Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Keral 12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: dexketoprofen 12.5 mg as dexketoprofen trometamol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.
White, round film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of pain of mild to moderate intensity, such as musculo-skeletal pain, dysmenorrhoea, dental pain.

4.2 Posology and method of administration

Posology

Adults
According to the nature and severity of pain, the recommended dosage is generally 12.5 mg every 4-6 hours or 25 mg every 8 hours. The total daily dose should not exceed 75 mg. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). Keral tablets are not intended for long term use and the treatment must be limited to the symptomatic period.

Elderly
In elderly patients it is recommended to start the therapy at the lower end of the dosage range (50 mg total daily dose). The dosage may be increased to that recommended for the general population only after good general tolerance has been ascertained.

Hepatic impairment
Patients with mild to moderate hepatic dysfunction should start therapy at reduced doses (50 mg total daily dose) and be closely monitored. KERAL tablets should not be used in patients with severe hepatic dysfunction.

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

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

Method of administration:
The tablet should be swallowed with a sufficient amount of fluid (e. g. one glass of water). Concomitant administration with food delays the absorption rate of the drug (see Pharmacokinetic Properties), thus in case of acute pain it is recommended that administration is at least 30 minutes before meals.

4.3 Contraindications

Keral tablets must not be administered in the following cases:

- patients hypersensitive to the active substance, to any other NSAID, or to any of the excipients listed in section 6.1.
- patients in whom substances with a similar action (e.g. acetylsalicylic acid, or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema.
- known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates
- patients with history of 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 bleedings 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).

4.4 Special warnings and precautions for use

Administer with caution in patients with a history of allergic conditions.
The use of Keral with concomitant other 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 GI and cardiovascular risks below).

Gastrointestinal safety

Gastrointestinal bleeding, ulceration or perforation which can be fatal, have 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 Keral, 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 the elderly.

Elderly: The elderly 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.

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

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and section 4.5). Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

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.

Elderly 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. Elderly 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 history of hypertension and/or mild to moderate heart failure. 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, since fluid retention and oedema have been reported in association with NSAIDs therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for dexketoprofen.

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 after careful consideration. Similar consideration should be made before initiating longer-term treatment of the 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. Therefore, the use of dexketoprofen in patients who are receiving other therapy that interferes with haemostasis, such as warfarin or other coumarins or heparins is not recommended (see Section 4.5).

Elderly 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. KERAL 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 Keral. 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 Keral in case of varicella.

Keral 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.

Paediatric population

The safe use in children and adolescents has not been established.

4.5 Interaction with other medicinal products and other forms of interactions

The following interactions apply to non-steroidal antiinflammatory drugs (NSAIDs) in general:

Inadvisable combinations:

- Other NSAIDs (including cyclooxygenase-2 selective inhibitors) and 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: there is an increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Lithium (described with several NSAIDs): NSAIDs increase blood lithium levels, which may reach toxic values (decreased renal excretion of lithium). This parameter therefore requires monitoring during the initiation, adjustment and withdrawal of treatment with dexketoprofen.
- Methotrexate, used at high doses of 15 mg/week or more: increased haematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory agents in general.
- Hydantoines and sulphonamides: the toxic effects of these substances may be increased.

Combinations requiring precautions:

- Diuretics, ACE inhibitors, antibacterial aminoglycosides and angiotensin II receptor antagonists: Dexketoprofen may reduce the effect of diuretics and 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 Special warnings and special precautions for use).
- Methotrexate, used at low doses, less than 15 mg/week: increased haematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory agents in general. Weekly monitoring of blood count during the first weeks of the combination. Increased surveillance in the presence of even mildly impaired renal function, as well as in the elderly.
- Pentoxyfilline: increased risk of bleeding. Increase 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: There is a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone, Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.
- Quinolone Antibiotics: Animal data indicate that high doses of quinolones in combination with NSAIDs can increase the risk of developing convulsions.
- Tenofovir: concomitant use with NSAID can increase plasma urea nitrogen and creatinine, renal function should be monitored in order to control a potential synergic influence on renal function.
- Deferasirox: concomitant use with NSAIDs can increase the risk of gastrointestinal toxicity. Close clinical monitoring is required when deferasirox is combined with these substances.
- Pemetrexed: concomitant use with NSAIDs may decrease pemetrexed elimination, therefore caution should be made when administering higher doses of NSAIDs. In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs doses should be avoided for 2 days before and 2 days following pemetrexed administration.

4.6 Fertility, pregnancy and lactation

Keral tablets are 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. Nevertheless, animal studies with dexketoprofen haven't shown reproductive toxicity (see 5.3). During the first and second trimester of pregnancy, dexketoprofen should not be given unless clearly necessary. If dexketoprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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

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

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

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

Breast-feeding

It is not known whether dexketoprofen is excreted in human milk. Keral is contraindicated during breast-feeding (see section 4.3).

Fertility

As with other NSAIDs, the use of Keral 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 should be considered.

4.7 Effects on ability to drive and use machines

Keral tablets may cause undesirable effects such as dizziness, visual disturbances or drowsiness. The ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in these cases.

4.8 Undesirable effects

The adverse events reported as at least possibly related with dexketoprofen in clinical trials, as well as the adverse reactions reported after the marketing of Keral tablets are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**
Blood and lymphatic system disorders				Neutropenia, thrombocytopenia
Immune system disorders			Laryngeal oedema	Anaphylactic reaction, including anaphylactic shock
Metabolism and nutrition disorders			Anorexia	
Psychiatric disorders		Insomnia, anxiety		
Nervous system disorders		Headache, dizziness, somnolence	Paraesthesia, syncope	
Eye disorders				Blurred vision
Ear and labyrinth disorders		Vertigo		Tinnitus
Cardiac disorders		Palpitations		Tachycardia
Vascular disorders		Flushing	Hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders			Bradypnoea	Bronchospasm, dyspnoea
Gastrointestinal disorders	Nausea and/or vomiting, abdominal pain, diarrhoea,	Gastritis, constipation, dry mouth, flatulence	Peptic ulcer, peptic ulcer haemorrhage or peptic ulcer perforation (see section	Pancreatitis

	dyspepsia.		4.4)	
Hepatobiliary disorders			Hepatocellular injury	
Skin and subcutaneous tissue disorders		Rash	Urticaria, acne, sweating increased	Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, facial oedema, photosensitivity reactions, pruritus
Musculoskeletal and connective tissue disorders			Back pain	
Renal and urinary disorders			Acute renal failure, Polyuria	Nephritis or nephrotic syndrome
Reproductive system and breast disorders			Menstrual disorder, prostatic disorder	
General disorders and administration site conditions		Fatigue, pain, asthenia, rigors, malaise	Peripheral oedema	
Investigations			Liver function test abnormal	

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

Oedema, hypertension and cardiac failure have been reported in association with NSAIDs 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; haematological reactions (purpura, aplastic and haemolytic anaemia, and 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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, immediately institute symptomatic therapy according to the patient's clinical condition. Activated charcoal should be administered if more than 5 mg/kg has been ingested by an adult or a child within an hour.
Dexketoprofen trometamol may be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 drug, which belongs to the non-steroidal anti-inflammatory group of drugs (M01AE).

Mechanism of action
The mechanism of action of non-steroidal antiinflammatory drugs 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 PG12 and thromboxanes (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 for 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. The onset of the analgesic activity was obtained in some studies at30 minutes post-administration. The analgesic effect persists for 4 to 6 hours.

5.2 Pharmacokinetic properties

Absorption
After oral administration of dexketoprofen trometamol to humans, the Cmax is reached at 30 min (range 15 to 60 min). When administered concomitantly with food, the AUC does not change, however the Cmax of dexketoprofen decreases and its absorption rate is delayed (increased tmax).

Distribution
The distribution half-life and elimination half-life valuesof dexketoprofen are 0.35 and 1.65 hours, respectively. As with other drugs with a high plasma protein binding (99%), its volume of distribution has a mean value below 0.25 l/kg. In multiple-dose pharmacokinetic studies, it was observed that the AUC after the last administration is not different from that obtained following a single dose, indicating that no drug accumulation occurs.

Biotransformation and elimination
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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and immunopharmacology. The chronic toxicity studies carried out in mice and monkeys gave a No Observed Adverse Effect Level (NOAEL)at doses 2 fold higher than maximum recommended human dose. In monkey, at higher doses,the main adverse effect observed were blood in faeces, decreased body weight gain and, at the highest dose, erosive gastrointestinal lesions. These effects appeared at doses determining a drug exposure 14-18 fold higher than that at the maximum recommended human dose.

There are not studies on the carcinogenic potential in animals.

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

Maize starch
Microcrystalline cellulose
Sodium starch glycollate
Glycerol distearate
Hypromellose
Titanium dioxide
Propylene glycol
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30ºC; keep the blister packs in the outer carton in order to protect from light.

6.5 Nature and contents of container

Tablets are provided in blister packs (PVC-aluminium blister)

10, 20, 30, 40, 50 or 500 film-coated tablets/pack

(Not all pack sizes may be marketed).

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare
1611 Luxembourg
Luxembourg

8 MARKETING AUTHORISATION NUMBER

PA0865/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06March 1998
Date of last renewal: 25 April 2006

10 DATE OF REVISION OF THE TEXT