IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1498/001/001
Case No: 2051459

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

HGH Regulatory Sciences Limited

Ledderhoser Weg 38, **D 55543 Bad Kreuznach**, **Germany**

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

Tradorec XL 100mg prolonged-release tablets

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 **07/08/2009** until **06/08/2014**.

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

Tradorec XL 100mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release tablet contains 100mg tramadol hydrochloride

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet
White to off white, plain, bevelled edge, round biconvex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

The dosage should be adjusted according to the severity of pain and the response of the individual patient. The prolonged-release tablets should be swallowed whole, with a sufficient quantity of liquid and not divided or chewed. The prolonged-release tablets can be taken with or without food.

Alternative strengths of Tradorec XL are available. Where necessary, appropriate strengths should be used to achieve the required dose.

Tradorec XL prolonged-release tablets should be taken once every 24 hours as follows:

Adults and adolescents (12 years and over):
The starting dose is 100 mg tramodol hydrochloride as prolonged-release tablet once daily. The usual dose is 200 mg tramadol hydrochloride as prolonged-release tablet once daily, to be taken preferably in the evening. If this does not provide sufficient pain relief, the dosage can be increased in 100 mg dose increments to 300 mg or to a maximum of 400 mg tramadol hydrochloride as prolonged-release tablet once daily.
In general, the lowest effective analgesic dose should be chosen. A daily dose of 400mg of Tradorec XL should not be exceeded except in special clinical cases.
Tradorec XL should not be used for a period longer than absolutely necessary. If continued pain treatment is necessary due to the nature and severity of the illness, careful regular surveillance should be carried out (including periods without treatment, if necessary) in order to determine the need for continued treatment.

Children (under 12):
Tradorec XL is not recommended for the treatment of children (under 12 years of age).

Elderly patients:
Dose adjustment is usually not necessary for elderly patients (75 years or older), in the absence of clinically relevant hepatic insufficiency or renal insufficiency (creatinine clearance ≥ 50 ml/min).

Renal impairment, dialysis and hepatic impairment:
Patients with severe hepatic or renal impairment should not be treated with Tradorec XL prolonged-release tablets (see section 4.3). Dose adjustment is usually not necessary in patients with mild renal impairment, in the absence of clinically relevant features. Caution should be exercised in patients with moderate hepatic or moderate renal impairment (see section 4.5).

4.3 Contraindications

Hypersensitivity to tramadol hydrochloride or to any of the excipients (see section 6.1).
Acute intoxication or overdose with CNS depressants (alcohol, hypnotics, other opioid analgesics, etc.).
Patients receiving concomitant treatment with MAO inhibitors or who have been treated with MAO inhibitors during the past 2 weeks (see section 4.5). Concomitant treatment with linezolid (see section 4.5).
Severe hepatic impairment (Child-Pugh Class C) or severe renal impairment (creatinine clearance < 30ml/min).
Epilepsy not adequately controlled by treatment (see section 4.4).
Tramadol hydrochloride must not be used as a substitute in opioid dependent patients.

4.4 Special warnings and precautions for use

Consumption of alcohol is not recommended during treatment with tramadol hydrochloride.
Concomitant treatment with carbamazepine is not recommended (see section 4.5).

Warnings and Precautions:

Tramadol hydrochloride should be used with caution in patients with opioid dependence, head trauma, in patients in shock, an altered state of consciousness (with no obvious cause), respiratory centre disorders or respiratory dysfunction, increased intracranial pressure.
Patients who are sensitive to opioids should be treated with caution.

Seizures have been reported at the therapeutic doses. There is an increased risk of seizures if the tramadol hydrochloride dose exceeds the maximum recommended daily dose (400 mg). There is an increased risk of seizures in patients taking concomitant medications which lower the seizure threshold (see section 4.5).
Patients with controlled epilepsy or patients with a known risk of seizure should only be treated with tramadol hydrochloride in cases of absolute necessity.

Tramadol hydrochloride has a low potential for dependence. However, with long-term use, tolerance and psychological and/or physical dependence may develop. In patients with a tendency to drug abuse or dependence, tramadol hydrochloride should only be used for short periods under strict medical surveillance.

Tramadol hydrochloride is not suitable as a substitute in opioid dependent patients. Although it is an opioid agonist, tramadol hydrochloride cannot suppress morphine withdrawal symptoms.

Respiratory depression or patient taking CNS depressants:
Caution is recommended with administration of tramadol hydrochloride in patients at risk for respiratory depression or receiving medicinal products likely to produce respiratory depression.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol hydrochloride must not be used in combination with selective or nonselective MAO inhibitors. Serotonin Syndrome (diarrhoea, tachycardia, sweating, tremor, confusion and coma) may develop (see section 4.3).
Linezolid: Treatment experience with non-selective MAOI indicates a risk of development of Serotonin Syndrome: diarrhoea, tachycardia, sweating, tremor, confusion and coma.

After premedication with MAO inhibitors during 14 days before treatment with the opioid pethidine life threatening interactions concerning the CNS, the cardiovascular and the respiratory system have been observed. Similar interactions cannot be excluded for tramadol hydrochloride .

Concomitant medication of tramadol hydrochloride and other CNS depressant substances including alcohol may increase CNS effects (see section 4.8).

According to pharmacokinetic studies a concomitant or previous administration with cimetidine (enzyme inhibitor) does not lead to clinically relevant interactions. Carbamazepine (enzyme inducer): Possibility of decreased plasma concentrations of tramadol hydrochloride and its pharmacologically active metabolite, resulting in reduction of the analgesic effect and a shorter duration of effect.

Concomitant treatment with mixed agonist-antagonists (buprenorphine, nalbuphine and pentazocine) and tramadol hydrochloride is not recommended because theoretically, this could reduce the analgesic effects of the pure agonist due to competitive blocking of receptors.

Tramadol hydrochloride can induce seizure and increase the risk of convulsions when taken concomitantly with medicinal products that reduce seizure threshold, notably tricyclic antidepressants (imipramine), selective serotonin re-uptake inhibitors (SSRIs), antipsychotics.

A serotonin syndrome was reported in individual cases and in temporal relation to the administration of tramadol hydrochloride and serotoninergic substances such as selective serotonin re-uptake inhibitors (SSRIs) or MAO inhibitors. Its symptoms may include confusion, tremor, fever, sweating, ataxia, tachycardia, and diarrhoea. Management of serotonin syndrome involves withdrawal of serotoninergic substances and initiation of supportive measures. Drug treatment of the serotonin syndrome depends on the severity of the symptoms.

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

Other CYP3A4 inhibitors such as ketoconazole and erythromycin inhibit the metabolism of tramadol hydrochloride (N-Demethylation) and possibly its O-demethylated metabolite. The clinical relevance of this interaction is not known (see section 4.8)

4.6 Pregnancy and lactation

There is insufficient data available to appropriately assess the safety of tramadol hydrochloride use in pregnant women. Animal studies with tramadol hydrochloride at high doses have shown effects on organogenesis, bone growth and mortality of the newborn. Teratogenic effects have not been observed. Tramadol hydrochloride crosses the placental barrier.
Therefore tramadol hydrochloride should not be used during pregnancy.

Tramadol hydrochloride, when administered before or during delivery, does not influence the contractility of the uterus. In the newborn tramadol hydrochloride may induce respiratory effects, which are normally not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Tramadol hydrochloride and its metabolites have been detected in human breast milk in small amounts of 0.1% of the single dose given to the mother. Therefore tramadol hydrochloride should not be administered to breastfeeding women on a long-term basis. A single administration of tramadol hydrochloride does not usually require breastfeeding to be interrupted.

4.7 Effects on ability to drive and use machines

Tramadol hydrochloride may cause dizziness and/or drowsiness and has, even when used according to the directions, an influence on the ability to drive and use machines. This effect may occur at the beginning of treatment, and may be potentiated by alcohol and concomitant use of other CNS-depressants or antihistamines. If patients are affected they should be warned not to drive or operate machinery.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most commonly reported undesirable effects, nausea and dizziness, have been observed in more than 10% of patients.

Cardiac disorders
Uncommon (≥1/1,000, <1/100): effects on cardiovascular regulation (palpitations, tachycardia, orthostatic hypotension or cardiovascular collapse). These undesirable effects occur in particular after intravenous administration and in patients undergoing physical exertion. Rare (≥1/10,000, <1/1,000): bradycardia, Increase in blood pressure

Nervous system disorders
Very common (≥1/10): dizziness.

Common (≥1/100, <1/10): headaches, confusion.

Rare (≥1/10,000, <1/1,000): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform seizures.

Respiratory depression may occur if the quantities administered greatly exceed the recommended doses and in the case of concomitant administration of other CNS depressant medicinal products (see section 4.5).

Epileptiform seizures primarily occurred following administration of high doses of tramadol hydrochloride or following concomitant treatment with medicinal products that lower the seizure threshold or trigger seizures (see sections 4.4 and 4.5).

Psychiatric disorders
Rare (≥1/10,000, <1/1,000): hallucinations, confusion, sleep disturbance, nightmares.

After the administration of tramadol hydrochloride, in rare cases, various psychiatric adverse events may occur, the nature and severity of which vary between patients (depending on the individual reactivity and the duration of treatment). Mood disorders (usually euphoria, occasionally dysphoria), changes in activity (usually reduced activity, occasionally an increase) and, altered cognitive and sensory capacities (for example the ability to make decisions, perception problems) may be observed. Dependence may occur.

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

Respiratory, thoracic and mediastinal disorders
An aggravation of asthma has been reported although a causal relationship was not confirmed.

Gastrointestinal disorders
Very common (≥1/10): nausea.

Common (≥1/100, <1/10): vomiting, constipation, dry mouth.

Uncommon (≥1/1,000, <1/100): gastro-intestinal irritation (a feeling of gastric heaviness, flatulence).

Skin and subcutaneous tissue disorders
Common (≥1/100, <1/10): sweating.

Uncommon (≥1/1,000, <1/100): dermal reactions (for example pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders
Rare (≥1/10,000, <1/1,000): muscular weakness.

Hepatobiliary disorders
In some isolated cases, an increase in hepatic enzymes was reported during the therapeutic use of tramadol hydrochloride.

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

General disorders and administration site conditions
Rare (≥1/10,000, <1/1,000): Allergic reactions (for example dyspnoea, bronchospasm, wheezing, Quincke's oedema) and anaphylaxis.

Withdrawal symptoms similar to those observed during withdrawal of opiates may occur, such as agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastro-intestinal symptoms. Other symptoms of withdrawal have also been reported, including: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and other CNS problems.

4.9 Overdose

Symptoms
In tramadol hydrochloride intoxication, in principle, the same symptoms occur as for all other central acting analgesics (opioids). In particular, these include miosis, vomiting, cardiovascular collapse, loss of consciousness leading to coma, convulsions, respiratory depression leading to respiratory failure.

Treatment
General emergency measures are applicable: including maintenance of respiratory and cardiocirculatory functions, emptying of the stomach by means of vomiting (patient to be conscious) or by means of pumping the stomach.
The antidote for respiratory depression is naloxone. There is a risk of increased convulsions with the use of naloxone. In animal tests naloxone proved to be ineffective against convulsions. In that case diazepam should be administered intravenously.
Tramadol hydrochloride is only minimally removed from plasma using haemodialysis or haemofiltration. Therefore treatment of acute overdose of tramadol hydrochloride using haemodialysis or haemofiltration alone is not a suitable way of detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other opioids
ATC code: N02A X02

Tramadol hydrochloride is a centrally acting analgesic. It is a pure non-selective μ, delta and k morphine receptor agonist with a higher affinity for μ receptors. Other mechanisms responsible for the product’s analgesic effects include the inhibition of the neuronal re-uptake of noradrenalin and an increase in serotonin release.
Tramadol hydrochloride has an antitussive effect. Unlike morphine, broad ranges of analgesic tramadol hydrochloride doses do not have any respiratory depressant effect. Nor is there any effect on gastro-intestinal motility. The effects on the cardiovascular system tend to be slight. Tramadol hydrochloride has 1/10 to 1/6 the potency of morphine.

5.2 Pharmacokinetic properties

Following oral administration of a single dose, Tradorec XL is almost completely absorbed (>90%).
The absolute bioavailability is approximately 70%, independent of food intake. The difference between the tramadol hydrochloride absorbed and the non-metabolised available tramadol hydrochloride is probably due to a weak first-pass effect. The first-pass effect following oral administration is a maximum of 30%.
Tramadol hydrochloride has a high tissue affinity (volume of distribution = 203 ± 40 litres). Approximately 20% is bound to plasma proteins.

Following single-dose administration of one 200 mg Tradorec XL prolonged- release tablet, in a fasted state, a mean maximum plasma concentration (C_{max}) of 241 ± 62 ng/ml is reached after a median time (tmax) of 6.0 hours.

Tramadol hydrochloride crosses the blood-brain barrier and the placenta. Very small quantities of the active substance and its *O*-demethylated derivative have been found in breast milk (0.1% and 0.02% of the administered dose respectively).
The elimination half-life is approximately 6 hours, regardless of route of administration. The half life can be prolonged by a factor of approximately 1.4 in patients over 75 years of age.
In man, tramadol hydrochloride is extensively metabolised by N- and *O*-demethylation and by conjugation of the *O*-demethylation products with glucuronic acid. Only the *O*-desmethyltramadol metabolite is pharmacologically active. Considerable quantitative inter-individual differences have been observed between the other metabolites: 11 different metabolites have been identified to date in urine. Tests on animals showed that *O*-desmethyltramadol is more potent than the parent molecule by a factor of 2 to 4. Its half life (6 healthy volunteers) is 7.9 hours (range 5.4 to 9.6 hours), similar to that of tramadol hydrochloride.
The inhibition of cytochrome CYP3A4 and/or CYP2D6, the isozymes responsible for biotransformation of tramadol hydrochloride could modify the plasma concentration of tramadol hydrochloride or its active metabolite. To date, no clinically significant interactions have been observed.
Tramadol hydrochloride and its metabolites are almost wholly excreted in urine. Cumulative urinary excretion accounts for 90% of the total radioactivity of the administered dose. The half-life may be slightly longer in the case of hepatic or renal impairment. In patients with liver cirrhosis, an elimination half-life of 13.3 ± 4.9 hours (tramadol hydrochloride) and 18.5 ± 9.4 hours (*O*-desmethyltramadol) has been observed, with one extreme case of elimination half-lives of 22.3 and 36 hours respectively. In renal insufficiency (creatinine clearance < 5 ml/min), elimination half-lives of 11 ± 3.2 and 16.9 ± 3 hours respectively have been observed, with one extreme case of 19.5 and 43.2 hours respectively.
Tradorec XL presents a linear pharmacokinetic profile within the recommended therapeutic dosing regimen.
The relationship between serum concentration and analgesic effect is dose-dependent but varies considerably between individuals. A serum concentration of 100 ng/ml to 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, but at high doses, foetotoxicity due to maternotoxicity appeared.
In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects observed from 125 mg/kg upwards and skeletal anomalies in the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
hydrogenated vegetable oil (from cotton seed)
magnesium stearate (vegetable origin)
silica colloidal anhydrous
hydroxypropyl distarch phosphate (E1442)

Tablet Coat
xanthan gum
hydrogenated vegetable oil (from cotton seed)
magnesium stearate (vegetable origin)
silica colloidal anhydrous
Kollidon SR (consisting of polyvinyl acetate, povidone K30, sodium laurilsulfate, silica colloidal anhydrous)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Blisters: Do not store above 30°C.
HDPE Bottles: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/PVDC blisters with aluminium backing foil (containing 3, 5, 10, 15, 20, 30, 50, 60 or 100 prolonged-release tablets).
PVC/PE/PCTFE (Aclar) blisters with aluminium backing foil (containing 3, 5, 10, 15, 30, 60 or 100 prolonged-release tablets).
HDPE bottles with PP cap containing 100 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

HGH Regulatory Sciences Limited
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8 MARKETING AUTHORISATION NUMBER

PA1498/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th August 2009

10 DATE OF REVISION OF THE TEXT