SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tilodol SR 100 mg prolonged-release tablets
Invodol SR 100 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 100 mg tramadol hydrochloride.

Excipient with known effect

Each prolonged-release tablet contains 56.1 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Flat, round bi-layer-tablet with facet, initial layer white, slow-release layer green with one-sided identification mark "$^{T\,R}_{100R}$".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 as prolonged-release 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 prolonged 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 prolonged-release 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 may be prolonged. 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 prolongation 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 prolonged-release tablets are not recommended.

Method of administration

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

Treatment goals and discontinuation

Before initiating treatment with Tilodol SR, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

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:

• **Population**	• **Prevalence %**
• African/Ethiopian	• 29%
• African American	• 3.4% to 6.5%
• Asian	• 1.2% to 2%
• Caucasian	• 3.6% to 6.5%
• Greek	• 6.0%
• Hungarian	• 1.9%
• Northern European	• 1% to 2%

Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

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 and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tilodol SR. Repeated use of Tilodol SR can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tilodol SR may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current

tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Tilodol SR and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

. 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.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic medicinal product usually brings about a rapid improvement.

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).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, decreasing the total opioid dose should be considered.

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 prolonged-release 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).

The concomitant use of tramadol hydrochloride with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

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-HT3 antagonist ondansetron increased the requirement of tramadol hydrochloride in patients with post-operative pain. Although not tested, other 5-HT3-receptor antagonists would be expected to interact similarly with tramadol hydrochloride.

4.6 Fertility, 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 (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)

Rare (≥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).**

Not known: serotonin syndrome

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.

Not known: hiccups

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

Drug dependence

Repeated use of Tilodol SR can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard.

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.

Serotonin syndrome has also been reported.

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 prolonged-release 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 μ, δ and κ opioid receptors with a higher affinity to the μ 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 ± 40 l). Protein binding is about 20%.

After administration of tramadol 100 mg prolonged release tablets the peak plasma concentration C_{max} 141 ± 40 ng/ml is reached after 4.9 hours. After administration of tramadol 200 mg prolonged release tablets a C_{max} 260 ± 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 t½ 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.

Elimination

Elimination half-life (t½ ß) is approximately 6 hours, irrespective of the mode of administration .In patients above 75 years of age it may be prolonged by 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 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.

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

Initial dose layer

Lactose monohydrate

Calcium hydrogen phosphate dihydrate

Maize starch

Cellulose, microcrystalline

Sodium starch glycolate (Type A)

Magnesium stearate

Silica, colloidal anhydrous

Slow release layer

Lactose monohydrate

Hypromellose

Povidone K25

Magnesium stearate

Silica, colloidal anhydrous

Castor oil, hydrogenated

Colouring agents

Quinoline yellow,

Indigo carmine

Aluminium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 20, 30, 50, 60 and 100 prolonged-release tablets in a PP/Aluminium blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1237

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26/07/2011

Date of latest renewal:

10 DATE OF REVISION OF THE TEXT

06/11/2024