

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

By-Madol SR 50 mg prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged-release capsule contains 50 mg of tramadol hydrochloride equivalent to 43.91 mg tramadol.

Excipients with known effects: 0.0038mg Methyl parahydroxybenzoate/prolonged-release capsule
0.0011 mg Propyl parahydroxybenzoate/prolonged-release capsule
5.35 mg Sucrose/prolonged-release capsule

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Capsules with opaque white cap and 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:

100-200 mg tramadol hydrochloride twice daily (corresponding to 200- 400 mg of tramadol hydrochloride/day), morning and evening administration recommended. If required, other forms of administration can be used.

The smallest effective analgesic dose should always be used. Daily doses of 400mg 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 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 dosage intervals should be carefully considered according to the patient's requirements.

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.

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).

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.

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.

Tramadol has a slight potential for dependence. In case of prolonged use, patients may develop tolerance, and psychic and physical dependence. At therapeutic doses, withdrawal symptoms have been reported with a frequency of 1 in 8,000. In patients with a tendency to drug abuse or drug dependence, treatment with BY-MADOL SR should only be for short periods and under strict medical supervision.

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.

The medicinal product contain 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, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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.

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

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-HT₃ 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

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.

Breast-feeding

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.

Tramadol is excreted in very small amounts (approx. 0.1% of an intravenous dose) in human breast milk.

For this reason tramadol should not be used during lactation. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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)).

Organ System	Frequency	Adverse drug reaction
Metabolism and nutrition disorders	Not known	- hypoglycaemia
Psychiatric disorders	Rare	-changes in mood (e.g. elation, dysphoria) - changes in activity (e.g. suppression, increase) - change in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders) - hallucinations -confusion - sleep disturbances - anxiety - nightmares - dependency
Nervous System disorders	Very common	-vertigo
	Common	- headaches - drowsiness
	Rare	- change in appetite - paraesthesia - trembling - respiratory depression - epileptiform seizures - involuntary muscle contractions, - abnormal coordination -syncope
Eye disorders	Rare	- blurred vision
Cardiac disorders	Uncommon	- effects on cardiovascular regulation: palpitations, tachycardia, faintness, cardiovascular collapse
	Rare	- bradycardia - elevated blood pressure
Respiratory, thoracic and	Rare	- dyspnea

mediastinal disorders		
Gastrointestinal disorders	Very common	- nausea
	Common	- vomiting, - constipation -dry mouth
	Uncommon	- retching, diarrhoea, gastric complaints (e.g., stomach pressure, bloating)
Hepatobiliary disorders	Very rare	- elevated transaminases
Skin and subcutaneous tissue disorders	Common	- sweating
	Rare	- skin manifestations (e.g., itching, rash, hot flushes)
Musculoskeletal and connective tissue disorders	Rare	- reduced muscle strength
Renal and urinary disorders	Rare	- disorders of micturition or reduced diuresis
General disorders and administration site conditions	Common	-fatigue
	Rare	- allergic reactions (e.g., dyspnea, bronchospasm, wheezing, angioneurotic oedema, swollen skin) - anaphylaxis

The long-term use of By-Madol SR can lead to dependence, even if the risk is low. Following cessation of treatment, symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastrointestinal symptoms.

Methyl parahydroxybenzoate and propylparahydroxybenzoate can cause hypersensitivity, even delayed hypersensitivity reactions.

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 Pharmacovigilance Section, Irish Medicines Board, Kevin O’Malley House, Earlsfort Centre, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

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.

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.

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 μ , δ , and κ opioid receptors with a higher affinity at the μ 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 (V_d , β 203 ± 40 l). 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 ($t_{1/2 \beta}$) (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. No clinically relevant interactions have been reported to date.

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 ($t_{1/2 \beta}$) 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

Polyacrylate dispersion 30% (ethyl acrylate, methyl methacrylate, nonoxynol)

Dimeticone emulsion (dimethicone, (t-octylphenoxy)polyethoxyethanol, Macrogol 600, polyethylene glycol-sorbitan-laurate, sodium benzoate, propyl-4-hydroxybenzoate (E216), methyl-4-hydroxybenzoate (E218), propylene glycol, sorbic acid)

Hypromellose

Talc

Capsule shell:

Gelatin

Titanium dioxide (E 171)

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 SA

194 Bureaux de la Colline

Bâtiment D

92213 Saint-Cloud cedex

France

8 MARKETING AUTHORISATION NUMBER

PA0549/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th October 2006

Date of last renewal: 12th July 2011

10 DATE OF REVISION OF THE TEXT

May 2017