PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Ranitidine Accord 150 mg and 300 mg, film-coated tablets
Accord Healthcare Ltd., United Kingdom

ranitidine (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2077/001-002/MR
Registration number in the Netherlands: RVG 25004-25005

24 April 2013

Pharmacotherapeutic group: H2-receptor antagonists
ATC code: A02BA02
Route of administration: oral
Therapeutic indication: duodenal ulcer, benign gastric ulcer, long-term treatment of duodenal ulcers (150 mg only), reflux oesophagitis, Zollinger-Ellison syndrome; children from 3-18 years - short-term treatment of peptic ulcer and treatment of gastroesophageal reflux, including reflux oesophagitis, and relief of the symptoms of gastroesophageal reflux disease.

Prescription status in NL: prescription only
Date of first authorisation in NL: 1 December 1999
Concerned Member States: Mutual recognition procedure with AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LV, MT, NO, PL, PT, RO, SE, SI, SK
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ranitidine Accord 150 mg and 300 mg, film-coated tablets from Accord Healthcare Ltd. The date of authorisation was on 1 December 1999 in the Netherlands.

The product is indicated for:
- duodenal ulcer
- benign gastric ulcer
- long-term treatment of duodenal ulcers (150 mg only)
- reflux oesophagitis
- Zollinger-Ellison syndrome.

Children from 3 to 18 years
- short-term treatment of peptic ulcer
- treatment of gastroesophageal reflux, including reflux oesophagitis, and relief of the symptoms of gastroesophageal reflux disease.

A comprehensive description of the indications and posology is given in the SPC.

Ranitidine is a competitive histamine H2-receptor antagonist. It inhibits basal gastric acid secretion and gastric acid secretion stimulated for example by histamine, pentagastrin and food. Ranitidine reduces the quantity of acid and to a lesser extent of pepsin, and reduces the volume of gastric juices.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Zantac 150 mg and 300 mg tablets (NL License RVG 09265 and 11161) which have been registered in the Netherlands by GlaxoSmithKline B.V. since 24 December 1982 (150 mg) and 4 June 1986 (300 mg). In addition, reference is made to Zantac authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Zantac 300 mg tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ranitidine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or pale yellow, crystalline powder. It is freely soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, very slightly soluble in methylene chloride. Two polymorphic forms are known. Form II is used.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specifications are in line with the Ph.Eur. and the CEP, and therefore acceptable. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from each manufacturer.

Stability of drug substance
The active substance is stable for 3 years for one manufacturer, and 4 years for the other, when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Ranitidine Accord 150 mg contains 167.5 mg ranitidine hydrochloride equivalent to 150 mg ranitidine, and is a creamish yellow, round, biconvex, film-coated tablet having approximately 10 mm diameter with the inscription "IL" on one side and plain on the other side.
Ranitidine Accord 300 mg contains 335 mg ranitidine hydrochloride equivalent to 300 mg ranitidine, and is a creamish yellow, round, biconvex, film-coated tablet having approximately 12.5 mm diameter with the inscription "II" on one side and plain on the other side.

The film-coated tablets are packed in aluminium blister packs.

The excipients are:
* Tablet core - microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silica, purified talc, magnesium stearate
Tablet coating - hypromellose, castor oil, titanium dioxide (E171), yellow iron oxide (E172), purified talc.

The two tablet strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concerned a bioequivalence study of Ranitidine Accord 300 mg in comparison with Zantac 300 mg tablets as well as comparative dissolution studies with the originator product. In vitro studies were conducted as well on the 150 mg tablet strength versus the innovator product in three different media. In all media more than 85% of the reference and test product were dissolved within 15 minutes. The choices of the packaging and manufacturing process are justified. The batch used in the bioequivalence was manufactured according to the finalized formulation and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a standard process mainly consisting of raw material sifting, blending, compression, film coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation has been carried out on two production-scale batches of each strength of tablets. The process validation protocol has been included in the dossier.

Control of excipients
The excipients are widely used for the manufacturing of pharmaceutical products and are in compliance with current Ph.Eur. monograph requirements. The specifications of the excipients are acceptable.

Quality control of drug product
The product specification includes tests for description, average weight, identification, uniformity of the dosage unit, dissolution, resistance to crushing, loss of drying, related substances, assay, residual solvent and microbiological limit tests. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches of 150 mg and 300 mg tablets, demonstrating compliance with the release specification.

Stability of drug product
The drug product was stored at long term (25°C/60% RH) and at accelerated (40°C/75% RH) conditions. The conditions used in the stability studies are according to the ICH stability guideline. At accelerated (6 months) and long-term conditions (36 months) no trends or out of specification results are observed. No changes were observed in photostability studies. Therefore, the drug product is considered to be photostable. Based on the data submitted, a shelf life was granted of 2 years when packed in Alu-Alu blisters without special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is derived from vegetable origin.

II.2 Non-clinical aspects
This product is a generic formulation of Zantac, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ranitidine released into the environment. It
II.3 Clinical aspects

Ranitidine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ranitidine Accord 300 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Zantac 300 mg tablets (GSK, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 20-54 years. Each subject received a single dose (300 mg) of one of the 2 ranitidine formulations. The tablet was orally administered with 240 ml water after overnight fasting. There were 2 dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.3, 2.7, 3, 3.3, 3.7, 4, 4.3, 4.7, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products. A single dose, crossover study to assess bioequivalence is considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn due to an adverse event. Twenty-seven subjects completed the study entirely and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of ranitidine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-4} ng.h/ml</th>
<th>AUC_{0-\infty} ng.h/ml</th>
<th>C_{\text{max}} ng/ml</th>
<th>t_{\text{max}} h</th>
<th>t_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>5413 ± 1412</td>
<td>5662 ± 1435</td>
<td>1039 ± 374</td>
<td>3.0 (1.5 – 4.0)</td>
<td>3.4 ± 0.6</td>
</tr>
<tr>
<td>Reference</td>
<td>5549 ± 1122</td>
<td>5829 ± 1144</td>
<td>1024 ± 269</td>
<td>2.67 (1.5 – 4.67)</td>
<td>3.5 ± 0.9</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.96 (0.90 - 1.02)</td>
<td>0.96 (0.90 - 1.02)</td>
<td>0.98 (0.86 - 1.12)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>13.5</td>
<td>12.9</td>
<td>27.8</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
AUC$_{0\rightarrow\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC$_{0\rightarrow t}$ area under the plasma concentration-time curve from time zero to $t$ hours
C$_{\text{max}}$ maximum plasma concentration
t$_{\text{max}}$ time for maximum concentration
t$_{1/2}$ half-life

*ln-transformed values

The 90% confidence intervals calculated for AUC$_{0\rightarrow t}$, AUC$_{0\rightarrow\infty}$ and C$_{\text{max}}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of ranitidine under fasted conditions, it can be concluded that Ranitidine Accord 300 mg and Zantac 300 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Ranitidine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ranitidine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation of the study results to the 150 mg strength was justified based on the following:
- The 150 and 300 mg ranitidine tablets are dose proportional.
- The tablets have been manufactured by the same manufacturing process.
- Ranitidine shows linear pharmacokinetics.
- Dissolution profiles were provided for both strengths in three media. The data indicate that dissolution was more than 85% within 15 min in all three media.

This rationale was accepted; separate bioequivalence testing is not required for the 150 mg strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Ranitidine was first approved in 1981, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ranitidine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Zantac.

Readability test
The package leaflet for Ranitidine Accord 150 mg and 300 mg tablets 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 user test consisted of two rounds with 10 participants each. A total of 14 questions were asked in random order. These questions sufficiently addressed the key safety messages. Results of the first round of testing were good. For all items the participants scored well on the diagnostic questions. At least 90% of the participants were able to find the information requested and at least 90% showed that they understood and acted upon it. Therefore no changes were made to the leaflet for the second round. Results of the second round confirmed the results of the first round. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ranitidine Accord 150 mg and 300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zantac 150 mg and 300 mg tablets. Zantac is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Ranitidine Accord 150 mg and 300 mg, film-coated tablets were authorised in the Netherlands on 1 December 1999.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ranitidine Accord 150 mg and 300 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 1 October 2012.

The date for the first renewal will be: 1 October 2017.

The following post-approval commitments have been made during the procedure:

**Quality - medicinal product**
- The MAH committed to submit the validation data of the third batch results as soon as available.
- The MAH committed to revise the limits based on the third batch validation/stability results, if required.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>C(\text{max})</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PIL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>(t_{\frac{1}{2}})</td>
<td>Half-life</td>
</tr>
<tr>
<td>(t_{\text{max}})</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
</tr>
</tbody>
</table>
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>