IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1328/008/001
Case No: 2077973

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

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

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

Zydol, 50 Milligram

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 **17/02/2010** until .

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 50 mg 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

Hard Capsule.

Product imported from the UK:
Hart gelatin capsule with a green cap and yellow body, imprinted with a black logo on both body and cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of 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 and 4.8).
As with all analgesic drugs, the dose of Zydol should be adjusted according to the severity of the pain and the clinical response of the individual patient.
Adults and children aged 14 years and over
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.
A total daily dose of more than 400mg is not recommended, except in special clinical circumstances.
Capsules should be swallowed whole, not divided or chewed, with sufficient liquid, and independent of meals.
Elderly
No adjustment of dosage is usually necessary in elderly patients (up to 75 years) as there is no significant difference in tramadol pharmacokinetics with increasing age. However, 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 and Hepatic impairment
In patients with impaired hepatic or renal functionthe elimination of tramadol may be prolonged. In these patients prolongation of dosage intervals should be carefully considered according to the patient's 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.
Renal dialysis
Tramadol is removed very slowly by haemodialysis or haemofiltration, therefore post-dialysis administration to maintain analgesia is not usually necessary.

Children under 14 years
On account of their high dosage strength Zydol 50 mg capsules are not recommended for use in children under 14 years.

4.3 Contraindications

Zydol should not be administered to patients who have previously demonstrated hypersensitivity towards tramadol or any of the excipients of Zydol capsules (see Section 6.1) or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see Section 4.5)
Zydol must not be used in epilepsy not adequately controlled by treatment.
Zydol 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*).
Zydol may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.
Zydol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, Zydol can not suppress morphine withdrawal symptoms.
Precautions
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 only be treated with tramadol if there are compelling circumstances.
Zydol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function, bilary tract disorders and in patients prone to convulsive disorders or in shock.
Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered or if the recommended dose is significantly exceeded, as the possibility of respiratory depression can not be excluded in these situations.
In one study use of Zydol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intraoperative recall. Until further information is available, use of Zydol with such anaesthesia should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Zydol should not be combined with MAO inhibitors (see Section 4.3).
On premedication 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 acting drugs including alcohol may potentiate CNS depressant effects (see Section 4.8).
In common with other opioid analgesics, there have been spontaneous reports of epileptiform convulsions which in most instances occurred after intravenous administration of a high single dose of Zydol or during concomitant use with anti-psychotics known to induce convulsions.
Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs), anti-psychotics and other seizure threshold-lowering drugs to cause convulsions.
Co-administration with serotonergic medicines such as SSRIs or with MAO inhibitors, may lead to an increase of serotonin associated effects which can include serotonin syndrome. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug 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 and ecchymoses in some patients.

Simultaneous administration with cimetidine, an enzyme inhibitor, is associated with clinically insignificant changes in absolute 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 be taken if prolonged co-administration with agents such as cimetidine is needed.
Simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol and the principal active metabolite to an extent that a decrease in analgesic effectiveness and a shorter duration of action should be expected.
Other drugs 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.

4.6 Pregnancy and lactation

Pregnancy
Animal studies using very high doses have shown effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placental barrier. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore, Zydol should not be used in pregnant women.
In neonates it may induce changes in the respiratory rate which are usually not clinically relevant.
Lactation
Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Zydol should not be used during breast-feeding.
After a single administration of Zydol it is not usually necessary to interrupt breast feeding.

4.7 Effects on ability to drive and use machines

Zydol may cause drowsiness and this effect may 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

The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10 % of patients.
Very common >1/10), Common >1/100, <1/10), Uncommon >1/1000, <1/100), Rare >1/10,000, <1/1000), Very rare (<1/10,000) and including isolated cases

Cardiac/vascular system disorders:
uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse), flushing. These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.
rare: bradycardia, increase in blood pressure

Central and peripheral nervous system disorders:
very common: Dizziness
common: headache, drowsiness
rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitant treatment with drugs which lower the seizure threshold (see Section 4.4 and 4.5).

Psychiatric disorders:
rare: hallucinations, confusion, sleep disturbance and nightmares. 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 ability (e.g. decision behaviour, perception disorders). Dependence, abuse and addiction may occur.

Vision disorders:
rare: blurred vision

Respiratory system disorders:
Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:
very common: nausea
common: constipation, dry mouth, vomiting
uncommon: retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating).

Skin and appendages disorders:
common: sweating
uncommon: dermal reactions (e.g. pruritus, rash, urticaria)

Musculo-Skeletal system disorders:
rare: muscle weakness

Liver and biliary system disorders:
In isolated cases, increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Urinary system disorders:
rare: micturition disorders (difficulty in passing urine and urinary retention)

Body as a whole:
rare: Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

Physical Dependence:
Dependence, abuse, addiction and withdrawal reactions may occur. The majority of withdrawal reaction symptoms are similar to those occurring during opiate withdrawal. Typical withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

4.9 Overdose

Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression.
Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
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

Zydol is a centrally acting analgesic. It is a non selective pure agonist of mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

5.2 Pharmacokinetic properties

The half-life of the terminal elimination phase (t½ b) 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 b was 6.5 ± 1.7h on oral administration. In volunteers aged over 75 years, t½ b was 7.0 ± 1.6h on oral administration.
Since tramadol is eliminated both metabolically and renally, the terminal half-life t½ b may be prolonged in impaired hepatic or renal function. However, the increase in the t½ b values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½ b, 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

In single and repeat-dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatotoxicity) is observed. Symptoms of toxicity are typical of opioids and include restlessness, ataxia, vomiting, tremor, dyspnoea and convulsions.
Exposure to tramadol (≥ that expected in man) in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a battery of *in-vitro* and *in-vivo* mutatgenicity tests were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate
Colloidal anhydrous silica

Capsule shell:
Gelatin
Indigotin (E 132)
Ferric oxide yellow (E 172)
Titanium dioxide (E171)

Printing ink:
Shellac
Black iron oxide (E172)
Soya lecithin
Antifoam DC 1510

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be 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^{O}C.
Store in the original package.

6.5 Nature and contents of container

PVC/Foil or PP/Foil blister strips in a cardboard carton.
Pack sizes 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.

7 Parallel Product Authorisation Holder

B&S Healthcare
Unit 4
Bradfield Road
Ruislip
Middlesex
HA4 0NU
United Kingdom

8 Parallel Product Authorisation Number

PPA 1328/8/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 8th September 2006

10 DATE OF REVISION OF THE TEXT

February 2007