פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר במאי 2012

## 1. NAME OF THE MEDICINAL PRODUCT

**Profenid 50 mg capsules**
**Profenid 100 mg suppositories**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Profenid 50 mg capsules**

Ketoprofen.....50 mg

For one hard capsule.

Excipient: lactose monohydrate

For a full list of excipients, see Section 6.1.

**Profenid 100 mg suppositories**

Ketoprofen.....100 mg

For one 2.7 g suppository.

For a full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

**Profenid® 50 mg hard capsules**

Hard capsules.

**Profenid® 100 mg suppositories**
Suppositories.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Anti inflammatory, anti-rheumatic, analgetic.

The therapeutic indications are based on the analgesic and anti-inflammatory properties of ketoprofen, the extent of the adverse effects related to the medicinal product, and its position in the range of currently available anti-inflammatory drugs.

Indications are restricted to the following, in adults and children aged 15 years and over:

- Long-term symptomatic treatment of:
  - chronic inflammatory rheumatism, particularly rheumatoid arthritis, ankylosing spondylitis (or related syndromes, such as Reiter's syndrome, and psoriatic arthritis),
  - certain types of painful and incapacitating osteoarthritis.
- Short-term symptomatic treatment of acute episodes of:
  - abarticular rheumatism such as scapulohumeral periarthritis, tendonitis, and bursitis,
  - gouty arthritis,
  - osteoarthritis,
  - lower back pain,
  - radicular pain,

- acute, minor, post-traumatic disorders of the musculoskeletal system.

**4.2 Posology and method of administration**

**- Profenid 50 mg hard capsules**

**Method of administration:**

Oral use.

The hard capsules are to be swallowed whole with a large glass of water.

**Dosage:**

Unwanted side effects may be reduced by using the lowest possible dose for the shortest time necessary to alleviate symptoms (see Section 4.4).

The maximum daily dose is 200 mg. The benefit/risk ratio should be carefully assessed before initiating treatment at a daily dose of 200 mg; the use of higher doses is not recommended (also see Section 4.4).

- Long-term symptomatic treatment: three 50 mg hard capsules per day, i.e. 150 mg per day.
- Short-term symptomatic treatment of acute episodes: four 50 mg hard capsules per day, i.e. 200 mg per day.

**Frequency of administration:**

The hard capsules are to be taken with meals.

The daily dose is to be taken as two or three divided doses.

**Populations at risk:**

- Patients with renal insufficiency and elderly subjects: the initial dose should be reduced then adjusted if necessary based on renal tolerance.
- Patients with hypovolemia: see Section 4.4.

- Patients with impaired heptic function : These patients should be carefully monitored and kept at the minimal effective daily dosage

- Children : The safety and effectivness of ketoprofen have not been established. It is restricted for adults and children above 15 years of age
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- Elderly: The elderly are at increased risk of serious adverse reactions from NSAIDs. If an NSAID is considered necessary, it is generally advisable to begin ketoprofen therapy at the lower end of the dose range and to maintain such patients on the lowest effective dosage, for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

**- Profenid 100 mg suppositories**

**Method of administration:**

Rectal use.

**Dosage:**

Unwanted side effects may be reduced by using the lowest possible dose for the shortest time necessary to alleviate symptoms (see Section 4.4).

The maximum daily dose is 200 mg. The benefit/risk ratio should be carefully assessed before initiating treatment at a daily dose of 200 mg; the use of higher doses is not recommended (also see Section 4.4).

- Long-term symptomatic treatment: one to two 100 mg suppositories per day, i.e. 100 mg to 200 mg per day.
- Short-term symptomatic treatment of acute episodes: two 100 mg suppositories per day, i.e. 200 mg per day.

**Frequency of administration:**

The daily dose is to be taken as 1 dose or 2 divided doses.

**Duration of treatment:**

Use of the rectal route should be as short as possible due to the risk of local adverse effects which occur in addition to those observed with oral administration.

**Populations at risk:**

- Patients with renal insufficiency and elderly subjects: the initial dose should be reduced then adjusted if necessary based on renal tolerance.
- Patients with hypovolemia: see Section 4.4.

- Patients with impaired heptic function : These patients should be carefully monitored and kept at the minimal effective daily dosage

- Children : The safety and effectivness of ketoprofen have not been established. It is restricted for adults and children above 15 years of age
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- Elderly: The elderly are at increased risk of serious adverse reactions from NSAIDs. If an NSAID is considered necessary, it is generally advisable to begin ketoprofen therapy at the lower end of the dose range and to maintain such patients on the lowest effective dosage, for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

**4.3. Contraindications**

This medicinal product is contraindicated in the following situations:

- from 24 weeks of pregnancy (5 full months) (see Section 4.6),
- hypersensitivity to ketoprofen or to any of the excipients of the drug,
- History of hypersensitivity reactions such as bronchospasm , asthma, rhinitis, urticaria or other allergic type reactions to ketoprofen, acetylsalicylic acid or other NSAIDs. Severe anaphylactic reactions, rarely fatal have been reported in these patients (see section 4.8).
- history of gastrointestinal bleeding or perforation during previous NSAID therapy,
- gastrointestinal bleeding, cerebrovascular bleeding or any other active bleeding, active peptic ulcer, history of recurrent bleeding or peptic ulcer (2 or more separate identified episodes of bleeding or ulceration),
- severe hepatic failure,
- severe renal failure,
- severe heart failure, cardiac disfunction

- In addition, for the suppositories form: recent episode of proctitis or proctorrhagia.

**4.4. Special warnings and precautions for use**

Concomitant use of Profenid with other NSAIDs, including cyclooxygenase-2 (cox-2) selective inhibitors, should be avoided.

The occurrence of adverse effects can be minimized by using the lowest possible dose for the shortest possible duration to obtain relief of symptoms (see Section 4.2 and "Gastrointestinal effects" and "Cardiovascular and cerebrovascular effects" below).

Patients with asthma associated with chronic rhinitis, chronic sinusitis and/or nasal polyposis are at a higher risk of allergic reactions when taking aspirin and/or non-steroidal anti-inflammatory drugs than the general population. Administration of this proprietary medicinal product may induce asthma attacks or bronchospasm, particularly in subjects allergic to aspirin or an NSAID (see Section 4.3).

**Elderly subjects**

The elderly have an increased risk of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation that can be fatal (see Section 4.2 and below).

**Gastrointestinal effects**

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, at any time during treatment, even without warning signs or a patient history of serious gastrointestinal adverse reactions..

The relative risk increases with age, patients who presents with platelet dysfunction or in patients undergoing anticoagulant or antiplatelet treatment (see section Interactions with other drugs and other forms of interaction).

Some epidemiological evidence suggests that ketoprofen may be associated with a higher risk of serious gastrointestinal toxicity than other NSAIDs, especially at high doses (also see Sections 4.2 and 4.3).

The risk of gastrointestinal bleeding, ulceration or perforation increases with the dose used in patients with a history of ulcer, particularly if complicated with bleeding or perforation (see Section 4.3), in elderly subjects, as well as in patients with low body weight. In these patients, treatment should be initiated at the lowest possible dose. Treatment providing protection of the mucosa (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring low-dose treatment with aspirin or treated with other medicinal products likely to increase the risk of gastrointestinal effects (see below and Section 4.5).

Patients with a history of gastrointestinal disorders, particularly elderly patients, should report any unusual abdominal symptoms (in particular gastrointestinal bleeding), especially at the start of treatment.

Special monitoring is required in patients receiving concomitant medication likely to increase the risk of ulceration or bleeding, such as glucocorticoids, oral anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) and antiplatelet agents such as aspirin (see Section 4.5).

If bleeding or ulceration occurs in patients receiving Profenid, treatment should be discontinued.

Caution should be exercised and close monitoring instituted when administering NSAIDs in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see Section 4.8).

**Cardiovascular and cerebrovascular effects**

Adequate monitoring and recommendations are required for patients with a history of hypertension and/or mild to moderate heart failure, since cases of water and sodium retention and edema have been reported in patients receiving treatment with NSAIDs.

Clinical studies and epidemiological data suggest that the use of certain NSAIDs (particularly when administered at high doses and over a long period) can be associated with a slight increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Currently available data do not make it possible to rule out this increased risk with ketoprofen.

As is the case for all NSAIDs, patients with uncontrolled hypertension, congestive heart failure, ischemic heart disease, peripheral arterial disease, and/or a history of stroke (including transient ischemic attack) should only be treated with ketoprofen after careful assessment.

Similar caution is required before initiating long-term treatment in patients with risk factors for cardiovascular disease (such as hypertension, hyperlipidemia, diabetes or smoking).

**Skin reactions**
Serious skin reactions, some of which have been fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and Lyell's syndrome, have been reported in very rare cases during treatment with NSAIDs (see Section 4.8).

The incidence of these adverse effects appears to be higher at the start of treatment, occurring within the first month of treatment in most cases. Treatment with Profenid should be discontinued as soon as skin rash, mucosal damage or any other signs of hypersensitivity occur.

**Functional renal failure**

By inhibiting the vasodilatory effects of renal prostaglandins, NSAIDs are likely to cause functional kidney failure as a result of decreased glomerular filtration. This adverse effect is dose-dependent.
At the start of treatment or after an increase in dose, monitoring of urine output and kidney function is recommended in patients with the following risk factors:

- advanced age,
- concomitant medication such as ACE inhibitors, sartans, diuretics (see Section 4.5),
- hypovolemia regardless of the cause,
- heart failure,
- chronic kidney failure,
- nephrotic syndrome,
- lupus nephropathy,
- cirrhosis.

**Water and sodium retention**

Water and sodium retention with possible edema, hypertension or exacerbation of hypertension, exacerbation of heart failure. Clinical monitoring is required from the start of treatment in patients with hypertension or heart failure. The effect of antihypertensive agents may be reduced (see Section 4.5).

**Hyperkalemia**
Hyperkalemia promoted by diabetes or concomitant treatment with hyperkalemic agents (see Section 4.5).

Regular monitoring of blood potassium levels is required in these patients.

The use of NSAIDs may affect fertility in female patients, and is not recommended in female patients hoping to conceive. Discontinuation of NSAID therapy should be considered in women having difficulty conceiving or undergoing infertility tests.

Like other NSAIDs, ketoprofen can mask the signs of worsening infection such as fever.

Patients with a history of photosensitivity or phototoxicity reactions must be closely monitored.

Regular transaminase monitoring is recommended in patients with abnormal liver function tests or a history of liver disease particularly during long term treatment.

Rare cases of jaundice and hepatitis have been described with ketoprofen.

During long term treatment, the blood count, as well as kidney and liver function, should be monitored.

Treatment must be discontinued if visual disturbances, such as blurred vision, occur.

Administration of this medicinal product should be avoided during treatment with another non-steroidal anti-inflammatory drug, oral anticoagulant, lithium, aspirin at analgesic, antipyretic or anti-inflammatory doses, methotrexate at doses higher than 20 mg per week, with low-molecular-weight heparins and related products, and unfractionated heparins (at curative doses and/or in the elderly), pemetrexed, and in patients with low to moderate kidney function (see Section 4.5).

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis

In addition, for the capsules form:
This medicinal product contains lactose and is therefore not recommended in patients with galactose intolerance, Lapp lactase deficiency or glucose or galactose malabsorption syndrome (rare hereditary diseases).

**4.5. Interaction with other medicinal products and other forms of interaction**

**Risk related to hyperkalemia:**

Certain medicinal products or therapeutic groups may promote hyperkalemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory drugs, heparins (low-molecular-weight or unfractionated), immunosuppressants such as cyclosporin or tacrolimus, trimethoprim.

This risk is potentiated when the above-mentioned drugs are used concomittantly with ketoprofen. It is particularly high with potassium-sparing diuretics, especially when more than one are used together or when they are co-administered with potassium salts, whereas co-administration of an ACE inhibitor and NSAID, for instance, presents a lesser risk as long as the recommended precautions are implemented.

In order to identify the risks and restrictions specific to hyperkalemic agents, the interactions specific to each substance should be referred to.

However, for certain substances, such as trimethoprim, no specific interactions have been described in terms of this risk. Nevertheless, these substances may act as promoting factors when combined with other medicinal products such as those mentioned above.

Patients require strict clinical and laboratory monitoring when the following agents are co-administered with ketoprofen:

**Inadvisable combinations**

+ **Other NSAIDs (including high-dose aspirin)**

Increased risk of gastrointestinal ulcers and bleeding (additive effects).

At anti-inflammatory doses of aspirin (≥ 1 g per dose and/or ≥ 3 g daily), or at analgesic or antipyretic doses (≥ 500 mg per dose and/or < 3 g daily).

+ **Oral anticoagulants**

Increased risk of bleeding related to the oral anticoagulant (damage to the gastroduodenal mucosa by NSAIDs). NSAIDs are liable to increase the effects of anticoagulants, such as warfarin (see Section 4.4).

If the combination cannot be avoided, close clinical and laboratory monitoring should be carried out.

+ **Unfractionated or low-molecular-weight heparins and related substances (at curative doses and/or in elderly subjects)**

Increased risk of bleeding (inhibition of platelet function and damage to the gastroduodenal mucosa by NSAIDs).

If the combination cannot be avoided, close clinical monitoring should be carried out.

+ **Lithium**

Increased blood lithium possibly reaching toxic levels (reduced renal excretion of lithium).

If the combination cannot be avoided, blood lithium levels should be closely monitored, and lithium dosage adjusted during co-administration and after discontinuation of the NSAID.

+ **Methotrexate used at doses higher than 15 mg/week**

Increased hematological toxicity of methotrexate (reduced renal clearance of methotrexate due to anti-inflammatory drugs).

An interval of at least 12 hours should be allowed between discontinuing or starting treatment with ketoprofen and administration of methotrexate.

+ **Pemetrexed (in patients with mild to moderate renal function impairment, creatinine clearance between 45 ml/min and 80 ml/min)**

Risk of increased pemetrexed toxicity (reduced renal clearance of pemetrexed due to NSAIDs).

**Combinations requiring precautions for use**

+ **Diuretics, ACE inhibitors, angiotensin II receptor antagonists**

Acute renal failure in patients at risk (elderly subjects and/or dehydrated patients) due to decreased glomerular filtration (inhibition of vasodilatory prostaglandins by NSAIDs).

In addition, decrease in the antihypertensive effect.

Patients should be hydrated and renal function monitored at the start of treatment.

+ **Methotrexate used at low doses (≤ 15 mg/week)**

Increased hematological toxicity of methotrexate (reduced renal clearance of methotrexate).

Weekly blood count monitoring during the first few weeks of the combination.

Monitoring should be increased if there is even minor impairment of renal function, and in elderly subjects.

+ **Pemetrexed (in patients with normal renal function)**

Risk of increased pemetrexed toxicity (reduced renal clearance of pemetrexed due to NSAIDs).

Laboratory monitoring of renal function should be carried out.

+ **Cyclosporin, tacrolimus**

Risk of additive nephrotoxic effects, particularly in elderly subjects.

Renal function should be monitored at the start of treatment.

+ **Corticosteroids** : increased risk of gastrointestinal ulceration and bleeding.

+ **Pentoxifylline**: There is an increased risk of bleeding. More frequent clinical monitoring and monitoring of bleeding time is required.

+ **Mifepristone** – NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

**Combinations to be taken into account**

+ **Acetylsalicylic acid used at antiplatelet doses (50 to 375 mg per day as one or more doses)**

Increased risk of gastrointestinal ulcers and bleeding.

+ **Glucocorticoids (except hydrocortisone as a replacement therapy)**

Increased risk of gastrointestinal ulcers and bleeding (see Section 4.4).

+ **Platelet aggregation inhibitors and selective serotonin reuptake inhibitors (SSRIs)**

Increased risk of gastrointestinal bleeding (see Section 4.4).

+ **Unfractionated and low-molecular-weight heparins (at preventive doses)**

Increased risk of bleeding.

+ **Deferasirox**

Increased risk of gastrointestinal ulcers and bleeding.

+ **Beta-blockers (except esmolol)**

Reduced antihypertensive effect (inhibition of vasodilatory prostaglandins by NSAIDs and water and sodium retention with pyrazole NSAIDs).

**+ other antiplatelet agents** (ticlopidine,clopidogrel, tirofiban, eptifibatide and abciximab, iloprost), heparin at prophylactic doses: increased risk of hemorrhage.

**+ other drugs inducing hyperkalemia**: potassium salts, potassium-containing diuretics, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, other non-steroidal anti-inflammatory drugs, low molecular weight or unfractionated heparin, cyclosporin, tacrolimus and trimethoprim: risk of hyperkalemia.

**+ Quinolone antibiotics:** Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
**+ Thrombolytics**: Increased risk of bleeding.

**+ Probenecid**: Concomitant administration of probenecid may markedly reduce the plasma clearance of ketoprofen

**4.6 Pregnancy and lactation**

**Pregnancy**

Prostaglandin synthesis inhibition may have a harmful effect on pregnancy and/or embryonic or fetal development. Epidemiological data, following the use of a prostaglandin synthesis inhibitor during the early stage of pregnancy, suggest an increased risk of miscarriage, cardiac malformation, and gastroschisis. The absolute risk of cardiac malformation is increased from less than 1% to approximately 1.5%.

This risk would seem to increase with dose and treatment duration.

In animal studies, administration of a prostaglandin synthesis inhibitor induces an increase in pre- and post-implantation losses, and embryo-fetal mortality.

Furthermore, an increased incidence of various malformations, including cardiovascular malformations, has been observed in animals having received a prostaglandin synthesis inhibitor during the organogenesis period.

Unless treatment is clearly shown to be absolutely necessary, the use of ketoprofen should be avoided during the first and second trimesters of pregnancy.

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

- Kidney function impairment:
  - in utero which may be observed from 12 weeks of amenorrhea (initiation of fetal diuresis): oligohydramnios (in most cases reversible on treatment discontinuation), or even severe oligohydramnios, particularly during prolonged exposure.
  - at birth, kidney failure (reversible or nonreversible) may persist, in particular in cases of late-stage or long term exposure (with a risk of severe, delayed hyperkalemia).
- Risk of cardiopulmonary damage:

Partial or complete in utero constriction of the ductus arteriosus. This can occur from 5 full months of pregnancy, and can lead to fetal or neonatal right heart failure or even fetal death in utero. This risk is increased when the drug is administered close to term (less reversibility). This effect can even occur following single administration.

- Risk of prolonged bleeding time for the mother and infant (due to the antiplatelet effect which may occur even at very low doses).
- inhibition of uterine contractions which can delay or prolong labor.

Consequently:

- Up to 12 weeks of amenorrhea: use of Profenid should only be considered if necessary.
- Between 12 and 24 weeks of amenorrhea (between the initiation of fetal diuresis and 5 full months of pregnancy): a brief course of treatment should only be prescribed if necessary. Prolonged use is strongly inadvisable.
- After 24 weeks of amenorrhea (5 full months): any use, even single administration, is contraindicated (see Section 4.3). Accidental use after 24 weeks of amenorrhea (5 full months) warrants cardiac and renal monitoring in the fetus and/or neonate depending on the stage at which exposure occurred. Duration of monitoring should be adjusted to the elimination half-life of the compound.

During use in women hoping to conceive, or in the second trimester of pregnancy, the lowest possible dose should be used for the shortest period possible.

**Lactation**

Since NSAIDs are excreted in breast milk, as a precaution, administration should be avoided in breast-feeding women.

### 4.7 Effects on ability to drive and use machines

Patients should be warned that dizziness, drowsiness, seizures or visual disturbances may occur. Patients should be advised not to drive or use machines if any of these symptoms occur.

### 4.8. Undesirable effects

Clinical studies and epidemiological data suggest that the use of certain NSAIDs (particularly when administered at high doses and over a long period) can be associated with a slight increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) (see Section 4.4).

The most commonly observed adverse effects are gastrointestinal. Peptic ulcers, gastrointestinal perforations or bleeding, sometimes fatal, may occur, particularly in elderly subjects (see Section 4.4).
Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, ulcerative stomatitis, abdominal pain, melena, hematemesis, exacerbation of colitis or Crohn's disease (see Section 4.4) have been reported further to administration of NSAIDs. Cases of gastritis have been observed less commonly.

Edema, hypertension and heart failure have been reported in patients treated with NSAIDs. Bullous reactions (Stevens-Johnson syndrome and Lyell's syndrome) have been observed in very rare cases.

Undesirable effects have been ranked by incidence, using the following system:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000), frequency unknown (cannot be estimated from the available data)

**Gastrointestinal disorders**

- common: dyspepsia, nausea, abdominal pain, gastric pain, vomiting,
- uncommon: diarrhea, constipation, flatulence, gastritis,
- rare: stomatitis, peptic ulcer, colitis,
- frequency unknown: exacerbation of colitis, Crohn's disease, gastrointestinal bleeding, and perforation.

At a dose of 200 mg per day, oral ketoprofen causes an increase in occult gastrointestinal bleeding. The incidence of this effect increases with dose and treatment duration.

**Immune system disorders**

- frequency unknown: angioedema, anaphylactic reactions (including anaphylactic shock).

**Skin and subcutaneous tissue disorders**

- uncommon: eruption, rash, pruritus,
- frequency unknown: urticaria, exacerbation of chronic urticaria, photosensitivity, alopecia, and bullous dermatoses (Stevens-Johnson syndrome and Lyell's syndrome).

**Respiratory, thoracic and mediastinal disorders**

- rare: asthma attack,
- frequency unknown: bronchospasm, particularly in subjects allergic to aspirin and to other NSAIDs, rhinitis.

**Nervous system disorders**

- uncommon: headache, dizziness, drowsiness,
- rare: paresthesia,
- frequency unknown: seizures, taste disorders.

**Psychiatric disorders**

- frequency unknown: mood disorders.

**Eye disorders**

- rare: blurred vision.

**Ear and labyrinth disorders**

- rare: tinnitus.

**Renal and urinary disorders**

- water and sodium retention, hyperkalemia (see Sections 4.4 and 4.5),
- functional acute renal failure (ARF) in patients with risk factors (see Section 4.4),
- organic impairment of the kidneys which may result in ARF: isolated cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome and papillary necrosis have been reported.

**Blood and lymphatic system disorders**

- rare: anemia due to bleeding, leukopenia,
- frequency unknown: agranulocytosis, thrombocytopenia, bone marrow depression.

**Hepatobialiary disorders**

- rare: transaminases increased, hepatitis, bilirubin increased related to hepatic disorders.

**Cardiac disorders**

- uncommon: edema,
- frequency unknown: heart failure.

**Vascular disorders**

- frequency unknown: hypertension, vasodilation.

**General disorders**

- uncommon: fatigue,
- rare: weight gain.

**Effects related to the route of administration - suppositories**

Risk of local toxicity, increasing in frequency and intensity the longer the treatment duration, and the higher the dose and rate of administration. Rectal irritation, such as burning sensations, may occur

### 4.9. Overdose

Cases of overdose have been reported for ketoprofen doses of up to 2.5 g.

In adults, the main signs of overdose are headache, dizziness, drowsiness, lethargy, nausea, vomiting, diarrhea and abdominal or epigastric pain. Hypotension, respiratory depression and gastrointestinal bleeding have been observed in cases of serious poisoning.

There is no specific antidote

The patient must be immediately transferred to a specialized hospital setting where symptomatic treatment must be initiated to rehydrate the patient, monitor renal function, and correct possible acidosis.

If kidney failure occurs, the medicinal product may be eliminated by hemodialysis.

Gastric lavage may be performed or activated charcoal administered to limit ketoprofen absorption.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Anti-inflammatory and antirheumatic products, non-steroids, ATC code: M01AE03
(M: musculo-skeletal system)

Ketoprofen is a non-steroidal anti-inflammatory drug derived from aryl carboxylic acid, and belongs to the propionic group. It has the following properties:

- peripheral and central analgesic properties,
- antipyretic properties,
- anti-inflammatory properties,
- short-term inhibition of platelet function.

All of these properties are related to prostaglandin synthesis inhibition.

In several experimental models, a central analgesic effect was observed for ketoprofen, as with other NSAIDs.

### 5.2. Pharmacokinetic properties

**Absorption**

Successive serum level determinations after administration of a therapeutic dose show that ketoprofen is very rapidly absorbed. Peak serum concentrations were reached 60 to 90 minutes after oral administration.
After rectal administration, the time to peak serum concentration is 45 to 60 minutes.

When ketoprofen is administered with food, the absorption rate is slower, causing delayed and reduced peak plasma concentrations (Cmax). However, total bioavailability remains unchanged.

**Distribution**
Following oral administration, the mean plasma elimination half-life is approximately 1.5 to 2 hours.
Following rectal administration, the mean plasma elimination half-life is 2.2 hours.

Ketoprofen is 99% plasma protein bound.

Ketoprofen is distributed into and remains in synovial fluid at concentrations higher than serum concentrations after the 4$^{th}$ hour following oral administration.

It crosses the placental and blood-brain barriers.

The volume of distribution is approximately 7 l.

**Metabolism**

Biotransformation of ketoprofen is characterized by two processes: a very minor process (hydroxylation) and a largely predominant process (glucuronide conjugation).

Less than 1% of the administered ketoprofen dose is recovered unchanged in the urine, while the glucuronide metabolite accounts for approximately 65 to 75%.

**Excretion**

**Profenid® 50 mg hard capsules**

Within 5 days of oral administration, 75 to 90% of the dose is excreted by the renal route and 1 to 8% in the feces.

Ketoprofen excretion, mainly in the urine, is rapid since 50% of the administered dose is eliminated within 6 hours, irrespective of the route of administration.

**Pathophysiological changes**
- Elderly subjects: the absorption of ketoprofen does not change, but the elimination half-life is longer (3 hours).
- Patients with renal insufficiency: total clearance is prolonged in proportion to the extent of renal insufficiency.

**Profenid® 100 mg suppositories**

Ketoprofen excretion, mainly in the urine, is rapid since 50% of the administered dose is eliminated within 6 hours, irrespective of the route of administration.

**Pathophysiological changes**

- Elderly subjects: the elimination half-life is longer.
- Patients with renal insufficiency: total clearance is prolonged in proportion to the extent of renal insufficiency.

### 5.3. Preclinical safety data

Not applicable.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

**Profenid® 50 mg capsules**

Lactose monohydrate, magnesium stearate.
Composition of the hard capsule shell: yellow iron oxide (E172), titanium dioxide (E171), gelatin.

**Profenid® 100 mg suppositories**

Hydrophobic silica colloidal anhydrous, hard fat.

### 6.2. Special precautions for storage

**Profenid® 50 mg capsules**

Store protected from moisture at a temperature not exceeding 25° C.

**Profenid® 100 mg suppositories**

Store at a temperature not exceeding 25° C.

## 7. MANUFACTURER

**Profenid® 50 mg hard capsules**

- FAMAR HEALTHCARE SERVICES MADRID S.A.U., Spain.

**Profenid® 100 mg suppositories**

- Unither Liquid Manufacturing, France.

## 8. MARKETING AUTHORIZATION HOLDER

**Sanofi-aventis Israel ltd.**