Mictra® Injection

(Tramadol HCl)

مِک ٹرا انجکشن

(ٹراماڈال ہائیڈروکلورائیڈ)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Mictra 100mg/2mL Injection
Each 2 mL contains:
Tramadol HCl BP……..100mg
(Product Specs: BP)

PHARMACEUTICAL FORM
Injection

CLINICAL PARTICULARS
Therapeutic indications
Mictra Injection is indicated for the treatment of moderate to severe pain
Mictra is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Posology and Method of Administration
Do not use concomitantly with other tramadol-containing products. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse.
The total daily dose of 400mg Mictra Injection should not be exceeded, except in special clinical circumstances. Unless otherwise prescribed, Mictra should be administered as follows:

Adults and adolescents above the age of 12 years:
The usual dose is 50 or 100mg 4-6 hourly. Intravenous injections must be given slowly over 2-3 minutes.
For post-operative pain administer an initial bolus of 100mg. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg - 100mg 4-6 hourly up to a total daily dose of 400mg.

Children: It is not suitable for children below the age of 12 years.

Geriatric patients
A dose adjustment is not usually necessary in elderly patients (up to 75 years) without clinically manifest hepatic or renal insufficiency. In elderly patients (over 75 years) elimination may be prolonged. Therefore, if necessary, the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis and hepatic insufficiency
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Method of administration
Mictra Injection is to be injected slowly or diluted in infusion solution and infused.

Duration of administration
It should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Mictra Injection is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out

Contraindications
Tramadol Injection is contraindicated.
- In hypersensitivity to tramadol in acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products.
- In patients who are receiving MAO inhibitors or who have taken them within the last 14 days.
- In patients with epilepsy not adequately controlled by treatment.
- For use in narcotic withdrawal treatment.

Special warnings and precautions for use
Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory center or function, increased intracranial pressure.

In patients sensitive to opiates tramadol should only be used with caution. Concomitant use of Tramadol Injection and sedating medicinal products such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol Injection concomitantly with sedating medicinal products, the lowest effective dose of Tramadol Injection should be used, and the duration of the concomitant treatment should be as short as possible.
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.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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.

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations. 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 drugs usually brings about a rapid improvement.

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). 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 on-line, 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. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
The opioid drug withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhea, increased blood pressure, increased respiratory rate or heart rate.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain.

CYP2D6 metabolism
Tramadol is metabolized 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.

Post-operative use in children
Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

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, and weight loss.
This medicine contains less than 1 mmol sodium (23mg) per 2mL, that is to say essentially 'sodium-free'

Interaction with other medicinal products and other forms of interaction
Tramadol should not be combined with MAO inhibitors. 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.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects. The concomitant use of opioids with sedating medicinal products such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose of Tramadol Injection and the duration of the concomitant use should be limited.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors(SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g., warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy:
Tramadol should not be used in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. Administration during labor may depress respiration in the neonate and an antidote for the child should be readily available.

Lactation:
Administration to nursing women is not recommended as tramadol may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility:
Post marketing surveillance does not suggest an effect of tramadol on fertility

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This medicine can impair cognitive function and can affect a patient's ability to drive safely.

UNDESIRABLE EFFECTS
The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients. The frequencies are defined as follows: Very common: ≥1/10 Common: ≥1/100, Uncommon: ≥1/1000, <1/100, Rare: ≥1/10 000, <1/1000, Very rare: <1/10 000, Not known: cannot be estimated from the available data.

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Cardiac Disorders	Uncommon	Cardiovascular regulation (palpitation, tachycardia)
	Rare	Bradycardia, increase in blood pressure
Vascular Disorders	Uncommon	Cardiovascular regulation (postural hypotension or cardiovascular collapse).
Metabolism and nutrition disorders	Rare	Changes in appetite
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression, dyspnea
	Not Known	Hiccups
Nervous system disorders	Very Common	Dizziness
	Common	Headache, somnolence
	Rare	Changes in appetite, tremor paranesthesia, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.
	Not Known	Serotonin syndrome
Psychiatric disorders	Rare	Hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares, changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g., decision behavior, perception disorders).
	Frequency not known	Drug dependence
Eye disorders:	Rare	Miosis, mydriasis, blurred vision
Gastrointestinal disorders	Very Common	Nausea
	Common	Constipation, dry mouth, vomiting
	Uncommon	Retching; gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhea
Skin and subcutaneous tissue disorders:	Common	Hyperhidrosis
	Uncommon	Dermal reactions (e.g., pruritus, rash, urticaria)
Musculoskeletal and connective tissue disorders:	Rare	Motorial weakness
Hepatobiliary disorders:	-	In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol
Renal and urinary disorders:	Rare	Micturition disorders (dysuria and urinary retention)
Immune system disorders:	Rare	Allergic reactions (e.g., dyspnea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
Metabolism and nutrition disorders:	Not Known	Hypoglycemia
General disorders and administration site conditions:	Common	Fatigue
	Uncommon	Drug withdrawal syndrome

Symptoms of drug withdrawal syndrome, 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, paranesthesia, tinnitus and unusual CNS symptoms (i.e., confusion, delusions, depersonalization, derealization, paranoia).

Overdose
Patients should be informed of the signs and symptoms of overdose. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest. Serotonin syndrome has also been reported.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group:
Analgesic other opioids; ATC code: N02AX02

Pharmacodynamic properties
Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also, gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight.

Pharmacokinetic properties
More than 90% of Tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. plasma concentrations were detectable within approximately 15 to 45 minutes within a mean Cmax of 280 to 208 mcg/L and Tmax of 1.6 to 2h.

Tramadol passes the blood-brain and placental barriers. 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).

Elimination half-life t1/2,ß 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

In humans tramadol is mainly metabolized by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

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.

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 isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

Pediatric population
The pharmacokinetics of tramadol and O-desmethyl tramadol after single-dose

and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults.

PHARMACEUTICAL PROPERTIES

Incompatibilities

Precipitation will occur if Tramadol injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.

Shelf life

2 Years

Special precautions for storage

Do not use if injection is leaking, solution is cloudy or contains un-dissolved particles.

PRESENTATION:

Mictra 100mg/2mL Injection: Pack of 5 x 2mL ampoules.

INSTRUCTIONS:

Protect from sunlight, heat and moisture,
store at or below 25°C.
The expiration date refers to the product correctly stored at the required condition. Keep out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

MARKETING AUTHORISATION HOLDER
Head Office:
Bosch Pharmaceuticals (Pvt.) Ltd.,
8, Modern Society, Tipu Sultan Road,
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Manufacturing Site:
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053436

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پٹھوں/وریدی اور جلد کے نیچے استعمال کے لئے۔

ہدایات: دھوپ، گرمی اور نمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ یا اس سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔

احتیاط: انجکشن لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

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