Granules for Oral Solution

DOLKETO™-T

(Dexketoprofen + Tramadol HCl)

Sachet

25mg + 75mg

ڈول کیٹو-ٹی

(ڈیکسکیٹوپروفن + ٹراماڈول ہائیڈروکلورائیڈ) ساشے

۲۵ ملی گرام + ۷۵ ملی گرام

QUALITATIVE AND QUANTITATIVE DESCRIPTION

Each sachet contains:
Tramadol HCl U.S.P. 75mg
Dexketoprofen (As Dexketoprofen trometamol)....25mg
Innovator's Specifications

DESCRIPTION

This medicine contains the active substances tramadol hydrochloride and dexketoprofen. Tramadol hydrochloride is a painkiller that belongs to a group of medicines called opioids (strong painkillers) that act on the central nervous system (brain and spinal cord). It relieves pain by acting on certain nerve cells in the brain and spinal cord. Dexketoprofen is a painkiller that belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs: a group of painkillers with anti-inflammatory and antipyretic effects).

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.

DOSAGE AND ADMINISTRATION

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).

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 this medicine should be used with caution in these patients.

Hepatic impairment: Patients with mild to moderate hepatic impairment should start therapy at reduced number of doses (total daily dose 2 sachets) and be closely monitored. This medicine should not be used in patients with severe hepatic impairment
Renal impairment: The initial total daily dosage should be reduced to 2 sachets in patients with mildly impaired renal function (creatinine clearance 60 – 89 ml / min). This medicine should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤59 ml / min).

Paediatric Population: The safety and efficacy of this medicine in children and adolescents have not been established. No data are available. Therefore should not be used in children and adolescents.

Method of administration

Dissolve the whole contents of each sachet in a glass of water and stir well to dissolve.

The obtained solution should be immediately ingested after reconstitution.
Concomitant administration with food delays the absorption rate of the drug, for a faster effect this medicine may be taken at least 30 minutes before meals.

CLINICAL PHARMACOLOGY

Mechanism of action: The mechanism of action of non-steroidal anti-inflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway. Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG2 and PGH2, which produce prostaglandins PGE1, PGE2, PGF2α and PGD2 and also prostacyclin PGI2 and thromboxanes (TxA2 and TxB2). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as kinins, causing an indirect action which would be additional to the direct action. 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. 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.
Pharmacodynamics: 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.
Pharmacokinetics: Dexketoprofen: Absorption Dexketoprofen is rapidly absorbed after oral administration. When given as 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 Cmax (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 Cmax of dexketoprofen decreases and its absorption rate is delayed (increased tmax). 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%. 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. 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 t½ β 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.

CONTRAINDICATIONS

Dexketoprofen must not be administered in the following cases:

- patients hypersensitive to the active substance, to any other NSAID, or to any of the excipients.
- patients in whom substances with a similar action (e.g. acetylsalicylic acid, or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema.
- known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates - patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- patients with active peptic ulcer/gastrointestinal haemorrhage or any history of gastrointestinal bleeding, ulceration or perforation.
- patients with chronic dyspepsia.
- patients who have other active bleedings or bleeding disorders.
- patients with Crohn's disease or ulcerative colitis.
- patients with severe heart failure.
- patients with moderate to severe renal impairment (creatinine clearance ≤59 ml/min).
- patients with severely impaired hepatic function (Child-Pugh score 10 - 15). patients with haemorrhagic diathesis and other coagulation disorders.
- patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

Tramadol must not be administered in the following cases:

- hypersensitivity to tramadol or to any of the excipients.
- 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.
- in patients with epilepsy not adequately controlled by treatment.
- severe respiratory depression.

This medicine is contraindicated during pregnancy and lactation.

WARNINGS AND PRECAUTIONS

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. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms

Gastrointestinal safety: Gastrointestinal bleeding, ulceration or perforation which can be fatal, have been reported with all NSAIDs 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 dexketoprofen, the treatment should be withdrawn. 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. 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. 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.

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.

Liver Safety: Caution should be exercised in patients with impairment of hepatic functions. As with other NSAIDs, it can cause transient small increases in some liver parameters, and also significant increases in SGOT and SGPT. In case of a relevant increase in such parameters, therapy must be discontinued.

Cardiovascular and cerebrovascular safety: Appropriate monitoring and advice are required for patients with history of hypertension and/or mild to moderate heart failure. Special caution should be exercised in patients with a history of cardiac disease, in particular those with previous episodes of heart failure as there is an increased risk of triggering heart failure, since fluid retention and oedema have been reported in association with NSAIDs therapy. Consequently, patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with dexketoprofen after careful consideration.

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

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.

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, or if the recommended dosage is significantly exceeded as the possibility of respiratory depression cannot be excluded in these situations. In addition tramadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs: Concomitant use of this medicine 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 this medicine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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. Sleep-related breathing disorders: Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia.

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 & 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.

INTERACTIONS

	Concomitant use not recommended	Combinations requiring precautions	Combinations needing to be taken into account
Dexketoprofen	-Other NSAIDs -Anticoaglants -Heparins -Corticosteroids -Lithium -Methotrexate -Hydantoines and sulphonamides	-Diuretics, ACE inhibitors, antibacterial aminoglycosides and angiotensin II receptor antagonists -Methotrexate -Pentoxyfilline -Zidovudine Sulfonylureas	-Beta -blockers -Cyclosporin and tacrolimus -Thrombolytics -Probenecid -Cardiac glycosides -Mifepristone -Quinolone - Antibiotics -Tenofovir -Deferasirox -Pemetrexed
Tramadol	-Monoamine Oxidase (MAO) inhibitors -Coumarin derivatives (e.g. warfarin) -mixed agonists/antagonists opioid receptors (e.g. buprenorphine, nalbuphine, pentazocine)	-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) . -sedative medicines such as benzodiazepines or related drugs	-Centrally depressant medicinal products -Cimetidine (enzyme inhibitor) -Carbamazepine (enzyme inducer) -Ondansetron -CYP3A4 inhibitors, such as ketoconazole and erythromycin

DOSAGE: As directed by the physician.

INSTRUCTIONS: Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of childern.

DIRECTION FOR USE: Disolve the whole contents of each sachet in a glass of water and stir well to dissolve. The obtained solution should be immediately ingested after re-constitution.

PRESENTATION: DOLKETO™-T (Dexketoprofen + Tramadol HCl) 25mg + 75mg sachet are available in triplex foil of 10 sachets (1 x 10's) in a carton.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
طریقہ استعمال: ساشے کے اجزاء کو ایک گلاس سادے پانی میں اچھی طرح حل کریں اور فوراً استعمال کریں۔

Manufactured by:
Genix Pharma (Pvt.) Ltd.
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.genixpharma.com

Manufactured for:
Daneen Pharma (Pvt.) Ltd.
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@daneenpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.daneenpharma.com