Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Tramadol 50 mg/ml Solution for Injection

tramadol hydrochloride

PL 56639/0010

SVP Pharma Ltd

LAY SUMMARY

Tramadol 50 mg/ml Solution for Injection
tramadol hydrochloride

This is a summary of the Public Assessment Report (PAR) for Tramadol 50 mg/ml Solution for Injection. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Tramadol Solution for Injection in this lay summary for ease of reading.

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

What is Tramadol Solution for Injection and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Zydol® 50mg/ml solution for injection.

Tramadol Solution for Injection is used for the treatment of moderate to severe pain in adults and adolescents above the age of 12 years.

How does Tramadol Solution for Injection work?
The active substance in Tramadol Solution for Injection belongs to a class of medicines called opioids, which are ‘pain relievers.

How is Tramadol Solution for Injection used?
The pharmaceutical form of this medicine is a solution for injection and the route of administration is intravenous (into a vein).
Tramadol Solution for Injection will be injected slowly usually into a blood vessel under the surface of the arm or injected into muscle (usually the buttocks) or under the skin.
Alternatively, Tramadol Solution for Injection will be diluted and infused into a vein.

The dosage should be adjusted to the intensity of the patient’s pain and individual pain sensitivity. In general, the lowest pain-relieving dose should be received.
Normally, daily doses up to 8 ml of Tramadol (equivalent to 400 mg tramadol hydrochloride) will be sufficient. Exceptionally, if clinically required, the patient’s doctor may direct to use a higher daily dose.
Unless otherwise prescribed by the patient’s doctor, the usual dose is:

Adults and adolescents from the age of 12 years
Depending on the pain the patient will receive 1-2 ml of Tramadol Solution for Injection (equivalent to 50–100 mg tramadol hydrochloride).
Depending on the pain, the effect lasts for about 4-8 hours.
The patient’s doctor may prescribe a different, more appropriate dosage of Tramadol Solution for Injection.

Use in children
Tramadol Solution for Injection is not suitable for children below the age of 12 years.

Elderly patients
In elderly patients (above 75 years), the excretion of tramadol may be delayed. If this applies to the patient, the patient's doctor may direct to prolong the dosage interval.

For further information on how Tramadol Solution for Injection is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Tramadol Solution for Injection have been shown in studies?
Tramadol Solution for Injection is a generic medicine that fulfils criteria meaning that no additional studies are required. Tramadol Solution for Injection has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Tramadol Solution for Injection?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Tramadol Solution for Injection is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Tramadol Solution for Injection approved?
It was concluded that, Tramadol Solution for Injection has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Tramadol Solution for Injection?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Tramadol Solution for Injection. The RMP details the important risks of Tramadol Solution for Injection, how these risks can be minimised, any uncertainties about Tramadol Solution for Injection (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Tramadol Solution for Injection:

Summary of safety concerns	
Important identified risks	– Convulsions (e.g. in patients with poorly controlled epilepsy); – Overdose; – Dependence, withdrawal syndrome, tolerance, abuse; – Concomitant use with anticoagulants; – Serotonin syndrome during concomitant use with serotonergic drugs; – Concomitant use with Central Nervous System (CNS) depressants.
Important potential risks	– Use in patients with a tendency of prolonged elimination [elderly above over seventy-five (75) years or hepatic/renal impairment]; – Use during pregnancy and breast-feeding.
Missing information	– Use in paediatric population under one (1) year of age.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Tramadol Solution for Injection are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Tramadol Solution for Injection
A marketing authorisation for Tramadol Solution for Injection was granted in the United Kingdom (UK) on 24 May 2024.

The full PAR for Tramadol Solution for Injection follows this summary.

This summary was last updated in June 2024.

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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) considered that the application for Tramadol 50 mg/ml Solution for Injection (PL 56639/0010) could be approved.

The product is approved for the following indication:

Treatment of moderate to severe pain.

The name of the active substance is tramadol hydrochloride, which belongs to the pharmacotherapeutic group of analgesics and other opioids.

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ-receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.
Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also, gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Zydol® 50mg/ml solution for injection that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required, and no new clinical studies were provided with this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Tramadol Solution for Injection was granted in the United Kingdom (UK) on 24 May 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a solution for injection, each solution for injection ampoule contains 100 mg tramadol hydrochloride in 2 ml colourless aqueous solution.

In addition to tramadol hydrochloride, this product also contains the excipients sodium acetate trihydrate and water for injections.

The finished product is packaged in type I colourless glass ampoules of 2 ml (packages of 10 and 50 ampoules). Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

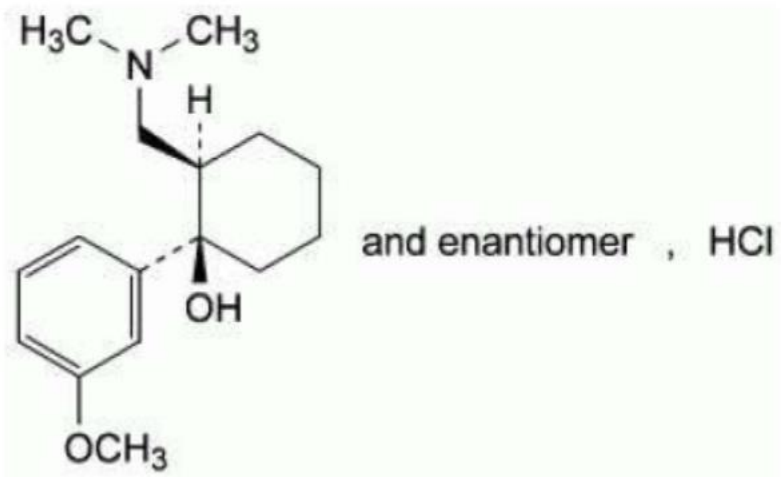
II.2 ACTIVE SUBSTANCE

rINN: tramadol hydrochloride

Chemical Name: (1RS,2RS)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride or (1RS,2RS)- 2-(dimethylaminomethyl)-1-(m- methoxyphenyl)cyclohexanol

Molecular Formula: $C_{16}H_{26}ClNO_2$

Chemical Structure:



Molecular Weight: 299.8 g/mol

Appearance: White or almost white, crystalline powder

Solubility: Freely soluble in water and in methanol, 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMOs).

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

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with storage conditions below 25ºC, is acceptable. This medicine should be used immediately after opening the ampoule/dilution as a single use only.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of tramadol hydrochloride 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.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of tramadol hydrochloride is well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics

No new pharmacokinetic data were submitted for this application, and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application, and none were required. The safety profile for this product is considered to be the same as Zydol® 50mg/ml solution for injection.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tramadol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**