Medicines & Healthcare products Regulatory Agency

Public Assessment Report

UKPAR

Tramadol 50mg/ml Solution for Injection or Infusion

(tramadol hydrochloride)

UK Licence No: PL 18157/0014

Beacon Pharmaceuticals Limited

LAY SUMMARY
Tramadol 50mg/ml Solution for Injection or Infusion (tramadol hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Tramadol 50mg/ml Solution for Injection or Infusion (PL 18157/0014). Tramadol 50mg/ml Solution for Injection or Infusion will be referred to as Tramadol injection throughout this lay summary, for ease of reading.

This summary explains how Tramadol injection was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Tramadol injection.

For practical information about using Tramadol injection, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Tramadol injection and what is it used for?
Tramadol injection is a 'generic medicine'. This means that this product is similar to a 'reference medicine', already authorised in the UK called Zydol 50 mg/ml Solution for Injection (PL 21727/0002; Grunenthal Limited).

Tramadol is used to relieve pain and can also be used to prevent pain.

How does Tramadol injection work?
Tramadol injection contains the active ingredient tramadol hydrochloride which belongs to a group of medicines known as analgesics or "pain-killers".

How is Tramadol injection used?
Tramadol injection is administered by a nurse or a doctor either into a vein or muscle.

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

The usual dose is one injection of 50mg or 100mg every 4 to 6 hours. After an operation, a patient may need injections more often.

In elderly patients (above 75 years) the excretion of tramadol may be delayed. A doctor may recommend prolonging the dosage interval.

Patients with severe liver or kidney disease (insufficiency)/dialysis should not be given Tramadol Injection. If the insufficiency is mild or moderate, a doctor may recommend prolonging the dosage interval.

Tramadol Injection should not be given to children under 12 years of age.

The dosage should be adjusted to the intensity of the pain and an individual pain sensitivity.
In general, the lowest dose to relieve pain should be given for the shortest possible time.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained with a prescription from a doctor.

How has Tramadol injection been studied?
Because Tramadol injection is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Zydol 50 mg/ml Solution for Injection. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Tramadol injection?
Because Tramadol injection is a generic medicine, and is bioequivalent to the reference medicine, Zydol 50 mg/ml Solution for Injection, the benefits and risks are taken as being the same as the reference medicine.

Why are Tramadol injection approved?
It was concluded that, in accordance with EU requirements, Tramadol injection has been shown to have comparable quality and to be bioequivalent to Zydol 50 mg/ml Solution for Injection. Therefore, the view was that, as for Zydol 50 mg/ml Solution for Injection, the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Tramadol injection?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Tramadol injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Tramadol injection
A Marketing Authorisation was granted in the UK on 30 August 2007.

The full PAR for Tramadol injection follows this summary.

This summary was last updated in August 2017.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Beacon Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Tramadol 50mg/ml Solution for Injection or Infusion (PL 18157/0014) on 30 August 2007. This product is a prescription-only medicine (POM), indicated for the treatment and prevention of moderate to severe pain.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming essential similarity to the original product, Tramal 100 Injectievloeistof 100mg/2ml, which was originally authorised in 1992 to Grunenthal GmbH in the Netherlands. The reference medicinal product in the UK is Zydol 50 mg/ml Solution for Injection, which was originally authorised on 19 March 1996 to GD Searle and Company Limited (PL 00020/0195). Following a Change of Authorisation Holder (CoA), which was granted on 1 December 2004, the current marketing authorisation holder is Grunenthal Limited (PL 21727/0002).

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.

No new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years. A bioequivalence study was not necessary to support this application for a parenteral product administered as an aqueous intravenous solution containing the same active substance as the reference product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

A satisfactory pharmacovigilance system was provided with this application. A justification for not submitting the risk management plan has also been provided.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Tramadol 50mg/ml Solution for Injection or Infusion outweigh the risks and a Marketing Authorisation was granted.

II Quality Aspects

II.1 Introduction

This product is presented as solution for injection or infusion, and each ampoule contains 100mg of tramadol hydrochloride in 2ml solution (50mg/ml), as active ingredient.

Other ingredients consist of pharmaceutical excipients, namely sodium acetate trihydrate and water for injections. Both 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.

The 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.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

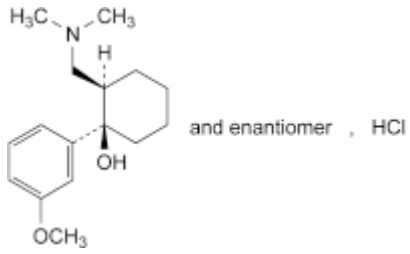
II.2. Drug Substance

Tramadol hydrochloride

INN: Tramadol hydrochloride

Chemical Name: (1*RS*,2*RS*)-2-[(dimethyl amino)methyl]-1-(3-methoxyphenyl) cyclohexanol, hydrochloride

Structure:



Molecular formula: $C_{16}H_{25}NO_2$ HCl

Molecular weight: 299.8 g/mol

Appearance: white to off-white crystalline powder.

Solubility: Freely soluble in water and in methanol and very slightly soluble in acetone.

Tramadol hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, tramadol hydrochloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain a stable solution for injection or infusion containing tramadol hydrochloride that could be considered as a generic medicinal product of Zydol Solution for Injection (Grunenthal Limited).

Satisfactory pharmaceutical development data have been submitted in support of the application.

Manufacture of the product
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.

Product Specification
The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with a storage condition "keep ampoule in the outer carton".

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III Non-Clinical Aspects
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of tramadol are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Tramadol 50mg/ml Solution for Injection or Infusion is intended for generic substitution, its use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of the originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV Clinical Aspects

IV.1 Introduction

Tramadol 50mg/ml Solution for Injection or Infusion is administered as an aqueous intravenous solution and contains the same active ingredient in the same concentration and pharmaceutical form using the same route of administration as the reference product. No bioequivalence studies have been submitted and none are required.

IV.2 Pharmacokinetics

No new data have been submitted and none are required for applciations of this type.

IV.3 Pharmacodynamics

No new data have been submitted and none are required for applciations of this type.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required.

IV.5 Clinical safety

No new safety data have been submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system

A satisfactory pharmacovigilance system was provided with this application. A justification for not submitting the risk management plan has also been provided.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with tramadol hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Tramadol 50mg/ml Solution for Injection or Infusion is presented below:

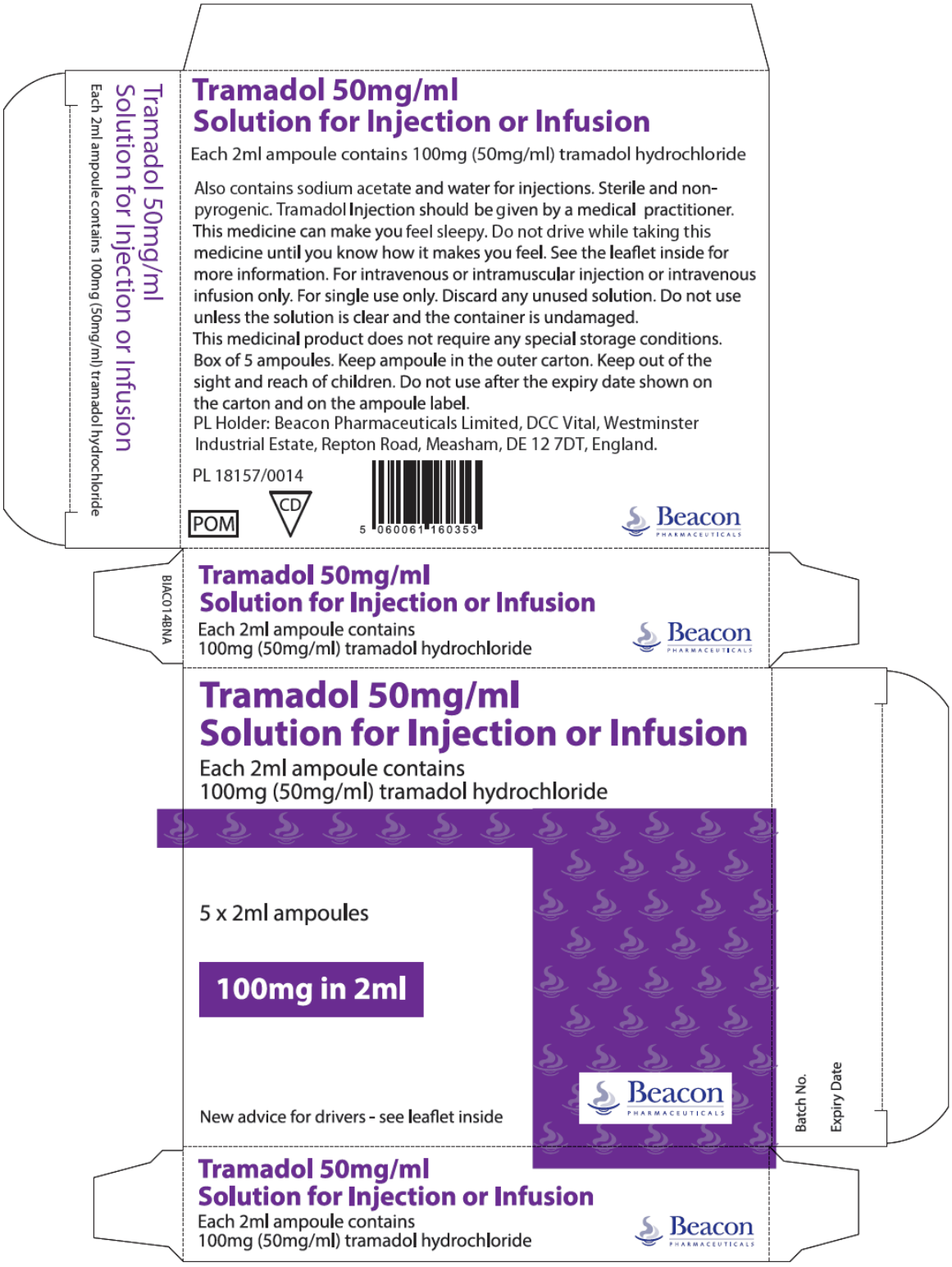


Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment

Date submitted	Application type	Scope	Outcome
03/07/2017	Type IB	To update sections 5.1 and 5.2 of the SmPC for the product Tramadol 50 mg/ml solution for injection or infusion, in line with the recommendations of the Article 45 work-sharing procedure.	24/07/2017

Annex 1

Our Reference: **PL 18157/0014 – 0034**

Product: **Tramadol 50mg/ml Solution for Injection or Infusion**

Marketing Authorisation Holder: **Beacon Pharmaceuticals Limited**

Active Ingredient(s): **Tramadol hydrochloride**

Type of Procedure: **National**
Submission Type: **Variation**
Submission Category: **Type IB**
Submission Complexity: **Standard**
EU Procedure Number (if applicable): **Not applicable**

Reason:
To update sections 5.1 and 5.2 of the SmPC for the product Tramadol 50 mg/ml solution for injection or infusion, in line with the recommendations of the Article 45 work-sharing procedure.

Supporting Evidence
Revised sections of 5.1 and 5.2 of the SmPC have been provided.

Evaluation
The proposed changes to the SmPC is in line with the reference product. The updated SmPC fragments have been incorporated into the Marketing Authorisation.

Conclusion
The proposed changes to the SmPC is acceptable.

Decision - Approved on 24 July 2017.