FRONT SIDE

its active metabolite. Up to now, clinically relevant interactions have not been reported.
Elimination: 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 metabolised by means of N- and O-demethylation and conjugation of the Odemethylation 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. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life t1/2,ß (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Magnesium stearate
Microcrystalline Cellulose
Purified Talc
Empty hard gelatin capsule size '4'

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 Months from the date of manufacture

6.4. Special precautions for storage
Store at temperature not exceeding 30°C, protect from light and moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container
10 × 10 Capsules in Alu-PVC Blister Pack

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURED BY :
ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India

Zeal & Innovation in Medicine

8. MARKETING AUTHORIZATION NUMBER(S)
NA

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
NA

10. DATE OF REVISION OF THE TEXT
02/06/ 2019

*PB145/X/XX/XX

TRAMAZIM

Tramadol Capsules BP 50 mg

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
1.1 Trade Name : TRAMAZIM
(Tramadol Capsules BP 50 mg)
1.2 Strength : 50 mg
1.3 Pharmaceutical Form : Hard gelatin capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard gelatin capsule contains:
Tramadol Hydrochloride BP 50 mg
'For full list of excipients, see section 6.1'.

3. PHARMACEUTICAL FORM
'Hard gelatin capsule'
Green/yellow colour, size '4' hard gelatin capsules filled with white powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of moderate to severe pain.

4.2 Posology and method of administration
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.
Unless otherwise prescribed, Tramadol should be administered as follows:
Adults and children aged 12 years and over:
***Acute pain*:** An initial dose is 50-100 mg depending on the intensity of pain. This can be followed by doses of 50 or 100 mg 4-6 hours later, and duration of therapy should be matched to clinical need. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.
***Pain associated with chronic conditions*:** Use an initial dose of 50 mg and then titrate dose according to pain severity. The initial dose may be followed if necessary by 50-100 mg every 4-6 hours. The recommended doses are intended as a guideline. Patients should always receive the lowest dose that provides effective pain control. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported.
Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.
Children: Tramadol capsules are not suitable for children below the age of 12 years.
Geriatric patients: A dose adjustment is not usually necessary in 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 impairment: 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. In cases of severe renal and/or severe hepatic insufficiency tramadol are not recommended.

Method of administration
Oral administration
The capsules are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals.

4.3 Contraindication
Tramadol is contraindicated:
- in hypersensitivity to tramadol hydrochloride or any of the excipients,

170 mm

180 mm

BACK SIDE

170 mm

- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or 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.

4.4 Special warnings and special 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 centre or function, increased intracranial pressure.

In patients sensitive to opiates the product should only 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.

Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

In patients with a tendency to drug abuse or dependence, treatment with Tramadol should only be carried out for short periods under strict medical supervision.

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

Tramadol should be used with caution in patients with impaired hepatic and renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitors.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects.

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

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants, anti-psychotics 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 toxicity. Serotonin syndrome is likely when one of the following is observed:
- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperrflexia
- Hypertonia and body temperature > 38°C and inducible or ocular clonus.

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.

Other medicinal products known to inhibit CYP3A4, such as ketoconazole, ritonavir and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) and probably also the metabolism of the active O-demethylated metabolite.

4.6 Fertility, pregnancy and lactation

Pregnancy: Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnant women.

Breast-feeding: During lactation about 0.1 % of the maternal dose is secreted into the milk. Tramadol is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, Tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

4.8 Undesirable effects

The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely (≥1/10,000 to <1/1,000). The reactions are classified according to frequency very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known.

Very Common: Nausea, dizziness.

Common: Headache, somnolence, vomiting, constipation, dry mouth, sweating, fatigue

Uncommon: Cardiovascular regulation (palpitations, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially in connection with intravenous administration and if the patient is experiencing physical stress, Retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea, dermal reactions (e.g. pruritus, rash, urticaria).

Rare: Hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic side-effects may occur following administration of tramadol, which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (mostly reduced, occasionally increased) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur, Blurred vision, Bradycardia, increased blood pressure, Dyspnoea, Motorial weakness, Micturition disorders (difficulty in passing urine and urinary retention), Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Not known: speech disorders, hypoglycaemia.

4.9 Overdose

Symptoms: Symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment: The general emergency measures apply. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The stomach is to be emptied by vomiting (conscious patient) or gastric irrigation. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore treatment of acute intoxication with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Analgesics, other opioids.

ATC code : N02AX02

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 may 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. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

Absorption: More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70%, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30%.

Distribution: Tramadol has a high tissue affinity (V d,ß = 203 + 40 l). It has a plasma protein binding of about 20 %.Following a single oral dose administration of tramadol 100 mg to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its Odesmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Biotransformation: 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

180 mm