IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1473/036/001
Case No: 2063357

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

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

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

Zydol 50mg Hard 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 **04/09/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zydol 50mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50mg Tramadol Hydrochloride

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (capsule)

Product imported from the UK:
Green/pale yellow hard gelatin capsules for oral administration, imprinted with the Grunenthal logo.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

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 Section 4.4, Special warnings and precautions for use and 4.8, Undesirable effects).*
The dose should be adjusted to the intensity of the pain and sensitivity of the individual patient.

Unless otherwise prescribed, Zydol should be administered as follows:
Adults and adolescents above the age of 12 years:

Oral administration
Depending on the severity of the pain, the initial dose is 50 or 100mg at 4-6 hourly intervals. For acute pain an initial dose of 100mg is usually necessary. For pain associated with chronic conditions an initial dose of 50mg is advised.

The lowest analgesically effective dose should generally be selected. Daily doses of 400 mg active substance should not be exceeded, except in special clinical circumstances.

Capsules should be swallowed whole, not divided or chewed, with sufficient liquid, and independent of meals.

Zydol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Zydol 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.

Geriatric patients
A dose adjustment is not necessary in elderly 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 patients requirements.

Renal insufficiency/Dialysis and Hepatic Insufficiency
In patients with impaired hepatic or renal function the elimination of tramadol may be prolonged. In these patients prolongation of dosage intervals should be carefully considered according to the patients requirements. It is recommended that the usual initial dosage be used and when repeated dosing is required the interval between doses is extended by a factor of 2. Subsequent dosing should be adjusted dependent on the frequency of recurrence of pain.

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

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

4.3 Contraindications

Zydol is contraindicated
- in hypersensitivity to Tramadol or any of the excipients *(see section 6.1, List of excipients)*,
- in acute intoxication with alcohol, hynotics, analgesics, opioids, or psychotropic medicinal products,
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days *(see section 4.5, Interaction with other medicinal products and other forms of interaction),*
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Zydol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

In patients sensitive to opiates the product should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered *(see section 4.5, Interaction with other medicinal products and other forms of interaction),* or if the recommended dosage is significantly exceeded *(see section 4.9, Overdose)* as the possibility of respiratory depression cannot be excluded in these situations.

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 dose limit (400 mg). In addition, Tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold *(see section 4.5, Interaction with other medicinal products and other forms of interaction)*. Patients with epilepsy or those susceptible to seizures should be only treated with Tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with Zydol should only be carried out for short periods under strict medical supervision.

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

4.5 Interaction with other medicinal products and other forms of interaction

Zydol should not be combined with MAO inhibitors *(see section 4.3, Contraindications)*. In patients treated with MAO inhibitors in the last 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular functions have been observed.

The same interactions with MAO inhibitors cannot be ruled out during treatment with Zydol.

Concomitant administration of Zydol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects *(see section 4.8, Undesirable effects).*

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and Tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products to cause convulsions.

In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of Tramadol in combination with other serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

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.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of Tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied *(see section 4.8, Undesirable effects).*

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.

4.6 Pregnancy and lactation

Animal studies using very high doses have shown effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta barrier. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore Zydol should not be used 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.

Chronic use during pregnancy may lead to neonatal withdrawal symptoms. During lactation about 0.1% of the maternal dose is secreted into the milk. Zydol is not recommended during breast-feeding. After a single administration of Tramadol it is not usually necessary to interrupt breast feeding.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, Zydol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

4.8 Undesirable effects

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

Cardiovascular disorders:
Uncommon (≥1/1000, <1/100): cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Rare (≥1/10000, <1000): Bradycardia, increase in blood pressure

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

Common (≥1/100, <1/10): headache, somnolence

Rare (*≥1/10000, <1/1000):* changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope..

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.
Epileptiform 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, Special warnings and precautions for use and 4.5, Interaction with other medicinal products and other forms of interaction).*

Psychiatric disorders:
Rare (≥1/10000, <1/1000): hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic adverse reactions may occur following administration of Zydol, which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually suppression, occassionaly increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:
Rare (≥1/10000, <1/1000): blurred vision

Respiratory disorders:

Rare (≥1/10000, <1/1000): dyspnoea

Worsening of asthma has been reported, though a casual relationship has not been established.

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

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

Uncommon (≥1/1000, <1/100): retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea

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

Uncommon (≥1/1000, <1/100): dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal disorders:
Rare (≥1/10000, <1/1000): motorial weakness

Hepatobiliary 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.

Renal and urinary disorders:
Rare (*≥1/10000, 1/1000):* micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:
Common (≥1/100, <1/10): fatigue
Rare (*≥1/10000, 1/1000):* allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; symptoms of withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with Tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms.

4.9 Overdose

Symptoms
In principle, on intoxication with Tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment
The general emergency measures apply. Keep open the respiratory tract (aspiration!), maintain respiration and circulation depending on symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

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.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Zydol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC-code N 02 AX 02

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 for μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of Tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

About 90% of tramadol is absorbed after oral administration. The bioavailabilty of tramadol from Zydol capsules is extremely high (about 70%) compared with other opioids analgesics. Peak serum concentrations are achieved after about 1 to 2 hours.

The half-life of the terminal elimination phase (t½ β) was 6.0 ± 1.5h in young volunteers. Tramadol pharmacokinetics show little age dependence, the minimal changes being therapeutically irrelevant. In patients above the age of 65 years, the t½ β was 6.5 ± 1.7h on oral administration. In volunteers aged over 75 years, t½ β was 7.0 ± 1.6h on oral administration.

Since tramadol is eliminated both metabolically and renally, the terminal half-life t½ β may be prolonged in impaired hepatic or renal function. However, the increase in the t½ β values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½ β, tramadol was a mean of 13.3 ± 4.9h; in patients with renal insufficiency (creatinine clearance < 5ml/min) it was 11.0 ± 3.2h.

5.3 Preclinical safety data

On repeated oral and parenteral administration of Tramadol for 6-26 weeks in rats and dogs and oral administration for 12 months in dogs haematological, clinicochemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats Tramadol dosages from 50mg/kg/day upwards caused toxic effects in dams 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 50mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125mg/kg upwards and skeletal anomalies in the offspring.

In some *in-vitro* test systems there was evidence of mutagenic effects. *In-vivo* studies showed no such effects. According to knowledge gained so far, Tramadol can be classified as non-mutagenic.

Studies on the tumourigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose dependent, non-significant increase from 15mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups(significant, but not dose-dependent).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Microcrystalline cellulose
Sodium Starch Glycollate (Type A)
Magnesium Stearate
Silica, colloidal anhydrous

Capsule Shell:
Gelatin
Sodium laurilsulfate
Indigotin (E132)
Yellow Iron Oxide (E172)
Titanium Dioxide (E171)

Logo printing ink:
Shellac
Soya Lecithin
Black Iron Oxide (E172)
Antifoam DC 1510

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C
Store in the original container

6.5 Nature and contents of container

PVC/Foil or PP/Foil blister strips in an overlabelled container. Pack size of 100 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals
4 Altona Road
Lisburn
N. Ireland
BT27 5QB

8 Parallel Product Authorisation Number

PPA 1473/36/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th September 2009

10 DATE OF REVISION OF THE TEXT