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PROFESSIONAL INFORMATION FEBRUARY 2025

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DOLTREX 50 mg (Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DOLTREX 50 mg Film-coated tablet

Each film-coated tablet contains tramadol hydrochloride 50 mg. Contains sugar (Lactose monohydrate 125.30 mg).

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

DOLTREX film-coated tablet 50 mg:

White to off-white, capsule shaped, biconvex, film coated tablets debossed with “ML 4” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to moderately severe pain.

4.2 Posology and method of administration

Posology:

The dosage should be adjusted to the intensity of pain and the sensitivity of theindividual patient.

In principle, the lowest pain-relieving dose should be selected. In general, a total oraldaily dose of 400 mg of Tramadol (equivalent to 8 **DOLTREX** tablets) should not beexceeded.

The recommended dosages are guidelines.

DOLTREX tablets should be taken as follows:

Adults and children over 12 years

Moderate pain:

Initial dose of 50 mg of Tramadol (1 **DOLTREX** tablets), followed by 50 mg or 100 mg4-6 hourly.

Severe pain:

Initial dose of 100 mg followed by 50 mg or 100 mg 4-6 hourly.

Tablets are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

Special populations:

Paediatric population

On account of the high dosage strength, **DOLTREX** tablets are not intended forchildren below the age of 12 years.

Elderly patients

A downward adjustment of the dose and/or prolongation of the interval betweendoses are recommended in the elderly over 75 years.

Patients with renal insufficiency/dialysis

In patients with renal insufficiency, the elimination of tramadol hydrochloride isdelayed. In these patients prolongation of the dosage intervals should be carefullyconsidered according to the patient's requirements. In cases of severe renalinsufficiency **DOLTREX** tablets are not recommended.

Patients with hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride isdelayed. In these patients prolongation of the dosage intervals should be carefullyconsidered according to the patient's requirements. In cases of severe hepaticinsufficiency **DOLTREX** tablets are not recommended.

Duration of treatment

Under no circumstances should **DOLTREX** tablets be given for longer than absolutelynecessary. If the nature and severity of the disease require long-term pain treatment,careful checks should be carried out initially and at regular intervals to assess efficacyand adverse events and to what extent further treatment with **DOLTREX** tablets isnecessary.

***Method of administration*:**

Oral

Tablets are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

4.3 Contraindications

- Known hypersensitivity to tramadol hydrochloride or opioids or any of the ingredients of DOLTREX.
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines.
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
- **DOLTREX** tablets should not be given to patients with epilepsy.

DOLTREX tablets must not be used for narcotic withdrawal treatment.

DOLTREX tablets should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.

DOLTREX tablets should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

DOLTREX tablets should not be used in pregnant and breastfeeding women (see Section 4.6).

4.4 Special warnings and precautions for use

DOLTREX tablets may only be taken with special care in opioid dependence.

DOLTREX tablets are not suitable for children under the age of 12 years.

DOLTREX tablets should be used with care in patients with increased reactivity toopioids.

Respiratory depression may develop if the recommended dosages are exceeded orother centrally depressant medicines are given concomitantly.

DOLTREX tablets should not be used in the treatment of minor pain.

DOLTREX tablets should be used with caution in patients with impairment of hepaticand renal function and in patients prone to convulsive disorders or in shock. (seeSection 4.2).

Seizures

Seizures have been reported in patients receiving **DOLTREX** tablets at dosageswithin the recommended dosage range. The risk of seizures may be enhanced inpatients exceeding the recommended dose, or in patients taking tricyclic antidepressantsor other tricyclic compounds e.g. promethazine, selective serotonin reuptakeinhibitors, MAO-inhibitors and neuroleptics.

Drug Abuse and Dependence

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) maydevelop. **DOLTREX** tablets have been associated with craving drug-seekingbehaviour and tolerance development. Symptoms of drug withdrawal syndrome,similar to those occurring during opiate withdrawal, may occur as follows: agitation,anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinalsymptoms. Other symptoms that have been seen with **DOLTREX** tabletsdiscontinuation include: panic attacks; severe anxiety, hallucinations, paraesthesias,tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation,derealisation and paranoia).

DOLTREX tablets should not be used in opioid-dependent patientsor in patients with a family history of substance abuse or mental health issues.**DOLTREX** tablets can reinstate physical dependence in patients that have been previouslydependent or chronically using other opioids. In patients with a tendency to drugabuse, a history of drug dependence or who are chronically using opioids, treatmentwith **DOLTREX** tablets are not recommended.

CYP2D6 Ultra-rapid metabolism of tramadol:

Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its activemetabolite (M1) more rapidly and completely than other patients. This rapidconversion may lead to higher than expected serum M1 levels which could lead to anincreased risk of respiratory depression. Alternative

medication, dose reduction and/orincreased monitoring for signs of tramadol overdose, such as respiratory depressionis recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Hyponatraemia:

Hyponatraemia has been reported with the use of DOLTREX, usually in patients withpredisposing risk factors, such as elderly patients and/or patients using concomitantmedications that may cause hyponatraemia. This hyponatraemia appeared to be theresult of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) andresolved with discontinuation of **DOLTREX** and appropriate treatment (e.g. fluidrestriction). During **DOLTREX** treatment, monitoring for signs and symptoms ofhyponatraemia is recommended for patients with predisposing risk factors.

Lactose

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **DOLTREX.**

4.5 Interaction with other medicines and other forms of interaction

DOLTREX tablets should not be combined with MAO inhibitors within 14 days ofwithdrawal of 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 of the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with **DOLTREX** tablets.

Concomitant administration of **DOLTREX** tabletswith other centrally depressant medicines including alcohol may potentiate the CNS effects (see Section 4.3).

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

DOLTREX tablets can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants,

anti-psychotics and other seizure thresholdlowering medicinal products (such as bupropion, mirtazapine, tetra-hydrocannabinol) to cause convulsions.

Concomitant therapeutic use of **DOLTREX** tabletsand serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see Section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. The 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 or ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement.

Treatment depends on the type and severity of the symptoms.

Caution should be exercised during concomitant treatment with **DOLTREX** tabletsand warfarin–like medicines due to reports of increased International Normalised Ratio (INR) with major bleeding and ecchymoses in some patients.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved inthe biotransformation of tramadol may affect the plasma concentration of tramadol orits active metabolite.

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 (see Section 5.1).

The antiemetic 5-HT3 antagonist ondansetron increases the requirement of **DOLTREX** tablets in patients with postoperative pain. **DOLTREX** tablets may decrease the antiemetic efficacy of ondansetron.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy and lactation has not been established. Therefore, **DOLTREX** tablets should not be used in pregnant women. **DOLTREX** crosses the placenta.Animal studies with **DOLTREX** revealed effects on organ development, ossification and neonatal mortality. The administration of **DOLTREX** tablets during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see Section 4.3).

Breastfeeding

DOLTREX passes into breastmilk. Mothers on**DOLTREX** tablets should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

DOLTREX tablets may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired. This applies particularly in conjunction with other psychotropic medicines including alcohol.

4.8 Undesirable effects

Table 1: The following adverse reactions have been reported in association with **DOLTREX** Tablets:

System Organ Class	**Frequency**	**Undesirable effects**
Immune system disorders:	Less frequent	Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioedema) and anaphylaxis.
Metabolism and nutrition disorders	Less frequent	Changes in appetite.

System Organ Class	**Frequency**	**Undesirable effects**
Psychiatric disorders:	Less frequent	Hallucinations, confusional states, sleep disturbances, delirium, anxiety and nightmares. Changes in mood (euphoria, dysphoria), decreased activity, restlessness and changes in cognitive and sensorial capacity (such as decision behaviour, perception disorders).
Nervous system disorders:	Frequent	Dizziness headaches, somnolence
	Less frequent	Speech disorders, paraesthesia, tremor, convulsions, involuntary muscle contractions, abnormal coordination, syncope.
Eye disorders:	Less frequent	Miosis, mydriasis, blurred vision.
Cardiac disorders:	Less frequent	Dysrhythmias, palpitation, tachycardia. bradycardia.
Vascular disorders	Less frequent	Postural hypotension, cardiovascular collapse. increase in blood pressure.
Respiratory, thoracic and mediastinal disorders:	Less frequent	Respiratory depression, dyspnoea, bronchospasm.
Gastrointestinal disorders:	Frequent	Nauseavomiting, constipation, dry mouth.

System Organ Class	Frequency	Undesirable effects
	Less frequent	Retching, gastrointestinal discomfort, acute pancreatitis, abdominal pain
Hepatobiliary disorders:	Less frequent	Increase in transaminases (ALT and AST) is expected.
Skin and subcutaneous tissue disorders:	Frequent	Hyperhidrosis
	Less frequent	Dermal reactions (e.g. pruritus, rash, urticaria).
Musculoskeletal and connective tissue disorders	Less frequent	Muscular weakness.
Renal and urinary disorders	Less frequent	Micturition disorders (dysuria and urinary
General disorders and administration site conditions:	Frequent	Fatigue.

Post marketing experience

Nervous system complaints

Speech disorders.

Eye disorders

Mydriasis.

Skin and subcutaneous tissue disorders

Stevens Johnson Syndrome,

Toxic Epidermal Necrolysis.

Gastrointestinal disorders:

Increased risk of abdominal pain, including pancreatitis has been reported.

Frequency: rare

Cases of hyponatraemia and/or SIADH have been reported in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medications that may cause hyponatraemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9Overdose

Symptoms

Following an overdose with **DOLTREX** tablets, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular constriction of the pupil of the eye, vomiting, cardiovascular collapse, consciousness disorders, coma, convulsions, respiratory depression and respiratory arrest.

Treatment

The general emergency measures apply. Keep open the respiratory tract, maintainrespiration and circulation depending on the symptoms. Suitable measures should be taken to avoid aspiration dangers.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone).

Convulsions should be treated with intravenous diazepam.

In cases of intoxication with oral formulations, gastrointestinal decontamination with activated charcoal is only recommended within 2 hours after **DOLTREX** tablets intake.

Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with **DOLTREX** tablets with haemodialysis or haemofiltration alone is therefore not suitable for detoxification

5. PHARMACOLOGICAL PROPERTIES

Pharmaceutical groups:

A.2.9.Other analgesics

ATC code: N02AX02.

5.1 Pharmacodynamic properties

Tramadol hydrochloride is a centrally acting analgesic with binding to specific opioid receptors. It is a non-selective, agonist at mu (μ), delta (δ) and kappa (k) opioid receptors with a higher affinity for the μ receptor. Other mechanisms, whichcontribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenalineacts as an anti-inflammatory, analgesic and as well as the enhancement of serotonin release. The relationship between serumconcentrations and the analgesic effect is dose-dependent, but varies considerably. Patients devoid of CYP2D6 may need higher doses of tramadol, to achieve adequate analgesia.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of **DOLTREX** tablets, tramadol hydrochloride is absorbed with an absorption half-life ($t½_{ka}$) of 0, 38± 0, 18 hours.

Distribution

The mean systemic bioavailability is 68 %, independent of food intake.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

Biotransformation and Elimination

The elimination half-life is 5 to 7 hours. Tramadol is mainly metabolised in the liver (90 %).

Tramadol hydrochloride and its metabolites are almost completelyexcreted by the renal route (95 %). Biliary excretion of these components is quantitatively insignificant and is therefore subject to hepatic metabolism and renal elimination.

The terminal half-life (t½ β) is prolonged in impaired hepatic or renal function. In patients with liver cirrhosis, the mean t½ β of tramadol was 13, 3 ± 4, 9 h, t½, β/M1 18, 5 ±

9, 4 h, in patients with renal insufficiency (creatinine clearance ≤ 5 m//min) the valueswere 11, 0 ± 3, 2 h (tramadol) and 16, 9 ± 3, 0 h (M1) respectively.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and coating agent containing hypromellose 6 cPs, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

Contains sugar (lactose).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months from the manufacturing date

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the HDPE containers closed.

Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Container Pack

Tablets are packed in a round white opaque plastic container (HDPE) and are closed with a white closure, packed with or without outer carton. Pack sizes include 100 tablets

Blister Pack

Clear, transparent PVC 250 µm as the forming material and silver coloured, plain 25 µm aluminium foil/ 6 - 8 gsm HSL in a pre-printed outer carton.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

DOLTREX 50 MG: 52/2.9/0749

MAKLODOL 50 MG: 52/2.9/0750.749

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DOLTREX 50 MG: 15 FEBRUARY 2022

MAKLODOL 50 MG: 15 FEBRUARY 2022

10. DATE OF REVISION OF THE TEXT

24 December 2024