, antirheumatic, nonsteroidal drugs. Propionic acid derivatives. ATC: M01AE03
Ketoprofen lysine salt is the lysine salt of 2-(3-benzoylphenyl)propionic acid, an analgesic, anti-inflammatory and antipyretic drug that belongs to the NSAID class (M01AE).
Ketoprofen lysine salt is more soluble than acid ketoprofen.
The mechanism of action of NSAIDs is related to the reduction of prostaglandin synthesis by inhibition of the enzyme cyclooxygenase.
Specifically, an inhibition of the transformation of arachidonic acid into the cyclic endoperoxides, PGG2 and PGH2, precursors of prostaglandins PGE1 , PGE2 , PGF2a and PGD2 and also of prostacyclin PGI2 and thromboxanes (TxA2 and TxB2) is observed. In addition, inhibition of prostaglandin synthesis may interfere with other mediators such as kinins, causing an indirect action that would add to the direct action.
Ketoprofen lysine salt possesses a marked analgesic effect, correlated with both its anti-inflammatory effect and a central effect.
Ketoprofen lysine salt exerts antipyretic activity without interfering with normal thermoregulatory processes.
Painful inflammatory manifestations are eliminated or alleviated by promoting joint mobility.

5.2 Pharmacokinetic properties
Ketoprofen lysine salt has more solubility respect to the acid ketoprofen.
The oral form allows intake of the active ingredient already in an aqueous solution and thus leads to a rapid increase in plasma levels and an early attainment of the peak value. This is expressed, clinically, by a more rapid onset and greater intensity of the antalgic and antiphlogistic effect.
The kinetic profile in children does not differ from that in adults.
Repeated administration does not change the kinetics of the drug or produce accumulation.
Ketoprofen is 95-99% bound to plasma proteins. Significant levels of ketoprofen were found in tonsillar tissue and synovial fluid after systemic administration.
Elimination is rapid and essentially by the renal route: 50% of the systemically administered product is excreted in the urine in 6 hours. Ketoprofen is extensively metabolized: about 60-80% of the systemically administered product is found as metabolites in the urine.

5.3 Preclinical safety data
DL_{50} of oral ketoprofen lysine salt in rat and mouse is 102 and 444 mg/kg, respectively, which is 30-120 times the active dose as an anti-inflammatory and analgesic in animal. By intraperitoneal way, DL_{50} of ketoprofen lysine salt is 104 and 610 mg/kg in rat and mouse, respectively.

Prolonged treatment in the rat, dog, and monkey with oral ketoprofen lysine salt at doses equal to or greater than the intended therapeutic dosages did not cause the appearance of any toxic phenomena. At high doses, gastrointestinal and renal changes attributable to the known side effects caused in animals by nonsteroidal anti-inflammatory drugs were found. In a prolonged toxicity study conducted in the rabbit by the oral or rectal route, ketoprofen was better tolerated when administered rectally than by the oral route. In a tolerability study conducted in the rabbit by the intramuscular route, ketoprofen lysine salt was shown to be well tolerated.
Ketoprofen lysine salt was found to be nonmutagenic in genotoxicity tests conducted "in vitro" and "in vivo."
Carcinogenesis studies with ketoprofen in mouse and rat showed the absence of carcinogenic effects.
Regarding embryofetal toxicity and teratogenesis of NSAIDs in animals, see section 4.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (Neosorb P60), sorbitol (Neosorb P30/P60), povidone, silica colloidal anhydrous, sodium chloride, saccharin sodium, ammonium glycyrrhizinate, mint flavor.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.
Expiration date shown refers to the product in intact packaging, properly stored.

6.4 Special precautions for storage

This medicinal product does not require any special precaution for storage.

6.5 Nature and contents of container

Heat-sealed paper/aluminum/polythene sachets.
Cardboard box containing 30 bipartite sachets of 2 g.

6.6 Special precautions for disposal and handling

No special instruction.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Aesculapius Farmaceutici S.r.l.
Via Cefalonia, 70
25124 Brescia

8. MARKETING AUTHORIZATION NUMBER(S)

SOLKET “80 mg powder for oral solution” 30 bipartite sachets
MA No. 038727018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First Authorization: 15/03/2010
Renewal of Authorization: 17/11/2015

10. DATE OF REVISION OF THE TEXT

February 2024