Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

By-Madol SR 200 mg prolonged-release

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged-release capsule contains 200 mg of tramadol hydrochloride equivalent to 175.64 mg tramadol.

Excipients with known effects:
21.40 mg Sucrose/prolonged-release capsule 14.5 ng benzoic acid/prolonged-release capsule

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Capsules with opaque yellow cap and opaque white body containing white spherical microgranules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For 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 aged 12 years and over:
200 mg tramadol hydrochloride twice daily (corresponding to 400 mg of tramadol hydrochloride/day), morning and evening administration recommended.

The smallest effective analgesic dose should always be used. Daily doses of 400 mg of active substance must not be exceeded, unless exceptional medical reasons require so. A minimum interval of 8 hours must be respected between administrations.

Paediatric population
By-Madol SR is not suitable for use in children below 25 kg body weight which in general does not allow for individualized dosage in children below 12 years of age. Consequently, a more suitable form of administration should be used.

Geriatric 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 insufficiencv/dialysis and hepatic impairment
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency By-Madol SR is not recommended.

Note:
The recommended dosages are indicative only. In general, the smallest effective analgesic dose should be used. For the treatment of chronic pain, a pre-established posology must be respected.

For doses not realisable/practicable with this medicinal product other strengths of this medicinal product or other pharmaceutical forms and products are available.

Method of administration
The prolonged-release capsule, hard, must be swallowed whole with sufficient liquid, irrespective of mealtimes.

By-Madol SR must never be used for longer than therapeutically absolutely necessary. Should prolonged pain treatment according to the nature and severity of the illness be necessary, a careful evaluation should be carried out at short regular intervals (if necessary by instituting treatment pauses) to check whether or to what extent prolonged treatment is medically necessary.
Treatment goals and discontinuation
Before initiating treatment with By-Madol 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

By-Madol SR must not be used in the following cases:

- hypersensitivity to tramadol or to any of the excipients listed in section 6.1;
- acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs;
- patients who are taking monoamine oxidase inhibitors or have been taking them within the previous two weeks (see section 4.5*);*
- epilepsy uncontrolled by treatment.

By-Madol SR must not be used for the treatment of opioid dependence.

By-Madol SR 50 mg is not suitable for use in children under 25 kg body weight (see also section 4.2).

This medicinal product is contraindicated in children below 12 years of age

4.4 Special warnings and precautions for use

By-Madol SR should only be used following a strict benefit-risk evaluation and appropriate precautionary measures in the following cases:

- opioid-dependent patients,
- impaired consciousness of unclear aetiology, shock
- impaired respiratory centre or function,
- increased intracranial pressure, head injury, or brain disease,
- impaired liver or kidney function

The medicinal product should be used with caution in patients showing sensitivity reactions to opiates.
Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.
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 By-Madol SR. Repeated use of By-Madol 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 By-Madol 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 By-Madol 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.
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, consider decreasing the total opioid dosage.
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.
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 drugs usually brings about a rapid improvement.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related active substances
Concomitant use of tramadol and sedative medicinal products such as benzodiazepines or related active substances 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 By-Madol SR 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).

Convulsions have been reported in patients taking tramadol at the recommended dosage. Increased risk may be associated with the administration of doses exceeding the recommended daily dose (400 mg). Tramadol can increase the risk of convulsions if combined with other medicinal products that lower the convulsion threshold (see section 4.5). Patients with a history of epilepsy or those susceptible to convulsions should only be treated with tramadol if there are compelling circumstances.

By-Madol SR is not suitable for use as a substitute in opioid-dependent patients. Although it is an opiate agonist, tramadol cannot suppress morphine withdrawal symptoms.

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 side effects 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%

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.
The medicinal product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Benzoic acid content
This medicine contains 14.5 ng of benzoic acid (E210) in each dosage unit containing 200 mg of tramadol.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitors (see section 4.3).
Life-threatening interactions affecting the central nervous system as well as respiratory and cardiovascular function have been observed in patients who had been treated with MAO inhibitors within 14 days prior to the administration of the opioid pethidine. The same interactions with By-Madol SR as with MAO inhibitors cannot be ruled out.

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

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

The concurrent administration of By-Madol SR with other centrally acting drugs, including alcohol, may mutually potentiate effects on the CNS (see section 4.8).

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs or with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
Based on available pharmacokinetic results, no clinically relevant interactions are expected with the co-administration or previous administration of tramadol with cimetidine (enzyme inhibitor). Concurrent or previous treatment with carbamazepine (enzyme inducer) may reduce and shorten the analgesic effect.

The combination of a mixture of agonists/antagonists (e.g., buprenorphine, nalbuphine, pentazocine) and tramadol is not recommended, since there is a theoretical possibility that the analgesic effect of a pure agonist becomes decreased in such conditions.

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.

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT_3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

Other CYP3A4 inhibitors, such as ketoconazole and erythromycin may inhibit both the metabolism of tramadol (N demethylation) and possibly also the metabolism of the active O-demethylated metabolites. The clinical significance of this interaction is not known.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality.

Tramadol crosses the placenta.

Insufficient experience is available on the chronic use of tramadol during pregnancy. The repeated administration of tramadol during pregnancy can lead to increased tolerance of tramadol in the foetus and consequently to withdrawal symptoms in the new-born infant after birth. For this reason By-Madol SR should not be used during pregnancy.

Tramadol administered before or during birth does not affect uterine contractility. In new-born infants it may induce respiratory rate changes which normally are not clinically significant.

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 dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. 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

By-Madol SR may cause drowsiness and blurred vision altering one's capacity to react, so that the ability to drive and use machines or work without a steady foothold is reduced. This applies especially at the start of treatment, when changing over to another treatment, in combination with other centrally active drugs, and particularly if combined with alcohol.

4.8 Undesirable effects

The most frequent side effects occurring during treatment with By-Madol SR are nausea and vertigo, which occur in more than 1 out of 10 patients.
The reactions are classified according to frequency (very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data)).

System organ class	**Very common (≥ 1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from the available data)**
Immune system disorders				allergic reactions (e.g., dyspnea, bronchospasm,	

				wheezing, angioneurotic oedema), anaphylaxis	
Metabolism and nutrition disorders				change in appetite	hypoglycaemia
Psychiatric disorders				hallucinations, confusion, sleep disturbances, delirium, anxiety, night-mares	
Nervous system disorders	dizziness	headaches, somnolence		paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders	Serotonin syndrome
Eye disorders				blurred vision, miosis, mydriasis	
Cardiac disorders			effects on cardiovascular regulation: palpitations, tachycardia.	bradycardia	
Vascular disorders			cardiovascular regulation (postural hypotension or cardiovascular collapse.		
Respiratory, thoracic and mediastinal disorders				dyspnoea, respiratory depression	Hiccups
Gastrointestinal disorders	nausea	vomiting, constipation, dry mouth	retching, diarrhoea, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating)		
Skin and subcutaneous tissue disorders		hyperhidrosis	dermal reactions (e.g., pruritus, rash, urticaria)		
Musculoskeletal and connective tissue disorders				motorial weakness	
Renal and urinary disorders				disorders of micturition (dysuria and urinary retention)	
General disorders and administration site conditions		fatigue			
Investigations				increased blood pressure	

Drug dependence
Repeated use of By-Madol 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).
For cardiac disorders, adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

For vascular disorders, adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

For nervous system disorders, convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).

Psychic adverse reactions may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (e.g. usually elation, occasionally dysphoria), changes in activity (e.g. usually suppression, occasionally increase), change in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).
Drug dependence may occur.

Symptoms of withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastroinstestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

For respiratory disorders, 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 been reported, though a causal relationship has not been established.

In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Reporting of suspected adverse reactions
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website www.hpra.ie, e-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

The symptoms of tramadol poisoning are typical of other centrally active analgesics (opioids). In particular, miosis, vomiting, cardiovascular collapse, impaired consciousness and coma, convulsions and respiratory depression as well as respiratory arrest may occur.
Serotonin syndrome has also been reported.

Management

Depending on symptoms, treatment ordinarily consists of general emergency measures for freeing the airways (beware of aspiration!) and for maintaining breathing and cardiovascular function. Naloxone can be used as antidote in case of respiratory depression. Naloxone has been shown to have no effect on convulsions in animal experiments. Intravenous Diazepam should be used instead.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

Tramadol is only slightly dialysable. For this reason, haemodialysis or haemofiltration on their own are not suitable for the treatment of acute poisoning with By-Madol SR.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other opioids.
ATC Code: N02AX02

Mechanism of action
Tramadol is a centrally-acting opioid analgesic. It is a non-selective pure agonist at micro t, d, and k opioid receptors with a higher affinity at the micro receptors. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline as well as increased serotonin release.

Clinical efficacy and safety
Tramadol has an antitussive effect. In contrast to morphine, tramadol in analgesic doses has no respiratory depression effect over a wide range and no effect on gastrointestinal motility.
It has only a slight effect on the cardiovascular system. Tramadol potency is given as 1/10 to 1/6 of that for 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 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 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
Following oral use tramadol absorption is greater than 90%. Absolute average bioavailability is 70%, irrespective of concurrent food intake. The difference between available absorbed and unmetabolized tramadol can be explained by the fact that there is only slight first-pass metabolism. First-pass metabolism following oral administration is 30% at most.

Distribution
Following oral use (100 mg) in liquid form, peak plasma concentrations (C_{max}) after 1.2 hours are calculated to be 309 ± 90 ng/ml and following a similar dose in solid oral form peak plasma concentrations (C_{max}) after 2 hours are 280 ± 49 ng/ml. Tramadol has high tissue affinity (Vd, β 203 ± 40 1). Serum protein binding is approximately 20%.

Following the administration of By-Madol SR 100 mg peak plasma concentrations (C_{max}) after 4.9 hours are 141 ± 40 ng/ml. Following the administration of By-Madol SR 200 mg, peak plasma concentrations (C_{max}) after 4.8 hours are 260 ± 62 ng/ml.

Tramadol crosses the blood-brain barrier and the placenta. Very slight amounts of the drug together with its O-demethyl derivative are found in maternal milk (0.1% and 0.02% of the administered dose, respectively).

Biotransformation
In humans, tramadol is essentially metabolized by N- and O-demethylation as well as by conjugation of the O- demethylation products with glucuronic acid. Only O-demethyl tramadol is pharmacologically active. There are considerable quantitative interindividual variations as regards the other metabolites. 11 metabolites have been found in urine to date. According to results of animal experiments, O-demethyl tramadol exceeds the potency of the parent substance by a factor of 2 to 4. Its half-life (t½ β) (6 healthy volunteers) is 7.9 hours (ranging between 5.4 to 9.6 hours) and is similar to that of tramadol.

Inhibition of the isoenzymes CYP3A4 and/or CYP2D6 involved in the biotransformation of tramadol can influence the plasma concentration of tramadol or that of its active metabolites.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. Tramadol half-life may be slightly prolonged in patients with impaired liver or kidney function. Elimination half-lives of 13.3 ± 4.9 hours (tramadol) and of 18.5 ± 9.4 hours (O-demethyl tramadol) and in extreme cases of 22.3 and 36 hours, respectively have been determined in patients with cirrhosis of the liver. Elimination half-lives of 11 ± 3.2 hours and 16.9 ± 3 hours, and in extreme cases of 19.5 hours and 43.2 hours, respectively have been determined in patients with renal insufficiency (creatinine clearance < 5 ml/min).

Elimination
The elimination half-life (t½ β) of tramadol is about 6 hours, irrespective of the method of administration. In patients over 75 years of age, elimination half-life may be prolonged by a factor of approx. 1.4.

Linearity/non-linearity
Tramadol at therapeutic doses shows a linear pharmacokinetic profile.

Pharmacokinetic/Pharmacodynamic relationship
The relation between serum concentrations and analgesic effect is dose-dependent while showing significant individual variations. As a rule, serum concentrations of 100- 300 ng/ml are 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

Some *in-vitro* test systems have indicated mutagenic effects. *In vivo* tests have given no indications of mutagenic effects. According to current knowledge tramadol can be classified as a non-mutagenic substance.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in the rat and mouse.
The rat study gave no indications of substance-related increases in tumour incidence. In the mouse study, increased incidence of liver cell adenoma was observed in the males (dose-dependent, non-significant increases from 15 mg/kg) and an increase in lung tumours in the females of all dose groups (significant but non-dose dependent increases).

In studies on reproduction toxicity tramadol dosages from 50 mg/kg/day in the rat produced maternal toxic effects and led to increased neonate mortality. Delayed growth in the form of disorders of ossification and delayed vaginal and eye opening occurred in the progeny. The fertility of male rats was not impaired. Females on high doses (from 50 mg/kg/day) showed a reduced gestation index.

From 125 mg/kg maternal toxic effects occurred in rabbits as well as skeletal anomalies in the progeny.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Sugar spheres (maize starch and sucrose)
Macrogol 4000
Polyacylate dispersion 30% (ethyl acrylate, methyl methacrylate, nonoxynol)
Simethicone emulsion (simethicone, polyoxyethylene sorbitan tristearate, methylcellulose, polyethylene glycol stearate, glycerides, xanthan gum, benzoic acid, sorbic acid, sulfuric acid)
Hypromellose

Talc

Capsule shell:
Gelatin
Titanium dioxide (E 171) Yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/PVC blisters
Pack sizes: 10, 20, 28, 30, 50, 56, 60, 100 prolonged-release capsules, hard.
Hospital packs: 500 prolonged-release capsules, hard
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194 Bureaux de la Colline - Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0549/016/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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