Public Assessment Report

Decentralised Procedure

Tramadol 50mg Capsules

UK/H/0953/01/DC

UK licence no: PL 20395/0065

Relonchem Ltd

LAY SUMMARY

The MHRA granted Relonchem Limited a Marketing Authorisation (licence) for the medicinal product Tramadol 50mg Capsules. This is a prescription-only medicine (POM) that is used for management (treatment and prevention) of moderate to severe pain.

Tramadol capsules are 'analgesics' which act on the central nervous system (the brain and spinal cord). This product relieves pain and can also be taken to prevent pain.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Tramadol 50mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Tramadol 50mg capsules
Type of Application	Generic, Article 10.1
Active Substance	tramadol hydrochloride
Form	Capsules
Strength	50mg capsules
MA Holder	Relonchem Ltd, 27 Old Gloucester Street, London WC1 3XX
RMS	UK
CMS	IE
Procedure Number	UK/H/0953/01/DC
Timetable	Day 210 – 24 August 2007

Module 2

Summary of Product Characteristics

1. Name of the medicinal product
Tramadol 50mg Capsules

2. Qualitative and quantitative composition
Each capsule contains 50mg tramadol hydrochloride

For excipients, see 6.1

3. Pharmaceutical form
Capsule, hard
White hard gelatine capsules for oral administration.

4.1. Therapeutic indications
Management (treatment and prevention) of moderate to severe pain.

4.2. Posology and method of administration
Treatment 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 & Special precautions For Use and Undesirable Effects section).*
As with all analgesic drugs, the dose of Tramadol 50mg Capsules should be adjusted according to the severity of the pain and the clinical response of the individual patient.

Adults and children aged 12 years and over:
Oral administration.
Acute Pain:
An initial dose of 100mg is usually necessary. This can then be followed by doses of 50mg or 100mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.
Pain associated with chronic conditions:
Use an initial dose of 50mg and then titrate dose accordingly to pain severity.
A total daily oral dose of 400mg should not be exceeded except in special clinical circumstances.
The capsules should be swallowed whole, not divided or chewed, with sufficient liquid and independently of meals.

Elderly
No adjustment of dosage is necessary in elderly patients up to 75 years, as there is no significant difference in tramadol pharmacokinetics with increasing age. However it should be noted that in volunteers aged over 75 years, the elimination half-life of tramadol was increased by 17% following oral administration. Therefore, if necessary, the dosage interval is to be extended according to the patients requirements.

Renal Impairment / renal dialysis
The elimination of tramadol may be prolonged, hence 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. For patients with creatinine clearance < 30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance < 10ml/min).
As tramadol is only removed very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Hepatic impairment
The elimination of tramadol may be prolonged. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours.

Children aged 12 years and under:
On account of their high dosage strength, Tramadol 50mg Capsules are not recommended for use in children under 12 years of age.

4.3. Contra - indications

Tramadol 50mg Capsules should not be administered to patients who have previously demonstrated hypersensitivity towards tramadol or any of the excipients (see Section 6.1 'List of Excipients') 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 (MAO) inhibitors or within two weeks of their withdrawal (see Section 4.5 'Interaction with Other Medicinal Products and Other Forms of Interaction').
Tramadol 50mg Capsules must not be used in epilepsy not adequately controlled by treatment.
Tramadol 50mg Capsules must not be used for narcotic withdrawal treatment.

4.4. Special warnings and precautions for use

Warnings
At therapeutic doses, Tramadol 50mg Capsules has the potential to cause withdrawal symptoms. At therapeutic doses withdrawal symptoms have been reported at a reporting frequency of 1 in 8,000. On long term use tolerance, psychic and physical dependence may develop, but reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.
In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.
Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, Tramadol cannot suppress morphine withdrawal symptoms.

Precautions
Tramadol 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.
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 Interactions with other Medicaments and other Forms of Interactions).
Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.
In one study using a nitrous oxide/opioid anaesthetic technique (with only intermittent administration of enflurane 'as required') tramadol hydrochloride was reported to enhance intra-operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.
Two studies of tramadol hydrochloride administration during anaesthesia comprising continuous administration of isoflurane have shown clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol hydrochloride may be used intra-operatively in the same way as other analgesic agents are routinely used.

4.5. Interactions with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitors (see Section 4.3 'Contraindications').
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 Tramadol hydrochloride.
Concomitant administration of Tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effects (see Section 4.8 'Undesirable Effects').
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 Tramadol or during concomitant use with antipsychotics known to induce convulsions.
Tramadol may increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions *(*see section 4.4 'Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties').
There is a theoretical possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.
Co-administration with serotonergic drugs, e.g. SSRIs or triptans 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 diarrhea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms.
There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.
Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of tramadol.
Simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol and the principle active metabolite to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.
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.
A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the tramadol C_{max} and AUC; T_{max} is unaffected. However, the increases in C_{max} and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.
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. Use during pregnancy and lactation

Pregnancy
Animal studies with tramadol have revealed that at very high doses, effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta, but animal studies have not revealed teratogenic effects. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore Tramadol 50mg Capsules should not be used in pregnant women.
In neonates it may include 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 about 0.1% of the dose given to the mother. Tramadol 50mg Capsules should not be administered during breast feeding.

4.7. Effects on ability to drive and use machines

Tramadol 50mg Capsules 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.

Cardiovascular system disorders:

Uncommon (< 1 %): 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 (< 0.1%): bradycardia, increase in blood pressure.
Central and peripheral nervous system disorders:
Very common > 10 %): dizziness.
Occassional (1-10%): headache, drowsiness
rare (< 0.1 %): somnolence, changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions.

Psychiatric disorders:

rare (< 0.1 %): 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 (< 0.1%): blurred vision
Respiratory system disorders:
Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:
*Very common > 10 %):*nausea
Common (1-10%): vomiting, constipation, diarrhoea, dry mouth
Uncommon (< 1 %): retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating)

Skin and appendages disorders:
Common (1-10 %): sweating
Uncommon (< 1 %): dermal reactions (e.g. pruritus, rash, urticaria)

Musculo-Skeletal system disorders:
rare (< 0.1%): 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 (< 0.1 %): micturition disorders (difficulty in passing urine and urinary retention)

Body as a whole:
rare (< 0.1 %): Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis. Cases of blood dyscrasias have been rarely observed during treatment with tramadol.

Physical Dependence:
Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: 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, emergency procedures, antidotes.

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 Tramadol 50mg Casules with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. Pharmacological properties

5.1. Pharmacodynamic properties

ATC code N 02: Analgesics.
Tramadol is a centrally acting analgesic. It is a non selective pure agonist at 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.
Tramadol has an antitussive effect.

5.2. Pharmacokinetic properties

After oral administration, tramadol is almost completely absorbed. Mean absolute bioavailability is approximately 70% following a single dose and increases to approximately 90% at steady state. Plasma protein binding of tramadol is approximately 20%. When ^{14}C-labelled tramadol was administered to

humans, approximately 90% was excreted via the kidneys with the remaining 10% appearing in the faeces.
Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The half-life of the terminal elimination phase (t½β) was 6.0 ± 1.5h in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the aged of 75 years. In volunteers aged over 75 years, t½β was 7.0 ± 1.6h on oral administration.
Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes with a mean C_{max} of 280 to 308 mcg/L and T_{max} of 1.6 to 2h.
Tramadol is metabolised by the cytochrome P450 isoenzyme CYP2D6. It undergoes biotransformation to a number of metabolites mainly by means of N- and O-demethylation. O-desmethyl tramadol appears to be the most pharmacologically active metabolite, showing analgesic activity in rodents. As humans excrete a higher percentage of unchanged tramadol than animals it is believed that the contribution made by this metabolite to analgesic activity is likely to be less in humans than animals. In humans the plasma concentration of this metabolite is about 25% that of unchanged tramadol.
Since tramadol is eliminated both metabolically and renally, the terminal half-life t½β may be prolonged in impaired hepatic or renal function. In patients with liver cirrhosis t½β 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 mutagenicity tests were negative.
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 adenomas in male animals (a dose dependent, non-significant increase from 1mg/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

The capsule core contains:
Calcium hydrogen phosphate, dihydrate
Magnesium Stearate
Colloidal Silica anhydrous
The capsule shell contains:
Gelatin
Titanium dioxide (E171)
The printing ink contains:
Shellac (E904)
Black Iron Oxide (E172)
Soya Lecithin (E322)
Antifoam (DC 1510)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

4 years

6.4. Special precautions for storage

Do not store above 30°C'

6.5. Nature and contents of container

PVC/aluminium foil blister packs of 30 or 100 capsules.

6.6. Special precautions for disposal

None

Administrative Data

7. Marketing authorisation holder
Relonchem Ltd
27 Old Gloucester Street
London
WC1 3XX
UK

8. Marketing authorisation number
PL: 20395 / 0065

9. Date of first authorisation or renewal
25/01/2008

10. Date of revision of the text
25/01/2008

Module 3

Tramadol 50mg Capsules

RelonChem

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1.WHAT ARE TRAMADOL 50mg CAPSULES AND WHAT ARE THEY USED FOR?

Tramadol 50mg Capsules are 'analgesics' which act on the central nervous system (the brain and the spinal cord). Analgesics are often called 'pain killers' or 'pain relievers'.

Tramadol 50mg Capsules relieve pain and can also be taken to prevent pain.

Pain is a symptom not an illness. There are many types of pain with many different causes, for example back-ache, toothache, pain after an operation or pain from broken bones.

Tramadol 50mg Capsules help your body's system for relieving pain. It does this in two ways:

- Acts directly on parts of your brain and spinal cord to reduce the amount of pain you feel
- Reduces the size of the pain message passed from one nerve to another.

Tramadol 50mg Capsules should only be taken by adults or children over 12.

2.BEFORE YOU TAKE TRAMADOL 50mg CAPSULES

Do not take Tramdol 50mg Capsules

- If you have had an allergic reaction, skin rash, swelling of the face, wheezing or difficulty breathing after taking tramadol or any of the other ingredients in Tramadol 50mg Capsules.
- If you are hypersensitive (allergic) to tramadol hydrochloride or any of the other ingredients in Tramadol 50mg Capsules
- If you are pregnant or if you are breast-feeding
- If you are taking a monoamine oxidase inhibitor (MAOI) or have taken one in the past two weeks. You should know if you are taking MAOI because your doctor or chemist will have told you, and you may also have a treatment card.
- If you suffer from epilepsy not controlled by treatment
- If you have drunk enough alcohol to make you feel whoozy or drunk.
- If you feel 'high' or excited because you have taken medicines that slow the nervous system. These medicines include tranquillisers, sleeping pills, psycho-tropic medicines (medicines that affect your mood or emotions) or other pain relievers such as morphine and codeine.
- If you have severe kidney disease.

Take special care with Tramadol 50mg Capsules

- If you have had a head injury or have brain disease. If you have a very bad headache or vomit without feeling sick first, this could be a sign of this.
- If you suffer from epilepsy, convulsions or seizures (fits) or have had them in the past.
- If you feel light-headed, faint, cold or clammy, or look pale.
- If you suffer from asthma, or other lung disease or have difficulty in breathing
- If you suffer from kidney or liver disease.

Taking other medicines

Please tell your doctor or pharmacist:-

- If you are taking other medicines including tranquilizers, sleeping pills, antidepressants and other pain relievers such as morphine and codeine. You may feel drowsier or feel that you might faint.
- If you are going to be given a general anaesthetic tell your doctor or dentist that you are taking Tramadol 50mg Capsules.
- If you are taking carbamazepine, a treatment for epilepsy, this may reduce the pain relieving effect of Tramadol 50mg Capsules. Your doctor will tell whether Tramadol 50mg Capsules is suitable for you.
- If you are taking antidepressants these may cause convulsions (fits). The chance of having a fit is rare, but if you are also taking Tramadol 50mg Capsules, the risk of having a fit may increase. Your doctor will tell you whether having Tramadol 50mg Capsules is suitable for you.
- If you are taking selective serotonin reuptake inhibitors (often referred to as SSRI's) or triptans or MAOI's because it has been shown that Tramadol may interfere with their action by enhancing their effects.
- If you are taking lithium, make sure your doctor or dentist knows. Tramadol 50mg Capsules could alter the effect of lithium
- If you are taking coumarin anticoagulants (blood thinning medicines) e.g. warfarin. Tramadol 50mg Capsules could alter their effects if taken at the same time.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription and herbal remedies.

Taking Tramadol 50mg Capsules with food and drink

You should avoid alcohol during treatment with Tramadol 50mg Capsules. If you use alcohol with Tramadol 50mg Capsules you may feel drowsier than when you are taking alcohol alone.

Pregnancy and breast feeding

Tramadol 50mg capsules should not be used in pregnant women or when breast feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Tramadol can cause drowsiness. Do not drive or operate any tools or machines if you feel tired or sleepy after treatment with Tramadol 50mg Capsules. These effects are made worse if alcohol and/or CNS depressants are taken at the same time.

3.HOW TO TAKE TRAMADOL 50mg CAPSULES

Follow your doctor's instructions on how many Tramadol 50mg Capsules to take and when to take them. You will also find this information on the label.

You should usually swallow one or two capsules at a time. Do not take them more often than every four hours and do not take more than eight capsules in any 24 hours unless your doctor tells you to. Swallow the capsules whole, not divided or chewed, with sufficient liquid. Tramadol capsules do not need to be taken with food. If you are not sure, ask your doctor or pharmacist.

Do not take a different amount of Tramadol 50mg Capsules or take it more often than your doctor has told you to. These Tramadol 50mg Capsules are for you. You must not give them to other people.

If you have chronic pain (pain that lasts for long periods of time) it is best to take Tramadol 50mg Capsules over short periods and only when you need it.

If you take more Tramadol 50mg Capsules than you should:-

If you take two single doses of Tramadol 50mg capsules at once by mistake, this will generally not be harmful. If pain returns, continue taking Tramadol 50mg Capsules as usual.

If high doses are taken accidentally (e.g. a dose of more than two Tramadol 50mg Capsules at once), a number of symptoms may occur. These might include:- pin-point pupils, vomiting, a fall in blood pressure, a fast heartbeat, collapse, disturbed consciousness including coma (deep unconsciousness), epileptic fits and difficulties in breathing. If you suspect that you or someone else has taken an overdose of Tramadol 50mg Capsules, contact your doctor or go to your local hospital immediately. Always take the carton and this leaflet with you if possible.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you forget to take Tramadol 50mg Capsules

If you forget to take the capsules, pain is likely to return. Do not take a double dose to make up for forgotten individual doses, simply continue taking the capsules as before.

If you stop taking Tramadol 50mg Capsules

Tramadol 50mg Capsules may cause dependence (addiction / reliance on a medicine). Although this is rare, when you stop taking Tramadol 50mg Capsules, you may feel agitated, anxious, nervous or shaky. You may become hyperactive and have difficulty sleeping. Very few people may experience unusual effects on the nervous system such as confusion, delusions or unusual perceptions such as itching, tingling or numbness or noise in the ear (tinnitus) or stomach and bowel disorders. These effects usually disappear after a few days. Tell your doctor if you experience any of these symptoms after stopping Tramadol 50mg Capsules.

4 POSSIBLE SIDE EFFECTS

Like all medicines. Tramadol 50mg Capsules can cause side effects, although not everybody gets them. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Very common (> 1/10)

- Some people may feel dizzy or nauseas

Common (< 1/100, 1> 1/10)

- Some people may vomit or sweat, have a dry mouth and have diarrhoea or constipation, or suffer headaches or drowsiness.

Uncommon (< 1/1000, 1> 1/100)

- Some people may suffer from palpitations (awareness of your heartbeat), or tachycardia (rapid heart beat), irregular heartbeat, retching, gastro-intestinal irritation, skin irritation and develop a rash. Some people may suffer postural hypotension (dizziness or light headedness when standing up too quickly).

Rare (< 1/10,000, 1 > 1/1000)

- Some people may develop high blood pressure, bradycardia (slow heartbeat) or changes in appetite. Parasthesia (pins and needles), convulsions, hallucinations, sleep pattern disturbances and nightmares can also occur. Some people may get blurred vision or have difficulty in passing urine. Very few people may experience unusual effects on the nervous system such as confusion, changes of mood, delusions, feelings of loss of identity or unusual perceptions such as itching, tingling or numbness. Rarely, people have also suffered allergic or anaphylactic reactions. These may include a rash, itching, swelling of the face or breathing problems (shortness of breath and wheezing). In a few isolated cases, blood disorders have also been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Contact your doctor immediately if:

- You have difficulty breathing
- Your asthma gets worse
- You get an allergic reaction, skin rash, swelling of the face, or wheezing
- You have a fit
- You constantly have a sore throat or high temperature

5. HOW TO STORE TRAMADOL 50mg CAPSULES

Keep out of the reach and sight of children.

Do not use Tramadol 50mg Capsules after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 30ºC.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tramadol 50mg Capsules contain

The active substance is called tramadol hydrochloride. Each Capsule contains 50mg of tramadol hydrochloride. The other ingredients are Calcium hydrogen phosphate (dihydrate), Magnesium Stearate and Silica (Colloidal anhydrous). The capsule is made of gelatine and contains the colour Titanium dioxide (E171). The printing ink contains the ingredients shellac, Black Iron oxide, Soya Lecithin and Antifoam DC 1510.

What Tramadol 50mg Capsules look like and the contents of the pack

Tramadol 50mg Capsules are all white and have 'TR50' printed on the outside. They are packed in blister strips and supplied in boxes of 30 or 100 capsules.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder:

Relonchem Ltd, 27 Old Gloucester Street, London, WC1 3XX. UK

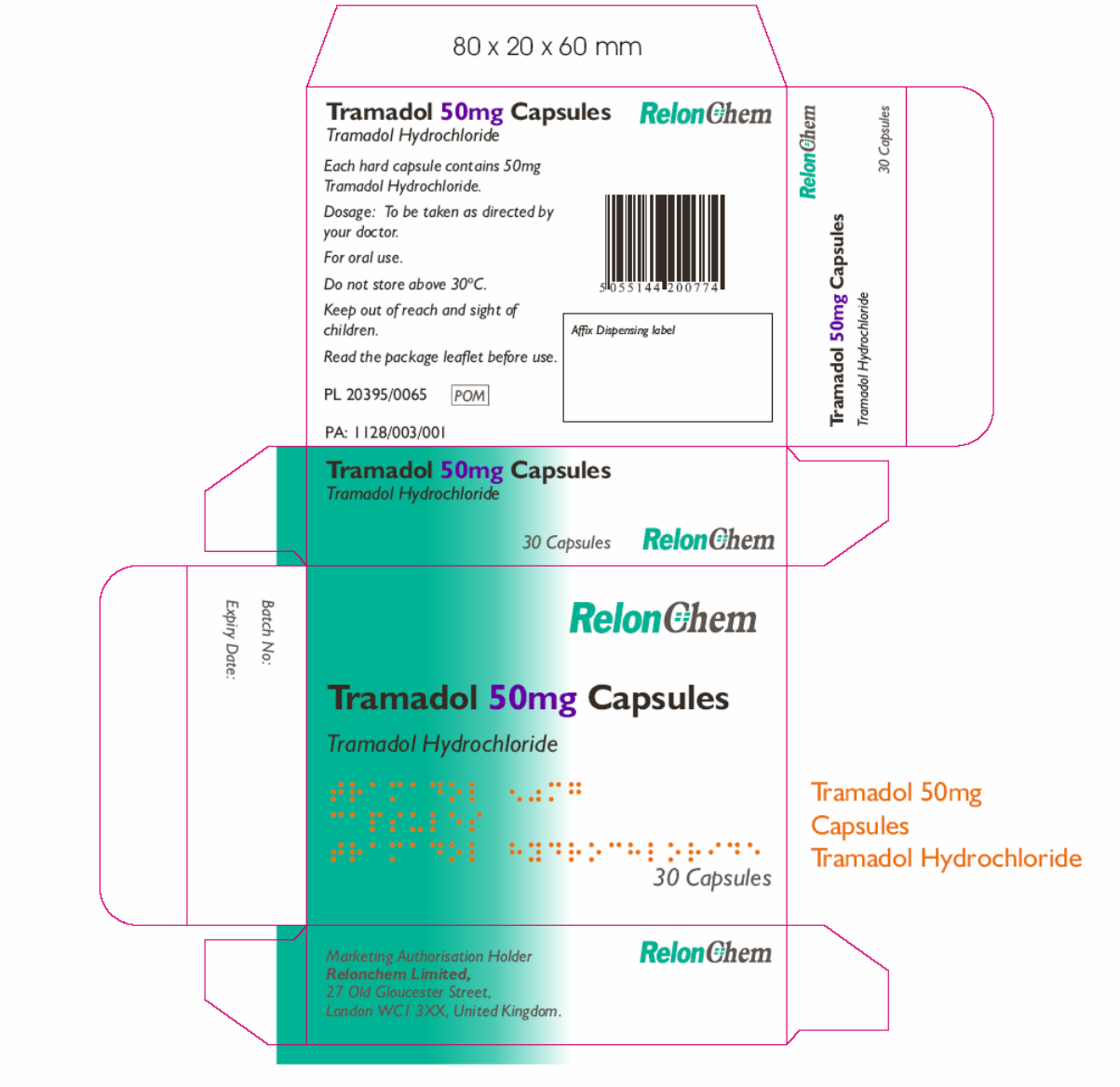
Manufacturer:

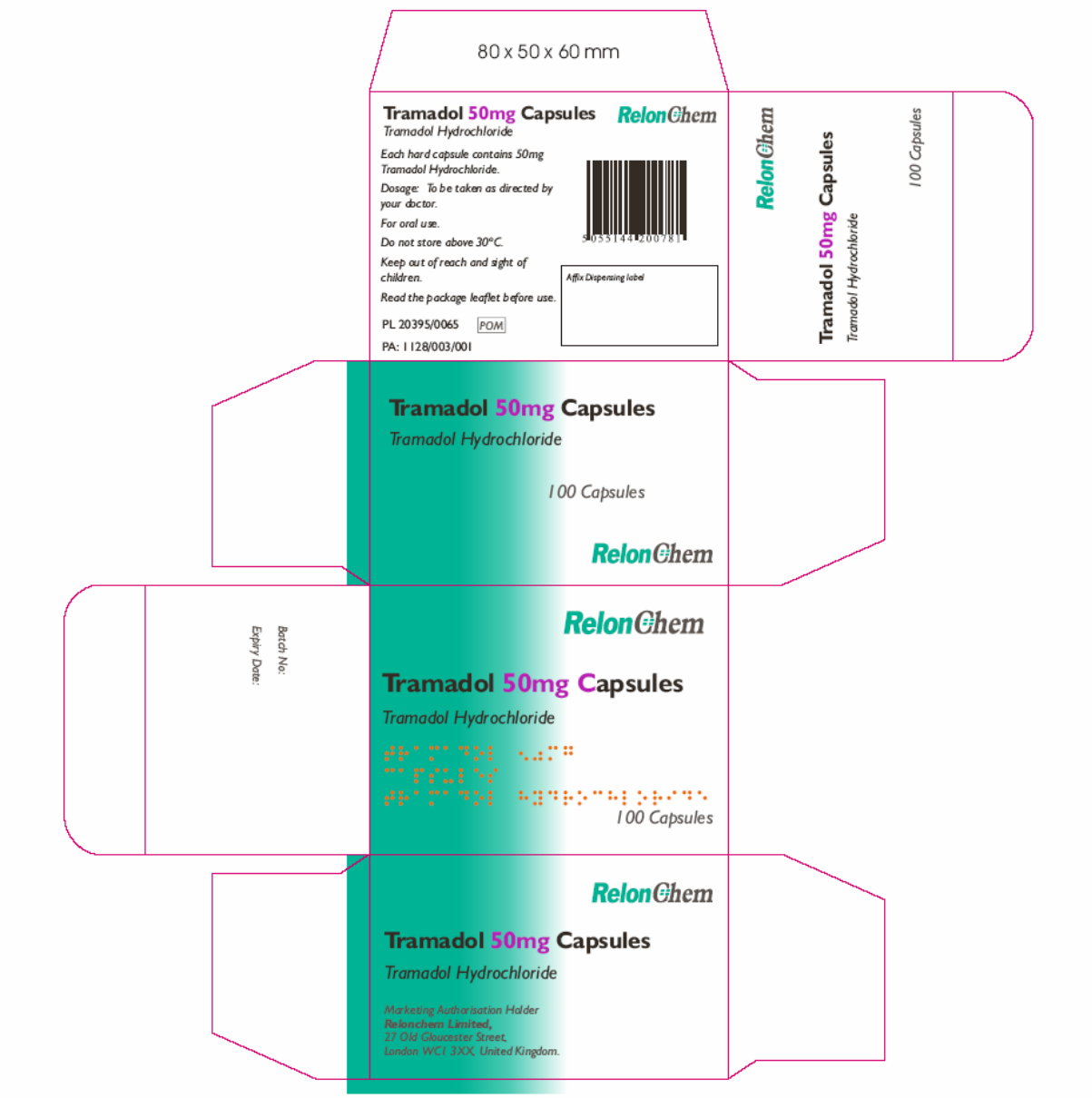
Famar Italia S.p.A, Via Zambeletti nº 25, I-20021 Baranzate di Bollate (MI), Italy.

This leaflet was last approved in: January 2008

Module 4

Labelling




80 x 50 x 60 mm
Tramadol 50mg Capsules
Tramadol Hydrochloride
RelonChem
Each hard capsule contains 50mg Tramadol Hydrochloride.
Dosage: To be taken as directed by your doctor.
For oral use.
Do not store above 30°C.
Keep out of reach and sight of children.
Read the package leaflet before use.
PL 20395/0065
POM
PA: 1128/003/001
Affix Dispensing label
RelonChem
Tramadol 50mg Capsules
Tramadol Hydrochloride
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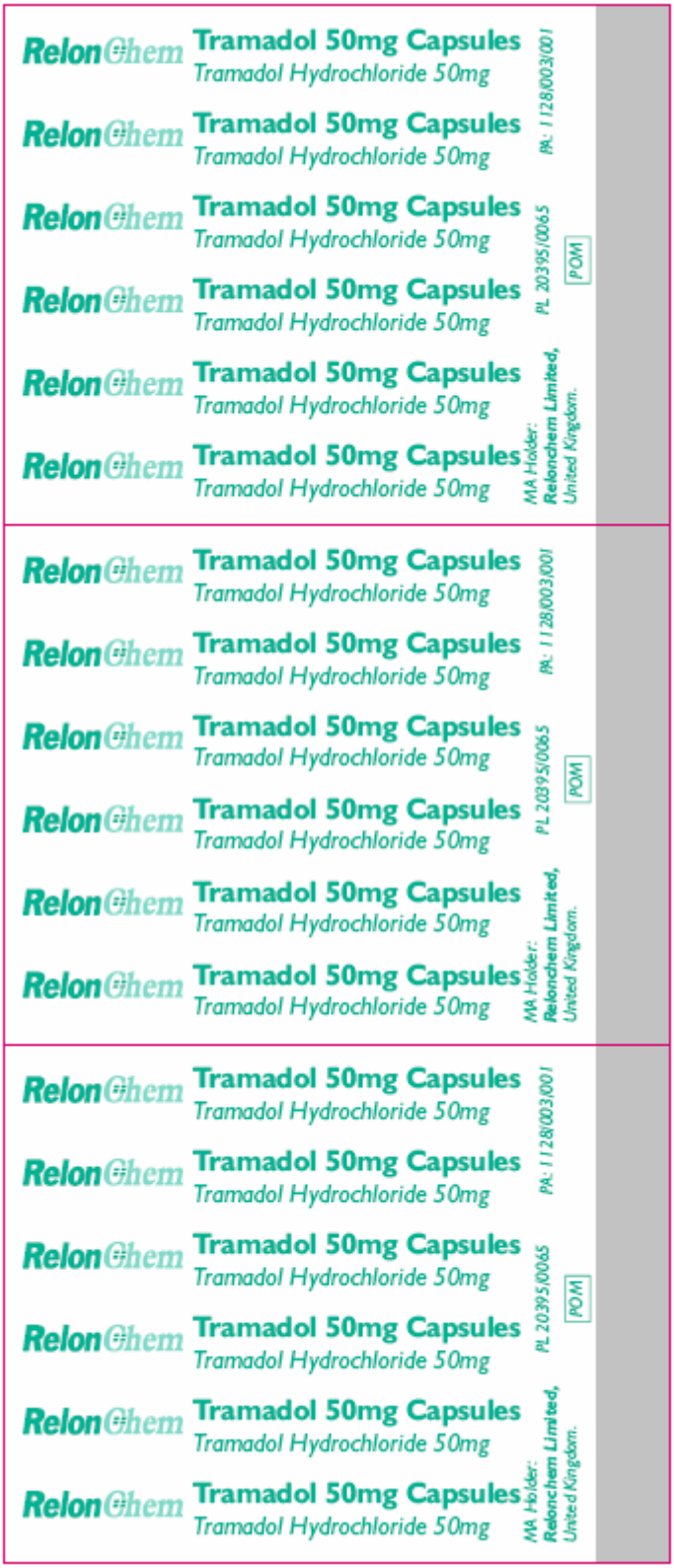
Marketing Authorisation Holder
Relonchem Limited,
27 Old Gloucester Street,
London WC1 3XX, United Kingdom.


Relonchem
Tramadol 50mg Capsules
Tramadol Hydrochloride 50mg
PA: 1128/003/001
PL 20395/0065
POM
MA Holder:
Relonchem Limited,
United Kingdom.

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Tramadol 50mg Capsules, in the management (treatment and prevention) of moderate to severe pain, is approvable.

This is an application made under Article 10.1 of 2001/83 EC, as amended, for Tramadol 50mg Capsules. The originator product is Zydol 50 mg Capsules, marketed by Gruenthal, which has undergone change of ownership application from Zydol 50mg capsules, marketed by GD Searle & Company, first registered in the EU since 17th November 1994.

With UK as the Reference Member State in this Decentralised Procedure, Relonchem Ltd is applying for the Marketing Authorisations for Tramadol 50 mg Capsules in Ireland only.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

Tramadol is a widely used, well-known product. It is a centrally acting analgesic indicated for the management (treatment and prevention) of moderate to severe pain.

The RMS has been assured that acceptable standards of GMP are in place for this type of product at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Tramadol 50mg Capsules
Name(s) of the active substance(s) (INN)	tramadol hydrochloride
Pharmacotherapeutic classification (ATC code)	ATC code N 02: Analgesics
Pharmaceutical form and strength(s)	50mg capsules
Reference numbers for the Mutual Recognition Procedure	UK/H/0953/01/DC
Reference Member State	United Kingdom
Member States Concerned	Ireland
Marketing Authorisation Number(s)	PL 20395/0065
Name and address of the authorisation holder	Relonchem Limited, 27 Old Gloucester Street, London, WC1 3XX

III SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug Substance

INN: Tramadol Hydrochloride

Chemical name: (1*RS*,2*RS*)-2-(Dimethylaminomethyl)-1-(3 methoxyphenyl)-cyclohexanol hydrochloride.

(±)-trans-2-(Dimethylaminomethyl)-1-(3 methoxyphenyl)-cyclohexanol hydrochloride.

It is a white to off white crystalline powder, freely soluble in water and methanol, very slightly soluble in acetone.

The drug substance does not exhibit polymorphism.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active tramadol hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Acceptable justification of the proposed specifications are provided.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a shelf-life of 5 years.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely colloidal silicon dioxide, titanium dioxide, dibasic calcium phosphate dehydrate, gelatine, magnesium stearate, shellac E904, soya lecithin E322, antifoam DC 1510, and Black Iron Oxide E172.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients. No materials of animal or human origin are contained in or used in the manufacture of this product. The manufacturer of magnesium stearate has confirmed that this is a vegetable origin.

Pharmaceutical development
The applicant has provided a suitable product development rationale and data. Comparable dissolution and impurity profiles have been provided for batches of the proposed product versus reference product.

Manufacture
A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The Product is packaged in aluminium/PVC blisters in pack sizes of 30 and 100 capsules. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 4 years when stored below 30^{o}C is proposed. This is satisfactory.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

Pharmacodynamic, pharmacokinetic and toxicological properties of tramadol are well known. As tramadol is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. There are no objections to approval of Tramadol 50mg Capsules from a non-clinical point of view.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a standard generic abridged application for Marketing Authorisation in the UK, submitted under Article 10.1 of Directive 2004/27/EC. This has been submitted under Decentralised Procedure number UK/H/953/001/DC with the UK as the Reference Member State. The only Concerned Member State is Ireland.

The reference product which has been authorised for not less than 6/10 years in the EEA is the UK product Zydol 50mg Capsules PL 21727/0001, marketed by Gurenthal Ltd, which underwent a change of ownership from PL 08821/0005 Zydol 50mg Capsules, marketed by Monsanto Plc, which in turn underwent a change of ownership from PL 00020/0197 Zydol 50mg capsules, marketed by GD Searle and Company Ltd. The latter licence was initially authorised 17 November 1994.

2. BACKGROUND

Tramadol is a well known centrally acting analgesic with high affinity particularly for the mu receptor. The indications, namely the management of moderate to severe pain are the same as those for the cross-referred product. The drug is well established for use in these indications.

3. INDICATIONS

The applicant has submitted the following indications: For the treatment and prevention of moderate to severe pain. These are consistent with the licensed indications approved for the UK reference product and are, therefore, satisfactory.

4. DOSE & DOSE SCHEDULE

The proposed posology is in line with currently agreed requirements and is therefore satisfactory.

5. TOXICOLOGY

No formal data are presented under this heading and none are required for this application.

6. CLINICAL PHARMACOLOGY

Bioequivalence

To support the application, the applicant has submitted a report of a single bioequivalence study. No clinical data are provided. This is acceptable in principle for a generic application of this type.

Tramadol 50 mg Capsules (test) has been compared to Zydol 50 mg Capsules (reference). The experimental samples were assayed for tramadol hydrochloride and O-desmethyltramadol using a liquid chromatography method, developed and validated in the laboratory of the Analytical Facility. The shelf life and storage conditions of the samples were validated at -20ºC for 30 months. Analysts were blinded about which of the formulations were administered during each period.

Volunteers were enrolled. The protocol appeared to state that there were to be 18 subjects plus 2 reserves in order to ensure that there would be 18 evaluable subjects and if more than 2 subjects dropped out additional subjects would be recruited. However the samples from all 20 subjects were analysed and the study report stated that all 20 subjects were evaluated in the PK analyses.

Bioequivalence assessment was initially based on AUCt, AUCinf and Cmax for tramadol only. Samples were analysed for the active metabolite O-desmethyl tramadol, which has significant analgesic activity and makes a significant contribution to the overall pharmacological activity of the product. Bioequivalence was also required to be demonstrated for this active metabolite. Satisfactory comprehensive documentation was provided including full individual subject data.

The analyses specified in the protocol are satisfactory. Satisfactory explanation was provided in the response documentation that the calculated confidence intervals are satisfactory.

Results

The individual plasma concentration – time curves show that in the majority of subjects the absorption of tramadol appeared to be faster for the reference product than for the test product. This is consistent with the estimated shorter mean T_{max} and higher mean C_{max} for the reference product in the presented analyses. However as standard 80-125% criteria are met, it can be concluded that bioequivalence for the parent drug has been demonstrated.

The new data for the active metabolite also showed bioequivalence according to the 80-125% criteria for AUC and C_{max}. Bioequivalence has been demonstrated.

7. EFFICACY

No new data are submitted and none are required for this application. The efficacy of Tramadol has been well documented.

8. SAFETY

No new data are submitted and none are required for this application.

9. EXPERT REPORTS

A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

10. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The summary of Product Characteristics is satisfactory.

11. PATIENT INFORMATION LEAFLET (PIL)

The patient information leaflet is satisfactory.

12. LABELLING

The labelling is satisfactory

13. APPLICATION FORM (MAA)

The MAA is satisfactory

14. CONCLUSION

The bioequivalence of Tramadol 50mg Capsules was evaluated in a two period, two sequence, crossover, controlled, block randomised, single dose bioequivalence study. The applicant's product was compared to Zydol 50mg Capsules and the two products were shown to be bioequivalent.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and packaging are satisfactory and consistent with those for the reference product.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Tramadol 50mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant's Tramadol 50mg Capsules and Zydol 50mg Capsules.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with tramadol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome