Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Crowther Tramadol Capsules (Tramadol Capsules BP 100 mg)

1.1 Strength

Each Hard Gelatin Capsule contains:
Tramadol Hydrochloride BP 100 mg
Excipients q.s.
Empty Gelatin capsule contains approved colors

1.2 Pharmaceutical form

Hard Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No	Ingredients	Spec	Label Claim (mg)	Qty/Cap (mg)	Category
Mixing					
1.	Tramadol Hydrochloride	BP	100	100.000	Active
2.	Lactose Monohydrate	BP	-	10.000	Filler
3.	Maize Starch	BP	-	15.00	Filler
4.	Calcium Hydrogen Phosphate (anhydrous)	BP	-	5.000	Diluent
5.	Cross carmellose Sodium	BP	-	7.000	Disintegrant
Lubrication					
6.	Magnesium Stearate	BP	-	3.000	Lubricant
Filling					
7.	Empty Hard gelatin capsules shell Green/White size: '4'	In-House	-	1 Nos	1 Nos
Total fill quantity				**140.00 mg**	

BP: British Pharmacopoeia

3. PHARMACEUTICAL FORM

Green/white colour size "4" capsule containing powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of moderate to severe pain.

4.2 Posology and method of administration

The capsules are intended for twice daily oral administration and can be taken independently of meal times, swallowed whole with water.
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:
The usual initial dose is 50-100 mg twice daily, morning and evening. This dose may be titrated up to 150-200 mg twice daily according to pain severity.
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.
A total oral daily dose of 400 mg should not be exceeded except in special clinical circumstances.
Elderly 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 capsules prolonged-release capsules is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. Capsules are not recommended for patients with severe hepatic and/or renal insufficiency.
Patients who have difficulty in swallowing:
Prolonged-release hard capsules can be opened, carefully, so that the pellets are deposited on a spoon. The spoon and pellets should be taken into the mouth, followed by a drink of water to rinse the mouth of all pellets. The pellets must not be chewed or crushed.
Children and adolescents:
Over 12 years: Dosage as for adults.

Under 12 years: Prolonged-release hard capsules have not been studied in children. Therefore, safety and efficacy have not been established and the product should not be used in children.

4.3 Contraindications

This Prolonged-release hard capsules should not be given to patients who have previously shown hypersensitivity to the active substance tramadol or to any of the other excipients.
The product should not be administered to patients suffering from acute intoxication with hypnotics, centrally acting analgesics, opioids, psychotropic drugs or alcohol.
Tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within 2 weeks of their withdrawal.
Contra-indicated in patients suffering from uncontrolled epilepsy.
Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Care Warnings:
Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment should be for short periods under strict medical supervision. In rare cases at therapeutic doses, tramadol has the potential to cause withdrawal symptoms.
Prolonged-release hard capsules are not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.
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.
This medicinal product contains sucrose and therefore should not be used by patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.
Precautions:
Prolonged-release hard capsules should be used with prudence in patients who have shown previous hypersensitivity to opiates, and in patients with severe renal or hepatic impairment, head injury, decreased level of consciousness, increased intracranial pressure, or patients in shock or at risk of convulsions.
At recommended therapeutic doses Prolonged-release hard capsules are unlikely to produce clinically relevant respiratory depression. Care should however be taken when administering Prolonged-release hard capsules to patients with existing respiratory depression or excessive bronchial secretion and in those patients taking concomitant CNS depressant drugs.

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 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 and the duration of the concomitant use should be limited
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.
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 (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 serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.
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 active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active Odemethylated metabolite. The clinical importance of such an interaction has not been studied.

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy
Prolonged-release hard capsules should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol 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.
Lactation
Prolonged-release hard capsules should not be administered during breast feeding as tramadol and its metabolites have been detected in breast milk. 0.1% of the dose administered to the mother may be excreted in milk.

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

4.8 Undesirable effects

The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10% of patients.
Immune system disorders:
Rare (≥ 1/10,000 to < 1/1,000): Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
Metabolism and nutrition disorders:
Rare (≥ 1/10,000 to < 1/1,000): Changes in appetite.

Frequency not known (cannot be estimated from the available data): Hypoglycaemia
Psychiatric disorders:
Rare (≥ 1/10,000 to < 1/1,000): 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 (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders), hallucinations, confusion, sleep disturbances and nightmares.
Prolonged administration of prolonged-release hard capsules may lead to dependence Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.
Nervous system disorders:
Very common (≥ 1/10) dizziness.
Common (≥ 1/100 to < 1/10): headache, drowsiness.
Rare (≥ 1/10,000 to < 1/1,000): epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (e.g. antidepressants or anti-psychotics, "Interaction with other medicinal products and other forms of interaction".
Paraesthesia and tremor.
Very rare (< 1/10,000): vertigo
Eye disorders:
Rare (≥ 1/10,000 to < 1/1,000): blurred vision.
Cardiac disorders:
Uncommon (≥ 1/1,000 to < 1/100): effects on cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.
Rare (≥ 1/10,000 to < 1/1,000): bradycardia, increase in blood pressure.
Vascular disorders:
Very rare (< 1/10,000): flushing.
Respiratory disorders:
Worsening of asthma has also been reported, though a causal relationship has not been established.
Respiratory depression has been reported. If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly "Interaction with other medicinal products and other forms of interaction") respiratory depression may occur.
Gastrointestinal disorders:
Very common (≥ 1/10): vomiting, nausea.
Common (≥ 1/100 to < 1/10): constipation, dry mouth.

Uncommon (≥ 1/1,000 to < 1/100): retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating).
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.
Skin and subcutaneous tissue disorders:
Common (≥ 1/100 to < 1/10): sweating.
Uncommon (≥ 1/1,000 to < 1/100): dermal reactions (e.g. pruritus, rash, urticaria).
Musculoskeletal, connective tissue and bone disorders:
Rare (≥ 1/10,000 to < 1/1,000): motorial weakness.
Renal and urinary system disorders:
Rare (≥ 1/10,000 to < 1/1,000): micturition disorders (difficulty in passing urine and urinary retention).
General disorders:
Common (≥ 1/100 to < 1/10): fatigue.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Symptoms of tramadol overdose include vomiting, miosis, sedation, seizures, respiratory depression and hypotension, with circulatory failure and coma. Respiratory failure may also occur. Such symptoms are typical of opioid analgesics.
Treatment of overdose requires the maintenance of the airway and cardiovascular functions. Respiratory depression may be reversed using naloxone and fits controlled with diazepam. Naloxone administration may increase the risk of seizures.
The treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not sufficient or suitable due to the slow elimination of tramadol from the serum by these routes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other opioids, **ATC code:** N02AX02

Tramadol is a centrally acting analgesic which possesses opioid agonist properties. Tramadol consists of two enantiomers, the (+)-isomer is predominantly active as an opioid with preferential activity for the μ-receptor. The (-)-isomer potentiates the analgesic effect of the (+)-isomer and is active as an inhibitor of noradrenaline and serotonin-uptake thereby modifying the transmission of pain impulses.

Tramadol also has an antitussive action. 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 to 1/6 of morphine.

Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 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 2mg/kg or multiple doses of up to 8mg/kg per day (to a maximum of 400mg per day) efficacy of tramadol 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 that 1 year.

5.2 Pharmacokinetic properties

About 90% of tramadol released from prolonged-release hard capsules 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 with an apparent volume of distribution of 203 ± 40 litres after oral dosing in healthy volunteers. Protein binding is limited to 20%.

After single dose administration of prolonged-release hard capsules the peak plasma concentration Cmax 70 ± 16 ng/ml is reached after 5.3 h. After administration of 100 mg prolonged-release hard capsules Cmax 137 ± 27 ng/ml is reached after 5.9 h. Following administration of 200 mg prolonged-release hard capsules Cmax 294 ± 82 ng/ml is reached after 6.5 h. The reference product (Tramadol Immediate Release Capsules, given as a total dose of 200 mg tramadol hydrochloride) reached a peak concentration of Cmax 640 ± 143 ng/ml after 2.0 hours.

The relative bioavailability for the slow release formulation after single dose administration is 89% and increases to 100% after multiple dose administration in comparison to the reference product.

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

Elimination of half-life t½β 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 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 t½β (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 cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite. The clinical consequences of any such interactions are not known.

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.

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 characterized. 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 - 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 body weight 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 fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. 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 dosage groups (significant, but not dose-dependent).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose Monohydrate	BP
Calcium Hydrogen Phosphate (anhydrous)	BP
Maize Starch	BP
Cross carmellose Sodium	BP
Magnesium Stearate	BP
Empty Hard gelatin capsule shell Green/white size: '4'	In-House

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 Preserve in air tight container.

6.5 Nature and contents of container

10 x 10 Alu-PVC Blister Pack

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.