Professional Information for DOLOTRAM 50/100

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DOLOTRAM 50 solution for injection

DOLOTRAM 100 solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DOLOTRAM 50:

Each 1 mL ampoule contains 50 mg tramadol hydrochloride.

DOLOTRAM 100:

Each 2 mL ampoule contains 100 mg tramadol hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless solution**.**

The pH of the solution is between 5,8 and 7,5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to severe pain.

4.2 Posology and method of administration

Posology:

DOLOTRAM should not be used to treat minor pain.

Unless otherwise prescribed, DOLOTRAM should be administered as follows:

Single dose for adults and children older than 12 years of age:

IV: 100 mg – injected slowly or diluted in solution for infusion and infused.

IM: 100 mg.

SC: 100 mg.

The total daily dose should not exceed 400 mg of tramadol.

An intravenous injection must be given slowly over 2 to 3 minutes.

For post-operative pain, administer an initial bolus of 100 mg. During the 90 minutes following the initial bolus further doses of 50 mg may be given every 30 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 mg or 100 mg, 4 to 6 hourly up to a total daily dose of 600 mg.

For less severe pain administer 50 mg or 100 mg 4 to 6 hourly.

The dosage should be adjusted to the intensity of the pain and the individual's response to the analgesic action.

Special populations:

Elderly:

A downward adjustment of the dose and/or prolongation of the interval between doses are recommended for patients older than 75 years.

Renal impairment/dialysis:

In patients with renal impairment, the elimination of tramadol may be prolonged. It is recommended that the usual initial dosage be used, but the dosage interval should be increased to 12 hours. Haemodialysis or haemofiltration removes tramadol very slowly and therefore post-dialysis administration to maintain analgesia is not usually necessary. In cases of severe renal insufficiency, DOLOTRAM is not recommended.

Hepatic impairment:

In patients with hepatic impairment, the elimination of tramadol may be prolonged. It is recommended that the usual initial dosage be used, but the dosage interval should be increased to 12 hours. In cases of severe hepatic insufficiency, DOLOTRAM is not recommended.

Paediatric population:

DOLOTRAM is not recommended for children younger than 12 years (see section 4.3).

Duration of treatment:

Under no circumstances should DOLOTRAM 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 DOLOTRAM is necessary.

Method of administration:

DOLOTRAM may be administered intramuscularly, by slow intravenous injection or subcutaneously.

4.3 Contraindications

- DOLOTRAM is contraindicated in known hypersensitivity to tramadol hydrochloride or opioids,

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or in patients that have previously shown hypersensitivity to any of the excipients listed in section 6.1.

- DOLOTRAM should not be administered during acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids and other psychotropic medicines.
- It should not be given to patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- It should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.
- DOLOTRAM should not be administered to patients receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.
- DOLOTRAM must not be used for narcotic withdrawal treatment.
- DOLOTRAM should not be used in pregnant and breastfeeding women (see section 4.6).
- DOLOTRAM should not be given to patients with epilepsy.
- All children younger than 12 years of age (see section 4.4).
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

4.4 Special warnings and precautions for use

DOLOTRAM is likely to intensify and prolong the CNS effects of central nervous system depressant medicines. Respiratory depression may develop if the recommended dosages are exceeded, or other centrally depressant medicines are given concomitantly.

DOLOTRAM may only be used with special care in opioid dependence, patients with head injury, shock, a reduced level of consciousness of uncertain origin or disorders of the respiratory centre or function.

Seizures:

Seizures have been reported in patients receiving tramadol, as in DOLOTRAM, at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients taking tricyclic antidepressants or other tricyclic compounds (such as promethazine) or selective serotonin reuptake inhibitors, MAO inhibitors and neuroleptics. The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with a recognised risk for seizures, e.g. drug and alcohol withdrawal and intracranial infections, head trauma, metabolic disorders and naloxone treatment with tramadol overdose. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with DOLOTRAM.

Substance abuse and dependence:

Although DOLOTRAM has a low dependence potential, tolerance, psychic and physical dependence of the morphine-type (μ-opioid) may develop with long-term use. DOLOTRAM has been associated with craving, drug-seeking behaviour and tolerance development. Withdrawal does not develop in all cases and is not as severe as with other opioids. Symptoms of withdrawal syndrome similar to those occurring during opiate withdrawal may occur as follows: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis, palpitations, agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms (abdominal

cramps, nausea, vomiting, diarrhoea). Other symptoms that have been seen with DOLOTRAM discontinuation include: irritability, panic attacks or severe anxiety, weakness, insomnia, anorexia, increased blood pressure, increased respiratory rate or heart rate, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation-derealisation, paranoia).

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with DOLOTRAM.

Withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

DOLOTRAM is not a suitable substitute in opioid dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

If women take tramadol during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome (see section 4.6).

Cases of abuse and dependence (addiction) on DOLOTRAM have been reported, even at therapeutic doses. DOLOTRAM should not be used in opioid-dependent patients or should be used with care in patients with increased reactivity to opioids. DOLOTRAM can reinitiate physical dependence in patients that have been previously dependent or chronically using other opioids.

Treatment with DOLOTRAM is not recommended in patients with a tendency to substance abuse, or with a current or past history of substance dependence (including alcohol misuse), mental health disorder (e.g. major depression) or who are chronically using other opioids.

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse. A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained online, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.

The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death.

Patients should be closely monitored for signs of misuse, abuse or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Opioid-induced hyperalgesia:

Opioid-induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalised pain (i.e. less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

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.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Hyponatraemia:

Hyponatraemia has been reported with the use of DOLOTRAM, 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 DOLOTRAM and appropriate treatment (e.g. fluid restriction). During DOLOTRAM treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Sleep-related breathing disorders:

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

Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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

Concomitant use of DOLOTRAM 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 DOLOTRAM 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).

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 severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite and weight loss.

Serotonin syndrome:

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

If concomitant treatment with other serotonergic medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic medicines usually brings about a rapid improvement.

Other:

DOLOTRAM should be used with caution in patients with renal or hepatic function impairment or in patients prone to convulsion disorders or in shock (see section 4.2).

Rapid intravenous administration should be avoided as it may be associated with higher incidence of adverse events.

DOLOTRAM should not be used for the treatment of minor pain.

4.5 Interaction with other medicines and other forms of interaction

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

Quinidine (or other CYP2D6 inhibitors such as paroxetine) inhibits tramadol metabolism but the clinical nature of the consequences is not known.

Cimetidine does not interact with tramadol. Alcohol, CNS depressants and MAO inhibitors all dangerously potentiate the effects of DOLOTRAM (see section 4.3).

DOLOTRAM must not be combined with an MAO inhibitor, or within 14 days of discontinuation of it, as potentiation of serotonergic and noradrenergic effect may result (see section 4.3).

In patients treated with MAO inhibitors in the 14 days prior to the use of the 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 DOLOTRAM.

Inhibitors of 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 (see sections 4.8 and 5.2).

The antiemetic 5-HT3 antagonist ondansetron increases the requirement of DOLOTRAM in patients with post-operative pain. DOLOTRAM may decrease the antiemetic efficacy of ondansetron.

DOLOTRAM 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, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of DOLOTRAM 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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

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 DOLOTRAM and warfarin-like medicines due to reports of increased international normalised ratio (INR) with major bleeding and ecchymoses in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety during pregnancy has not been established (see section 4.3). Therefore, DOLOTRAM should not be used in pregnant women. DOLOTRAM crosses the placenta. DOLOTRAM (administered before or during birth) does not affect uterine contractility. In neonates it may induce changes in the respiratory rate.
The administration of DOLOTRAM injection during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see section 4.3).

Breastfeeding:

Safety during lactation has not been established (see section 4.3). DOLOTRAM passes into breast milk. Mothers on DOLOTRAM should not breastfeed their infants.

Fertility:

Post-marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

Patients should be warned not to operate machinery or drive a vehicle, as DOLOTRAM 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

The following side effects have been reported:

Immune system disorders:

Less frequent: Allergic reactions (dyspnoea, bronchospasm, wheezing, angioedema) and anaphylaxis.

Metabolism and nutrition disorders:

Less frequent: Changes in appetite.

Frequency unknown: Hypoglycaemia.

Psychiatric disorders:

Less frequent: Hallucinations, confusional states, sleep disturbance, delirium, anxiety, nightmares,

anorexia, changes in mood (euphoria, dysphoria), decreased activity, restlessness and changes in cognitive and sensorial capacity (such as decision behaviour, perception disorders).

Frequency unknown: Unusual CNS symptoms (i.e confusion, delusions, despersonalisation-derealisation, paranoia, drug dependence (see section 4.4).

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, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation-derealisation, paranoia).

Nervous system disorders:

Frequent: Dizziness, headache, drowsiness, somnolence.

Less frequent: Paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.

Frequency unknown: Serotonin syndrome.

Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicines which can lower the seizure threshold (see sections 4.4 and 4.5).

Eye disorders:

Less frequent: Blurred vision, miosis, mydriasis.

Cardiac disorders:

Less frequent: Dysrhythmias, cardiovascular regulation (palpitation, tachycardia), bradycardia.

These adverse reactions may occur especially with intravenous administration and in patients who are physically stressed.

Vascular disorders:

Less frequent: Cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially with intravenous administration and in patients who are physically stressed.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Respiratory depression, dyspnoea, bronchospasm. *Frequency unknown:* Hiccups.

If the recommended doses are considerably exceeded and other centrally depressant medicines are administered concomitantly (see section 4.5), respiratory depression may occur.

Worsening of asthma has been reported, but it has not been established whether it was caused by the active substance tramadol.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, constipation and dry mouth.

Less frequent: Retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), heartburn and diarrhoea.

Hepato-biliary disorders:

Less frequent: Increase in liver enzyme values.

In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders:

Frequent: Sweating (hyperhidrosis), flushing.

Less frequent: Dermal reactions (e.g. pruritus, rash, urticaria), toxic epidermal necrolysis and Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders:

Less frequent: Muscle weakness.

Renal and urinary disorders:

Less frequent: Difficulty in passing urine, dysuria, urinary retention.

General disorders and administration site conditions:

Frequent: Fatigue.

Less frequent: Withdrawal syndrome.

Investigations:

Less frequent: Increase in blood pressure.

Reporting of suspected adverse reactions:

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

4.9 Overdose

Symptoms of overdosage:

Symptoms are typical of opioids and include pinpoint pupils (constriction of pupils or miosis), vomiting, cardiovascular collapse, consciousness disorders, coma, convulsions. respiratory depression and respiratory arrest. Side effects of DOLOTRAM may be exacerbated (see section 4.8).

Serotonin syndrome has also been reported.

Treatment of overdose:

Depending on the symptoms, the general emergency measures apply. Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. Suitable measures should be taken to avoid aspiration dangers.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone). Naloxone may precipitate seizures and should be used cautiously.

Convulsions and/or restlessness can be treated with symptomatic and supportive therapy (benzodiazepines/barbiturates or intravenous diazepam).

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration and therefore it is not suitable for detoxification treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics.

Pharmacotherapeutic group: Analgesics, other opioids.

ATC code: N02AX02.

Tramadol is a centrally-acting synthetic opioid analgesic from the aminocyclohexanol group with binding to specific opioid receptors. Tramadol is not derived from the natural sources of opiates nor is it chemically related to opiates.

Tramadol is an opioid agonist at the μ (mu) receptors. It is an inhibitor of neuronal reuptake of noradrenaline and enhances serotonin release.

Tramadol causes significantly less respiratory and cardiac depression than morphine, pethidine and buprenorphine and possesses a much lower dependence potential. In contrast to morphine, tramadol does not promote the release of histamine.

Patients devoid of CYPD6 may need higher doses of tramadol to achieve adequate analgesia.

5.2 Pharmacokinetic properties

After intramuscular administration, tramadol has mean absolute bioavailability of 100 %.

After intravenous administration, tramadol is distributed rapidly. It crosses the blood-brain and placental barrier and is excreted in very small amounts in breast milk, unchanged or as metabolite M1. Plasma protein binding is 20 %. Plasma concentrations of tramadol are consistently well correlated with its analgesic activity.

Tramadol is mainly metabolised in the liver (90 %). Following the hepatic metabolism, tramadol hydrochloride and its metabolites are almost completely excreted via the renal route (95 %). The elimination half-life is 5 to 7 hours.

The terminal half-life is likely to be prolonged in patients with impaired hepatic or renal function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (pH adjuster).

Water for injection.

6.2 Incompatibilities

Precipitation will occur if DOLOTRAM is mixed in the same syringe with injections of diazepam, diclofenac sodium, indometacin, midazolam, piroxicam, flunitrazepam, glyceryl trinitrate and phenylbutazone.

6.3 Shelf life

Unopened ampoules:

24 months.

After first opening:

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after first opening of the ampoule, see section 6.3.

6.5 Nature and contents of container

DOLOTRAM 50: 1 mL clear glass OPC ampoule with a yellow ring and blue dot.

DOLOTRAM 100: 2 mL clear glass OPC ampoule with a maroon ring and blue dot.

Pack size:

5 ampoules are packed in a plastic tray per carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1, Roodepoort

Johannesburg 1724

8. REGISTRATION NUMBERS

DOLOTRAM 50: 36/2.9/0337

DOLOTRAM 100: 36/2.9/0338

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 November 2004

10. DATE OF REVISION OF THE TEXT

03 June 2022

Namibia Registration Details:

Scheduling status: NS3

DOLOTRAM® 50: 06/2.9/0170

DOLOTRAM® 100: 06/2.9/0171

Signed: