SUMMARY OF PRODUCT CHARACTERISTICS

1. **NAME OF THE MEDICINAL PRODUCT**
   TRAMADOL 50mg CAPSULE is an oral Capsule
   Composition:
   Each Hard Gelatin Capsule contains:
   TRAMADOL HCL BP……50mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Excipients: Each Capsule also contains Starch
   For a full list of excipients, see section 6.1

3. **Pharmaceutical Form**
   Oral Capsule
   TRAMADOL 50mg is a Green/Yellow colour size "2" hard gelatin capsules containing a white colour free flowing powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Tramadol hydrochloride is indicated for the management (treatment and prevention) of moderate to severe pain.

4.2 Posology and method of administration:

Posology

Adults and children over 12 years: One or two Tramadol capsules (equivalent to 50 mg – 100 mg tramadol hydrochloride)

Method of Administration

For oral administration.

4.3 Contraindications

Do not take TRAMADOL if you are allergic to TRAMADOL or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

4.4 Special warnings and precautions for use

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods and 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.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold.

Tramadol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.
Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses, respiratory depression has infrequently been reported.
Do not exceed the stated dose. Keep out of the reach of children. If symptoms persist, consult your doctor.

4.5 Interaction with other medicinal products and other forms of interaction:
Tramadol should not be combined with MAO inhibitors.
Patients treated with monoamine oxidase inhibitors within 14 days prior to administration of the opioid pethidine have experienced life-threatening interactions affecting the central nervous system as well as the respiratory and circulatory centres. The possibility of similar interactions occurring between monoamine oxidase inhibitors and tramadol cannot be ruled out.
Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effect.
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 reuptake 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 toxicity.
Simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.
Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients.

4.6 Pregnancy and Lactation
Do not take TRAMADOL if you pregnant, planning a pregnancy or breast-feeding, unless your doctor has advised you to, as it may affect the development of your baby. Ask your doctor for advice before taking any medicines.

4.7 Effects on the ability to drive and use machines
Not Applicable

4.8 Undesirable effects:
TRAMADOL 50mg Side effects include; Nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, or headache may occur.

4.9 Overdose
Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression up to respiratory arrest.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other opioids
ATC Code: N02AX02

Mechanism of action:
Tramadol, a cyclohexanol derivative, 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 appears to modify the transmission of pain impulses by inhibition of monoamine reuptake. The duration of analgesia with orally administered tramadol has been shown to be 3-6 hours with maximum pain relief at 1-4 hours post-dosing. Tramadol also has an antitussive action but has no effect on gastrointestinal motility. At the recommended dosages, the effects of tramadol given orally on the respiratory and cardiovascular systems appear to be clinically insignificant. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

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 $\pm$ 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 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 metabolised by means of N- and O-demethylation and conjugation of the O-demethylation 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. Up to now, clinically relevant interactions have not been reported.

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 $\pm$ 4.9 h (tramadol) and 18.5 $\pm$ 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 $\pm$ 3.2 h and 16.9 $\pm$ 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 Pre-clinical Safety data
Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Starch
Magnesium Stearate
Purified Talc
Microcrystalline Cellulose
Lactose

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
36 months.

6.4 Special Precautions for storage
Store below 30^{o}C, protect from light.
Keep out of reach and sight of children.

6.5 Nature and contents of container
Alu-PVC blister of 10 Capsules, such 10 blisters are packed in carton along with the pack insert

6.6 Special precautions for disposal and other handling
No special requirements.

7. **SUPPLIER**

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