TRAMADOL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 18157/0014

UKPAR

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TRAMADOL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

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LAY SUMMARY

The MHRA has granted Beacon Pharmaceuticals Ltd a Marketing Authorisation (licence) for the medicinal product Tramadol 50mg/ml Solution for Injection or Infusion (PL 18157/0014). This is a prescription only medicine (POM) for the treatment and prevention of moderate to severe pain.

This product contains tramadol, which acts on pathways known as opioid receptors in the brain and spinal cord to relieve pain.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Tramadol 50mg/ml Solution for Injection or Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

TRAMADOL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 18157/0014

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Tramadol 50mg/ml Solution for Injection or Infusion (PL18157/0014) on 30th August 2007. The product is a prescription-only medicine.

This application was submitted as an abridged application according to Article 10(1) of Directive 2001/83/EC, claiming essential similarity to the original product, Tramal 100 Injectievloeistof 100mg/2ml authorised to Grunenthal GmbH in the Netherlands in 1992. The reference medicinal product in the UK is Zydol Solution for Injection 50mg/ml (PL 21727/0002) authorised to Grunenthal Limited in December 2004 following a change in ownership application from PL 08821/0004 (Monsanto plc, trading as Searle).

This product contains tramadol hydrochloride and is indicated for the management (treatment and prevention) of moderate to severe pain.

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 noradrenalines and enhancement of serotonin release.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Tramadol hydrochloride

Chemical names:
(1RS, 2RS)-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol hydrochloride
(±)-trans-2-[(Dimethylamino)methyl)-1-(3-methoxyphenyl)-cyclohexanol hydrochloride

Structure

$C_{16}H_{25}NO_2.HCl$ MW: 299.84 CAS Number: 36282-47-

White to off-white crystalline powder. Freely soluble in water and in methanol, very slightly soluble in acetone.

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 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 retest period of 3 years when stored in double polyethylene bags in a steel drum.
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DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium acetate trihydrate and water for injections. All excipients used comply with their respective European Pharmacopoeia monograph.

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.

There were no novel excipients used and no overages.

Impurity profiles

Satisfactory information was provided on levels of impurities in the proposed 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.

Satisfactory tests and acceptance criteria have been set for in-process testing.

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

Product is packaged in colourless 2ml neutral Type I glass ampoules. 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 2 years when kept in the outer container has been set, which is satisfactory.

Conclusion

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

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance and pharmaceutical form. It was not necessary to demonstrate bioequivalence.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a national abridged standard application for Tramadol 50mg/ml solution for injection to be used intravenously or intramuscularly, under article 10(1), cross-referring to Zydol Solution for Injection, 50 mg/ml marketed by Monsanto plc, trading as Searle, PL 08821/0004. The original product Tramal 100, injectier/oeistof 100mg/2ml was first licensed to Grunethal GmbH by the Netherlands on 21.12.1992.

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: 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. It is not recommended in children under 12 years of age.

5. TOXICOLOGY

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

6. CLINICAL PHARMACOLOGY

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

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

There is a satisfactory clinical expert report/overview. The report covers all forms of administration including capsules and suppositories, as well as ampoules for injection, the subject of this application. A curriculum vitae is included as are those for the preclinical and pharmaceutical experts.

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. DISCUSSION

The data presented is adequate for the company's application.

15 RECOMMENDATION

Marketing Authorisation should be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Tramadol 50mg/ml Solution for Injection or Infusion 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.

PRECLINICAL

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

EFFICACY

There was no need for bioequivalence to be demonstrated between the applicant's Tramadol 50mg/ml Solution for Injection or Infusion and the originator product.

No new or unexpected safety concerns arise from this application.

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

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The benefit/risk balance is considered to be positive.

TRAMADOL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 21st May 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 22nd June 2004
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 20th April 2005, 4th January 2007 and on the 23rd May 2007. Information relating to the clinical dossier was requested on 17th November 2004.
4	The applicant responded to the MHRA's request, providing further information on 14th July 2006, 9th February 2007, 14th February 2007 and 28th May 2007 for the quality section and on 14th December 2004 for the clinical dossier.
5	The application was determined on 30th August 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Tramadol 50mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule contains 100mg tramadol hydrochloride in 2ml solution (50mg/ml).

For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM
Solution for Injection or Infusion
A clear colourless solution in glass ampoules.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
For the treatment and prevention of moderate to severe pain.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of pain and the clinical response of the patient. The tramadol solution is for parenteral injection either intramuscularly, by slow intravenous injection or diluted in solution (see Section 6.6 Special instructions for use and handling) for administration by infusion or patient controlled analgesia.

Adults and children 12 years and over:
The usual dose is 50mg or 100mg 4 to 6 hourly by either intramuscular or intravenous routes. Intravenous injections must be given slowly over 2–3 minutes. The dose should be adjusted according to the severity of the pain and the response.

For post-operative pain, an initial bolus of 100mg is administered. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4-6 hourly up to a total daily dose of 600mg.

Elderly:
The usual dosages may be used. However, it is reported that in volunteers aged over 75 years, 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 adult dosage may be used but the dosage interval should be adjusted. For patients with creatinine clearance <30ml/min, the dosage interval should be increased to 12 hours. For patients with severe renal impairment (creatinine clearance of <10ml/min) tramadol is not recommended. As tramadol is only removed slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

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

Children under 12 years:
Not recommended.

4.3 CONTRAINDICATIONS
Tramadol 50mg/ml Solution for Injection should not be given to patients who have previously demonstrated hypersensitivity towards tramadol or any of the other ingredients (see Section

6.1 for 'list of excipients'). Tramadol 50mg/ml Solution for injection should not be given to patients suffering from acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.
In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5 'Interaction with other medicinal products and other forms of interaction').

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings
At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.
At therapeutic 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 to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.
Tramadol 50mg/ml Solution for Injection is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.
Tramadol 50mg/ml Solution for Injection 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 (see section 4.7 Effects on the ability to drive and use machines)

Precautions
Tramadol 50mg/ml Solution for Injection 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 Medicinal Products 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 (tramadol) anaesthetic technique (with only intermittent administration of enflurane 'as required') tramadol 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 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 may be used intra-operatively in the same way as other analgesic agents are routinely used.

This medicinal product contains approximately 8.29mg sodium acetate trihydrate (1.4mg sodium) per 2ml dose.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Tramadol 50mg/ml Solution for Injection should not be combined with MAO inhibitors (see Section 4.3 'Contraindications').
Concomitant administration of Tramadol 50mg/ml Solution for Injection with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects (see Section 4.8 'Undesirable Effects').

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').
Theoretically there is a possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.
Serotonergic drugs: Co-administration with serotonergic drugs, e.g. SSRIs or triptans, may lead to an increase of serotonin-associated effects, which can include serotonin syndrome.
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.
Carbamazepine – The 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.
Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.
Quinidine - A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the tramadol Cmax and AUC; Tmax is unaffected. However, the increases in Cmax and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.

4.6 PREGNANCY AND LACTATION

Pregnancy
Animal studies with tramadol at very high doses have revealed effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore Tramadol 50mg/ml Solution for Injection 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 dose given to the mother. Tramadol 50mg/ml Solution for Injection should not be administered during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tramadol 50mg/ml Solution for Injection 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

Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided. The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10 % of patients.

Cardiovascular system disorders: Uncommon (< 1 %) cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially after intravenous administration and in patients who are physically stressed. Rarely (< 0.1%) bradycardia, increase in blood pressure.

Central and peripheral nervous system disorders: Common (1-10 %) headache, muzziness. Rarely (< 0.1 %) changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions.

Psychiatric disorders: Rarely (< 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 may occur.

Vision disorders: Rarely (< 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: Rarely (< 0.1%) muscle weakness.

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

Urinary system disorders: Rarely (< 0.1 %) micturition disorders (difficulty in passing urine and urinary retention)

Body as a whole: Rarely (< 0.1 %) allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis. Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal 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 tramadol intoxication with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code N 02A X02: Analgesics – other opioids

Tramadol 50mg/ml Solution for Injection 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.

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 14C-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 ($t_{½\beta}$) 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 aged over 75 years, $t_{½\beta}$ was 7.0 + 1.6h on oral administration.
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 < 5 ml/min) it was 11.0 + 3.2h.

The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP 2D6, involved in the metabolism of tramadol may affect the plasma concentrations of tramadol or its active metabolite. The clinical consequences of any such interactions are unknown.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium acetate trihydrate
Water for injections

6.2 INCOMPATIBILITIES

Precipitation will occur if Tramadol 50mg/ml Solution for Injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indometacin, midazolam and piroxicam.

Tramadol 50mg/ml Solution for Injection must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 SHELF LIFE

3 years.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Keep ampoule in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

2ml neutral glass type I glass ampoules.
Box of 5 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The prepared infusion solution should be made up immediately before use.
Tramadol 50mg/ml Solution for Injection is physically and chemically compatible for up to:
- 24 hours with 4.2% sodium bicarbonate and Ringer's solution.
Or up to 5 days with the following infusion solutions:
- 0.9% sodium chloride
- 0.18% sodium chloride and 4% glucose
- sodium lactate compound
- 5% glucose

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Ltd.
Tunbridge Wells
Kent TN1 1YG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 18157/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/08/2007

10 DATE OF REVISION OF THE TEXT

30/08/2007

Patient Information Leaflet

Tramadol 50mg/ml Solution for Injection or Infusion
(referred to as Tramadol Injection throughout this leaflet)
Please read all of this leaflet carefully before being given your medicine.
Keep the leaflet in case you want to refer to it again.
If you want to know more about Tramadol 50mg/ml Injection or Infusion, or have any questions, you should ask your doctor or pharmacist.
This medicine has been prescribed for you. You should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
The name of this medicine is Tramadol 50mg/ml Solution for Injection (referred to as Tramadol Injection). The active substance is tramadol hydrochloride and the other ingredients are sodium acetate and water for injections.
Product Licence holder: Beacon Pharmaceuticals Ltd., Tunbridge Wells, Kent TN1 1YG, UK.
Manufacturer: Edmond Pharma Srl, 20037 Paderno Gugnano, Italy

1. What is Tramadol Injection and what is it used for?
Tramadol Injection is supplied in glass ampoules containing 50mg/ml of tramadol hydrochloride. Tramadol hydrochloride belongs to a group of medicines known as analgesics or "pain-killers".
Each ampoule contains 2ml of solution and there are 5 ampoules per box.
Tramadol is used to relieve pain and can also be taken to prevent pain.

2. Before being given Tramadol Injection
You must not be given Tramadol Injection if:
- You are a child under 12 years of age.
- You are allergic to tramadol hydrochloride or any of the other ingredients of the solution. Allergic reactions to tramadol could include skin rash, swelling of the face, wheezing or difficulty breathing.
- You are pregnant or breast-feeding.
- You are taking any of the following medicines: sleeping tablets or tranquillizers such as nitrazepam, other pain-killers such as codeine or morphine, psychotropic medicines such as chlorpromazine.
- You are taking a monoamine oxidase inhibitor (MAOI, a medicine to treat depression) or if you have taken one in the past two weeks.
- If you have been drinking alcohol.
- You are suffering from uncontrolled epilepsy.

Take special care if:
- You have liver or kidney disease. You may need a lower dose or a longer interval between doses.
- You have had a head injury or have brain disease.
- You are in a state of shock. You may feel light headed, faint, cold or clammy or look pale.
- You suffer from epilepsy, convulsions or seizures (fits) or if you have had them in the past.
- You suffer from asthma, other lung diseases or have difficulty in breathing.
- You are taking tricyclic antidepressants, such as amitriptyline, as this may increase the chance of having a fit (although this is very rare).
- You are taking carbamazepine a treatment for epilepsy, as this may reduce the effectiveness of the tramadol.
- You are taking triptans, such as sumatriptan, used to treat migraines, as this may increase the effectiveness of the triptans.
- You are taking coumarin anticoagulants, used to thin the blood, such as warfarin, as this may alter the effectiveness of the anticoagulant.
- You are taking selective serotonin reuptake inhibitors (SSRI's), used to treat depression, such as fluoxetine, as this may increase the effect of the SSRI's.
- You are taking lithium, used to treat psychotropic disorders, as this may alter the effect of lithium.
- You are taking any other medicine, even those not prescribed.

This medicinal product contains less than 1 mmol sodium (23mg) per 2ml dose i.e. essentially 'sodium free'.

Technical Leaflet

Tramadol 50mg/ml Solution for Injection or Infusion

Please read this information carefully before using Tramadol 50mg/ml Solution for Injection or Infusion (referred to as Tramadol Injection). Further information is contained in the Summary of Product Characteristics.

Presentation

Tramadol Injection is presented as a clear colourless solution in a neutral glass ampoule. Each ampoule contains 2ml of tramadol hydrochloride 50mg/ml.

Dosage and Method of Administration

Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Only a clear solution should be used.

Tramadol Injection is for parenteral injection either intramuscularly, by slow intravenous injection or diluted in solution for administration by infusion or patient controlled analgesia.

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

Adults and Children over 12 years

The usual dose is 50 or 100mg 4 to 6 hourly by either intramuscular or intravenous routes. Intravenous injections must be given slowly over 2–3 minutes. The dose should be adjusted according to the severity of the pain and the response.

For post-operative pain, an initial bolus of 100mg is administered. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4-6 hourly up to a total daily dose of 600mg.

Elderly

The usual dosages may be used. However, it has been shown that in the elderly (over 75 years) the elimination of half-life of tramadol is increased following oral administration.

Renal impairment/renal dialysis

The elimination of tramadol may be prolonged. The usual adult dosage may be used but the dosage interval should be adjusted. For patients with creatinine clearance <30ml/min, the dosage interval should be increased to 12 hours. For patients with severe renal impairment (creatinine clearance of <10ml/min) tramadol is not recommended. As tramadol is only removed 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. In cases of severe hepatic impairment the dosage interval should be increased to 12 hours.

Children under 12 years Not recommended.

Contraindications

Tramadol Injection should not be given to patients who have previously demonstrated hypersensitivity towards tramadol or any of the other ingredients in this medicine. Tramadol Injection should not be given to patients suffering from acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

Precautions

Tramadol Injection 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 (also see 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.

Pregnancy and breastfeeding

There is very little information on the safety of tramadol in pregnancy, therefore Tramadol Injection should not be used if you are pregnant

Tramadol may be harmful to the breast fed baby. Women must stop breastfeeding before starting treatment with Tramadol Injection.

Driving and using machinery

Tramadol Injection may cause drowsiness. Do not drive or use machinery if you are affected.

3. How should Tramadol Injection be given and how much will I receive?

Your doctor or nurse will usually give you Tramadol Injection. The solution may be given by an injection into either a vein or muscle.

You will usually have one injection of 50mg or 100mg every 4 to 6 hours. After an operation you may need injections more often.

If you are in hospital you may receive tramadol through a drip (infusion) or from a small machine that allows you to have tramadol when you need it by pushing a button. The doctor or nurse will explain how to use the machine.

Tramadol Injection is not recommended for children under 12 years of age.

If you receive too much Tramadol Injection.

If you think you have been given or given yourself too much Tramadol Injection tell a doctor or nurse immediately.

If you stop receiving Tramadol Injection

Rarely when some people stop treatment with tramadol they get withdrawal symptoms. These symptoms include agitation, nervousness, shaking, hyperactivity and difficulty in sleeping.

What side effects are possible?

Like all medicines, Tramadol Injection can cause side effects. However, do not be alarmed as most patients do not have problems with this medicine.

Tell your doctor or a nurse immediately if the following happens:

- If you experience swelling around the throat, tightness in your chest or difficulty in breathing.

You may have had an allergic reaction, these are rare but, if severe, can be serious and you may need urgent medical attention.

Tell a doctor or nurse if you get other side effects:

Very common side effects:

- Nausea, dizziness

Common side effects:

- Headache, muzziness
- Vomiting, constipation, diarrhoea, dry mouth, sweating

Uncommon side effects:

- Changes in heart beat or rhythm which may make you feeling faint or dizzy especially if you stand up quickly.
- Retching, stomach irritation or feeling bloated
- Rash

Rare side effects:

- Changes in appetite, abnormal touch sensations, trembling, difficulty breathing, fits
- Slowing of the heart rate, increased blood pressure
- Nightmares, disturbed sleep patterns, hallucinations (seeing things), feeling confused, changes in mood, activity or awareness
- Blurred vision
- Muscle weakness
- Increase in liver enzymes
- Difficulty in passing water
- Rarely when some people stop taking tramadol they get withdrawal symptoms. These symptoms include agitation, nervousness, shaking, hyperactivity and difficulty in sleeping.
- If you suffer from asthma, this may get worse

If you notice any other side effects please tell your doctor or nurse.

How should Tramadol Injection be stored?

This medicinal product does not require any special storage conditions.

Keep ampoule in the outer carton.

Do not use this product if there are signs of damage to the ampoule or if the solution is cloudy or contains particles.

Further information: This leaflet does not include all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Date of last revision: June 2007

Beacon PHARMACEUTICALS

In one study using a nitrous oxide/opioid (tramadol) anaesthetic technique (with only intermittent administration of enflurane 'as required') tramadol was reported to enhance intra- operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Tramadol administration during anaesthesia comprising continuous administration of isoflurane may lead to 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 may be used intra-operatively in the same way as other analgesic agents are routinely used.

Pregnancy and lactation

There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore Tramadol Injection should not be used in pregnant women.

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. Tramadol Injection should not be administered during breast-feeding.

Interactions with other Medicinal Products and other Forms of Interaction

Tramadol Injection should not be combined with MAO inhibitors. Concomitant administration of Tramadol Injection with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects.

Tramadol may increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions. Theoretically there is a possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

Serotonergic drugs: Co-administration with serotonergic drugs, e.g. SSRIs or triptans, may lead to an increase of serotonin-associated effects, which can include serotonin syndrome.

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.

Carbamazepine – The 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.

Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine - 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.

Pharmaceutical Information

Excipients Sodium acetate trihydrate and Water for Injections.

Incompatibilities

Precipitation will occur if Tramadol Injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.

Shelf-life 3 years

Storage Precautions Keep ampoule in the outer carton. This medicinal product does not require any special storage conditions.

Nature of Container 2ml neutral glass type I glass ampoules for injections. Box of 5 ampoules.

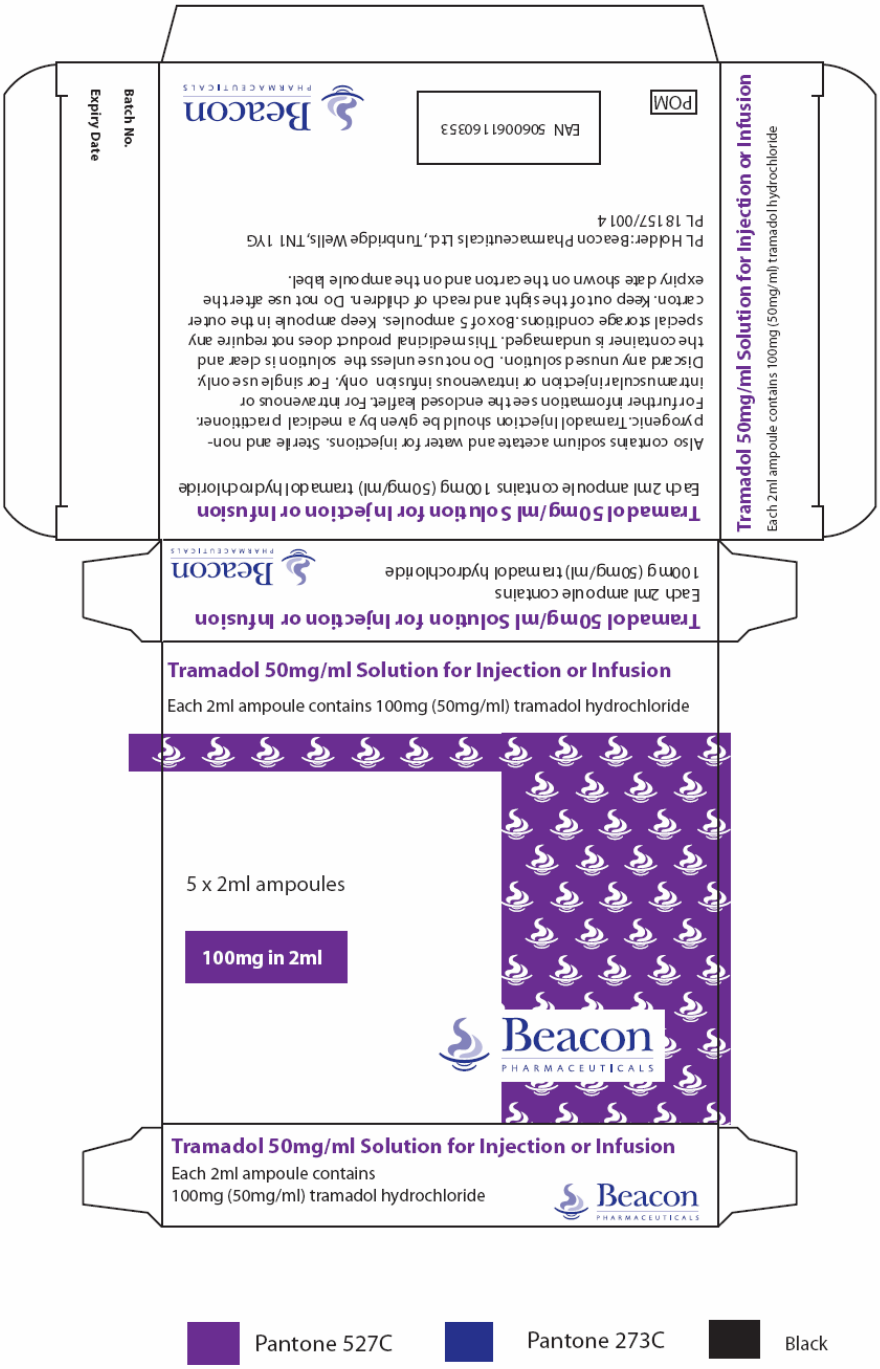
Instructions for Use and Handling.

The prepared infusion solution should be made up immediately before use.

Tramadol Injection is physically and chemically compatible for up to 24 hours with 4.2% sodium bicarbonate and Ringer's solution; and for up to 5 days with the following infusion solutions:

0.9% sodium chloride
0.18% sodium chloride and 4% glucose
sodium lactate compound
5% glucose

Carton Dimensions: 85x19x99mm



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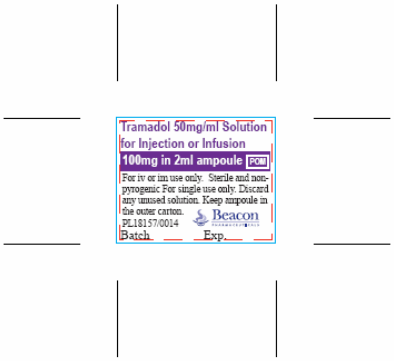

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