1. NAME OF THE MEDICINAL PRODUCT

SIVOTRAM 100 mg capsule

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each Capsule contains:

Tramadol Hydrochloride BP : 100 mg

Excipients : Q.S.

Approved coloured capsule shell used.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dark green/Light green coloured size "4" capsule printed TRM 100 on cap and body.

4. Clinical particulars

4.1 Therapeutic indications

Sivotram is indicated for:

Treatment of moderate to severe pain

4.2 Posology and method of administration

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

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.

A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

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

Children

Tramadol capsules are not suitable for children below the age of 12 years.

Method of administration: Oral

4.3 Contraindications

Tramadol is contraindicated:

-In hypersensitivity to tramadol hydrochloride or any of the excipients.

- 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 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.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold. Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Tolerance, psychic and physical dependence may develop, especially after long-term use. 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.
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 results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.
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.

4.6 Pregnancy and Lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. 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.

Tramadol - administered before or during birth - does not affect uterine contractility. In new-born infants it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.

Psychiatric disorders

Rare: Hallucinations, confusion, sleep disturbance, anxiety and nightmares.

Nervous system disorders

Very common: Dizziness.

Common: Headache, somnolence.

Rare: Changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, abnormal coordination, involuntary muscle contractions, and syncope.

Eye disorders

Rare: Blurred vision.

Cardiac disorders

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.

Rare: Bradycardia, increased blood pressure.

Metabolism and nutrition disorders

Not known: hypoglycaemia

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnoea

Frequency not known: Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders

Very common: Nausea.

Common: Vomiting, constipation, dry mouth.

Uncommon: Retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

Frequency not known: 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

Common: Sweating.

Uncommon: Dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders

Rare: Motorial weakness.

Renal and urinary disorders

Rare: Allergic reactions (e.g. Rare: Micturition disorders (difficulty in passing urine and urinary retention).

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol 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 Pharmacodynamics properties

Pharmacotherapeutic group: Analgesics, other opioids

ATC Code: N02AX02

Mechanism of Action:
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.

5.2 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. 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 %.
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 as capsules or tablets 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).
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.
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. In patients with cirrhosis of the liver, elimination half-lives of 13.3 + 4.9 h (tramadol) and 18.5 + 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 + 3.2 h and 16.9 + 3 h, in an extreme case 19.5 h and 43.2 h respectively.
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.

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch	BP
Dibasic Calcium Phosphate	BP
Starch + Dibasic Calcium Phosphate Granules	IHS
Soluble Starch	IHS
Purified Talc	BP
Dark Green/ Light Green coloured size "4" capsule priented TRM 100 on cap & body	IHS

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light, and moisture.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

10 X 10 Capsules of Alu/PVC is packed in a carton with package insert.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/MANUFACTURER

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Ahmedabad
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URL : www.sagalabs.com