

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TRAMADOL HYDROCHLORIDE 50mg CAPSULES

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50mg Tramadol hydrochloride
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Yellow and green, opaque, hard gelatin capsules (size 4) printed "C" and "TK" in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of moderate to severe pain.

4.2 Posology and method of administration

The dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. The capsules are taken orally, independent of meals, swallowed whole with water

Adults and children over 12 years

Acute pain: Adults and children over age 12 years: 50-100mg 3-4 times daily. Patients with low weight should use 0.7mg/kg bodyweight. Duration of therapy depends upon clinical need.

Chronic pain: An initial dose of 50mg or 100mg is followed by doses of 50mg or 100mg, every 4 to 6 hours, according to pain severity. The need for continued treatment should be assessed at regular intervals (as withdrawal symptoms and dependence have been reported).

A total daily dose of 400mg should not be exceeded.

Elderly patients

The normal adult doses may be given but the dosage interval should be extended to 9 hours. However, it should be noted that in volunteers aged over 75 years the elimination half life of tramadol was increased by 17% following oral administration.

Renal impairment/renal dialysis

The elimination of tramadol may be prolonged in these patients. The usual initial dosage should be used. For patients with creatinine clearance <30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended in patients with severe renal impairment (creatinine clearance <10ml/min). Tramadol is removed very slowly by haemodialysis or haemofiltration so post-dialysis administration to maintain analgesia is not usually necessary.

Patients with hepatic impairment

The elimination of tramadol may be prolonged. The usual dosage should be divided in 2, or the dosage interval should be extended to 12 hours. In severe hepatic impairment, the product is contraindicated.

Dosage in Children

Children under 12 years: Not recommended.

4.3 Contraindications

This product is contraindicated in the following situations:

- Previously demonstrated hypersensitivity to tramadol or any of the other ingredients in the capsule.
- Acute intoxication with central nervous system depressants (alcohol, hypnotics, centrally acting analgesics, opioids, psychotropic drugs).
- Patients receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5).
- Severe hepatic impairment.
- Severely impaired kidney function (creatinine clearance less than 10ml/min).
- Severe respiratory impairment.
- Epilepsy not controlled by adequate treatment.
- Tramadol must not be administered during breastfeeding if long term treatment, i.e more than 2 to 3 days, is necessary (see section 4.6).

4.4 Special warnings and precautions for use

Care should be taken and the risk/benefit of treatment determined prior to administration of tramadol in the following situations:

- Withdrawal symptoms. At therapeutic doses tramadol has the potential to cause withdrawal symptoms. A reporting frequency of 1 in 8000 has been stated.
- Drug dependence and abuse. Reports of these are rare and less frequent than withdrawal reactions. The clinical need for analgesic treatment should be reviewed regularly.
- Patients with a tendency to drug abuse or dependence. Treatment should only be for short periods and under medical supervision.
- Opioid-dependent patients. Tramadol is not suitable as a substitute in these patients and cannot suppress morphine withdrawal symptoms.
- Tramadol should be used with caution in patients with head injury, increased intracranial pressure, impairment of hepatic (metabolism of tramadol and

active metabolite is reduced) and renal (decreased rate and extent of excretion of tramadol and the active metabolite) function, decreased level of consciousness and in patients prone to convulsive disorder or in shock.

- Patients prone to convulsive disorders. 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 clinical reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that lowers the seizure threshold (see Interactions with other medicaments and other forms of interactions section).
- Respiratory depression or patients taking CNS depressant drugs. (tramadol may decrease the respiratory drive and increase airway resistance in patients with this condition. Caution is recommended with administration of oral tramadol in patients at risk for respiratory depression or receiving medicines likely to produce respiratory depression).
- The concomitant use of carbamazepine or concomitant intake of alcohol with tramadol is not recommended (see section 4.5)
- Buprenorphine and other mixed agonists-antagonists, naltrexone: see section 4.5

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications for concomitant use (see section 4.3):

- *MAO inhibitors* – a serotonergic syndrome is likely to occur: diarrhoea, tachycardia, sweating, tremor, confusion, coma. In case of treatment with MAOI, a 15 day interval has to be respected before starting a treatment with tramadol.
Concomitant use not recommended (see section 4.4)
- *Alcohol, hypnotics, sedatives and antipsychotics* The sedative effects of *alcohol, hypnotics, sedatives and antipsychotics* may be enhanced when they are given concomitantly with tramadol.
- *Carbamazepine* - simultaneous administration may decrease plasmatic concentrations of tramadol.
- *Analgesics* The combination of mixed agonists/antagonists (*eg* buprenorphine, nalbuphine, pentazocine) or naltrexone and tramadol is not recommended because it is theoretically possible that the analgesic effect of a pure agonist is attenuated under these circumstances.
Combinations to be taken into account:
- *Other morphine derivatives (including antitussives, substitution treatments), benzodiazepines and barbiturates* – increased risk of respiratory depression, that may be fatal in case of overdosage.
- Tramadol may increase the potential for selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), anti-psychotics and other seizure threshold lowering drugs (mefloquine, bupropion) to cause convulsions (see section 4.4).
- 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.

- Isolated cases of serotonergic syndrome have been reported with the therapeutic use of tramadol in combination with other serotonergic agents such as selective serotonin re-uptake inhibitors (SSRIs). Serotonergic syndrome can be manifested by symptoms such as confusion, restlessness, fever, sweat, ataxia, hyperreflexia, myoclonia and diarrhoea. The withdrawal of the serotonergic agent produces a rapid improvement.

4.6 Pregnancy and lactation

Pregnancy

As a precautionary measure, it is preferable to avoid the use of tramadol during pregnancy. In humans, there is insufficient data available to appropriately assess the safety of tramadol use in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. As with other opioid analgesics:

- Chronic use of tramadol may induce – at any dosage- a withdrawal syndrome in newborns.
- At the end of pregnancy, high dosages, even for short-term treatment, may induce respiratory depression in the newborn.

Animal studies have not shown any teratogenic effects, but at high doses, foetotoxicity due to maternotoxicity appeared (see section 5.3).

Lactation

Tramadol and its metabolites have been detected in human breast milk in small amounts. An infant could ingest 0.1% of the single dose given to the mother. A single administration of tramadol does not usually require breastfeeding to be interrupted. If repeated administration is needed for several days, i.e. more than 2 to 3 days, breastfeeding should be suspended. If long-term treatment after birth is necessary, breastfeeding is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

4.8 Undesirable effects

- ***Immune system disorders:***
Rare adverse effects (>1/10,000, <1/1,000): anaphylactic reaction with urticaria, Quincke's oedema, bronchospasm and exceptionally anaphylactic shock that may be fatal. Allergic reactions also include dyspnoea, wheezing and angiooedema (oedema of the oral cavity/pharynx/larynx).
- ***Metabolic and nutrition disorders:***
Rare adverse effects (>1/10,000, <1/1,000): changes in appetite.
- ***Psychiatric disorders:***
Rare adverse effects (>1/10,000, <1/1,000): neuropsychiatric disorders, depending on the individual sensibility, and essentially in elderly patients; confusion and exceptionally hallucinations or delirium. Also reported euphoria, sleep disturbance and nightmares. Psychiatric 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 ability (e.g. decision behaviours or perception disorders).

- ***Nervous system disorders:***
Very common adverse effects (>1/10): dizziness.
Common adverse effects (>1/100, <1/10): somnolence, headache, sweating, drowsiness, tiredness, paraesthesia and tremor.
Rare adverse effects (>1/10,000, <1/1000): convulsions, essentially in cases in treatment with high doses, or in the case of concomitant treatment with drugs that lower the epileptic threshold (see section 4.4).
- ***Eye disorders:***
Rare adverse effects (>1/10,000, <1/1000): blurred vision.
- ***Cardiac disorders:***
Uncommon adverse effects (>1/1,000, <1/100): disorders of cardiovascular regulation, tachycardia, hypotension, palpitations and syncope.
Rare adverse effects (>1/10,000, <1/1,000): increase in blood pressure and bradycardia.
- ***Respiratory, thoracic and mediastinal disorders:***
Respiratory depression may occur if therapeutic doses are largely exceeded, or if other centrally depressant drugs are concomitantly administered (see section 4.5). Also worsening of asthma has been reported, though a casual relationship has not been established.
- ***Gastrointestinal disorders:***
Very common adverse effects (>1/10): vomiting and nausea.
Common adverse effects (>1/100, <1/10): dry mouth, constipation in case of prolonged treatment, abdominal pain.
Uncommon adverse effects (>1/1,000, <1/100): gastrointestinal irritation (a feeling of pressure in the stomach or bloating) and retching.
- ***Hepato-biliary disorders:***
Few isolated reports of increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.
- ***Skin and subcutaneous tissue disorders:***
Uncommon adverse effects: (>1/1,000, <1/100): dermal reactions (e.g. rash, pruritus or urticaria).
Very rare adverse effects (<1/10,000): flushing.
- ***Musculoskeletal, connective tissue and perinatal disorders:***
Rare adverse effects >1/10,000, <1/1,000): muscle weakness.
- ***Renal and urinary disorders:***
Rare adverse effects (>1/10,000, <1/1000): difficulty in passing urine or urinary retention
- ***Withdrawal and dependence:*** Dependence and withdrawal reactions have been reported. Typical opiate withdrawal reactions include agitation, severe anxiety, nervousness, tremor, insomnia, hyperkinesias. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms.

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.

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam. Tramadol is minimally eliminated by haemodialysis and haemofiltration. Therefore treatment of acute intoxication with tramadol by haemodialysis or haemofiltration is not recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02A X02

Tramadol is a centrally acting synthetic analgesic compound. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline (norepinephrine) and enhancement of serotonin release. Tramadol opioid activity derives from low affinity binding of the parent compound to mu-opioid receptors and higher affinity binding of the active metabolite, O-desmethyl tramadol. Compared to morphine, tramadol does not show respiratory depression when given within the analgesic dosage interval. The effect of tramadol is considered 1/10 to 1/6 the effect of morphine. The gastrointestinal motility is not affected. There is minimal effect on the cardiovascular system. The contribution to human analgesia of tramadol relative to the active metabolite is unknown. Tramadol has an antitussive effect. Animal studies have revealed a reduced dependence potential compared with morphine and a very slight tolerance potential.

5.2 Pharmacokinetic properties

Absorption

Racemic tramadol is almost completely absorbed after oral administration 75%. After administration of a single dose of 50mg to 100mg, bioavailability is between 70 and 90%. After repeated oral administration every 6 hours, of doses of 50 to 100mg, the steady state is quickly reached, in about 36 hours, and bioavailability increases to more than 90%. Oral administration of tramadol with food does not significantly affect its rate and extent of absorption. Peak plasma concentration after oral administration of 100mg tramadol is approximately 300ng/ml (C_{max}) and is reached after about 2 hours. The mean plasma concentration of O-desmethyl tramadol was measured as 55±20ng/ml and occurred at approximately three hours post dose. The inhibition of one or both types of the iso-enzymes CYP3A4 (e.g. ketoconazole or erythromycin) and CYP2D6 (fluoxetine, paroxetine, quinidine or ritonavir) involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. The same applies for

enzyme inducers (e.g. rifampicin or phenytoin). Up to now, no clinically relevant interactions have been reported.

Distribution

The plasma protein binding is about 20% and the distribution volume is important. The volume of distribution of tramadol was 2.6 and 2.9 l/kg in male and female subjects, respectively following a 100mg intravenous dose. Tramadol crosses the placental barrier and is found in very small amounts in breast milk (about 0.1% of the dose administered to the mother).

Metabolism

Tramadol is extensively metabolised after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation and sulphation in the liver. Only one metabolite, O-desmethyl tramadol, is pharmacologically active.

Elimination

The half-life of the terminal phase is between 5 and 7 hours in healthy volunteers; 90% of the administered tramadol is metabolised, mostly by the liver. One of the desmethyl derivatives has analgesic properties, its half life is approximately that of tramadol. Tramadol and its metabolites are mainly eliminated renally (95%). The rest is eliminated in faeces. In the case of renal impairment, tramadol clearance decreases in proportion to creatinine clearance, the half life is about 12 hours. In the case of hepatic impairment, tramadol clearance decreases in proportion to the severity of hepatic impairment. Since tramadol is eliminated both metabolically and renally the terminal half life may be prolonged in patients with impaired hepatic or renal function.

Specific patient groups

Pharmacokinetics of tramadol show little age-dependence in volunteers up to the age of 75 years; in patients over 75, the half life is slightly increased.

The O-demethylation is catalysed by the enzyme CYP2D6. This enzyme is absent in 5-10% of Caucasians, the so-called “poor metabolisers”. In these patients the plasma concentrations of tramadol are increased and the concentrations of O-desmethyltramadol are reduced.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential. In animal studies, toxic symptoms occurring after repeated administration of high doses are compatible with a morphinic intoxication. Fertility and reproductive performance were unaffected.

Studies in mice, rats and rabbits have revealed no teratogenic effects.

In reproductive studies, there was evidence of a raised neonate mortality, delayed development of some organs, and delayed ossification, but the doses were considerably above the therapeutic range.

Transient delays in developmental or behavioural parameters were seen in pups from rat dams allowed to deliver.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch, microcrystalline cellulose, magnesium stearate.
The capsule shell contains: gelatin, iron oxide (E172), titanium dioxide (E171), indigo carmine (E132).
The printing ink contains: shellac glaze and iron oxide black (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life
3 years.

6.4 Special precautions for storage

Do not store above 30°C. Keep the container tightly closed (securitainers).
Store in the original package (blisters).

6.5 Nature and contents of container

Al/PVC/PVDC/aluminium blisters: 7s, 10s, 20s, 28s, 30s, 50s, 100s, 112s
Polypropylene containers with snap-on polyethylene lids: 7s, 10s, 20s, 28s, 30s, 50s, 100s, 112s

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis UK Limited (Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0484

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

August 2000

10 DATE OF REVISION OF THE TEXT

April 2007

11 DOSIMETRY (IF APPLICABLE)

**12 INSTRUCTIONS FOR PREPARATION OF
RADIOPHARMACEUTICALS (IF APPLICABLE)**