Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Skudexa 75 mg/25 mg granules for oral solution in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains: 75 mg of tramadol hydrochloride and 25 mg of dexketoprofen (as dexketoprofen trometamol).

Excipient(s) with known effect: sucrose 2.7 g per sachet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral solution in sachet.
The granules are white to almost white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic short term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen.

4.2 Posology and method of administration

Posology
The recommended dosage is one sachet (corresponding to 75 mg of tramadol hydrochloride and 25 mg of dexketoprofen). Additional doses can be taken as needed, with a minimum dosing interval of 8 hours. The total daily dose should not exceed three sachets per day (corresponding to 225 mg of tramadol hydrochloride and 75 mg of dexketoprofen).

Skudexa is intended for short term use only and the treatment must be strictly limited to the symptomatic period and in any case not more than 5 days. Switching to a single agent analgesia should be considered according to pain intensity and response of the patient.
Undesirable effects may be minimised by using the lowest number of doses for the shortest duration necessary to control symptoms (see section 4.4).

Elderly:
In elderly patients the starting recommended dosage is one sachet; additional doses can be taken as needed with the minimum dose interval of 8 hours and not exceeding the total daily dose of 2 sachets (corresponding to 150 mg of tramadol hydrochloride and 50 mg of dexketoprofen). The dosage may be increased to a maximum of 3 sachets as recommended for the general population only after good general tolerance has been ascertained.
Limited data are available in patients over 75 years, therefore Skudexa should be used with caution in these patients (see section 4.4).

Hepatic impairment:
Patients with mild to moderate hepatic impairment should start therapy at reduced number of doses (total daily dose 2 sachets Skudexa) and be closely monitored.

Skudexa should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment:
The initial total daily dosage should be reduced to 2 sachets Skudexa in patients with mildly impaired renal function (creatinine clearance 60 – 89 ml / min) (see section 4.4).

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

Paediatric population
The safety and efficacy of Skudexa in children and adolescents have not been established. No data are available.
Therefore Skudexa should not be used in children and adolescents.

Method of administration
Oral use.
Dissolve the whole contents of each sachet in a glass of water; shake/ stir well to help to dissolve.
Prepared solution is colourless, opalescent. The obtained solution should be immediately ingested after reconstitution.
Concomitant administration with food delays the absorption rate of the drug (see section 5.2), for a faster effect Skudexamay be taken at least 30 minutes before meals.

4.3 Contraindications

The contraindications reported for dexketoprofen and tramadol as single agents should be taken into account.

Dexketoprofen must not be administered in the following cases:

- hypersensitivity to dexketoprofen, 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 active peptic ulcer/gastrointestinal haemorrhage or any history of gastrointestinal bleeding ulceration or perforation.;
- patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy;
- 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 impairment (creatinine clearance ≤59 ml/min);
- patients with severely impaired hepatic function (Child-Pugh C);
- patients with haemorrhagic diathesis and other coagulation disorders;
- patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

Tramadol must not be administered in the following cases:

- hypersensitivity to tramadol or to any of the excipients listed in section 6.1;
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products;
- in patients receiving MAO inhibitors, or who have taken them within the last 14 days (see section 4.5);
- in patients with epilepsy not adequately controlled by treatment (see section 4.4);
- severe respiratory depression.

Skudexa is contraindicated during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

The special warnings and precautions reported for dexketoprofen and tramadol as single agents should be taken into account.

Dexketoprofen
Administer with caution in patients with a history of allergic conditions.
The use of dexketoprofen with concomitant other NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal 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 dexketoprofen, the treatment should be withdrawn.
The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in older people.

As with all NSAIDs, any history of oesophagitis, gastritis and/or peptic ulcer must be identified 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 used with caution in 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.

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 aspartate transaminase (AST) also known as serum glutamic oxaloacetic transaminase (SGOT) and Alanine transaminase (ALT), also known as serum glutamic-pyruvic transaminase (SGPT). In case of a relevant increase in such parameters, therapy must be discontinued.

Cardiovascular and cerebrovascular safety
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAIDs therapy. Special caution should be exercised in patients with a history of cardiac disease, in particular those with previous episodes of heart failure as there is an increased risk of triggering heart failure.

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

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 long-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).

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 (see section 4.8). 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. Dexketoprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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.
Elderly are more likely to be suffering from impaired renal cardiovascular or hepatic function (see section 4.2).

Masking of symptoms of underlying infections
Dexketoprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When this medicine is administered for pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.
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 dexketoprofen in case of varicella.

Other information:
Particular caution is required in patients with:
- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- dehydration
- directly after major surgery.

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 dexketoprofen.
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).

Dexketoprofen should be administered with caution to patients suffering from haematopoietic disorders, systemic lupus erythematosus or mixed connective tissue disease.

This medicinal product contains 2.7 g of sucrose per dose, this should be taken into account in patients with diabetes mellitus.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

<u>Paediatric population</u>
The safety and efficacy of Skudexa in children and adolescents have not been established. Therefore Skudexa should not be used in children and adolescents.

Tramadol
Tramadol should be used with particular caution in addicted patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, or increased intracranial pressure.
In patients sensitive to opiates the product should be used with caution.
Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.
Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg).
In addition tramadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold (see section 4.5.). Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.
Tolerance, psychic and physical addiction may develop, especially after long-term use. In patients with a tendency to drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.
When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Skudexa and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Skudexa concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.
Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

CYP2D6 metabolism
Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing of opioid toxicity even at commonly prescribed doses. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children
There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical studies have been performed to evaluate the potential impact of drug-drug interactions on safety profile of Skudexa. However, those reported for dexketoprofen and tramadol as single agents should be taken into account.

Dexketoprofen

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

Concomitant use not recommended:

- Other NSAIDs (including cyclooxygenase-2 selective inhibitors) including high doses of salicylates (≥ 3 g/day): administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect.
- Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin, 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.
- Lithium (described with several NSAIDs): NSAIDs increase blood lithium levels, which may reach toxic values (decreased renal excretion of lithium). This parameter therefore requires monitoring during the initiation, adjustment and withdrawal of treatment with dexketoprofen.
- Methotrexate, used at high doses of 15 mg/week or more: increased haematological toxicity of methotrexate via a decrease in its renal clearance by anti-inflammatory agents in general.
- Hydantoines (including phenytoin) and sulphonamides: the toxic effects of these substances may be increased.

Combinations requiring precautions:

- Diuretics, Angiotensin-converting-enzyme (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 co-administration 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 and periodically thereafter. Co-administration of dexketoprofen and potassium-sparing diuretics can lead to hyperkalaemia. Monitoring of blood potassium concentrations is required (see section 4.4).
- Methotrexate, used at low doses, less than 15 mg/week: increased haematological toxicity of methotrexate via a decrease in its renal clearance by anti-inflammatory agents in general. Weekly monitoring of blood count during the first weeks of the combination. Increased surveillance in the presence of even mildly impaired renal function, as well as in the elderly.
- 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 glucurono conjugation and requires adjustment of the dose of dexketoprofen.
- Cardiac glycosides: NSAIDS may increase plasma glycoside concentration.
- Mifepristone: because of a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone, NSAIDS should not be used for 8-12 days after mifepristone administration.

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 potentialsynergic 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, thereforecaution 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.

Tramadol
Concomitant use not recommended:

- Tramadol should not be combined with Monoamine Oxidase (MAO) inhibitors (see section 4.3). In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with tramadol.
- Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of elevated International Normalized Ratio (INR) with major bleeding and ecchymoses in some patients.
- The combination of mixed agonists/antagonists opioid receptors (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Combinations requiring precautions:

- Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal product (such as bupropion, mirtazapine, tethrahydrocannabinol) to cause convulsions.
- Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).
- The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Combinations needing to be taken into account:

- Concomitant administration of tramadol with other centrally depressant medicinal products or alcohol may potentiate the central nervous system effects (see section 4.8).
- The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.
- Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.
- In a limited number of studies the pre- or postoperative administration of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.
- Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No cases of pregnancy occurred during the Skudexa clinical development. The safety profile of Skudexa during pregnancy has not been established in the clinical studies included in this section. Data reported for dexketoprofen and tramadol as single agents should be taken into account.

Dexketoprofen

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 section 5.3).

From the 20th week of pregnancy onward, dexketoprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see below);

At the end of pregnancy, the mother and the neonate may be exposed to:

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

Tramadol

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy.

Tramadol – administered before or during birth – does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Considering the above Skudexa is contraindicated in pregnancy (see section 4.3).

Breast-feeding
No controlled trials have been conducted to study the excretion of Skudexa in human milk. Data reported for dexketoprofen and tramadol as single agents should be taken into account.

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

Tramadol
Tramadol and its metabolites are found in small amounts in human breast milk.

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Considering the above Skudexa is contraindicated during breastfeeding (see section 4.3).

Fertility
As with other NSAIDs, the use of dexketoprofen 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

The effects known for the single components of Skudexa apply to the fixed combination.

Dexketoprofen
Dexketoprofen has minor or moderate influence on the ability to drive and use machines, due to possible occurrence of dizziness or somnolence.

Tramadol
Even when taken according to instructions, tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators.
This applies particularly in conjunction with other psychotropic substances and alcohol.

4.8 Undesirable effects

The adverse events at least possibly related reported in the clinical trials performed with Skudexa and the adverse reactions reported in dexketoprofen and tramadol oral formulations SmPCs are tabulated below, classified by system organ class.

The frequencies are defined as follows:
Very common: ≥ 1/10
Common: ≥ 1/100 to <1/10
Uncommon: ≥1/1000 to <1/100
Rare: ≥ 1/10 000 to <1/1000
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

MedDRA SYSTEM ORGAN CLASS	Adverse Reaction	Frequency		
		Skudexa	Dexketoprofen	Tramadol
Blood and lymphatic system disorders	Thrombocytosis	Uncommon		
	Neutropenia,		Very rare	
	thrombocytopenia		Very rare	

Immune system disorders	Hypersensitivity (e.g. dyspnoea, bronchospasm, wheezing, Angioedema)		Very rare	Rare
	Anaphylactic reaction, including anaphylactic shock		Very rare	Rare
	Laryngeal oedema	Uncommon	Rare	
Metabolism and nutrition disorders	Appetite disorder			Rare
	Decreased appetite		Rare	
	Hypoglycaemia			not known
	Hypokalaemia	Uncommon		
Psychiatric disorders	Anxiety		Uncommon	Rare
	Cognitive disorder			Rare
	Confusional state			Rare
	Dependence			Rare
	Hallucination			Rare
	Insomnia		Uncommon	
	Mood altered			Rare
	Nightmare			Rare
	Psychotic disorder	Uncommon		
	Sleep disorder			Rare
Nervous system disorders	Coordination abnormal			Rare
	Amnesia	Uncommon		
	Dizziness	Common	Uncommon	Very common
	Epilepsy			Rare
	Headache	Uncommon	Uncommon	Common
	Muscle contractions involuntary			Rare
	Paraesthesia		Rare	Rare
	Sensory disturbance			Rare
	Serotonin syndrome			Not known
	Somnolence	Common	Uncommon	Common
	Speech disorder			not known
	Syncope		Rare	Rare
	Tremor			Rare
Eye disorders	Blurred vision		Very rare	Rare
	Mydriasis			not known
	Miosis			Rare
	Periorbital oedema	Uncommon		
Ear and labyrinth disorders	Tinnitus		Very rare	
	Vertigo	Uncommon	Uncommon	
Cardiac disorders	Bradycardia			Rare
	Palpitations		Uncommon	Uncommon
	Tachycardia	Uncommon	Very rare	Uncommon
Vascular disorders	Circulatory collapse			Uncommon
	Flushing		Uncommon	
	Hypertensive crisis	Uncommon		
	Hypotension	Uncommon	Very rare	
	Orthostatic hypotension			Uncommon
Respiratory, thoracic and mediastinal disorders	Bradypnoea,		Rare	

	Bronchospasm		Very rare	
	Dyspnoea		Very rare	Rare
	Respiratory depression			Uncommon
	Hiccups			Not known
Gastrointestinal disorders	Abdominal discomfort	Uncommon		Uncommon
	Abdominal distension	Uncommon		Uncommon
	Abdominal pain		Common	
	Constipation	Uncommon	Uncommon	Common
	Diarrhoea		Common	Uncommon
	Dry mouth		Uncommon	Common
	Dyspepsia	Uncommon	Common	
	Flatulence		Uncommon	
	Gastritis		Uncommon	
	Gastrointestinal tract irritation		Uncommon	
	Nausea	Common	Common	Very common
	Pancreatitis		Very rare	
	Peptic ulcer haemorrhage		Rare	
	Peptic ulcer perforation		Rare	
	Peptic ulcer,		Rare	
	Retching			Uncommon
	Vomiting	Common	Common	Common
Hepatobiliary disorders	Hepatitis		Rare	
	Hepatocellular injury		Rare	
	Hepatic enzyme increased including Liver function test abnormal and Gamma-glutamyl transferase increased	Uncommon	Rare	Very rare
Skin and subcutaneous tissue disorders	Acne		Rare	
	Face oedema	Uncommon	Very rare	
	Hyperhidrosis	Uncommon	Rare	Common
	Photosensitivity reaction		Very rare	
	Pruritus		Very rare	Uncommon
	Rash		Uncommon	Uncommon
	Stevens Johnson syndrome		Very rare	
	Toxic epidermal necrolysis (Lyell's syndrome)		Very rare	
	Urticaria	Uncommon	Rare	Uncommon
Musculoskeletal and connective tissue disorders	Back pain		Rare	
	Weakness			Rare
Renal and urinary disorders	Dysuria			Rare
	Haematuria	Uncommon		
	Micturition disorder			Rare
	Nephritis		Very rare	
	Nephrotic syndrome		Very rare	
	Polyuria		Rare	
	Renal failure acute		Rare	
	Urinary retention			Rare
Reproductive system and breast disorders	Menstrual disorder		Rare	
	Prostatic disorder		Rare	

General disorders and administration site conditions	Asthenia	Uncommon	Uncommon	
	Chills	Uncommon	Uncommon	
	Discomfort	Uncommon		
	Feeling abnormal	Uncommon		
	Drug withdrawal syndrome (agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms: rare; panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus, and unusual CNS symptoms-i.e. confusion, delusions, depersonalisation, derealisation, paranoia)			Rare/very rare
	Fatigue		Uncommon	Common
	Malaise	Uncommon	Uncommon	
	Oedema peripheral		Rare	
	Pain		Uncommon	
Investigations	Blood pressure increased	Uncommon	Rare	Rare
	Blood alkaline phosphatase increased	Uncommon		
	Blood lactate dehydrogenase increased	Uncommon		

Dexketoprofen-tramadol
In clinical studies the most commonly observed adverse reactions were nausea, somnolence, vomiting and dizziness (3.8%, 3.6%, 3.0% and 2.8% of patients, respectively).

Dexketoprofen
Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 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 increase in the risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Tramadol
The most commonly reported adverse reactions due to tramadol are nausea and dizziness, both occurring in more than 10% of patients.
If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5) respiratory depression may occur.
Worsening of asthma has been reported, though a causal relationship has not been established.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with drugs, which can lower the seizure threshold or themselves induce cerebral convulsions (see section 4.4 and section 4.5).

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows; agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus, and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

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 the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

No cases of overdose have been reported in the clinical studies. Data reported for dexketoprofen and tramadol as single agents should be taken into account.

Symptoms

Dexketoprofen
The symptomatology following overdose due to dexketoprofen is not known.
Medicinal products containing dexketoprofen have produced gastrointestinal (vomiting, anorexia, abdominal pain) and neurological (somnolence, vertigo, disorientation, headache) disorders.

Tramadol
In tramadol overdose, in principle, the same symptoms occur as for all other central acting analgesics (opioids). In particular, these include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest. Serotonin syndrome has also been reported.

Management

Dexketoprofen
In case of accidental or excessive intake, immediately initiate symptomatic therapy according to the patient's clinical condition. If more than 5 mg/kg has been ingested by an adult or a child, activated charcoal should be administered within the first hour after ingestion. Dexketoprofen may be removed by dialysis.

Tramadol
Keep the respiratory tract open (and avoid aspiration), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such case diazepam should be given intravenously.
In case of orally intoxication, gastrointestinal decontamination with activated charcoal is recommended within two hours after tramadol intake.

Tramadol may be removed by dialysis, but it is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics, ATC code: N02AJ14

Mechanism of action
Dexketoprofen 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).

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, $PGG_2$and PGH^2, which produce prostaglandins PGE^1, PGE^2, $PGF_{2\alpha}$and $PGD_2$and also prostacyclin $PGI_2$and thromboxanes ($TxA_2$and TxB^2). 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.

Dexketoprofen has been demonstrated to be an inhibitor for COX-1 and COX-2 activities in experimental animals and humans.

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. It is a non-selective, partial agonist of μ-, δ- and κ-opioid receptors with a higher affinity for μ-receptors. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding.
Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Tramadol has an antitussive action. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

Pharmacodynamic effects
Preclinical studies have shown a synergistic interaction between the active ingredients observed during both acute and chronic inflammation models and suggest that lower doses of each active ingredient allow to obtain effective analgesia.

Clinical efficacy and safety
Clinical studies performed on several models of moderate to severe nociceptive pain (including dental pain, somatic pain and visceral pain) demonstrated effective analgesic activity of Skudexa.

In a multiple-dose, double-blind, randomised, parallel group study in 606 patients with moderate to severe pain after abdominal hysterectomy, mean age 47.6 (range 25 to 73), the analgesic efficacy of the combination versus the individual components was assessed by means of the sum of pain intensity difference values over the interval of 8 hours (SPID8) after the first dose of study medication, with pain intensity been assessed on a 100 mm visual analogue scale (VAS). Higher value of SPID indicates greater pain relief. The treatment with Skudexa resulted in an analgesic effect significantly greater than those of the individual components given at the same dose (dexketoprofen 25 mg) or at a higher dose (tramadol 100 mg), being the results as follows: Skudexa (241.8), dexketoprofen 25 mg (184.5), tramadol 100 mg (157.3).

Over the first 8 hours following Skudexa, patients reported a significantly lower Pain Intensity (mean PI-VAS= 33.6) with a statistically significant ($p < 0.0001$) difference over dexketoprofen 25 mg (mean PI-VAS= 42.6) and tramadol 100 mg (mean PI-VAS= 42.9). Superior analgesia was also demonstrated over 56 hours following repeated doses administered according to the posology scheme in an ITT population in which patients who did not receive active treatment as first single dose were excluded, with statistically significant ($p < 0.0001$) difference between Skudexa and dexketoprofen 25 mg (-8.4) and tramadol 100 mg (-5.5).

Patients treated with Skudexa were in need of less rescue medication to control pain (11.8% of patients in comparison with 21.3% ($p = 0.0104$) and 21.4% ($p = 0.0097$) under dexketoprofen 25 mg and tramadol 100 mg, respectively). When the impact of rescue medication use is taken into account, the superior analgesic effect of Skudexa in the repeat use over 56 hours becomes more evident, reaching a difference in PI-VAS favouring Skudexa over dexketoprofen (-11.0) and tramadol (-9.1) with a statistical significance of $p = <0.0001$.

In a multiple-dose, double-blind, randomised, parallel group study in 641 patients with moderate to severe pain after total hip arthroplasty, mean age 61.9 (range 29 to 80), the analgesic efficacy of the combination versus the individual components was assessed over 8 hours after the first dose of study medication ($SPID^8$). The treatment with Skudexa resulted in an analgesic effect significantly greater than those of the individual components given at the same dose (dexketoprofen 25 mg) or at a higher dose (tramadol 100 mg); Skudexa (246.9), dexketoprofen 25 mg (208.8), tramadol 100 mg (204.6). Over the first 8 hours following Skudexa, patients reported a significantly lower Pain Intensity (mean PI-VAS= 26.3) with a statistically significant ($p < 0.0001$) difference over dexketoprofen 25 mg (mean PI-VAS= 33.6) and tramadol 100 mg (mean PI-VAS= 33.7).

Superior analgesia was also demonstrated over 56 hours following repeated doses administered according to the posology scheme in an ITT population in which patients who did not receive active treatment as first single dose were excluded, with statistically significant ($p < 0.0001$) difference between Skudexa and dexketoprofen 25 mg (-8.1) and tramadol 100 mg (-6.3), respectively.

Rescue medication to control pain was required by 15.5% of patients under Skudexa, in comparison with 28.0% ($p = 0.0017$) and 25.2% ($p=0.0125$) under dexketoprofen 25 mg and tramadol 100 mg, respectively. When the impact of rescue medication

use is taken into account, the superior analgesic effect of Skudexa in the repeat use over 56 hours becomes more evident, reaching a statistical (p= <0.0001) difference in PI-VAS favouring Skudexa over dexketoprofen (-10.4) and tramadol (-8.3).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Skudexa in all subsets of the paediatric population in the treatment of moderate to severe acute pain (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Concomitant administration of dexketoprofen and tramadol had no effects on the pharmacokinetic parameters of either component in healthy subjects.

One bioequivalence study in healthy volunteers was carried out to compare Skudexa 75 mg/25 mg granules for oral solution in sachet versus film-coated tablet. For dexketoprofen, the two formulations were bioequivalent in terms of the extent of bioavailability (AUC); peak concentrations (C_{max}) were approximately 15% higher after granules for oral solution compared to the film-coated tablet. Regarding tramadol, the two formulations were bioequivalent in terms of both rate and extent of absorption.

Dexketoprofen

Absorption
Dexketoprofen is rapidly absorbed after oral administration. When given as Skudexa 75 mg/25 mg granules for oral solution in sachets, detectable plasma concentrations are reached as early as 5 minutes (848.5 ng/mL, SD=459.51 ng/mL) and the C_{max} (3192.0 ng/mL) is achieved after 17 minutes (range 15 - 50 minutes). When administered concomitantly with food, the AUC does not change, however the C_{max} of dexketoprofen decreases and its absorption rate is delayed (increased t_{max}).

Distribution
The distribution half-life and elimination half-life values of 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 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.

Tramadol

Absorption
More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70%, irrespective of concomitant intake of food.

The difference between absorbed and non-metabolised available tramadol is probably due to low first-pass effect. The first-pass effect after oral administration is a maximum of 30%.

Tramadol has a high tissue affinity ($V_{d,\beta}$=203±40l). Protein binding is about 20%.

Tramadol is administered as a racemate and both the [+] and [-] enantiomers are detected in the circulation. When administered as Skudexa 75 mg/25 mg granules for oral solution in sachets, maximum plasma concentrations of [+] and [-] tramadol enantiomers are 158.9 and 142.0 ng/mL, respectively, and are achieved within 38 minutes (range 15 minutes - 2 hours).

Distribution
Tramadol passes the blood-brain and placenta barrier. Very small amounts of the substance and its O-desmethyl derivative are found in the breast milk (0.1 % and 0.02 % respectively of the applied dose).

Biotransformation

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 – 4. Its half-life $t_{½β}$ (6 healthy volunteers) is 7.9 h (range 5.4–9.6 h) and is approximately that of tramadol.

The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite.

Elimination
Elimination half-life $t_{½β}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml / min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case19.5 h and 43.2 h, respectively.

Linearity/non-linearity
Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 – 300 ng/ml is usually effective.

5.3 Preclinical safety data

Tramadol hydrochloride-dexketoprofen combination
Preclinical data with the combination revealed no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.
The combination of dexketoprofen and tramadol had not significant effect on cardiovascular system as assessed by both *in vitro* and *in vivo* tests. Less effect on gastrointestinal transit were observed with the combination as compared to tramadol alone.
A 13-week chronic toxicity study in rats, gave No Observed Adverse Effect Levels (NOAELs) of 6 mg/kg/day for dexketoprofen and 36 mg/kg/day for tramadol (highest tested doses), when administered both singularly or in combination (corresponding to AUC-based exposures at the NOAEL after single doses of 25.10 times and 1.38 times the human exposure to dexketoprofen and tramadol, respectively, at a single clinical dose of 25 mg dexketoprofen and 75 mg tramadol).
No new toxicities, different from those previously described for dexketoprofen or tramadol were observed.

Dexketoprofen
Preclinical data on dexketoprofen revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and immunopharmacology. The chronic toxicity studies carried out in mice and monkeys gave a No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day. The main adverse effect observed at high doses was gastrointestinal erosions and ulcers that developed dose-dependently.

Tramadol
In repeated oral and parenteral administration of tramadol during 6 to 26 weeks to rats and dogs and oral administration for 12 months in dogs haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.
In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.
In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects.
According to knowledge gained so far, tramadol can be classified as non-mutagenic.
Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased

incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Lemon Flavour
Acesulfame potassium (E-950)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Granules for oral solution are provided in sachets formed by thermo-sealed Paper/Aluminium/Polyethylene multilayer foil (as copolymer with vinylacetate) in a carton box.

Packs containing 2, 3, 10, 15, 20, 50, 100 and 500 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
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

PA0865/020/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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