APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

DOLTREX 50 MG50 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 50 MG film-coated tablet:

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 the individual patient.

In principle, the lowest pain-relieving dose should be selected. In general, a total oral daily dose of 400 mg of Tramadol (equivalent to 8 **DOLTREX 50 MG** tablets) should not be exceeded.

The recommended dosages are guidelines.

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DOLTREX 50 MG tablets should be taken as follows:

Adults and children over 12 years

Moderate pain:

Initial dose of 50 mg of Tramadol (1 **DOLTREX 50 MG** tablets), followed by 50 mg or 100 mg 4-6 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 50 MG** tablets are not intended for children below the age of 12 years.

Elderly patients

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

Patients with renal insufficiency/dialysis

In patients with renal insufficiency, the elimination of tramadol hydrochloride is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal insufficiency **DOLTREX 50 MG** tablets are not recommended.

Patients with hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe hepatic insufficiency **DOLTREX 50 MG** tablets are not recommended.

Duration of treatment

Under no circumstances should **DOLTREX 50 MG** tablets be given for longer than absolutely necessary. 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 efficacy and adverse events and to what extent further treatment with **DOLTREX 50 MG** tablets is necessary.

***Method of administration*:**

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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 50 MG**.

- 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 50 MG** tablets should not be given to patients with epilepsy.

DOLTREX 50 MG tablets must not be used for narcotic withdrawal treatment.

DOLTREX 50 MG tablets should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.

DOLTREX 50 MG tablets should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

DOLTREX 50 MG tablets should not be used in pregnant and breastfeeding women (see Section 4.6).

4.4 Special warnings and precautions for use

DOLTREX 50 MG tablets may only be taken with special care in opioid dependence.

DOLTREX 50 MG tablets are not suitable for children under the age of 12 years.

DOLTREX 50 MG tablets should be used with care in patients with increased reactivity to opioids.

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

DOLTREX 50 MG tablets should not be used in the treatment of minor pain.

DOLTREX 50 MG tablets should be used with caution in patients with impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. (see Section 4.2).

Seizures

Seizures have been reported in patients receiving **DOLTREX 50 MG** tablets at dosages within the recommended dosage range. The risk of seizures may be enhanced in patients exceeding the recommended dose, or in patients taking tricyclic antidepressants or other tricyclic compounds e.g. promethazine, selective serotonin reuptake inhibitors, MAO-inhibitors and neuroleptics.

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Drug Abuse and Dependence

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop. **DOLTREX 50 MG** tablets have been associated with craving drug-seeking behaviour 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-intestinal symptoms. Other symptoms that have been seen with **DOLTREX 50 MG** tablets discontinuation include: panic attacks; severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation and paranoia).

DOLTREX 50 MG tablets should not be used in opioid-dependent patients. **DOLTREX 50 MG** tablets can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with **DOLTREX 50 MG** tablets are not recommended.

CYP2D6 Ultra-rapid metabolism of tramadol:

Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Hyponatraemia:

Hyponatraemia has been reported with the use of **DOLTREX 50 MG**, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of **DOLTREX 50 MG** and appropriate treatment (e.g. fluid restriction). During **DOLTREX 50 MG** treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Lactose

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Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **DOLTREX 50 MG.**

4.5 Interaction with other medicines and other forms of interaction

DOLTREX 50 MG tablets should not be combined with MAO inhibitors within 14 days of withdrawal 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 50 MG** tablets.

Concomitant administration of **DOLTREX 50 MG** tablets with 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 50 MG 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 threshold lowering medicinal products (such as bupropion, mirtazapine, tetra-hydrocannabinol) to cause convulsions.

Concomitant therapeutic use of **DOLTREX 50 MG** tablets and 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.

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Caution should be exercised during concomitant treatment with **DOLTREX 50 MG** tablets and 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 in the biotransformation of tramadol may affect the plasma concentration of tramadol or its 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 50 MG** tablets in patients with postoperative pain. **DOLTREX 50 MG** 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 50 MG** tablets should not be used in pregnant women. **DOLTREX 50 MG** crosses the placenta. Animal studies with **DOLTREX 50 MG** revealed effects on organ development, ossification and neonatal mortality. The administration of **DOLTREX 50 MG** 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 50 MG passes into breastmilk. Mothers on **DOLTREX 50 MG** tablets should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

DOLTREX 50 MG 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.

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4.8 Undesirable effects

Table 1: The following adverse reactions have been reported in association with **DOLTREX 50 MG** 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.
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.

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System Organ Class	Frequency	Undesirable effects
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	Nausea, vomiting, constipation, dry mouth.
	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,

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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.

4.9 Overdose

Symptoms

Following an overdose with **DOLTREX 50 MG** 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, maintain respiration 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 50 MG** tablets intake.

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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 50 MG** 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, which contribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenaline acts as an anti-inflammatory, analgesic and as well as the enhancement of serotonin release. The relationship between serum concentrations 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 50 MG** tablets, tramadol hydrochloride is absorbed with an absorption half-life ($t_{½\ ka}$) 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 %).

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Tramadol hydrochloride and its metabolites are almost completely excreted 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 values were 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

24 months from the manufacturing date

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the HDPE containers closed.

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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 child resistant closure, packed in an 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.

HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

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1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

REGISTRATION NUMBER

DOLTREX 50 MG: 52/2.9/0749

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DOLTREX 50 MG: 15 FEBRUARY 2022

DATE OF REVISION OF THE TEXT

14 April 2023

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