Package Leaflet: Information For The User

Keral 50 mg/2 ml
solution for injection/infusion

Dexketoprofen

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Keral is and what it is used for
2. What you need to know before you use Keral
3. How to use Keral
4. Possible side effects
5. How to store Keral
6. Contents of the pack and other information

1. What Keral is and what it is used for

Keral is a pain killer from the group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
It is used to treat acute moderate to severe pain, when taking tablets is not appropriate, such as post-operative pain, renal colic (severe kidney pain) and low back pain.

2. What you need to know before you use Keral

Do not use Keral:

- If you are allergic to dexketoprofen or any of the other ingredients of this medicine (listed in section 6);
- If you are allergic to acetylsalicylic acid or to other non-steroidal anti-inflammatory medicines;
- If you have asthma or have suffered attacks of asthma, acute allergic rhinitis (a short period of inflamed lining of the nose), nasal polyps (lumps within the nose due to allergy), urticaria (skin rash), angioedema (swollen face, eyes, lips, or tongue, or respiratory distress) or wheezing in the chest, after taking acetylsalicylic acid or other non-steroidal anti-inflammatory medicines;
- If you have suffered from photoallergic or phototoxic reactions (a particular form of reddening and/or blistering of the skin exposed to sunlight) while taking ketoprofen (a non-steroidal anti-inflammatory drug) or fibrates (drugs used to lower the level of fats in the blood);
- If you have a peptic ulcer/ stomach or bowel bleeding or if you have suffered in the past from stomach or bowel bleeding, ulceration or perforation;
- If you have chronic digestive problems (e.g. indigestion, heartburn)
- If you have or have suffered in the past from stomach or bowel bleeding or perforation, due to previous use of non-steroidal anti-inflammatory drugs (NSAIDs) used for pain;
- If you have bowel disease with chronic inflammation (Crohn's disease or ulcerative colitis);
- If you have serious heart failure, moderate or serious kidney problems or serious liver problems;
- If you have a bleeding disorder or a blood clotting disorder;
- If you are severely dehydrated (have lost a lot of body fluids) due to vomiting, diarrhoea or insufficient intake of fluids;

- If you are in third trimester of pregnancy or breast feeding.

Warnings and precautions
Talk to your doctor or pharmacist before using Keral:

- If you have suffered in the past from a chronic inflammatory disease of the bowel (ulcerative colitis, Crohn's disease);
- If you have or have suffered in the past from the other stomach or bowel problems;
- If you are taking other medicines that increase the risk of peptic ulcer or bleeding, e.g. oral steroids, some antidepressants (those of the SSRI type, i.e. selective serotonin reuptake inhibitors), agents that prevent blood clots such as aspirin or anticoagulants such as warfarin. In such cases, consult your doctor before taking Keral: he/she may want you to take an additional medicine to protect your stomach (e.g. misoprostol or medicines that block the production of stomach acid);
- If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist; Medicines such as Keral may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment;
- If you are elderly: you may be more likely to suffer from side effects (see section 4). If any of these occur, consult your doctor immediately;
- If you suffer from allergy, or if you have had allergy problems in the past;
- If you have kidney, liver or heart problems (hypertension and/or heart failure) as well as fluid retention, or have suffered from any of these problems in the past;
- If you are taking diuretics or you suffer from very poor hydration and reduced blood volume due to an excessive loss of fluids (e.g. from excessive urination, diarrhoea or vomiting);
- If you are a woman with fertility problems (Keral may impair your fertility, therefore you should not use it if you are planning to become pregnant or you are doing fertility tests);
- If you are in the first or second trimester of pregnancy;
- If you suffer from a disorder in the formation of blood and blood cells;
- If you have systemic lupus erythematosus or mixed connective tissue disease (immune system disorders that affect connective tissue);
- If you have an infection - please see heading "Infections" below;
- If you suffer from asthma combined with chronic rhinitis, chronic sinusitis, and/or nasal polyposis as you have a higher risk of allergy to acetylsalicylic acid and/or NSAIDs than the rest of the population. Administration of this medicine can cause asthma attacks or bronchospasm, particularly in patients allergic to acetylsalicylic acid or NSAIDs.

Infections
Keral may hide signs of infections such as fever and pain. It is therefore possible that Keral may delay appropriate treatment of infection, which may lead to an increased risk of complications. This has been observed in pneumonia caused by bacteria and bacterial skin infections related to chickenpox. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor without delay.
During chicken pox it is advisable to avoid use of this medicine.

Children and adolescents

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

Other medicines and Keral
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. There are some medicines that should not be taken together and others that may need their doses to be altered when taken together.
Always inform your doctor, dentist or pharmacist if you are using or receiving any of the following medicines in addition to Keral:

Inadvisable combinations:
- Acetylsalicylic acid, corticosteroids or other anti-inflammatory drugs
- Warfarin, heparin or other medicines used to prevent blood clots
- Lithium, used to treat certain mood disorders
- Methotrexate (anti-cancer medicine or immunosuppressant), used at high doses of 15 mg/week
- Hydantoins and phenytoin, used for epilepsy
- Sulfamethoxazole, used for bacterial infections

Combinations requiring precautions:
- ACE inhibitors, diuretics, and angiotensin II antagonists, used for high blood pressure and heart problems
- Pentoxifylline and oxpentifylline, used to treat chronic venous ulcers
- Zidovudine, used to treat viral infections
- Aminoglycosides antibiotics, used to treat bacterial infections
- Sulfonylureas (e.g. chlorpropamide and glibenclamide) used for diabetes
- Methotrexate, used at low doses, less than 15 mg/week

Associations to be considered carefully:
- Quinolone antibiotics (e.g. ciprofloxacin, levofloxacin) used for bacterial infections
- Cyclosporin or tacrolimus, used to treat immune system diseases and in organ transplant
- Streptokinase and other thrombolytic or fibrinolytic medicines, i.e. medicines used to break-up blood clots
- Probenecid, used in gout
- Digoxin, used to treat chronic heart failure
- Mifepristone, used as an abortifacient (to terminate a pregnancy)
- Antidepressants of the selective serotonin reuptake inhibitors type (SSRIs)
- Anti-platelet agents used to reduce platelet aggregation and the formation of blood clots
- Beta-blockers, used for high blood pressure and heart problems
- Tenofovir, deferasirox, pemetrexed

If you have any doubt about taking other medicines with Keral, consult your doctor or pharmacist.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use Keral during the final three months of the pregnancy or when breast feeding. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected. You should not take Keral during the first 6 months of pregnancy unless absolutely necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used.

If taken for more than a few days from 20 weeks of pregnancy onward, Keral can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment for longer than a few days, your doctor may recommend additional monitoring.
The use of Keral is not recommended while attempting to conceive or during investigation of infertility.
With regard to potential effects on female fertility, see also section 2, "Warnings and precautions".

Driving and using machines
Keral may slightly affect your ability to drive and handle machines, due to the possibility of dizziness or drowsiness as side effects of treatment. If you notice such effects, do not drive or use machines until the symptoms wear off. Ask your doctor for advice.

Keral contains ethanol and sodium
This medicine contains up to 200 mg of alcohol (ethanol) in each ampoule of 2 ml, which is equivalent to 3 mg/kg/dose (10% w/v). The amount in one ampoule (2 ml) of this medicine is equivalent to 5 ml beer or 2 ml wine.
The small amount of alcohol in this medicine will not have any noticeable effects.

This medicinal product contains less than 1 mmol sodium (23mg) per dosage unit, that is to say essentially "sodium-free".

3. How to use Keral

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. If you have an infection, consult a doctor without delay if symptoms (such as fever and pain) persist or worsen (see section 2).

Your doctor will tell you what is the dose of Keral that you need, according to the type, severity and duration of your symptoms. The recommended dose is generally 1 ampoule (50 mg) of Keral every 8 - 12 hours. If needed, the injection can be repeated after only 6 hours. Do not exceed a total daily dose of 150 mg of Keral (3 ampoules) in any case.
Use the injection treatment only in the acute period (i.e. no longer than two days). Switch to an oral pain killer when possible.
The elderly with renal dysfunction and patients with kidney or liver problems should not exceed a total daily dose of 50 mg of Keral (1 ampoule).

Method of administration:
Keral can be administered either by intramuscular or by intravenous route (technical details for the intravenous injection are given in the section 7**).**

When Keral is given intramuscularly, the solution should be injected immediately after its removal from the coloured ampoule, by slow injection deep into the muscle.
Only a clear and colourless solution should be used.

Use in children and adolescents
This medicine should not be used in children and adolescents (under age 18).

If you use more Keral than you should
If you use too much of this medicine, tell your doctor or pharmacist immediately or go to the emergency department of your nearest hospital. Please remember to take this medicine pack or this leaflet with you.

If you forget to use Keral
Do not use a double dose to make up for a forgotten dose. Use the next regular dose when it is due (according to section 3 "How to use Keral**"**).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Possible side effects are listed below according to how likely they are to occur.
Common side effects: may affect up to 1 in 10 people
Nausea and/or vomiting, injection site pain, injection site reactions, e.g. inflammation, bruising or haemorrhage.

Uncommon side effects: may affect up to 1 in 100 people
Vomiting blood, low blood pressure, fever, blurred vision, dizziness, sleepiness, sleep disturbances, headache, anaemia, abdominal pain, constipation, digestive problems, diarrhoea, dry mouth, flushing, rash, dermatitis, itching, sweating increased, tiredness, pain, feeling cold.

Rare side effects: may affect up to 1 in 1,000 people
Peptic ulcer, peptic ulcer haemorrhage or peptic ulcer perforation, high blood pressure, fainting, too-slow breathing, inflammation of a superficial vein due to a blood clot (superficial thrombophlebitis), isolated heart skip (extrasystole), fast heartbeat, peripheral oedema, laryngeal oedema, loss of appetite (anorexia), abnormal sensation, feeling feverish and shivering, ringing in the ears (tinnitus), itchy rash, jaundice, acne, back pain, renal pain, passing water frequently, menstrual disorders, prostate problems, muscle stiffness, joint stiffness, muscle cramp, abnormal liver tests (blood tests), increased blood sugar level (hyperglyceaemia), decreased blood sugar level (hypoglyceaemia), increased triglyceride fats concentration in blood (hypertriglyceridaemia), ketone bodies in the urine (ketonuria), proteins in the urine (proteinuria), liver cell injury (hepatitis), acute renal failure.

Very rare: may affect up to 1 in 10,000 people
Anaphylactic reaction (hypersensitive reaction which may also lead to a collapse), ulceration of the skin, mouth, eyes and genital areas (Stevens Johnson and Lyell's syndromes), facial swelling or swelling of the lips and throat (angioedema), breathlessness due to contraction of the muscles around the airways (bronchospasm), shortness of breath, pancreatitis, skin sensitivity reactions and skin over-sensitivity to light, renal damage, reduced white blood cell count (neutropenia), reduced platelet count (thrombocytopenia).

Tell your doctor immediately if you notice any stomach/bowel side effects at the start of treatment (e.g. stomach pain, heartburn or bleeding), if you have previously suffered from any such side effects due to long-term use of anti-inflammatory drugs, and especially if you are elderly.

Stop using Keral as soon as you notice the appearance of a skin rash, or any lesion on the mucous surfaces (e.g. the surface along the inside of the mouth), or any sign of allergy.

During treatment with non-steroidal anti-inflammatory drugs, fluid retention and swelling (especially in the ankles and legs), a raise in blood pressure and heart failure have been reported.

Medicines such as Keral may be associated with a small increased risk of heart attack ("myocardial infarction") or cerebrovascular accident (stroke).

In patients with systemic lupus erythematosus or mixed connective tissue disease (immune system disorders that affect connective tissue), anti-inflammatory medicines may rarely cause fever, headache and stiffness of the back of the neck.

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, worsening of colitis and Crohn's disease have been reported following administration. Less frequently, inflammation of the stomach lining (gastritis) has been observed.

As with other NSAIDs haematological reactions (purpura, aplastic and haemolytic anaemia, and rarely agranulocytosis and medullar hypoplasia) may appear.

Tell your doctor immediately if signs of infection occur or get worse whilst using Keral.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Keral

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the ampoule. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice that the solution is not clear and colourless, but shows signs of deterioration (e.g. particles). Keral solution for injection/ infusion is for single use only and should be used immediately once opened. Discard any unused quantity of the product (please see "disposal" subsection below).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use and how to properly dispose of your used needles and syringes. These measures will help to protect the environment.

6. Contents of the pack and other information

What Keral contains

- The active substance is dexketoprofen (as dexketoprofen trometamol). Each ampoule contains 50 mg of dexketoprofen.
- The other ingredients are alcohol (ethanol, see section 2, Keral contains ethanol and sodium), sodium chloride, sodium hydroxide and water for injections.

What Keral looks like and contents of the pack

Keral is a solution for injection/ infusion. It is supplied in packs containing 1, 5, 6, 10, 20, 50 and 100 type I glass coloured ampoules each one with 2 ml of a clear and colourless solution.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

MENARINI INTERNATIONAL O.L.S.A.
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Manufacturer

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or

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This medicinal product is authorised in the Member States of the European Economic Area under the following names:

Spain (RMS), Belgium, Finland, France, Italy, Luxembourg, Portugal: Ketesse
Cyprus, Greece: Nosatel
Austria, Czech Republic: Dexoket
Estonia, Latvia, Lithuania: Dolmen
Germany: Sympal

Hungary: Ketodex forte
Ireland, Malta: Keral
Poland:Dexak
Slovakia: Dexadol
Slovenia: Menadex
The Netherlands: Stadium

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7. Information for the Health Professional

The following information is intended for healthcare professionals only:

Intravenous use:

Intravenous infusion: the content of one ampoule (2 ml) of Keral should be diluted in a volume of 30 to 100 ml of Normal Saline, 5% glucose or ringer lactate solution. The diluted solution should be given 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) Keral can be given in a slow intravenous bolus over no less than 15 seconds.

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

Instructions on handling the product:
When Keral is given as intravenous bolus the solution should be injected immediately after its removal from the coloured ampoule.
For administration as intravenous infusion, the solution should be diluted aseptically and protected from natural daylight.
Only a clear and colourless solution should be used.

Compatibilities:
Keral has shown to be compatible when **mixed in small volumes** (e.g. in a syringe) with injectable solutions of heparin, lidocaine, morphine and theophylline.
The solution for injection diluted as indicated is a clear solution. Keral diluted **in a volume of 100 ml** of normal saline or glucose solution has been shown to be compatible with the following solutions for injection: dopamine, heparin, hydroxyzine, lidocaine, morphine, pethidine and theophylline.
No absorption of the active ingredient has been found when diluted solutions of Keral 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).