TRAMADOL HYDROCHLORIDE 50MG CAPSULES
PL 08553/0210

UKPAR

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TRAMADOL HYDROCHLORIDE 50MG CAPSULES
PL 08553/0210

LAY SUMMARY

The MHRA granted Dr Reddy's Laboratories (UK) Limited a Marketing Authorisation for the medicinal product Tramadol Hydrochloride 50mg Capsules (PL08553/0210) on 11th July 2007. This prescription-only medicine (POM) is used in the management (treatment and prevention) of moderate to severe pain.

The active ingredient, tramadol hydrochloride is a centrally acting analgesic (a pain killer that acts on pain centres in the brain), which is used to relieve pain in the body.

This application is identical to a previously granted application for Tramadol Hydrochloride 50mg Tablets (PL 10622/0050, granted to PLIVA Pharma Limited on 30th January 2000) which had, in turn, demonstrated essential similarity or equivalence to the approved product, Zydol Capsules 50mg and, as such, these products can be used interchangeably.

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

TRAMADOL HYDROCHLORIDE 50MG CAPSULES
PL 08553/0210

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Tramadol Hydrochloride 50mg Capsules (PL 08553/0210) to Dr Reddys Laboratories (UK) Ltd on 11th July 2007. The product is a prescription-only medicine.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Tramadol Hydrochloride 50mg Capsules (PLIVA Pharma Ltd, UK, PL 10622/0050), approved on 30th January 2000. The original product had previously been shown to be essentially similar to Zydol Capsules 50mg licensed in the UK since 21st April 1994.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.

The product contains the active ingredient tramadol hydrochloride which is a centrally acting analgesic used in the management (treatment and prevention) of moderate and severe pain within the body.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 08553/0210
PROPRIETARY NAME: Tramadol Hydrochloride 50mg Capsules
ACTIVE(S): Tramadol hydrochloride
COMPANY NAME: Dr Reddy's Laboratories (UK) Limited
E.C. ARTICLE: Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION

This is a simple, informed consent application for Tramadol Hydrochloride 50mg Capsules submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Dr Reddy's Laboratories (UK) Limited, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK.

The application cross-refers to Tramadol Hydrochloride 50mg Capsules, approved on 30th January 2000 to the marketing authorisation holder PLIVA Pharma Ltd, UK. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Tramadol Hydrochloride 50mg Capsules. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains tramadol hydrochloride, equivalent to 50mg. It is to be stored in blisters composed of aluminium and polyvinyl chloride (PVC). The proposed shelf-life (36 months) and storage conditions ("Do not store above 25°C. Store in the original package") are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

Dr Reddy's Laboratories (UK) Limited, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product with the exception of an additional test for moisture.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
With the exception of lactose monohydrate, magnesium stearate and gelatin, no materials of animal or human origin are included in the product. This is consistent with the cross-reference product.

A declaration has been provided that lactose used in lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. TSE certificates of suitability have been provided for all suppliers of gelatin and one supplier of magnesium stearate (the other supplier has stated that it is sourced from vegetable origins).

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

Tramadol hydrochloride is a well known drug and has been used as an analgesic for many years. This application is identical to previously granted application for Tramadol Hydrochloride Capsules (PL 10622/0050) in which the applicant demonstrated essential similarity to the innovator product Zydol Capsules 50mg.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product which, in turn, has been shown to be interchangeable with the innovator product. 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.

TRAMADOL HYDROCHLORIDE 50MG TABLETS
PL 08553/0210

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 24/03/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 19/04/2004.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 27th January 2005, 25th October 2005 and 17th November 2006
4	The applicant responded to the MHRA's requests, providing further information on 9th June 2005, 14th November 2006 and 3rd December 2006.
5	The application was determined on 11th July 2007

TRAMADOL HYDROCHLORIDE 50MG TABLETS
PL 08553/0210

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

TRAMADOL HYDROCHLORIDE 50MG TABLETS
PL 08553/0210

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tramadol Hydrochloride 50mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50mg Tramadol Hydrochloride
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Hard Capsule.
Tramadol capsules are white capsules imprinted with "T 50" on the top.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

As with all analgesic drugs, the dose of Tramadol hydrochloride should be adjusted according to the severity of pain and the clinical response of the individual patient.

Adults and children aged 12 years and over:
Acute pain: An initial dose of 100mg is usually necessary. This can be followed by doses of 50 or 100 mg not more frequently than 4 hourly, and duration of therapy should be related to clinical need.

Pain associated with chronic conditions: Use an initial dose of 50mg and then titrate dose according to severity of pain. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 'Special warnings and precautions for use'). A total daily dose of 400mg should not be exceeded except in special clinical circumstances.

Elderly:
The usual doses may be used although it should be noted that in volunteers over 75 years old, the elimination half-life of tramadol was increased by 17% following oral administration.

Renal Impairment/ renal dialysis:
The elimination of tramadol may be prolonged. The usual initial dosage should be used. 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 under 12 years old:
Not recommended.

4.3. Contraindications

Tramadol hydrochloride should not be administered to patients who have previously demonstrated hypersensitivity to it or in cases of acute intoxication with alcohol, hypnotics, centrally active analgesics, opioids or pychotropic 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

4.4. Special warnings and precautions for use

Warnings:
At therapeutic doses, Tramadol hydrochloride has the potential to cause withdrawal symptoms. Rarely cases of dependence and abuse have been reported. At such doses, withdrawal symptoms have been reported at a frequency of 1 in 8,000. 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 of drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

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

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions:
Tramadol hydrochloride should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of renal and hepatic 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 'Interaction with other medicinal products and other forms of interaction').

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 nitrous oxide/opioid (Tramadol hydrochloride) 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 recent studies of Tramadol hydrochloride administration during anaesthesia continuous administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agents is followed, Tramadol hydrochloride may be used intra-operatively in the same way as other analgesic agents are routinely used.

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

Concomitant administration of Tramadol hydrochloride with other centrally acting drugs including alcohol may potentiate CNS depressant effects.

Serotoninergic drugs: co-administration with serotoninergic drugs e.g. SSRIs or triptans, or with MAOIs may lead to an increase of serotonin associated effects, which can include serotonin syndrome.

Tramadol may increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (see section 'Special Warnings and Precautions for Use' and 'Pharmacokinetic Properties'). There is a theoretical possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

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

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the Tramadol hydrochloride dosage regimen is recommended for patients receiving chronic cimetidine therapy.

A study of 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the C_{max} and AUC; T_{max} is unaffected. However, the increased C_{max}

and AUC fall within the normal therapeutic range for tramadol and hence no dosage adjustment is required.

4.6. Pregnancy and lactation

Pregnancy:
Animal studies (rats and rabbits, exposure to tramadol up to 7 times that expected in man) have not revealed teratogenic effects and minimal embryo-toxicity (delayed ossification). Fertility, reproductive performance and development of offspring were unaffected. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore tramadol hydrochloride should not be used in pregnant women.

Lactation:
Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dosage given to the mother. Tramadol hydrochloride should not be administered during breast feeding.

4.7. Effects on ability to drive and use machines

Tramadol hydrochloride may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. It may also cause blurred vision. Ambulant patients should be warned not to drive or operate machinery if affected by either or both of these side-effects.

4.8. Undesirable effects

Gastrointestinal system:
Nausea, vomiting and occasionally dry mouth. Both diarrhoea and constipation have been reported. In controlled trials the incidence of constipation is lower than that of comparator agents.

Central nervous system and psychiatric:
Tiredness, fatigue, drowsiness, somnolence, dizziness, headache, confusion, hallucinations and rarely respiratory depression.

Psychiatric side-effects may occur following administration of tramadol, which vary in intensity and nature (depending on the premorbid personality of the individual and quantity and duration of medication). These include changes in mood (usually euphoria, occasionally dysphoria), changes in behaviour and lifestyle interests (usually suppression, occasionally overactivity) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders).

Dependence and convulsions have been reported occasionally (see ‘Interactions with other medicaments and other forms of interaction').

Physical dependence:
Dependence, abuse and withdrawal symptoms have been reported. Typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia,

hyperkinesia, tremor and gastrointestinal symptoms (see 'Special Warnings and Precautions for Use' and 'Posology and Method of Administration').

Allergic/anaphylactic reaction:
Dyspnoea, wheezing, bronchospasm and worsening of existing asthma.

Other adverse events:
Diaphoresis, urticaria and pruritus have been reported. Skin rashes, blurred vision, difficulty passing urine or urine retention, tachycardia, orthostatic hypotension, increase in blood pressure, bradycardia, flushing, syncope and anaphylaxis have been rarely reported. Cases of blood dyscrasias have been rarely observed during treatment with tramadol, but causality has not been established.

4.9. Overdose

Symptoms of overdose 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 potency of the airway and maintaining cardiac function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
Tramadol is mainly eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with tramadol hydrochloride with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Tramadol hydrochloride is a centrally acting analgesic. It is a non selective pure agonist at mu, delta and kappa opioid receptors with 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

After oral administration, tramadol is almost completely absorbed. Mean absolute bioavailability is approximately 70% following a single dose and increases to approximately 90% at a steady state. Plasma protein binding of tramadol is approximately 20%. When C_{14}-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 ($t½\beta$) was 6.0±1.5h in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the age of 75 years. In volunteers over 75 years, $t½\beta$ was about 7.0±1.6h after oral administration.

Since tramadol is eliminated both metabolically and renally, the terminal half life t½β may be prolonged in impaired hepatic or renal function. However, the increase in the t½β values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½β tramadol was a mean of 13.3±4.9 h; in patients with renal insufficiency (creatine clearance ≤ 5ml/min) it was 11.0±3.2 h.

5.3. Preclinical safety data

In single and repeated-dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatoxicity) 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tramadol capsules contain microcrystalline cellulose, povidone K30, α-lactose monohydrate, magnesium stearate and sodium starch glycolate (type A).

The capsule shell contains gelatin and titanium dioxide (E171).

The black ink contains shellac, industrial methylated spirit 74 OP, soya lecithin, antifoam DC 1510, n-butyl alcohol and black iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Do not store above 25° C. Store in the original package.

6.5. Nature and contents of container

PVC/PVDC Aluminium foil blister packs.
Pack sizes: 30 or 100 capsules.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road,
Beverley, East Yorkshire,
HU17 0LD

8. MARKETING AUTHORISATION NUMBER

PL 08553/0210

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/07/2007

10 DATE OF REVISION OF THE TEXT

11/07/2007

TRAMADOL HYDROCHLORIDE 50MG TABLETS
PL 08553/0210

PATIENT INFORMATION LEAFLET

Component code

TRAMADOL HYDROCHLORIDE 50mg CAPSULES
PATIENT INFORMATION LEAFLET

Please read this leaflet carefully before you start taking this medicine.
Keep this leaflet until you have finished all the prescribed course of Tramadol Hydrochloride 50mg Capsules. You may need to read it again. If you have any questions concerning your medicine ask your doctor or pharmacist for more information. This medicine has been prescribed for you personally and you should not pass it onto others. It may harm then, even if their symptoms are the same as yours.

What Tramadol Hydrochloride is and what it is used for
The name of this medicine is Tramadol Hydrochloride 50mg Capsules. Each capsule contains 50mg of Tramadol Hydrochloride as the active ingredient.

The capsules also contain: microcrystalline cellulose, povidone K30, lactose monohydrate, magnesium stearate and sodium starch glycolate. The capsule shell contains gelatin and titanium dioxide (E171). The black printing contains shellac, soya lecithin, antifoam DC 1510, and black iron oxide (E172).

Tramadol Hydrochloride 50mg Capsules are available in blister packs of 30 or 100 capsules.
Tramadol Hydrochloride is a centrally acting analgesic (a pain killer which acts on the pain centre of the brain) which is used to relieve pain within the body. Tramadol Hydrochloride capsules are used in the management (treatment and prevention) of moderate to severe pain.

Manufacturers:
Losan Pharma GmbH, Otto Hahnstrasse 13, D 79395, Neuenburg, Germany

Cardinal Health Germany 405 GmbH, Steinbeisstrasse 2, D 73164, Schomdorf, Germany

Chamelle Medical Ltd, IDA Industrial Estate, Loughrea, Co.Galway, Ireland

Marketing Authorisation Holder: Dr Reddy's Laboratories (UK) Ltd,
6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK

Before you take Tramadol Hydrochloride Capsules
Do not take Tramadol Hydrochloride capsules if you are hypersensitive (allergic) to Tramadol Hydrochloride or any of the other ingredients listed above. It is important that your doctor is aware of any other medication you are taking whether prescribed or not. Make sure to tell your doctor or pharmacist if you have any other medical problems.

Ask yourself the following questions
- Do you suffer from epilepsy
- Are you suffering from a head injury or increased intracranial pressure (within the skull)?
- Are you suffering form severe kidney or liver problems?
- Are you prone to convulsive disorders (fits)?
- Could you be in shock? (This could involve feeling cold, clammy, faint or light headed.)
- Have you ever had any problems of dependence on any drugs, for example painkillers or sleeping capsules?

If the answer to any of these questions is YES, tell you doctor or pharmacist as soon as possible and before taking any capsules.

DO NOT take these capsules if you suffer from respiratory depression or breathing difficulties.

Use in pregnancy
Do not use Tramadol Hydrochloride if you are pregnant, or likely to become pregnant.

Breast-feeding
If you are breast-feeding tell you doctor or pharmacist before taking any capsules.

Driving and using machines
Some side-effects (drowsiness, headache, dizziness, blurred vision etc) have occurred during treatment with Tramadol Hydrochloride capsules. If affected you should not drive, operate machinery or carry out activities where these effects may be a danger to you or others.

Can you take Tramadol Hydrochloride 50mg Capsules with other medicines?
It is very important to tell you doctor or pharmacist about all the medicines which you are taking, whether or not any medicines were prescribed by your doctor or bought without a prescription from the pharmacy or elsewhere. It is also important to check whether you have recently been taking other medicines or alcohol before you start taking Tramadol Hydrochloride capsules. In particular, ask yourself about the following products:
- Have you recently been or are you currently taking alcohol, sleeping capsules, centrally acting pain killers, opioids (a particular class of pain killers, including codeine, morphine and others) or psychotropic drugs (drugs which have an affect on the brain)?
- Are you taking a monoamine oxidase inhibitor, a type of antidepressant which includes phenelzine (Nardil), tranylcypromine (Parnate or Parstelin) or isocarboxazid, or have you stopped taking one during the last 2 weeks?

If the answer to any of these questions is YES and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking any capsules.

Other medicines which may affect Tramadol Hydrochloride capsules:
- Centrally acting drugs including these may increase central nervous system depressant effects
- Carbamazepine (a drug for epilepsy) may decrease the painkilling effect of Tramadol Hydrochloride capsules
- Selective serotonin reuptake inhibitors (SSRIs), a type of antidepressant including Fluoxetine, or tricyclic antidepressants (TCAs) including dothiepin and Amitriptyline may increase the risk of fits. There is also a theoretical chance Tramadol Hydrochloride capsules may interact with lithium.

Special precautions and warnings
Each 50mg capsule contains 103mg of lactose (as alpha-lactose monohydrate). Lactose is a sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

How to take Tramadol Hydrochloride Capsules
Always take Tramadol Hydrochloride capsules exactly as your doctor has instructed you. If you are not sure, ask your doctor or pharmacist. Swallow the capsules whole with a drink of water. Do not chew the capsules. Do not exceed the stated dose.

Adults and Children over 12 years old: For short term treatment of pain, the usual dose is initially 2 capsules (100mg) followed by 1 to 2 capsules (50-100mg) not more often than every 4 hours. For long term conditions, an initial dose of 1 capsules (50mg) is usually given, and then the dosage adjusted by your doctor. A total of 8 capsules (400mg) daily should not usually be exceeded except in special circumstances.
Elderly: The usual adult doses may be used.
Liver or kidney problems: if your suffer from liver or kidney problems, or are on dialysis due to reduced kidney function, your doctor may reduce the dose or how often you take Tramadol Hydrochloride capsules.
Children under 12 years old: Tramadol Hydrochloride capsules are not recommended for children under 12 years old.

If after taking your medicine you have any problems consult your doctor.

If your forget to take Tramadol hydrochloride
If you forget to take a dose, take it as soon as your remember. However, if it is almost time for your next dose, miss the forgotten dose altogether and continue with the rest of the capsules as normal.

If you take more Tramadol Hydrochloride than you should
It is important to stick to the dose on the label of your medicine. If you or someone else swallows a lot of these capsules all together, or you think a child has swallowed any of these capsules contact your doctor or hospital emergency department immediately. Take with you any remaining capsules and packaging so that they can be identified.

Possible side effects
Like all medicines, Tramadol Hydrochloride capsules can have side effects. If you suffer from any of the following side-effects, **stop** taking the capsules and tell your doctor **immediately** or go to your nearest hospital. This kind of reaction is extremely rare and it may mean you are suffering from a severe allergic reaction to the capsules:
- Sudden wheeziness or tightness of the chest.
- Swelling of the eyelids, face or lips; with or without a lumpy skin rash ('hives') anywhere on the body.
- Unexplained fever
- Feeling faint, especially on standing up

Other more common undesirable effects which may sometimes happen while taking Tramadol Hydrochloride capsules include those listed below. If you suffer from any of these reactions, and they are severe or prolonged, you should stop taking your capsules and contact your doctor or pharmacist.
- *Gastrointestinal;* feeling or being sick, dry mouth, diarrhoea or constipation
- *Central nervous system;* tiredness, fatigue (exhaustion), drowsiness, feeling sleepy, dizziness, headache, confusion, hallucinations and infrequently shallow slowed breathing. Rarely a feeling of needing to continue taking this medicine, a general feeling of uneasiness and convulsions have been reported.
- *Physical dependence;* physical dependence, abuse and withdrawal symptoms have been reported. Physical dependence occurs when your body becomes used to the drug and begins to need it to continue functioning normally. If you stop taking it your body will need to readjust, which may result in the following symptoms: agitation, anxiety, nervousness, difficulty sleeping, hyperkinesias (strong movements), trembling and gastrointestinal symptoms.
- *Other effects:* sweating, skin rash or itching, blurred vision, difficulty passing urine or urine retention, change in heart rate, reduced blood pressure when standing upright which may cause dizziness or light headedness, increase in blood pressure, flushing, temporary loss of consciousness and allergic reaction have rarely been reported. Cases of blood disorders have rarely been observed but causality has not been established.

If you suffer from any side effects listed above, if they are severe or prolonged or if you notice any side effects not mentioned in this leaflet, inform your doctor or pharmacist immediately.

Storing Tramadol Hydrochloride Capsules
Do not store above 25°C
Store in the original package
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
On the packaging you will find a printed expiry date. This is the date when the medicine is no longer fit for use. Do not use Tramadol Hydrochloride capsules after this date. If you have any capsules which are out of date, return them to your pharmacist for disposal.

A reminder
Remember this medicine id for you. Never give it to someone else, even if their symptoms are the same as yours. This leaflet does not contain the complete information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist for access to additional information.

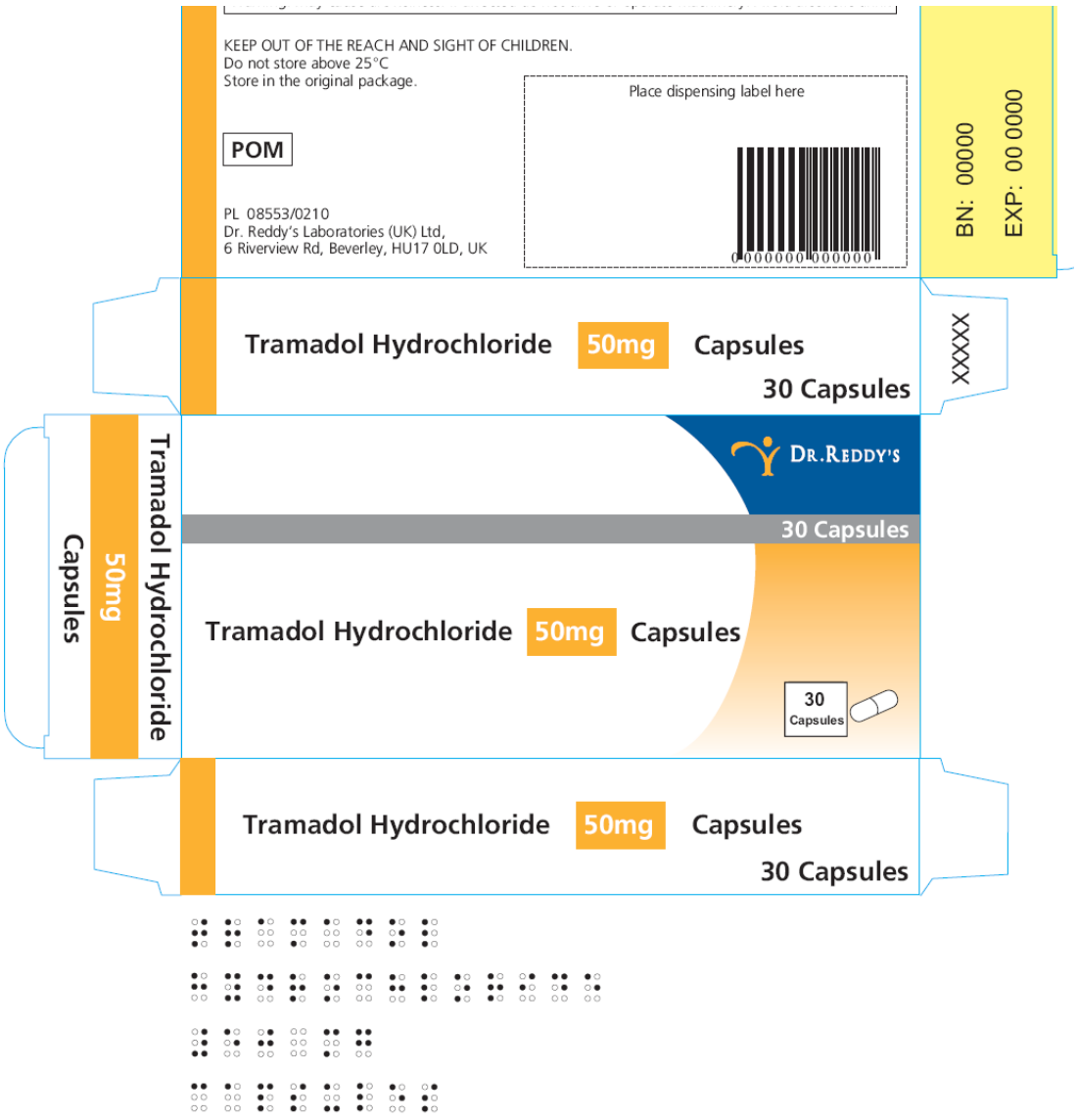
Date of preparation:19/01/06
Tramadol Hydrochloride 50mg Capsules, PL08553/0210

Component code

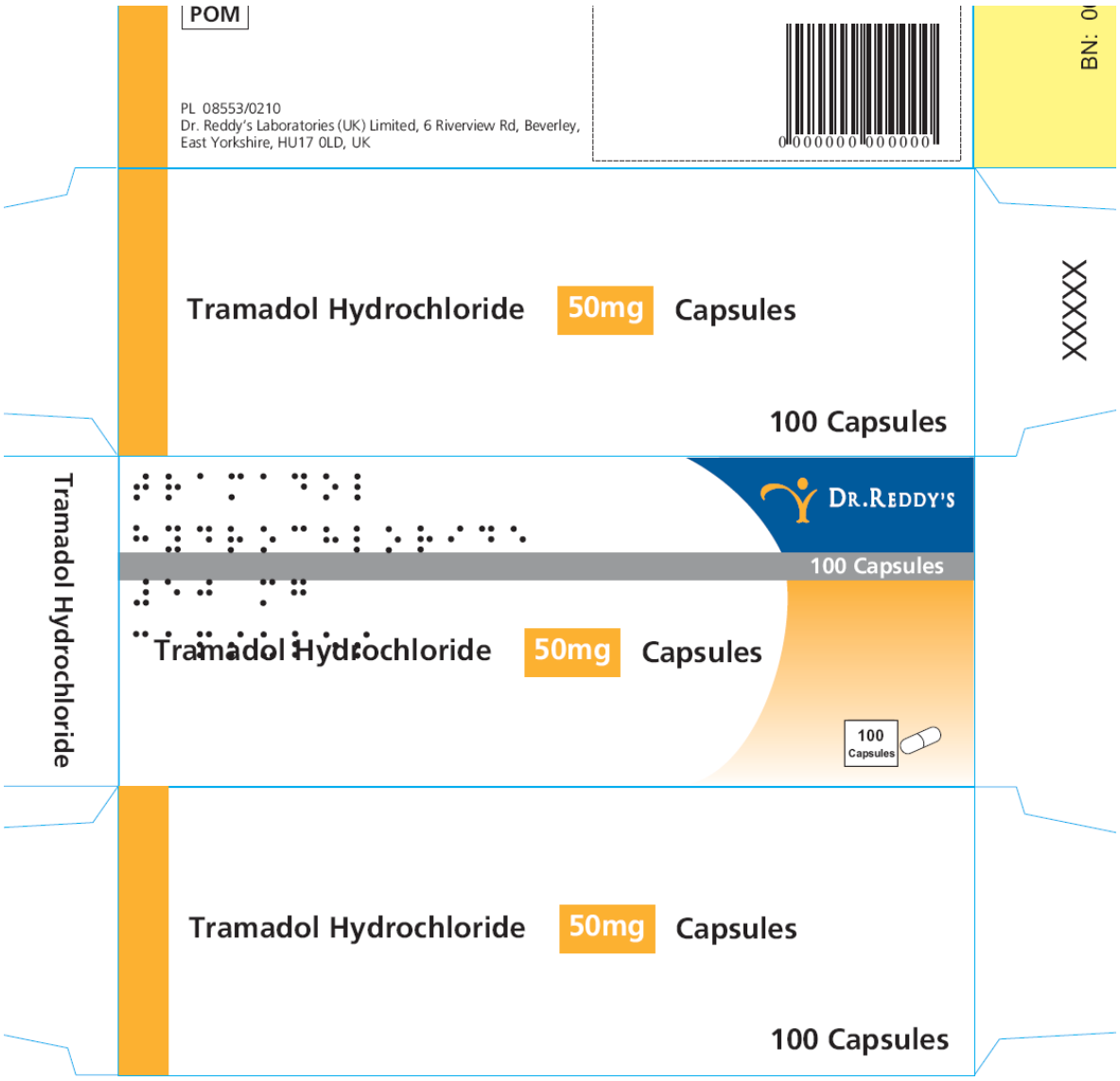
TRAMADOL HYDROCHLORIDE 50MG TABLETS
PL 08553/0210

LABELLING

CARTON
PACK SIZE-30 CAPSULES



PACK SIZE-100 CAPSULES



CONTAINER
BLISTER FOIL