

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0915/026/001**

Case No: 2080524

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

**Helsinn Birex Therapeutics Ltd**

**Damastown, Mulhuddart, Dublin 15, Ireland**

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

**By-Madol 50mg 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 **11/05/2010**.

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

By-Madol 50mg Capsules

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg tramadol hydrochloride.

Excipients: Lactose monohydrate 103.0mg

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Capsule, hard.

Capsules have a hard, yellow cap and a green body. Each capsule is printed 'TRA50' on the cap and body.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Management (treatment and prevention) of severe pain.

##### 4.2 Posology and method of administration

As with all analgesics, the dose of By-Madol should be adjusted according to the severity of the pain and the clinical response of the individual patient. 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 & Precautions for Use and Undesirable Effects Sections).

*Adults and adolescents over the age of 12 years:*

Depending upon the severity of the pain, the initial dose is 50 to 100mg tramadol, then 50mg to 100mg 4-6 hourly. If tramadol is used for the treatment of acute pain, it should be taken into account that the effect starts slightly later than that of other analgesics. For acute pain an initial dose of 100 mg is usually required. For pain associated with chronic conditions, an initial dose of 50 mg is recommended. A total daily dose of more than 400mg is not usually required.

*Elderly:*

The usual dosages may be used since no significant change of the pharmacokinetic parameters appears.

*Renal and hepatic impairment:*

In patients with renal or hepatic impairment the usual initial dose may be used, however the interval between subsequent doses should be twice as long. In patients with both renal and hepatic impairment, the use of tramadol should be avoided.

*Renal Dialysis:*

Tramadol is removed very slowly by haemodialysis or haemofiltration, therefore postdialysis administration to maintain analgesia is not usually necessary.

*Children under 12 years:*

On account of their high dosage strength By-Madol 50 mg capsules are not recommended for use in children under 12 years.

Route of administration: Oral.

### 4.3 Contraindications

Hypersensitivity to tramadol or any of the excipients or other opioids.

Acute intoxication with alcohol, hypnotics, centrally acting analgesics or other centrally acting drugs. Tramadol should not be administered to patients concomitantly with monoamine oxidase inhibitors or within two weeks of their withdrawal.

### 4.4 Special warnings and precautions for use

Tramadol has the potential to cause physical dependence at therapeutic doses (See Undesirable Effects).

By-Madol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

Care should be taken when treating patients with severe respiratory depression, if concomitantly CNS depressant drugs are being administered or if the recommended dose is exceeded considerably, since the possibility of respiratory depression cannot be excluded in these situations.

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

For physical dependency, addiction and habituation: see Undesirable Effects.

In one study use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intraoperative recall. Until further information is available use of By-Madol with such anaesthesia should be avoided.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily limit (400mg). In addition, tramadol may increase the seizure risk in patients taking other medication that affects the seizure threshold (see Interactions). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

### 4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of tramadol with monoamine oxidase inhibitors or within two weeks of their withdrawal is contraindicated. Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effects.

There have been isolated spontaneous reports of epileptiform convulsions which in most instances occurred after intravenous administration of a high single dose of tramadol or during concomitant use with antipsychotics known to induce convulsions.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. The elimination half-life of tramadol may be slightly prolonged by some 1-2 hours. Under normal circumstances this should be insufficient to have clinical relevance. However, because of inter-individual variation, it is recommended that care should be taken if prolonged co-administration with agents such as cimetidine is needed.

Simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to the extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Tramadol can induce convulsions and increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions.

## 4.6 Pregnancy and lactation

There is inadequate evidence available on safety of tramadol in human pregnancy, but it has been in wide use for many years without apparent ill consequences. Animal studies have not revealed harmful effects. As tramadol crosses the placenta, use during pregnancy should only be considered if there is no safer alternative.

Tramadol may be used during delivery.

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of a dose given to the mother. Tramadol should not be administered during lactation.

## 4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness and dizziness and this effect can be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

## 4.8 Undesirable effects

As with other opioids the following adverse effects have been reported: dyspnoea, wheeze, bronchospasm and worsening of existing asthma, nausea, vomiting, dry mouth, tiredness, fatigue, drowsiness, dizziness, headache, pruritus, urticaria, sweating, flushing.

Orthostatic effects e.g. postural hypotension and tachycardia, particularly after rapid intravenous administration have been reported rarely. Other rare adverse effects include gastrointestinal irritation, constipation, rash and CNS excitation.

Physical Dependence:

Dependence, abuse and withdrawal reactions have been reported. The majority of withdrawal reaction symptoms are similar to those occurring during opiate withdrawal and include agitation, anxiety, nervousness, insomnia, hypertension, tremor and gastrointestinal symptoms (See Posology and Administration and Special Warnings).

## 4.9 Overdose

The symptoms of overdose are typical for opioid-analgesics and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression. Supportive measures such as maintaining respiratory and cardiovascular functions should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam. As tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration, treatment of acute intoxication with By-Madol with haemodialysis or haemofiltration alone is not suitable for detoxification.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Tramadol is a centrally acting analgesic, effective for moderate to severe acute and chronic pains. Tramadol consists of two enantiomers. The (+)-isomer is predominantly active as an opiate with a higher affinity for the  $\mu$ -opiate receptor (20 times higher affinity than the (-)-isomer).

The (+)-desmethyl metabolite will certainly contribute to its action as an opiate as well. The metabolite has a six times stronger affinity for the  $\mu$ -receptor in vivo than tramadol. In vitro this affinity is 170 times stronger. The (-)-isomer acts as an inhibitor of the re-uptake of noradrenaline and potentiates the analgetic action of the (+)-isomer. The contribution of the stimulation of the serotonin release is considered low.

Tramadol has an analgesic and anti-tussive effect. Unlike morphine respiratory suppression is hardly observed at therapeutic doses. The influence on gastro-intestinal motility and on the cardiovascular system is low at these doses.

## 5.2 Pharmacokinetic properties

Tramadol is absorbed rapidly and completely after oral administration. The absolute biological availability is 60-95%, (on average 72%). Maximum serum concentrations are reached after approx. 1 hour.

Plasma protein binding amounts to 20%. Tramadol passes the blood-brain barrier and the placenta. The excretion of tramadol or its metabolites in human breast milk is small ( $\pm 0.1\%$ ). Tramadol is especially metabolised by demethylation followed by glucuronidation of the 0-desmethyl-metabolite. Only 0-desmethyl-tramadol is pharmacologically active. Tramadol and its metabolites are almost completely excreted renally, of which approximately 10% is unchanged tramadol. The half life of the terminal elimination phase of both tramadol and its metabolites is approximately 6 hours, both in young volunteers and in elderly patients. Since tramadol is eliminated both metabolically and renally, the half life of the terminal elimination phase may be prolonged in impaired hepatic and renal function. In those cases the half life of the terminal elimination phase is twice as long. In patients with both renal and hepatic impairment, the use of tramadol should be avoided.

## 5.3 Preclinical safety data

No particulars.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Microcrystalline cellulose  
Polyvidone K30  
Lactose monohydrate  
Magnesium stearate  
Sodium starch glycolate (Type A)

### Hard gelatin capsule shell:

#### Body:

Yellow L520  
Gelatin  
Water  
Erythrosine (E127)  
Titanium Dioxide (E171)  
Yellow iron oxide (E172)

#### Cap:

Green L730  
Gelatin  
Water  
Indigocarmine (E132)  
Titanium dioxide (E171)  
Yellow iron oxide (E172)

Printing Ink Colorcon S-1-27794:

Shellac

Industrial methylated spirit 740P

n-butyl alcohol

Black iron oxide (E172)

Purified water

Propylene glycol

Isopropyl alcohol

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf Life**

5 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**

By-Madol 50mg capsules are packed in a PVC/PVDC blister strip with aluminium foil, packed in a cardboard carton. Available in pack sizes of 10, 30, 60 or 100.

Not all pack sizes may be marketed.

## **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**

Helsinn Birex Therapeutics Ltd

Damastown

Mulhuddart

Dublin 15

## **8 MARKETING AUTHORISATION NUMBER**

PA 915/26/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 24<sup>th</sup> August 2001

## **10 DATE OF REVISION OF THE TEXT**

May 2010