Public Assessment Report

UKPAR

Trazodone Hydrochloride 150mg Film-coated Tablets

(Trazodone hydrochloride)

UK Licence Number: PL 43461/0033

Flamingo Pharma (UK) Limited
LAY SUMMARY

Trazodone Hydrochloride 150mg Film-coated Tablets

This is a summary of the Public Assessment Report (PAR) for Trazodone Hydrochloride 150mg Film-coated Tablets (PL 43461/0033). It explains how Trazodone Hydrochloride 150mg Film-coated Tablets 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 Trazodone Hydrochloride 150mg Film-coated Tablets.

The product will be referred to as ‘Trazodone Tablets’ throughout the remainder of this public assessment report (PAR).

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

What are Trazodone Tablets and what are they used for?
Trazodone Tablets are a ‘generic medicine’. This means that Trazodone Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Molipaxin 150mg Tablets/Trazodone hydrochloride 150mg Tablets (Winthrop Pharmaceuticals UK Limited). The reference product will be referred to as ‘Molipaxin 150mg Tablets’ throughout the remainder of this public assessment report (PAR).

Trazodone Tablets can be used to treat depression and anxiety.

How do Trazodone Tablets work?
This medicine contains the active substance called trazodone hydrochloride. This belongs to a group of medicines called antidepressants. It affects chemicals in the brain that may be unbalanced in people with depression.

How are Trazodone Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth). The tablets should be swallowed whole with a drink of water.

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

Taking this medicine
• The patient can take this medicine with or after food. This will help lower the chances of side effects.
• If the patient has been told to take this medicine only once each day then they should take it before going to bed
• If the patient feels the effect of this medicine is too weak or strong, the patient should not change the dose themselves but ask their doctor.

The recommended dose is:

Adults:
Depression
• Adults usually start by taking 150mg tablets each day
• The patient’s doctor may increase the dose to 300mg each day depending on their 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.

**Children and adolescents**
Children and adolescents under 18 years should not take Trazodone Tablets.

Please note that for doses which cannot be achieved using this product the doctor will prescribe and pharmacist supply trazodone tablets from other manufacturers.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Trazodone Tablets are 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.

**What benefits of Trazodone Tablets have been shown in studies?**
Because Trazodone Tablets are a generic medicine, studies in patients have been limited to tests to determine that Trazodone Tablets are bioequivalent to the reference medicine Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited).

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 Tablets?**
Because Trazodone Tablets are a generic medicine and they are bioequivalent to the reference medicine Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited), their benefits and possible side effect are taken as being the same as those of the reference medicine.

For a full list of all the side effects reported with Trazodone Tablets see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

**Why are Trazodone Tablets approved?**
It was concluded that, in accordance with EU requirements, Trazodone Tablets have been shown to have comparable quality and to be bioequivalent to Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited). Their benefits are greater than the risks and it was recommended that Trazodone Tablets can be approved for use.
What measures are being taken to ensure the safe and effective use of Trazodone Tablets?
A risk management plan (RMP) has been developed to ensure that Trazodone Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Trazodone Tablets 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/reviewed continuously.

Other information about Trazodone Tablets
A marketing authorisation was granted in the UK on 26 June 2018.

The full PAR for Trazodone Tablets follows this summary.

For more information about treatment with Trazodone Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.
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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 Flamingo Pharma (UK) Limited, a marketing authorisation for the medicinal product Trazodone Tablets (PL 43461/0033). This product is a prescription-only medicine (POM).

Trazodone Tablets are indicated for the relief of symptoms in all types of depression including depression accompanied by anxiety.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference product for this application is Molipaxin 150 mg Tablets/ Trazodone Hydrochloride 150mg Tablets which was first authorised in the UK to the marketing authorisation holder (MAH) Roussel Laboratories Limited (PL 00109/0133) on 08 May 1986. Following a subsequent change of ownership procedure, to Aventis Pharma Limited, UK (PL 04425/0606) on 30 January 2010, a marketing authorisation was granted to the current marketing authorisation holder (MAH) Winthrop Pharmaceuticals UK Limited (PL 17780/0616) on 05 November 2012.

Trazodone 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. It possesses anti-serotonin-adrenergic blocking and analgesic effects.

Whilst the mode of action of trazodone 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.

No new non-clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years.

One bioequivalence study (single dose, two-period crossover in healthy volunteers) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

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 manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
II QUALITY ASPECTS

II.1 Introduction

The finished product is formulated as a film-coated tablet containing 150 mg trazodone hydrochloride per tablet. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, calcium hydrogen phosphate dihydrate (E341), sodium starch glycolate Type A, povidone (PVP-K30), purified water, colloidal anhydrous silica and magnesium stearate. The film coating Instacoat Sol IC-S-5585 peach, contains hypromellose, polyethylene glycol, talc, titanium dioxide (E171), iron oxide red (E172) and iron oxide yellow (E172).

The product is packaged in aluminium-polyvinyl chloride/ polyvinylidene chloride white opaque film (Alu- PVC/PVDC) blister packs containing 20, 28, 30, 56, 84 and 100 tablets. The product is also available in white opaque high-density polyethylene (HDPE) bottles which have a white polypropylene child resistant cap containing packs of 100, 250 and 500 tablets. 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 European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Trazodone hydrochloride

Chemical name:
2,3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride
2-[3-{4-(3-Chlorophenyl)-1-piperazinyl}propyl]-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one monohydrochloride
2-[3-{4-(m-Chlorophenyl)-1-piperazinyl}propyl]-s-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride

Structure:

![Trazodone Hydrochloride Structure](image)

Molecular formula: C_{19}H_{23}Cl_{2}N_{5}O
Molecular weight: 408.3 g/mol
Appearance: White or almost white, crystalline powder
Solubility: Soluble in water and methanol, sparingly soluble in chloroform, very slightly soluble in acetone

The drug substance is the subject of an active substance master file (ASMF).

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 specification tests 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 specifications. Batch analyses data are provided that comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to develop a safe, efficacious, film-coated tablet containing 150mg trazodone hydrochloride per tablet that is a generic version of the reference product Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited). The development of the product has been described, the choice of excipients is justified, and their functions explained.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and reference products.

Instacoat Sol IC-S-5585 peach conforms to its in-house specifications, whilst its individual constituents are in compliance with the current EC directive requirements of Commission Regulation (EU) No 2009/35/EC. Purified water complies with the British Pharmacopeia monographs. All other excipients comply with their respective European Pharmacopeia monographs.

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

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

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

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial batch sizes have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unused product for both presentation types (bottles and blisters) with an in-
use shelf-life of 100 days once the HDPE bottles have been opened. This medicinal product does not require any special storage conditions.

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

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 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.

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.

Impurities

A risk assessment on Elemental Impurities (EI) for the drug product was performed in accordance with the Guideline on Elemental Impurities; ICH Q3D. None of the EI as defined by Q3D is likely to be present or prone to reach a level exceeding 30% of the Permitted Daily Exposure (PDE) set for each element. The EI assessment is accepted.

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 Trazodone Tablets are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

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

IV CLINICAL ASPECTS

IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of trazodone hydrochloride are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of trazodone hydrochloride.
Based on the results of the bioequivalence study, Trazodone Tablets can be considered bioequivalent to the reference product, Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited).

IV.2 Pharmacokinetics
In support of this application, the following bioequivalence study was submitted:

STUDY
An open labelled, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of the test product Trazodone hydrochloride 150 mg tablets (Flamingo pharma (UK) Limited) versus the reference product Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited) in healthy human, adult subjects under fed conditions.

A single dose of 150mg of the test or reference formulation was administered orally with 240 ml of water 30 minutes after receiving a high calorific high fat breakfast in each study period as per the randomisation scheme. A single oral dose of the test or reference product was administered on two occasions separated by a washout period of 7 days between treatments. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after the drug administration.

The main pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric LSM (Test)</th>
<th>Geometric LSM (Reference)</th>
<th>Power (%)</th>
<th>Intra-Subject Variability (CV %)</th>
<th>Ratio (%)</th>
<th>90% Confidence Intervals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt;</td>
<td>25543.82</td>
<td>25340.17</td>
<td>≈99.99</td>
<td>8.23</td>
<td>100.80</td>
<td>97.40 to 104.32</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1922.61</td>
<td>2041.41</td>
<td>99.65</td>
<td>18.55</td>
<td>94.18</td>
<td>87.22 to 101.70</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for trazodone lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the test product Trazodone Tablets (Flamingo Pharma (UK) Limited) are bioequivalent to the reference product Molipaxin 150mg Tablets (Winthrop Pharmaceuticals UK Limited).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
With the exception of the safety data collected during the bioequivalence study, no new data on safety have been submitted and none are required for applications of this type. No new or unexpected adverse events were observed in the bioequivalence study.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.
There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL), which is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the competent authority;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

**IV.7 Discussion on the clinical aspects**
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

**V User consultation**
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to called Molipaxin 150mg Tablets/Trazodone hydrochloride 150mg Tablets (Winthrop Pharmaceuticals UK Limited). The bridging report submitted by the applicant has been found 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 results of the clinical study confirm that the product is bioequivalent to the reference product and its benefit-risk 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 MAH has submitted the following approved labelling for this medicine which is presented below:
Annex 1

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, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>