Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

Decentralised Procedure

Trazodone Hydrochloride 50mg capsules
Trazodone Hydrochloride 100mg capsules

(trazodone hydrochloride)

PRODUCT LICENCE NUMBERS:
PL 00142/0876-0877

EUROPEAN PROCEDURE NUMBERS:
UK/H/6575/001-002/DC

Accord-UK Limited

LAY SUMMARY

Trazodone hydrochloride 50mg Capsules
Trazodone hydrochloride 100mg Capsules

(trazodone hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Trazodone hydrochloride 50mg and 100mg Capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Trazodone hydrochloride capsules in this lay summary, for ease of reading.

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

What are Trazodone hydrochloride capsules and what are they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Molipaxin 50mg and 100mg capsules/Trazodone Hydrochloride 50mg and 100mg capsules.

Trazodone hydrochloride capsules can be used in patients to treat anxiety and depression.

How do Trazodone hydrochloride capsules work?
Trazodone hydrochloride capsules contain a medicine called trazodone hydrochloride, which belongs to a group of medicines called antidepressants,

How are Trazodone hydrochloride capsules used?
The pharmaceutical form of these medicines is capsules and the route of administration is oral (taken by mouth).

Taking these medicines
- The capsules should be swallowed whole with a drink of water.
- The patient should take these medicines with or after food. This can help lower the chances of side effects.
- If the patient has been told to take Trazodone hydrochloride capsules only once each day, then they should take the capsules before going to bed.
- If the patient feels that the effect of their medicine is too weak or strong, they should not change the dose themselves, but should ask their doctor.

How much to take
Adults:
Depression
- Adults usually start by taking 150mg each day
- The patient's doctor may increase the dose to 300mg each day depending on the patient's condition
- For adults in hospital the dose may be as high as 600mg each day.

Anxiety
- Adults usually start by taking 75mg each day
- the patient's doctor may increase the dose to 300mg each day.

Elderly
Older people or those who are frail will usually be given a starting dose of 100mg each day.

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

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

These medicines can only be obtained with a prescription.

The patient should always take these medicines 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 hydrochloride capsules have been shown in studies?
Because Trazodone hydrochloride capsules are generic medicines, studies in healthy volunteers have been limited to tests to determine that these medicines are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Trazodone hydrochloride capsules?
Because Trazodone hydrochloride capsules are generic medicines and are bioequivalent to the reference medicines, the benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the SmPCs available on the MHRA website.

Why were Trazodone hydrochloride capsules approved?
It was concluded that, in accordance with EU requirements, Trazodone hydrochloride capsules have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Trazodone hydrochloride capsules?
A Risk Management Plan (RMP) has been developed to ensure that Trazodone hydrochloride capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPCs 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 hydrochloride capsules
Marketing Authorisations for Trazodone hydrochloride capsules were granted in the UK on 29 October 2020.

The full PAR for Trazodone hydrochloride capsules follows this summary.

This summary was last updated in December 2020.

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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 applications for Trazodone Hydrochloride 50mg and 100mg Capsules (PL 00142/0876-0877; UK/H/6575/001-002/DC) could be approved.

The products are approved for the following indications:

- Anxiety, depression, mixed anxiety and depression.

The Reference Member State (RMS) for these procedures was the UK; the applicant withdrew the sole Concerned Member State (CMS) during the procedure.

The active substance, trazodone hydrochloride, is a potent antidepressant. It also has anxiety reducing activity. Trazodone hydrochloride is a triazolopyridine derivative chemically unrelated to known tricyclic, tetracyclic and other antidepressant agents. It has negligible effect on noradrenaline re-uptake mechanisms. Whilst the mode of action of trazodone hydrochloride is not known precisely, its antidepressant activity may concern noradrenergic potentiation by mechanisms other than uptake blockade. A central antiserotonin effect may account for the drug's anxiety reducing properties.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Molipaxin 50mg and 100mg Capsules/Trazodone Hydrochloride 50mg and 100mg capsules that have 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 applications are based on being generic medicinal products of reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been in clinical use for over 10 years. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

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

The UK considered that the applications could be approved at the end of procedure (Day 210) on 22 September 2020. After a subsequent national phase, Marketing Authorisations were granted in the UK on 29 October 2020.

II QUALITY ASPECTS

II.1 Introduction

These products contains 50 mg or 100 mg of trazodone hydrochloride in each capsule.

In addition to trazodone hydrochloride, these products also contain the excipients lactose monohydrate, magnesium stearate, gelatin, titanium dioxide (E171), quinoline yellow (E104), Ponceau 4R red (E124), Patent blue V (E131; 50 mg capsule strength only), black iron oxide E172, shellac, propylene glycol, strong ammonia solution (pH adjustment) and potassium hydroxide (pH adjustment).

The finished products are packaged in polyvinylchloride/polyvinylidine chloride/aluminium blisters, in pack sizes of 84 (50 mg strength only) and 56 (100 mg strength only) capsules.

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.

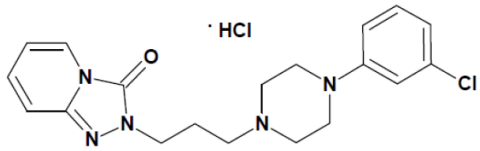
II.2 ACTIVE SUBSTANCE

rINN: Trazodone hydrochloride

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

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

Chemical Structure:



Molecular Weight: 408.3 g/mol

Appearance: A white or almost white, crystalline powder

Solubility: Trazodone hydrochloride is 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 PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and 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.

With the exception of lactose monohydrate and gelatin, no excipients of animal or human origin are used in the final products. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the capsules is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

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

Satisfactory batch formulae have been provided for the manufacture of the products, 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 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 18 months for the 50 mg strength product and 2 years for the 100 mg strength product, with the storage conditions ‘Do not store above 25°C’, is acceptable.

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 Marketing Authorisations 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of trazodone hydrochloride are well known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study:

STUDY
This study was an open-label, randomised, single-dose, two-sequence, two-treatment, two-period, oral, cross-over bioequivalence study comparing the test product Trazodone Hydrochloride capsules 100 mg versus the reference product Molipaxin capsules 100 mg in healthy, adult, human, male subjects under fed conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 100 mg tablet) of either treatment with approximately 240 ml of water 30 minutes after a high fat, high calorie breakfast. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of nine days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Tablet 1: Relative Bioavailability results for trazodone

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	1313.769	1299.838	101.1	94.34 - 108.29	22.2	100.0
$lnAUC_{0-t}$	17280.117	16733.056	103.3	98.69 - 108.06	14.5	100.0
$lnAUC_{0-\infty}$	17975.263	17365.935	103.5	98.88 - 108.35	14.7	100.0

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 100mg product strength can be extrapolated to the other strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

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 Marketing Authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) 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. The results show that the PIL 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

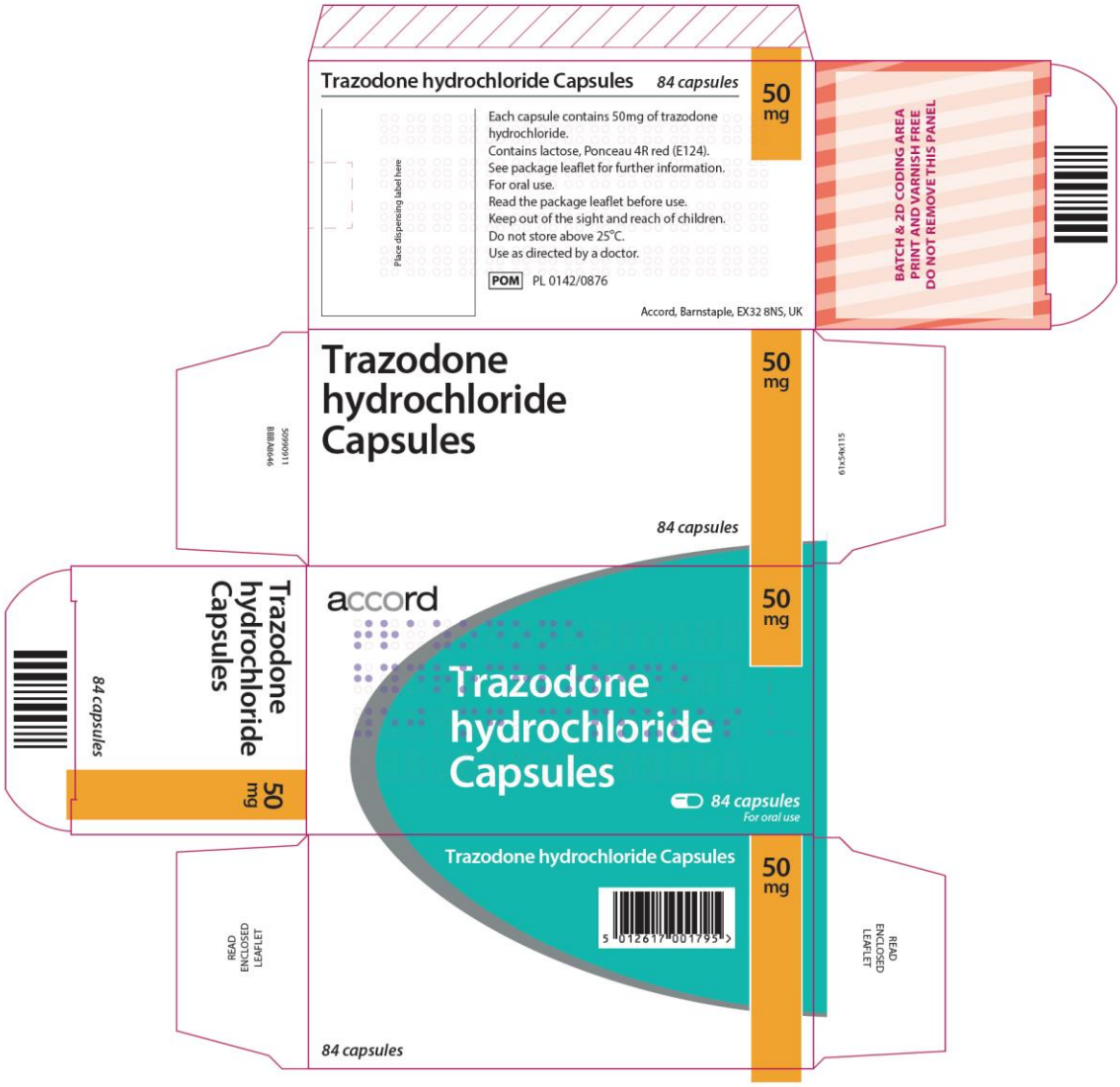
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with trazodone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

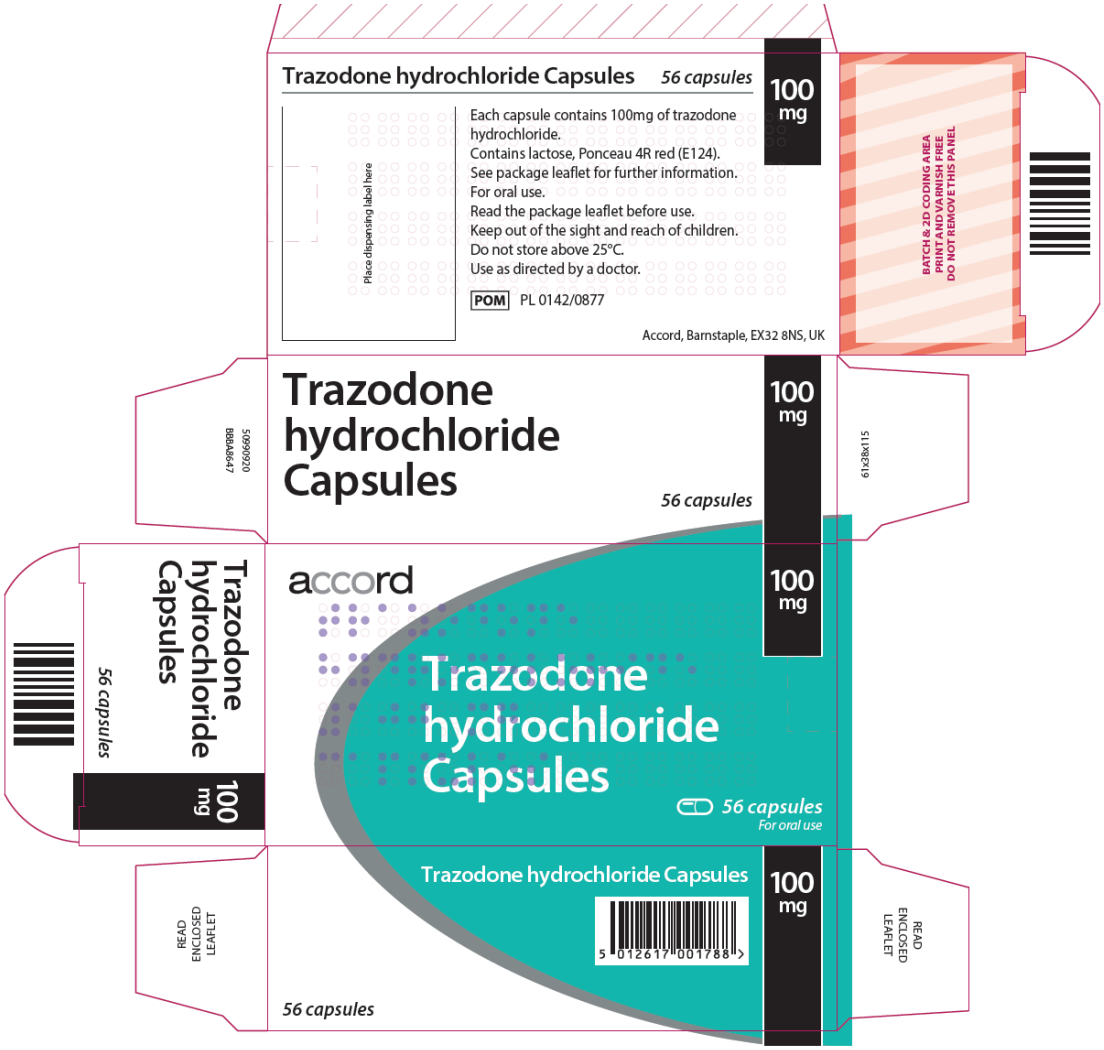
Representative copies of the labels at the time of UK licensing are provided below.

Trazodone hydrochloride 50mg Capsules




12mm
pharmacode
height
25mm
maximum
pharmacode
length
accord
Trazodone hydrochloride
50 mg Capsules
50990946 BBBA8643
116mm

Trazodone hydrochloride 100mg capsules




12mm
pharmacode
height
25mm
maximum
pharmacode
length
accord
Trazodone hydrochloride
100 mg Capsules
50990938 BBBA8644
116mm

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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**