Public Assessment Report

Ranitidine 150mg/10ml Oral Solution
(Ranitidine hydrochloride)

UK Licence Number: PL 39307/0081

Syri Limited t/a Thame Laboratories
LAY SUMMARY
Ranitidine 150mg/10ml Oral Solution
(Ranitidine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Ranitidine 150mg/10ml Oral Solution (PL 39307/0081). For ease of reading, this medicinal product will be referred to as Ranitidine Oral Solution.

This summary explains how Ranitidine Oral Solution 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 Ranitidine Oral Solution.

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

What is Ranitidine Oral Solution and what is it used for?
Ranitidine Oral Solution is a ‘generic medicine’. This means that Ranitidine Oral Solution is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Zantac Syrup (Glaxo Wellcome UK Ltd.).

How does Ranitidine Oral Solution work?
Ranitidine Oral Solution contains the active ingredient ranitidine hydrochloride. Ranitidine hydrochloride belongs to a group of medicines called H2-receptor antagonists. It lowers the amount of acid in the stomach.

How is Ranitidine Oral Solution used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth).

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

This medicinal product can only be obtained with a prescription.

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

What benefits of Ranitidine Oral Solution have been shown in studies?
No additional studies were needed as Ranitidine Oral Solution is a generic medicine that contains the same active substance in the same concentration as the reference medicine, Zantac Syrup. For this reason, Ranitidine Oral Solution is expected to be bioequivalent with the reference medicine. Two medicines are considered bioequivalent when they produce the same levels of active substance in the body.

What are the possible side effects of Ranitidine Oral Solution?
Like all medicines, Ranitidine Oral Solution can cause side effects, although not everybody gets them.

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 Ranitidine Oral Solution approved?
It was concluded that, in accordance with EU requirements, Ranitidine Oral Solution has been shown to have comparable quality and is considered bioequivalent to Zantac Syrup. Therefore, the MHRA decided that, for Ranitidine Oral Solution, 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 Ranitidine Oral Solution?
A Risk Management Plan has been developed to ensure that Ranitidine Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Ranitidine Oral Solution, 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 Ranitidine Oral Solution
A Marketing Authorisation was granted in the UK on 11 May 2018.

The full PAR for Ranitidine Oral Solution follows this summary.
This summary was last updated in July 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 Syri Limited trading as Thame Laboratories a Marketing Authorisation for the medicinal product Ranitidine 150mg/10ml Oral Solution (PL 39307/0081) on 11 May 2018. The product is a prescription only medicine (POM), indicated in

- **Adults** for the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents. In addition, Ranitidine oral solution is indicated for the prevention of NSAID associated duodenal ulcers. Ranitidine oral solution is also indicated for the treatment of post-operative ulcer, Zollinger-Ellison Syndrome and oesophageal reflux disease including long term management of healed oesophagitis. Other patients with chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but is not associated with the preceding conditions may benefit from ranitidine treatment. Ranitidine oral solution is indicated for the following conditions where reduction of gastric secretion and acid output is desirable; the prophylaxis of gastro-intestinal haemorrhage from stress ulceration in seriously ill patients, the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers and before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour.

- **Children (3 to 18 years)** for short term treatment of peptic ulcer. Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Zantac Syrup, which was granted a Marketing Authorisation to Glaxo Wellcome UK Ltd. in November 1993 following a national procedure (PL 10949/0108).

Ranitidine is a specific, rapidly acting H2-antagonist which inhibits basal and stimulated secretion of gastric acid.

No new clinical studies or non-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.

Ranitidine 150mg/10ml Oral Solution is an oral solution at the time of administration and in line with the CHMP ‘Guideline on the Investigation of Bioequivalence ’ (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a bioequivalence study was not necessary to support this application.

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

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

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 Ranitidine 150mg/10ml Oral Solution outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction

The finished product is presented as an oral solution. Each 10 ml of oral solution contains 150 mg of ranitidine as ranitidine hydrochloride. Other excipients are non-crystallising liquid sorbitol (E420), saccharin sodium (E954), potassium dihydrogen phosphate (E340), anhydrous disodium phosphate, (E339), ethyl parahydroxybenzoate (E214), butyl parahydroxybenzoate, hypromellose (E464), garden mint flavour (contains propylene glycol (E1520)), and purified water

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the garden mint flavour which is controlled to an in-house specification. Satisfactory Certificates of Analysis have been provided for these excipients.

The finished product is packaged in 100 and 300 ml Type III amber glass bottles each fitted with a tamper evident child-resistant white plastic cap with polypropylene inner, polyethylene outer and expanded polyethylene (EPE) liner. Each bottle is provided in an outer cardboard carton along with a 10ml dispensing oral syringe with 0.25 ml graduations and a bottle adapter.

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:

Chemical name(s): N-[2-[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]thio]ethyl]-N'-methyl-2-nitroethene-1,1-diamine, hydrochloride

Or


Structure:

![Structure diagram]

Molecular formula: \( C_{13}H_{22}N_{4}O_{5}S \) HCl
Molecular weight: 350.87
Appearance: White to pale yellow crystalline powder.
Solubility: Freely soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, and very slightly soluble in methylene chloride

Ranitidine hydrochloride is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, ranitidine hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a generic oral solution containing ranitidine as the active moiety, that could be considered generic medicinal products of the currently licensed product, Zantac Syrup (Glaxo Wellcome UK Ltd.)

None of the excipients are sourced from animal or human origin. These products do not contain or consist of genetically modified organisms (GMO).

A satisfactory account of the pharmaceutical development has been provided.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three commercial scale batches of finished product. The results are satisfactory.

Finished Product Specification
The proposed finished product specification 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 results from these studies support a shelf-life of 18 months for the unopened product with storage conditions ‘Do not store above 25°C’ and ‘Keep the container in the outer carton in order to protect from light’. Once the bottle is opened the product must be used within 90 days.

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
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of ranitidine hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

III.2 Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Ranitidine 150mg/10ml Oral Solution is 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
It is recommended that a Marketing Authorisation is granted for Ranitidine 150mg/10ml Oral Solution, from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
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 ranitidine hydrochloride. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
A bioequivalence study was not submitted as the product meets the criteria specified in the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as the reference product.

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

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical safety
No new data on safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system
The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ranitidine 150mg/10ml Oral Solution.
A summary of safety concerns, as approved in the RMP, is listed below:

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<th>Summary of safety concerns</th>
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<td><strong>Important identified risks</strong></td>
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<td>- Hypersensitivity to the active substance or to any of the excipients</td>
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<td>- Use in patients with gastric carcinoma</td>
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<td>- Use in patients with renal impairment</td>
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<td>- Concomitant use with coumarin anticoagulants (e.g. warfarin)</td>
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<td>- Community acquired pneumonia</td>
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<td>- Concomitant use with drugs eliminated by renal tubular secretion (e.g. procaainamide and N-acetylprocaainamide)</td>
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<td>- Use in patients with acute porphyria</td>
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<td>- Mental confusion, depression and hallucinations in particular in severely ill and elderly patients</td>
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| **Important potential risks** |
| - Use in pregnancy and lactation |

| **Missing information** |
| - Effects on fertility |
| - Long term safety in children under 18 years |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**

It is recommended that a Marketing Authorisation is granted for Ranitidine 150mg/10ml Oral Solution.

**V User consultation**

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

**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. The data supplied support the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with ranitidine hydrochloride is considered to have demonstrated the therapeutic value of the compound. 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 Ranitidine 150mg/10ml Oral Solution is presented below:
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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