Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Ranitidine 150mg/10ml Oral Solution

UK/H/0913/001/DC
UK licence no: PL 20046/0046

Focus Pharmaceuticals Ltd

LAY SUMMARY

Ranitidine 150mg/10ml Oral Solution
(ranitidine hydrochloride, oral solution, 150mg/10ml)

This is a summary of the Public Assessment Report (PAR) for Ranitidine 150mg/10ml Oral Solution (PL 20046/0046; UK/H/0913/001/DC). It explains how Ranitidine 150mg/10ml Oral Solution 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 Ranitidine 150mg/10ml Oral Solution.

For practical information about using Ranitidine 150mg/10ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ranitidine 150mg/10ml Oral Solution and what is it used for?
Ranitidine 150mg/10ml Oral Solution is a 'generic medicine'. This means that Ranitidine 150mg/10ml Oral Solution is similar to a 'reference medicine' already authorised in the European Union (EU) called Zantac Syrup (Glaxo Wellcome UK Ltd, trading as Glaxo SmithKline UK).

Ranitidine 150mg/10ml Oral Solution is used:
For adults including the elderly, Ranitidine 150mg/10ml Oral Solution is used to:

- Heal and stop ulcers in the stomach or the part of the gut it empties into (the duodenum);
- Help clear up infection in the stomach, when taken with antibiotic medicines (medicines taken to treat germs) stop stomach ulcers when they are a side effect of some medicines; to stop ulcers from bleeding;
- Improve problems caused by acid in the food pipe (oesophagus) or too much acid in the stomach. Both of these can cause pain or discomfort sometimes known as 'indigestion', 'dyspepsia' or 'heartburn';
- Stop acid coming up from the stomach while under anaesthetic during an operation.

For children (3 to 18 years) Ranitidine 150mg/10ml Oral Solution is used to:

- Heal ulcers in the stomach, of the part of the gut it empties into (the duodenum) heal and stop problems caused by acid in the food pipe (oesophagus) or too much acid in the stomach. Both of these can cause pain or discomfort sometimes known as 'indigestion', 'dyspepsia' or 'heartburn'.

How does Ranitidine 150mg/10ml Oral Solution work?
This medicine contains the active ingredient, ranitidine, which belongs to a group of medicines called acid antagonists or H_2 antagonists. They lower the amount of acid produced in your stomach.

How is Ranitidine 150mg/10ml 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 always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose depends on the patient's age and the reason why this medicine has been prescribed. Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

Ranitidine 150mg/10ml Oral Solution is for oral use only.

This medicine can only be obtained with a prescription.

What benefits Ranitidine 150mg/10ml Oral Solution have been shown in studies?
No additional studies were needed as Ranitidine 150mg/10ml Oral Solution is a generic medicine that is taken orally, as a solution, and contains the same active substance, in the same concentration, as the reference medicine, Zantac Syrup (Glaxo Wellcome UK Ltd, trading as Glaxo SmithKline UK).

What are the possible side effects of Ranitidine 150mg/10ml Oral Solution?
Because Ranitidine 150mg/10ml Oral Solution is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

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

For the full list of all side effects reported with Ranitidine 150mg/10ml Oral Solution, see section 4 of the package leaflet available on the MHRA website.

Why was Ranitidine 150mg/10ml Oral Solution approved?
It was concluded that, in accordance with EU requirements, Ranitidine 150mg/10ml Oral Solution has been shown to have comparable quality and to be comparable to Zantac Syrup (Glaxo Wellcome UK Ltd, trading as Glaxo SmithKline UK). Therefore, the MHRA decided that, as for Zantac Syrup (Glaxo Wellcome UK Ltd, trading as Glaxo SmithKline UK), the benefits are greater than their risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ranitidine 150mg/10ml Oral Solution?
Safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Ranitidine 150mg/10ml 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 150mg/10ml Oral Solution
Ireland and the UK agreed to grant a Marketing Authorisation for Ranitidine 150mg/10ml Oral Solution on 15 March 2007. A Marketing Authorisation was granted in the UK on 20 June 2007.

The full PAR for Ranitidine 150mg/10ml Oral Solution follows this summary.

For more information about treatment with Ranitidine 150mg/10ml Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2015.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Ranitidine 150mg/10ml Oral Solution (PL 20046/0046) on 20 June 2007. The product is a prescription-only medicine.

This application was made under Article 10.1 of 2001/83 EC, as amended, claiming that Ranitidine 150mg/10ml Oral Solution is a generic product of Zantac Syrup (Glaxo Wellcome UK Ltd, trading as Glaxo SmithKline UK), which was granted a licence in November 1993.

The product contains the active ingredient ranitidine.

In adults Ranitidine 150mg/10ml Oral Solution is indicated for:

- the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
- the prevention of NSAID associated duodenal ulcers.
- 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.
- 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.

In children (3 to 18 years) Ranitidine 150mg/10ml Oral Solution is indicated for:

- Short term treatment of peptic ulcer
- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

See section 4.4 of the SmPC 'Special warnings and precautions for use'.

Ranitidine is an H_2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume of the acid and pepsin content of the secretion.

No new non-clinical studies were conducted, which is acceptable given that the application referred to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given the nature of the product and that the application referred to a product that has been licensed for over 10 years.

The RMS 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 and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 210 (15 March 2007), with the RMS and the CMS agreeing that the licence was approvable. The national phase of the decentralised procedure was completed in the UK on 20 June 2007.

II.1 QUALITY ASPECTS

II.1 Introduction

Each 10ml of oral solution contains 150mg ranitidine as ranitidine hydrochloride. Other ingredients consist of the pharmaceutical excipients sorbitol, ethanol, disodium hydrogen phosphate dihyrate, sodium dihydrogen phosphate dihydrate, hydroxyethyl cellulose, peppermint flavour, saccharin sodium and purified water.

The finished product is packaged into amber Ph. Eur type III glass bottles containing 300ml oral solution with child resistant, tamper-evident, polypropylene lid.

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

All aspects of the manufacture and control of ranitidine hydrochloride are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of ranitidine hydrochloride for inclusion in this medicinal product.

Appropriate stability data have been provided to support a retest period of 3 years when stored in the proposed packaging below 30°C.

II.3 Medicinal Product

Pharmaceutical Development

The applicant has provided suitable product development rationale and data.

The excipients used comply with their respective European Pharmacopoiea monographs with the exception of peppermint flavour which meets the EU directive for use in foodstuffs. Satisfactory certificates of analysis have been provided.

None of the excipients used contain material of animal or human origin.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and the results are satisfactory.

Finished Product Specification

The proposed finished product specification is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Reference Standards or Materials

Certificates of analysis for all reference standards used have been provided and are satisfactory.

Stability of the Drug Product

The stability data provided support a shelf-life of 18 months, with storage conditions “Do not store above 25°C. Store in original carton/bottle in order to protect from light” and an in use shelf-life of 3 months.

Bioequivalence/Bioavailability
A bioequivalence study was not required for this application due to the nature of the 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.2 NON-CLINICAL ASPECTS
III.1 introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ranitidine hydrochloride are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology 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.

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 Ranitidine 150mg/10ml Oral Solution is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new 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.

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

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of ranitidine hydrochloride is well-known. No new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

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.

IV.2 Pharmacokinetics
No new pharmacokinetic data have been provided and none are required for an application of this type.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been provided and none are required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data have been provided and none are required for an application of this type. The applicant has provided an extensive review of clinical trial data published in the literature which confirms the efficacy and safety of ranitidine in the treatment and prevention of relapse of peptic ulceration and the associated disease conditions.

IV.5 Clinical safety

No new safety data have been provided and none are required for an application of this type.

IV.6 Discussion on the clinical aspects

SmPC, PIL, Labels

The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of a marketing authorisation is recommended.

V User consultation

The package leaflet 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 language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet 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

QUALITY

The important quality characteristics of Ranitidine 150mg/10ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK-BENEFIT ASSESSMENT

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

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The Summary of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) 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:


Ranitidine
150mg/10ml
Oral Solution
POM
PL: 20046/0046
PA: TBA
300ml
Each 10ml of oral solution contains 150mg ranitidine (as hydrochloride). It also contains ethanol, sodium and sorbitol, liquid (non-crystallising).
For oral use. Use only as directed by a doctor.
Read the package leaflet before use.
Do not store above 25°C.
Store in the original carton/bottle in order to protect from light.
Once opened, use within 1 month.
Keep out of reach and sight of children.
PL/PA Holder: Focus Pharmaceuticals Ltd
Unit 5 Faraday Court
Burton upon Trent
DE14 2WX, UK.
BN
EXP
Focus Pharmaceuticals Ltd

Module 6

Steps Taken After Initial Procedure - Summary

The following table lists non-urgent safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
07/05/2015	Type IB	**PL 20046/0046-0040:** To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 and 6.6 of the SmPC in line with the brand leader (Zantac Syrup). Consequentially the PIL has been updated.	Approved on 01/10/2015-see Annex 1

ANNEX 1

Our Reference: PL 20046/0046-0040

Product: Ranitidine 150mg/10ml Oral Solution

Marketing Authorisation Holder: Focus Pharmaceuticals Limited
Active Ingredient(s): Ranitidine hydrochloride

Type of Procedure: Mutual recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/0913/001/IB/026

Reason:
To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 and 6.6 of the SmPC in line with the brand leader (Zantac Syrup). Consequentially the PIL has been updated.

Supporting Evidence
Revised SmPC fragments and PIL.

Evaluation
The proposed changes to the SmPC and PIL are in line with the reference product Zantac Syrup. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisation.

Conclusion
The proposed changes to the SmPC and PIL are acceptable.

Decision - Approved on 01 October 2015.