Professional Information for SKUDEXA

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

SKUDEXA film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg tramadol hydrochloride and 25 mg dexketoprofen.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Almost white to slightly yellow, oblong, film-coated tablets with a break-mark on one side and a debossed “M” on the other side. The dimension of the film-coated tablet is approximately 14 mm in length and 6 mm in width.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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 film-coated tablet (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 film-coated tablets 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, with a maximum duration of 5 days. Switching to a single component medicine for 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 patients (≥ 65 years of age)

In elderly patients the starting recommended dosage is one film-coated tablet; additional doses can be taken as needed with the minimum dose interval of 8 hours and not exceeding the total daily dose of two film-coated tablets (corresponding to 150 mg of tramadol hydrochloride and 50 mg of dexketoprofen). The dosage may be increased to a maximum of 3 daily film-coated tablets as for adults < 65 years of age 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 dysfunction should not exceed a total daily dose of two film-coated tablets SKUDEXA and be closely monitored.
SKUDEXA should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment

The total daily dosage should be reduced to two film-coated tablets 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 < 18 years of age have not been established. No data are available.

Therefore SKUDEXA should not be used in children and adolescents < 18 years of age.

Method of administration

Oral use.

SKUDEXA should be swallowed with a sufficient amount of fluid (e.g. one glass of water) at least 30 minutes before a meal as concomitant administration with food delays the absorption rate of SKUDEXA (see section 5.2).

4.3 Contraindications

The contraindications reported for dexketoprofen and tramadol as single medicines, are contraindications for the use of SKUDEXA.

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 medicines with a similar action (e.g. acetylsalicylic acid, or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioedema.
- 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 dysfunction (creatinine clearance ≤ 59 mL/min).
- Patients with severe hepatic impairment (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).

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 medicines.
- 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.
- In patients with a head injury and a decreased level of consciousness.

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 medicines, apply to the use of SKUDEXA.

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 and cardiovascular risks below).

Gastrointestinal safety

Gastrointestinal bleeding, ulceration or perforation which can be fatal, have been reported with NSAIDs such as contained in SKUDEXA at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. When gastrointestinal bleeding or ulceration occurs in patients receiving SKUDEXA, the treatment should be discontinued.
The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in older people.
Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with SKUDEXA. Patients with gastrointestinal symptoms or history of gastrointestinal disease should be monitored for digestive disturbances, especially gastrointestinal bleeding.
SKUDEXA should not be given to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) (see section 4.3) as their condition may be exacerbated (see section 4.8).
Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any abdominal symptoms (especially gastrointestinal bleeding) during treatment with SKUDEXA.
Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet medicines such as acetylsalicylic acid (see section 4.5).

Renal safety

Caution should be exercised in patients with impairment of renal function. In these patients, the use of SKUDEXA may result in deterioration of renal function, fluid retention and oedema. The risk of nephrotoxicity is increased in patients on diuretic therapy and patients with hypovolaemia.

Adequate fluid intake should be ensured during treatment to prevent dehydration/hypovolaemia.

SKUDEXA can increase plasma urea and creatinine and is associated with nephrotoxicity which may present as glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute kidney injury (AKI) (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 function.
SKUDEXA can cause increases in liver function parameters, such as 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). Progressive significant increases in liver function parameters indicate deterioration of liver function, necessitating discontinuation of treatment.

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 such as contained in SKUDEXA. 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 precipitating heart failure. SKUDEXA should not be used in patients with severe cardiac failure (see section 4.3).

Clinical trial and epidemiological data suggest that use of NSAIDs such as contained in SKUDEXA may be associated with an increased 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 SKUDEXA after careful consideration.

SKUDEXA can inhibit platelet aggregation and prolong bleeding time via inhibition of prostaglandin synthesis. Therefore, the use of SKUDEXA in patients who are receiving other therapy that interferes with haemostasis, such as warfarin, other anticoagulants 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 in association with the use of NSAIDs, such as contained in SKUDEXA (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy. SKUDEXA should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients

The elderly has an increased frequency of adverse reactions to NSAIDs, such as contained in SKUDEXA especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). These patients should commence treatment on the lowest dose available.
Elderly patients are more likely to be suffering from impaired renal cardiovascular or hepatic function (see section 4.2).

Other information

Particular caution is required in patients with:

- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- dehydration/hypovolaemia
- directly after major surgery.

Severe acute hypersensitivity reactions (anaphylactic shock, for example) have been observed. Treatment must be discontinued and appropriate therapy initiated at the first signs of severe hypersensitivity reactions following intake of SKUDEXA.

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 SKUDEXA can cause asthma attacks or bronchospasm, particularly in subjects allergic to acetylsalicylic acid or NSAIDs (see section 4.3).
Varicella can cause serious cutaneous and soft tissues infectious complications. A contributing role of NSAIDs, such as contained in SKUDEXA in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of SKUDEXA in case of varicella.

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

SKUDEXA can mask the symptoms of infectious diseases. Aggravation of soft tissue infections have been described in temporal connection with the use of NSAIDs, such as contained in SKUDEXA.

Paediatric population

The safety and efficacy of SKUDEXA in children and adolescents < 18 years of age have not been established. Therefore SKUDEXA should not be used in children and adolescents < 18 years of age.

Tramadol-related special warnings and precautions

Due to the tramadol component, SKUDEXA 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 SKUDEXA should be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant medicines are being administered (see section 4.5), or if the recommended dosage is 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 medicines that lower the seizure threshold (see section 4.5). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances (see section 4.3).

Tolerance, psychic and physical addiction may develop with the use of SKUDEXA. There is an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders. In patients with a tendency to drug abuse or dependence, treatment with SKUDEXA should only be carried out for short periods under strict medical supervision. SKUDEXA has a maximum treatment duration of 5 days.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines

Concomitant use of SKUDEXA and sedative medicines such as benzodiazepines or related medicines 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).

CYP2D6 metabolism

Tramadol as contained in SKUDEXA, 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. 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 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 %

Use in children

There have been reports in the published literature that tramadol given post-operatively to children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, or in any child with compromised respiratory function from any cause, led to life-threatening adverse events. SKUDEXA is not for use in children or adolescents under 18 years of age (see sections 4.1 and 4.2).

SKUDEXA contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

No clinical studies have been performed to evaluate the potential impact of interactions on safety profile of SKUDEXA. However, those reported for dexketoprofen and tramadol as single medicines apply to the use of SKUDEXA.

Dexketoprofen

The following interactions apply to nonsteroidal anti-inflammatory drugs (NSAIDs) such as dexketoprofen in SKUDEXA:

Concomitant use not recommended

- 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 anticoagulants, 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 appropriate laboratory indicators 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 levels (decreased renal excretion of lithium). Lithium levels should be monitored during the initiation, adjustment and withdrawal of treatment with dexketoprofen as contained in SKUDEXA.

- Methotrexate, used at high doses of 15 mg/week or more: Increased haematological toxicity of methotrexate may occur due to a decrease in its renal clearance by anti-inflammatory medicines such as dexketoprofen contained in SKUDEXA.
- Hydantoins 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 medicines. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the coadministration of medicines 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 SKUDEXA 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).
- Methotrexate, used at low doses, less than 15 mg/week: Increased haematological toxicity of methotrexate may occur due to a decrease in its renal clearance by anti-inflammatory medicines, such as dexketoprofen contained in SKUDEXA. Frequent monitoring of the full blood count and renal function is indicated especially in elderly patients.
- Pentoxifylline: An increased risk of bleeding. Frequent clinical monitoring and checking of the bleeding time are required.
- Zidovudine: An increased risk of red cell line toxicity via action on reticulocytes, with severe anaemia during treatment with SKUDEXA. Check complete blood count and reticulocyte count during treatment with SKUDEXA.
- Sulfonylureas: SKUDEXA 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 SKUDEXA may decrease their antihypertensive effect via inhibition of prostaglandin synthesis.
- Ciclosporin and tacrolimus: Nephrotoxicity may be enhanced by SKUDEXA via renal prostaglandin mediated effects. During combination therapy, renal function should be monitored.
- Thrombolytics: Increased risk of bleeding.
- Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Probenecid: Plasma concentrations of dexketoprofen may be increased due to an inhibitory mechanism at the site of renal tubular secretion and of glucurono-conjugation. This may require adjustment of the dose of SKUDEXA.
- Cardiac glycosides (digoxin): SKUDEXA may increase plasma digoxin concentration.
- Mifepristone: Because of a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone, NSAIDs such as dexketoprofen in SKUDEXA 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 such as contained in SKUDEXA can increase the risk of developing convulsions.
- Tenofovir: Concomitant use with SKUDEXA, may increase plasma urea and creatinine, renal function should be monitored in order to detect impairment of renal function or deterioration thereof.
- Deferasirox: Concomitant use with SKUDEXA can increase the risk of gastrointestinal toxicity. Close clinical monitoring is required when deferasirox is combined with NSAID containing medicines such as SKUDEXA.
- Pemetrexed: Concomitant use with NSAIDs such as dexketoprofen may decrease

pemetrexed elimination, therefore caution is advised when administering higher doses of SKUDEXA. In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min), the concomitant administration of pemetrexed with SKUDEXA should be avoided for 2 days before and 2 days following pemetrexed administration.

Tramadol

Concomitant use not recommended

- Due to the tramadol component SKUDEXA 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 normalised ratio (INR) with major bleeding and ecchymoses in some patients.
- The combination of mixed opioid receptor agonist/antagonist medicines (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable because the analgesic effect of a pure agonist may theoretically be reduced in such circumstances.

Combinations requiring precautions

- Tramadol as contained in SKUDEXA 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 medicines (such as bupropion and mirtazapine) and including substances such as tetrahydrocannabinol to cause convulsions.
- Concomitant use of tramadol as contained in SKUDEXA and serotonergic medicines, 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 toxicity. Serotonin syndrome is likely when one of the following is observed: spontaneous clonus, inducible or ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, hypertonia and body temperature > 38 °C and inducible ocular clonus. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

- The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines 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 as contained in SKUDEXA with other centrally depressant medicines or alcohol may potentiate the central nervous system effects (see section 4.8).
- The results of pharmacokinetic studies have shown no clinically relevant interactions relating to previous administration or concomitant administration with cimetidine (enzyme inhibitor).
- 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) and 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

SKUDEXA is contraindicated during pregnancy and lactation (see section 4.3).

Dexketoprofen

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal 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 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo- fetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors such as contained in SKUDEXA 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 oligohydramnios;

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

Tramadol

Animal studies with tramadol as contained in SKUDEXA revealed at high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta and may induce respiratory depression in the neonate. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breastfeeding

SKUDEXA is contraindicated during breastfeeding (see section 4.3).

Dexketoprofen

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

Tramadol

Tramadol and its metabolites are found in human breast milk. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol.

Fertility

The use of SKUDEXA may impair female fertility and is not recommended in women attempting to conceive.

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 may cause dizziness and somnolence which impair the patient's ability to drive or to use machines.

Tramadol

Tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators.

4.8 Undesirable effects

The adverse events reported in the clinical trials performed with SKUDEXA and the adverse

reactions reported in dexketoprofen and tramadol oral formulations 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: ≥ 1/1 000 to < 1/100

Rare: ≥ 1/10 000 to < 1/1 000

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
	Dizziness	Common	Uncommon	Very common
	Epilepsy			Rare
	Headache	Uncommon	Uncommon	Common
	Muscle contractions involuntary			Rare
	Paraesthesia		Rare	Rare
	Sensory disturbance			Rare

	Somnolence	Uncommon	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
Gastrointestinal disorders	Abdominal discomfort			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	Menstrual disorder		Rare	

system and breast disorders	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 e.g. confusion, delusions, depersonalisation, derealisation, paranoia)			Rare/very rare
	Fatigue		Uncommon	Common
	Malaise		Uncommon	
	Oedema peripheral		Rare	

	Pain		Uncommon	
Investigations	Increased blood pressure	Uncommon	Rare	Rare
	Increased blood alkaline phosphatase	Uncommon		
	Increased blood lactate dehydrogenase	Uncommon		

Dexketoprofen-tramadol combination SKUDEXA

In clinical studies the most commonly observed adverse reactions were vomiting, nausea and dizziness (2,9 %, 2,7 % and 1,1 % 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 elderly patients, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Oedema, hypertension and cardiac failure have been reported in association with NSAIDs such as contained in SKUDEXA.

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 NSAIDs such as contained in SKUDEXA (particularly at high doses and in long-term treatment) may be associated with an increased 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 exceeded or if 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 have occurred especially after administration of high doses of tramadol or after concomitant treatment with medicines, 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).

Post-marketing experience

The following side effects have been reported for opioid containing medicines as contained in SKUDEXA:

Gastrointestinal disorders: Increased risk of abdominal pain, including pancreatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of SKUDEXA is important. It allows continued monitoring of the benefit/risk balance of SKUDEXA. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Data reported for dexketoprofen and tramadol as single medicines should be taken into account.

Symptoms

Dexketoprofen

In dexketoprofen overdose symptoms included gastrointestinal (vomiting, anorexia, abdominal pain) and neurological (somnolence, vertigo, disorientation, headache) adverse events.

Tramadol

In tramadol overdose, symptoms included miosis, vomiting, cardiovascular collapse, consciousness disorders, coma, convulsions, respiratory depression and respiratory arrest.

Management

Dexketoprofen

In case of accidental or excessive intake, immediately initiate symptomatic and supportive 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. When convulsions occur, a benzodiazepine such as 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, haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: propionic acid derivatives

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 nonsteroidal anti-inflammatory group of drugs (M01AE).

The mechanism of action of nonsteroidal anti-inflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway. There is inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG2 and PGH2, which produce prostaglandins PGE1, PGE2, PGF2α and PGD2 and also prostacyclin PGI2 and thromboxanes (TxA2 and TxB2). 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*. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Tramadol has an antitussive action. 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 suggesting that effective analgesia can be achieved by lower doses of each active ingredient, which was confirmed in clinical trials.

5.2 Pharmacokinetic properties

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

In normal healthy adults, peak plasma concentrations of dexketoprofen and tramadol are reached in about 30 min (range 15 to 60 min) and 1,6 to 2 hours, respectively.

Dexketoprofen

Absorption

After oral administration of dexketoprofen to humans, the C_{max} is reached at 30 min (range 15 to 60 min).

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. It has a high plasma protein binding (99 %), with a mean volume of distribution below

0,25 L/kg.

Multiple-dose pharmacokinetic studies indicated no dexketoprofen accumulation.

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 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1,6 to 2 h.

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. 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 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 < 15 mL/min) the values were 11 ± 3,2 h and 16,9 ± 3 h, in an extreme case 19,5 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 patients. A serum concentration of 100 – 300 ng/mL is usually effective.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Maize starch, pregelatinised

Croscarmellose sodium

Sodium stearyl fumarate

Silica colloidal, anhydrous.

Film-coating:

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol/PEG 3350

Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

The film-coated tablets are provided in PVC/PVDC/aluminium blisters.

Pack sizes: 15 or 20 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Menarini South Africa (Pty) Ltd

Waterside Place, Unit 02D, South Gate Office Park

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8. REGISTRATION NUMBER

SKUDEXA: 54/2.8/0538

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

18 May 2021

10. DATE OF REVISION OF THE TEXT

26 September 2025