

**1.3.1 Summary of Product Characteristics (SmPC)**

**1. Name of Medicinal Product**

**TRAMADOL HYDROCHLORIDE TABLETS USP 100MG**

**2. Qualitative and Quantitative Composition**

**2.1. Qualitative declaration:**

**Composition of the Drug product:**

Each Film coated tablet contains:

Tramadol Hydrochloride USP 100 mg.

Excipients Q.S.

Colour: Ponceau 4R

**Qualitative & Quantitative Composition Formula:**

**Batch Size: 1,00,000Tablets**

Sr. No.	Name of raw material	Specification	LabelQty /Tab (mg)	Overages	Qty. per Tab (mg) with overages	StdQty. Per Batch (kg)	Function
1.	*Tramadol Hydrochloride	USP	100 MG	100.00 MG	0%	100.00 MG	Active
2.	**Lactose	BP		151.00 MG	3 %	155.53 MG	Diluent
3.	Povidone K-30%	BP		10.00 MG		10.00 MG	Disintegrant
4.	Purified water	BP					Solvent
5.	Magnesium stearate	BP		3.00 MG		3.00 MG	Lubricant
6.	Purified Talc	BP		3.00 MG		3.00 MG	Glidant
7.	Colloidal silicon Dioxide	BP		1.00 MG		1.00 MG	Absorbent
8.	Sodium lauryl sulphate	BP		2.00 MG		2.00 MG	Surfactant

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9.	Maize Starch	BP		20.00 MG		20.00 MG	Binder
				<b>290 MG</b>		<b>29.00 KG</b>	
<b>Coating formula</b>							
10.	Isopropyl Alcohol	BP		5.80 ml		5.80 LTR	Solvent
11.	Ready mix of Ponceau 4R	IHS		9.00 mg		0.90 KG	Coloring agent
12.	Methylene Chloride	BP		8.60 ml		8.60 LTR	Solvent
				299.00		29.90 kg	

**\*Compensate the qty of actives with lactose to maintain the average weight.**

**\*\* Compensate of overages of lactose loss on drying.**

### **3. Pharmaceutical form**

Film coated Tablets

A Red coloured, Round shaped, Biconvex, Film coated tablet.

### **4. Clinical particulars**

#### **4.1 Therapeutic indications**

The treatment of moderate to severe pain.

#### **4.2 Posology and method of administration**

Posology

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.

*Adults and adolescents above the age of 12 years:*

The recommended doses are intended as a guideline. Patients should always receive the lowest dose that provides effective pain control. Chronic pain management should be preferably given on a fixed dosing schedule.

The starting dose is usually 100 mg tramadol hydrochloride tablet twice daily, in the morning and in the evening. If the pain relief is not sufficient, the dose may be increased to 150 mg twice daily or 200 mg twice daily.

The dose interval must not be less than 8 hours.

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

Tramadol hydrochloride should never be used longer than absolutely necessary for pain control. If the nature and severity of the underlying disease suggest the need for pain management, continued medical need for tramadol hydrochloride analgesia should be reviewed carefully at short, regular intervals (with breaks in treatment if necessary).

### **Paediatric population**

Tramadol tablets are not suitable for children under 12 years of age.

### **Elderly**

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly people over 75 years elimination. Therefore, if necessary the dose 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 of the dose intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency tramadol hydrochloride tablets are not recommended.

### **Method of administration**

The tablets must be swallowed whole, not divided or chewed, with sufficient liquid, irrespective of mealtimes.

## **4.3 Contraindications**

Tramadol hydrochloride is contraindicated

- in hypersensitivity to the active substance or to any of the excipients listed in section 6.
- in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or other psychotropic medicinal products

- in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days (see section 4.5)
- in patients with epilepsy not adequately controlled by treatment
- for use in narcotic withdrawal treatment

#### **4.4 Special warnings and precautions for use**

Tramadol hydrochloride 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,
- renal and hepatic impairment (see section 4.2).

In patients sensitive to opiates tramadol hydrochloride should only be used with caution.

#### **• CYP2D6 metabolism**

• Tramadol is metabolised 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. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing adverse reactions of opioid toxicity even at commonly prescribed doses. 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.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

<b>• Population</b>	<b>• Prevalence %</b>
• African/Ethiopian	• 29%
• African American	• 3.4% to 6.5%

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• Asian	• 1.2% to 2%
• Caucasian	• 3.6% to 6.5%
• Greek	• 6.0%
• Hungarian	• 1.9%
• Northern European	• 1% to 2%

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events. 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.

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 hydrochloride should only be carried out for short periods under strict medical supervision.

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

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that can lower the seizure threshold (see section 4.5). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol hydrochloride if there are compelling circumstances.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS-depressant medicinal products are being administered (see section 4.5) or if the recommended dose is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

Concomitant use of tramadol and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe tramadol concomitantly with sedative medicinal products, 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).

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

Tramadol hydrochloride must not be combined with monoamine oxidase (MAO) inhibitors (see section 4.3).

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 hydrochloride.

Concomitant administration of tramadol hydrochloride with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

Sedative medicinal products such as benzodiazepines or related medicinal products:

The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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.

Other morphine derivatives (including anti-tussives, substitution treatments), benzodiazepines, barbiturates: Increased risk of respiratory depression, that may be fatal in overdose.

Mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine): The analgesic effect of tramadol hydrochloride which is a pure agonist may be reduced, and a withdrawal syndrome may occur

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 medicinal products, 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 toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic medicinal products usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

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

Other active substances which inhibit the enzyme 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. The clinical importance of such an interaction has not been studied.

The analgesic effect of tramadol hydrochloride is in part mediated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In a limited number of studies the pre- or post-operative application of the antiemetic 5-HT<sub>3</sub> antagonist ondansetron increased the requirement of tramadol hydrochloride in patients with post-operative pain. Although not tested, other 5-HT<sub>3</sub>-receptor antagonists would be expected to interact similarly with tramadol hydrochloride.

#### **4.6 Pregnancy and lactation**

##### *Pregnancy*

Tramadol crosses the placenta. Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. There is inadequate evidence available on the safety of tramadol hydrochloride in human pregnancy. Therefore, tramadol hydrochloride should not be used in pregnant women.

Tramadol - administered before or during birth does not affect uterine contractility. In neonates 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 dose up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dose. 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.

##### 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**

Even when taken according to instructions, tramadol hydrochloride may cause adverse reactions such as somnolence, dizziness and blurred vision and therefore may impair the reactions of drivers, machine operators and workers without a safe hold. This applies particularly in conjunction with alcohol and other psychotropic substances. If patients are affected they should be warned not to drive or operate machinery.

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
- However, you would not be committing an offence (called 'statutory defence') if:
  - o The medicine has been prescribed to treat a medical or dental problem and
  - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - o It was not affecting your ability to drive safely.

#### **4.8 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 ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

#### **Immune system disorders**

Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

**Metabolism and nutrition disorders**

Rare: changes in appetite

Not known: hypoglycaemia

**Psychiatric disorders**

Rare: hallucination, confusion, delirium, anxiety, sleep disturbances and nightmares.

Psychic adverse reactions may occur following administration of tramadol hydrochloride which vary individually in intensity and nature (depending on personality and duration of treatment).

These include changes in mood (usually euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).

Dependence may occur (see section 4.4).

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

**Nervous system disorders**

Very common: dizziness

Common: headache, somnolence

Rare: paraesthesia, tremor, convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders

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

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

**Eye disorders**

Rare: blurred vision, miosis

**Cardiac disorders**

Uncommon: cardiovascular regulation (palpitation, tachycardia,). These adverse reactions may occur especially on intravenous administration of tramadol hydrochloride and in patients who are physically stressed.

Rare: bradycardia

#### **Vascular disorders**

Uncommon: cardiovascular regulation (postural hypotension or cardiovascular collapse).

These adverse reactions may occur especially on intravenous administration of tramadol hydrochloride and in patients who are physically stressed.

#### **Respiratory, thoracic and mediastinal disorders**

Rare: respiratory depression, dyspnoea

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

Worsening of asthma has also been reported, though a causal relationship has not been established.

#### **Gastrointestinal disorders**

Very common: nausea

Common: constipation, dry mouth, vomiting

Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea

#### **Hepato-biliary disorders**

Very rare: An increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol hydrochloride.

#### **Skin and subcutaneous tissue disorders**

Common: hyperhidrosis Uncommon: pruritus, rash, urticaria

#### **Musculoskeletal and connective tissue disorders**

Rare: motorial weakness

#### **Renal and urinary disorders**

Rare: micturition disorders (dysuria and urinary retention)

#### **General disorders and administration site conditions**

Common: fatigue

#### Investigations

Rare: increase in blood pressure

#### **4.9 Overdose**

##### *Symptoms*

In principle, on intoxication with tramadol hydrochloride 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 antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication with oral formulations, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol hydrochloride intake.

Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or formulations.

Tramadol hydrochloride is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with tramadol hydrochloride 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

Mechanism of action

Tramadol hydrochloride is a centrally acting opioid analgesic. It is a non-selective pure agonist at  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors with a higher affinity to the  $\mu$  receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Clinical efficacy and safety

Tramadol hydrochloride has an antitussive effect. In contrast to morphine, analgesic doses of tramadol hydrochloride over a wide range have no respiratory-depressant effect. Also gastrointestinal motility is less affected. Effects on the cardio-vascular system tend to be slight. The potency of tramadol hydrochloride is reported to be 1/10(one tenth) to -1/6(one sixth) that of morphine.

Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2,000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol hydrochloride was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

## **5.2 Pharmacokinetic properties**

### Absorption

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

Tramadol has a high tissue affinity ( $V_{d,\beta} = 203 \pm 40$  l). Protein binding is about 20%.

After administration of tramadol 100 mg tablets the peak plasma concentration  $C_{max}$   $141 \pm 40$  ng/ml is reached after 4.9 hours. After administration of tramadol 200 mg tablets a  $C_{max}$   $260 \pm 62$  ng/ml is reached after 4.8 hours.

### Distribution

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

#### Biotransformation

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-desmethyl-tramadol 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 compound by the factor 2-4. Its half-life  $t_{1/2 \beta}$  (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.

#### Elimination

Elimination half-life ( $t_{1/2 \beta}$ ) is approximately 6 hours, irrespective of the mode of administration. In patients above 75 years of age it may be a factor of approximately 1.4.

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 case of impaired hepatic and renal function the half-life may be slightly.

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.

#### Linearity

Tramadol has a linear pharmacokinetic profile within the therapeutic dose 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.

#### Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol 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 when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterised. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

### **5.3 Preclinical safety data**

On repeated oral and parenteral administration of tramadol for 6 to 26 weeks in rats and dogs, and oral administration for 12 months in dogs haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range restlessness, salivation, convulsions and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg, and 10 mg/kg body weight respectively and dogs rectal doses of 20 mg/kg bodyweight, without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male and female fertility was not affected. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dose groups (significant, but not dose-dependent).

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

<b>Sr. No.</b>	<b>Ingredients Name</b>	<b>Specification</b>
1.	Lactose	BP
2.	Povidone K-30%	BP
3.	Purified water	BP
4.	Magnesium stearate	BP
5.	Purified Talc	BP
6.	Colloidal silicon Dioxide	BP
7.	Sodium lauryl sulphate	BP
8.	Maize Starch	BP
9.	Isopropyl alcohol	BP
10.	Ready mix of ponceau4r	IHS
11.	Methylene Chloride	BP

**6.2 Incompatibilities:** Not Applicable

**6.3 Shelf-life:** 36 Months

**6.4 Special precautions for storage:**

Store in a cool, dry place below 30<sup>0</sup>C.

**6.5 Nature and contents of container:**

Each Alu/PVC blister contains 10 tablets and such 10 Alu/PVC blisters are pack in a carton with pack insert.

**6.6 Special precautions for disposal and other handling**

No special instructions for use/handling

**7- Marketing Authorization Holder:**

**SUITELIFE PHARMACEUTICAL LTD.,**

**4, Ayo Davies Close, Off. Ekolou Street,**

**Surulere, Lagos, Nigeria.**



**SUITELIFE TRAMADOL 100  
TRAMADOL HYDROCHLORIDE TABLETS USP 100MG**

**INDIA**

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**8- Marketing Authorization Number (s):  
Product license / registration Number (s)**

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**9- Manufacturer Name:**

**SWISS PHARMA PVT. LTD.**

**3709, G.I.D.C., Phase IV, Vatva, Ahmedabad-382 445, GUJARAT, INDIA.**

**10- Date of first authorization/renewal of the authorization:**

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**11- Date of revision of the text:**

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**SWISS PHARMA PVT. LTD.**

**3709, G.I.D.C., Phase IV, Vatva, Ahmedabad-382 445, GUJARAT, INDIA**