IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1332/021/001
Case No: 2032305

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Transferred from PA1058/008/001.

Meda Health Sales Ireland

Office 10, Dunboyne Business Park, **Dunboyne**, **Co. Meath**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Zamadol SR 50mg Prolonged-Release Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/01/2007** until **09/12/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zamadol SR 50mg Prolonged-Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg tramadol hydrochloride.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard.

Dark green capsules, marked ‘T50R’.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of severe pain.

4.2 Posology and method of administration

The capsules are intended for twice daily oral administration and can be taken independently of meal times, swallowed whole with water.

As with all analgesic drugs the dosing of Zamadol SR Prolonged-Release Capsules should be adjusted depending on the severity of the pain and the individual clinical response of the patient. The dose used should be the lowest dose that provides pain relief.

Adults:
The usual initial dose is 50-100 mg twice daily, morning and evening. This dose may be titrated up to 150-200 mg twice daily according to pain severity.

If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Treatment periods should be short and intermittent as dependence can occur with tramadol. The benefits of continued use should be reviewed in order to ensure that they outweigh the risks of dependence (see Special Warnings and Precautions for Use and Undesirable Effects sections).

A total oral daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Elderly patients:
Dosing as for adults, however it should be noted that in patients over 75 years there tends to be an increase in absolute bioavailability of 17% and a prolongation of the terminal half-life of tramadol. An adjustment of the dosage or the dose interval may be required**.**

Patients with renal or hepatic insufficiency:
As the elimination of tramadol may be prolonged in patients with severe renal and/or hepatic impairment, the use of Zamadol SR Prolonged-Release Capsules is not recommended. In moderate cases an adjustment of the dosage interval may be required.

Patients who have difficulty in swallowing:
Zamadol SR Prolonged-Release Capsules can be opened, carefully, so that the pellets are deposited on a spoon. The spoon and pellets should be taken into the mouth, followed by a drink of water to rinse the mouth of all pellets. The pellets must not be chewed or crushed.

Children:
Over 12 years: Dosage as for adults

Under 12 years: Zamadol SR Prolonged-Release Capsules have not been studied in children. Therefore, safety and efficacy have not been established and the product should not be used in children.

4.3 Contraindications

Zamadol SR Prolonged-Release Capsules should not be given to patients who have previously shown hypersensitivity to the active substance tramadol or to any of the excipients.

The product should not be administered to patients suffering from acute intoxication with hypnotics, centrally acting analgesics, opioids, psychotropic drugs or alcohol.

Tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within 2 weeks of their withdrawal.

Tramadol should not be given to patients suffering from uncontrolled epilepsy.

Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Warnings:

Tramadol has the potential to cause physical dependence at therapeutic doses (see Undesirable Effects). On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment should be for short periods under strict medical supervision. In rare cases at therapeutic doses, tramadol has the potential to cause withdrawal symptoms.

Zamadol SR Prolonged-Release Capsules are not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold (see section 4.5).

Precautions:
Zamadol SR Prolonged-Release Capsules should be used with prudence in patients who have shown previous hypersensitivity to opiates, and in patients with severe renal or hepatic impairment, head injury, decreased level of consciousness, increased intracranial pressure, or patients in shock or at risk of convulsions.

At recommended therapeutic doses Zamadol SR Prolonged-Release Capsules are unlikely to produce clinically relevant respiratory depression. Care should however be taken when administering Zamadol SR Prolonged-Release Capsules to

patients with existing respiratory depression or excessive bronchial secretion and in those patients taking concomitant CNS depressant drugs.

4.5 Interaction with other medicinal products and other forms of interaction

Patients treated with monoamine oxidase inhibitors within 14 days prior to the administration the opioid pethidine have experienced life-threatening interactions affecting the central nervous system as well as the respiratory and circulatory centres. The possibility of similar interactions occurring between monoamine oxidase inhibitors and tramadol cannot be ruled out.

Tramadol may potentiate the CNS depressant effects of other centrally acting drugs (including alcohol) when administered concomitantly with such drugs.

Tramadol can induce convulsions and may increase the potential for selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions (See section 4.4).

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. Withdrawal of the serotonergic agent produces a rapid improvement.

Administration of Zamadol SR Prolonged-Release Capsules together with carbamazepine results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivative (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients.

The combination of mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not recommended because it is theoretically possible that the analgesic effect of a pure agonist is attenuated under these circumstances.

There is no interaction with food.

4.6 Pregnancy and lactation

Pregnancy:
Zamadol SR Prolonged-Release Capsules should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant.

Lactation:
Zamadol SR Prolonged-Release Capsules should not be administered during breast feeding as tramadol and its metabolites have been detected in breast milk. 0.1% of the dose administered to the mother may be excreted in milk.

4.7 Effects on ability to drive and use machines

Zamadol SR Prolonged-Release Capsules may cause drowsiness and this effect may be potentiated by alcohol, anti-histamines and other CNS depressants. If patients are affected they should be warned not to drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10% of patients.

Immune system disorders:
Rare (>1/10,000, <1/1,000): Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

Metabolism and nutrition disorders:
Rare (>1/10,000, <1/1,000): Changes in appetite.

Psychiatric disorders:
Rare (>1/10,000, <1/1,000): psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders), hallucinations, confusion, sleep disturbances and nightmares.

Prolonged administration of Zamadol SR Prolonged-Release Capsules may lead to dependence (see section 4.4). Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastrointestinal symptoms.

Nervous system disorders:
Very common (>1/10): dizziness.
Common: (>1/100, <1/10): headache, drowsiness.
Rare (>1/10,000, <1/1,000): epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (e.g. antidepressants or anti-psychotics, see section 4.5 “Interaction with other medicinal products and other forms of interaction”. Paraesthesia and tremor.
Very rare (<1/10,000): vertigo

Eye disorders:
Rare (>1/10,000, <1/1,000): blurred vision.

Cardiac disorders:
Uncommon (>1/1,000, <1/100): effects on cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.
Rare (>1/10,000, <1/1,000): bradycardia, increase in blood pressure.

Vascular disorders:
Very rare (<1/10,000): flushing

Respiratory disorders:
Worsening of asthma has also been reported, though a causal relationship has not been established.
Respiratory depression has been reported. If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5 “Interaction with other medicinal products and other forms of interaction”) respiratory depression may occur.

Gastrointestinal disorders:
Very common (>1/10): nausea.
Common (>1/100, <1/10): vomiting, constipation, dry mouth.
Uncommon (>1/1,000, <1/100): retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating).

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

Skin and subcutaneous tissue disorders:
Common (>1/100, <1/10): sweating.
Uncommon (>1/1,000, <1/100): dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal, connective tissue and bone disorders:
Rare (>1/10,000, <1/1,000): motorial weakness.

Renal and urinary system disorders:
Rare (>1/10,000, <1/1,000): micturition disorders (difficulty in passing urine and urinary retention).

General disorders:
Common (>1/100, <1/10): fatigue.

4.9 Overdose

Symptoms of tramadol overdose include vomiting, miosis, sedation, seizures, respiratory depression and hypotension, with circulatory failure and coma. Respiratory failure may also occur. Such symptoms are typical of opioid analgesics.

Treatment of overdose requires the maintenance of the airway and cardiovascular functions. Respiratory depression may be reversed using naloxone and fits controlled with diazepam. Naloxone administration may increase the risk of seizures.

The treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not sufficient or suitable due to the slow elimination of tramadol from the serum by these routes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Analgesic, ATC code N02AX02

Tramadol is a centrally acting analgesic which possesses opioid agonist properties. Tramadol consists of two enantiomers, the (+)-isomer is predominantly active as an opioid with preferential activity for the μ-receptor.

The (-)-isomer potentiates the analgesic effect of the (+)-isomer and is active as an inhibitor of noradrenaline and serotonin uptake thereby modifying the transmission of pain impulses.

Tramadol also has an antitussive action. At the recommended dosages, the effects of tramadol given orally on the respiratory and cardiovascular systems appear to be clinically insignificant. The potency of tramadol is reported to be 1/10 to 1/6 of morphine.

5.2 Pharmacokinetic properties

About 90% of Tramadol released from Zamadol SR Prolonged-Release Capsules is absorbed after oral administration. The mean absolute bioavailability is approximately 70%, irrespective of concomitant intake of food.

The difference between absorbed and non-metabolised available Tramadol is probably due to low first-pass effect. The first pass-effect after oral administration is a maximum of 30%.

Tramadol has a high tissue affinity with an apparent volume of distribution of 203 ± 40 litres after oral dosing in healthy volunteers. Protein binding is limited to 20%.

After single dose administration of Zamadol SR Prolonged-Release Capsules 50 mg the peak plasma concentration C_{max} 70 ± 16 ng/ml is reached after 5.3 h. After administration of Zamadol SR Prolonged-Release Capsules 100 mg C_{max} 137 ± 27 ng/ml is reached after 5.9 h. Following administration of Zamadol SR Prolonged-Release Capsules 200 mg C_{max} 294 ± 82 ng/ml is reached after 6.5 h. The reference product (Tramadol Immediate Release Capsules, given as a total dose of 200 mg Tramadol hydrochloride) reached a peak concentration of C_{max} 640 ± 143 ng/ml after 2.0 hours.

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

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

Elimination of half-life t½β is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of 1.4.

The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite. The clinical consequences of any such interactions are not known.

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 substance by the factor 2-4. Its half life t½β (6 healthy volunteers) is 7.9 h (range 5.4-9.6 h) and is approximately that of tramadol.

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

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. Studies of tramadol in rats and rabbits have revealed no teratogenic effects. However, embryo toxicity was shown in the form of delayed ossification. Fertility, reproductive performance and development of offspring were unaffected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres (sucrose and maize starch)
Colloidal anhydrous silica
Ethylcellulose
Shellac
Talc

Capsule shell:

Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigotin (E132)

Printing Ink:

Shellac
Iron oxide black (E172)
Soya lecithin
Antifoam DC 1510

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

White opaque PVC/PVDC and aluminium foil blister strips. Each strip contains 10 size 4 capsules.

The blister strips are packed in cartons containing 30 or 60 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Meda Health Sales Ireland Ltd.
Office 10, Dunboyne Business Park,
Dunboyne,
Co. Meath

8 MARKETING AUTHORISATION NUMBER

PA 1332/21/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 December 1998

Date of last renewal: 10 December 2003

10 DATE OF REVISION OF THE TEXT

January 2007