Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Trazodone hydrochloride 50 mg/5ml oral solution

(trazodone hydrochloride)

PL 13606/0238

Strides Pharma UK Ltd.

LAY SUMMARY

Trazodone hydrochloride 50 mg/5ml oral solution (trazodone hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Trazodone hydrochloride 50 mg/5ml oral solution. 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 Trazodone in this lay summary for ease of reading.

For practical information about using Trazodone, patients should read the package leaflet or contact their doctor or pharmacist.

What is Trazodone and what is it used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Trazodone hydrochloride 50mg/5ml Oral solution.

Trazodone can be used to treat anxiety and depression.

How does Trazodone work?
Trazodone contains the active ingredient trazodone hydrochloride which belongs to a group of medicines called antidepressants. It works by affecting the chemicals in the brain that may be unbalanced in people with depression.

How is Trazodone used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (via the mouth). Take with or after food. This can help lower the chances of getting side effects.

If the patient has been told to take trazodone only once each day, then they should take it before going to bed. If the patient feels the effect of their medicine is too weak or strong, they should not change the dose themselves, but ask their doctor.

The recommended doses are:
To treat depression
Adults: the starting dose is 150 mg (15 ml) each day. The patient's doctor may increase the dose to 300 mg (30 ml) each day, depending on their condition.
For adults in hospital, the dose may be as high as 600 mg (60 ml) each day.

To treat anxiety
Adults: the starting dose is 75 mg (7.5 ml) each day. The patient's doctor may increase the dose to 300mg (30ml) each day.

Use in children
Children and adolescents under 18 years should not take Trazodone.

Use in elderly
Older people or those who are frail will usually be given a starting dose of 100 mg (10 ml) each day.
Doses of more than 300 mg (30 ml) will not normally be given.

For further information on how Trazodone is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Trazodone have been shown in studies?
Trazodone is a generic medicine that fulfils criteria meaning that no additional studies are required. Trazodone 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 Trazodone?
Because Trazodone is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Trazodone approved?
It was concluded that, in accordance with EU requirements, Trazodone has been shown to 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 Trazodone?
A Risk Management Plan (RMP) has been developed to ensure that Trazodone is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Trazodone
A Marketing Authorisation for Trazodone was granted in the UK on 17 December 2020.

The full PAR for Trazodone follows this summary.

This summary was last updated in January 2021.

TABLE OF CONTENTS

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 Trazodone hydrochloride 50 mg/5ml oral solution (PL 13606/0238) could be approved.

The product is approved for the following indications:
Relief of symptoms in all types of depression including depression accompanied by anxiety. Symptoms of depression likely to respond in the first week of treatment include depressed mood, insomnia, anxiety, somatic symptoms and hypochondriasis.

Trazodone hydrochloride is a triazolopyridine derivative which differs chemically from other currently available antidepressants. Although trazodone bears some resemblance to the benzodiazepines, phenothiazines and tricyclic antidepressants, its pharmacological profile differs from each of these classes of drugs. The basic idea for the development of trazodone was the hypothesis that depression involves an imbalance of the mechanism responsible for the emotional integration of unpleasant experiences. Consequently, new animal models of depression consisting of responses to unpleasant or noxious stimuli, instead of the current tests related to the aminergic theory of depression, were used in studying the drug. Trazodone inhibits serotonin uptake into rat brain synaptosomes and by rat platelets at relatively high concentrations and inhibits brain uptake of noradrenaline *in vitro* only at very high concentrations. It possesses antiserotonin-adrenergic blocking and analgesic effects. The anticholinergic activity of trazodone is less than that of the tricyclic antidepressants in animal studies and this has been confirmed in therapeutic trials in depressed patients.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine of a suitable originator medicinal product, Trazodone hydrochloride 50mg/5ml Oral solution that has been licensed within the EU 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 based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

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.

Advice was sought from the Commission of Human Medicines (CHM) on 21 June 2019, who on the evidence before them had reason to think that on grounds relating to quality, safety and efficacy, they might be unable to advise the grant of this application. In response to the CHM advice, the applicant provided further data to address these concerns. The information provided was adequate and the issues were resolved and a Marketing Authorisation was granted for this product on 17 December 2020.

II QUALITY ASPECTS

II.1 Introduction

Each 5ml of oral solution contains 50mg of trazodone hydrochloride.

In addition to trazodone hydrochloride, this product also contains the excipients glycerol (E 422), sorbitol solution 70% non-crystallising (E 420), benzoic acid (E 210), saccharin sodium, orange flavour 501071, sodium hydroxide (for pH adjustment) and purified water.

The finished product is packaged in 125 ml Type III amber coloured glass bottles, sealed with a child resistant closure and cap with a tamper evident ring, containing 120 ml of solution.

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

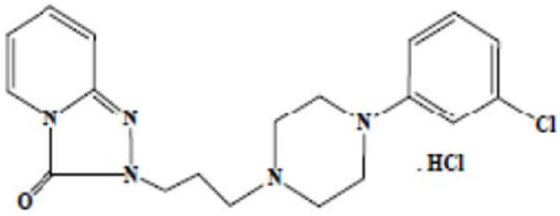
II.2 ACTIVE SUBSTANCE

rINN: Trazodone Hydrochloride

Chemical Name: 2,3-[4-(3-chloro)phenylpiperazin-1-yl]propyl-1,2,4- triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride

Molecular Formula: $C_{19}H_{22}ClN_5O \cdot HCl$

Chemical Structure:



Molecular Weight: 408.37

Appearance: A white or almost white crystalline powder

Solubility: Soluble in water; sparingly soluble in ethanol (96%); practically insoluble in ether..

Trazodone hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been 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 have been 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 (GMO).

Manufacture of the product

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

A satisfactory batch formula has 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 Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. 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 12 months for the unopened bottle, with the storage conditions ‘Store below 25°C. Store in the original bottle to protect from light’, is acceptable. The in-use shelf life of the product is 30 days after first opening the bottle.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of trazodone 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
Suitable justification has been 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 is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety trazodone hydrochloride are 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 have been submitted for this application and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been 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 Trazodone hydrochloride 50mg/5ml Oral solution.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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 is recommended for this application.

V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Trazodone Hydrochloride 50mg/100mg Capsule, Hard (PL 13606/0240 - 0241; Strides Pharma UK Ltd). The bridging report submitted by the applicant is acceptable.

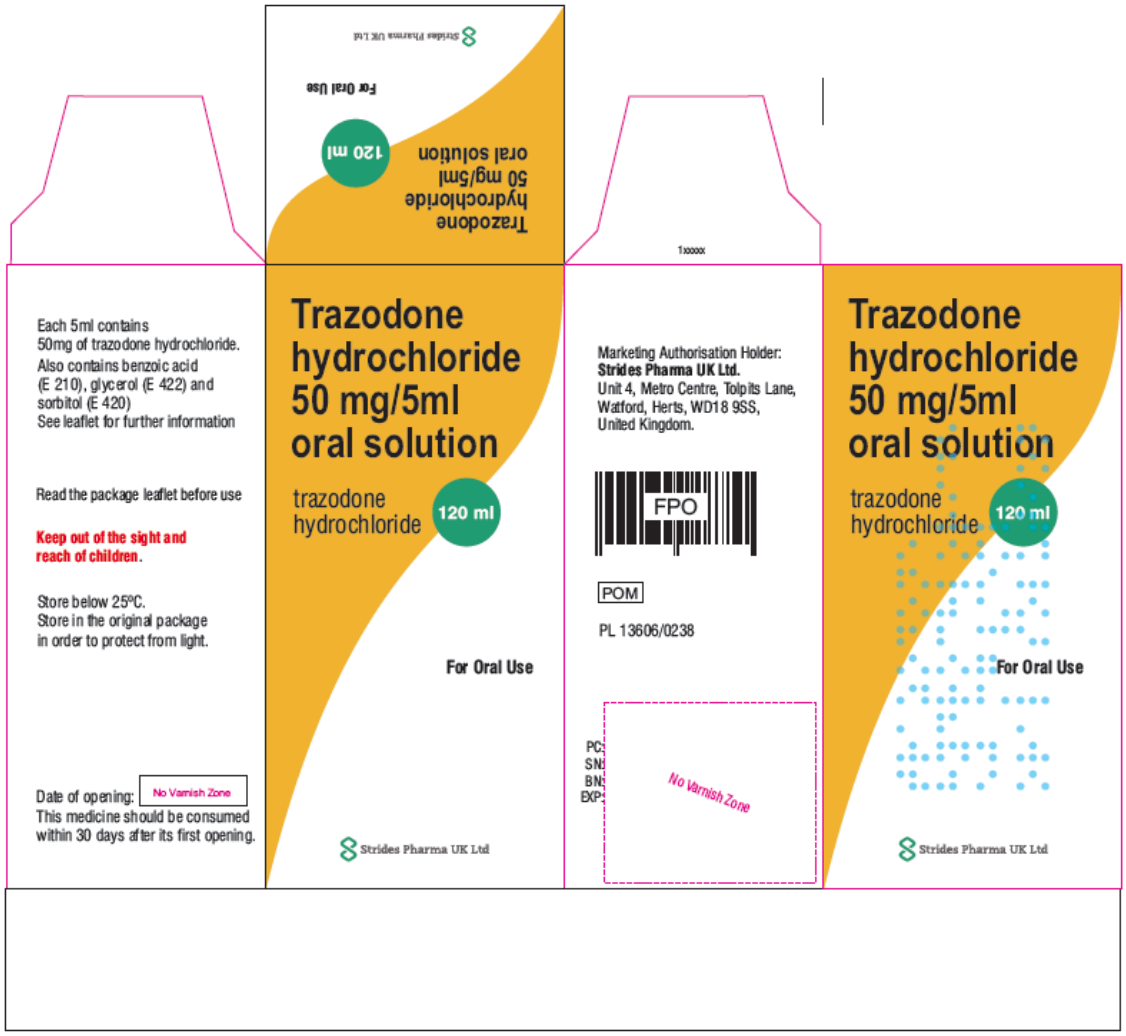
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

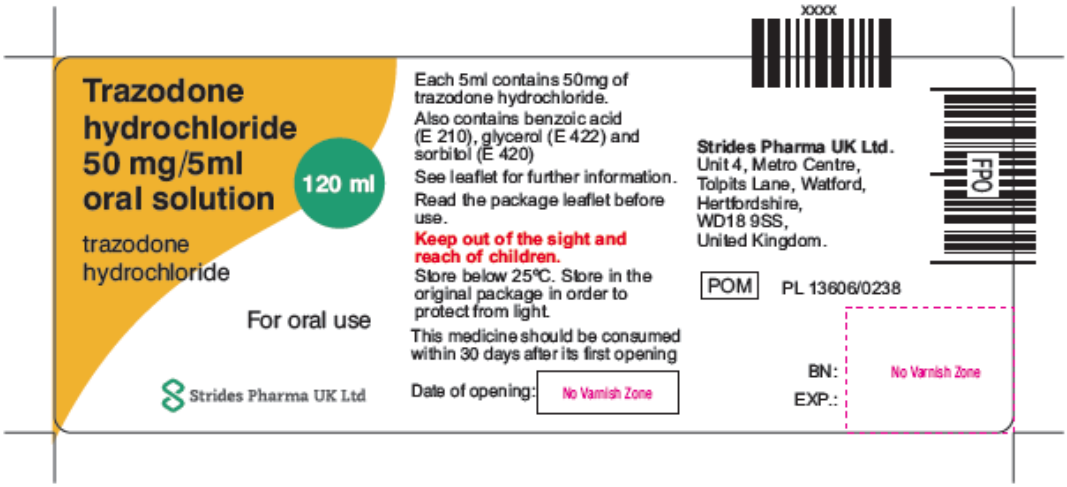
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with trazodone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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 Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.





Dimension: 115 x 45 mm

TABLE OF CONTENT OF THE PAR UPDATE

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**