PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Riluzol Hexal 50 mg film-coated tablets
Hexal AG, Germany

riluzole

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/1935/001/DC
Registration number in the Netherlands: RVG 106639

23 February 2011

Pharmacotherapeutic group:	other nervous system drugs
ATC code:	N07XX02
Route of administration:	oral
Therapeutic indication:	to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS) (not in children or patients with impaired renal or liver function)
Prescription status:	prescription only
Date of authorisation in NL:	26 January 2011
Concerned Member States:	Decentralised procedure with DE
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.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Riluzol Hexal 50 mg film-coated tablets, from Hexal AG. The date of authorisation was on 26 January 2011 in the Netherlands. The product is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

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

Although the pathogenesis of ALS is not completely elucidated, it is suggested that glutamate (the primary excitatory neurotransmitter in the central nervous system) plays a role for cell death in the disease. Riluzole is proposed to act by inhibiting glutamate processes. The mode of action is unclear.

This decentralised procedure concerns a generic application claiming essential similarity with Rilutek 50 mg film-coated tablets (EU License EU/1/96/010/001) which have been registered through a centralised procedure by Aventis Pharma S.A. since 1996. This marketing authorisation was renewed on 10 June 2001 and 10 June 2006.

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Rilutek 50 mg tablets, registered in France. 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 generic medicinal products.

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 riluzole, an established active substance not described in any Pharmacopoeia*. The active substance is slightly soluble in water. Solubility increases as pH decreases. There are no polymorphic forms and chiral centers.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The manufacturing process consists of four steps. The process has been adequately described. The active substance has been adequately characterized.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. 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 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The batches were adequately stored. No trends or changes are observed. The proposed re-test period of 36 months is acceptable. No specific storage conditions are required.

** A Pharmacopoeia is an official handbook in which methods of analysis with specifications for substances are laid down by the authorities.*

Medicinal Product

Composition
The drug product is a film-coated tablet containing 50 mg riluzole.
Riluzol Hexal – are white to off white, film coated, capsule shaped tablets with '*RLZ*' debossed on one side and plain on other side.
The excipients are:
Tablet core - anhydrous calcium hydrogen phosphate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and colloidal anhydrous silica
Tablet coating - Opadry: hypromellose, macrogol 6000, and titanium dioxide (E171)

The film-coated tablets are packaged in PVC-Alu blisters and HDPE bottles. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choice for the manufacturing process has been adequately justified. The test product has the same qualitative composition as the innovator product. The pharmaceutical development of the product has been adequately performed.

Container closure system
Riluzole tablets are packaged in PVC-Alu blisters and HDPE bottles. The stability of the drug product has been analysed for related substances, assay and dissolution during development. Three batches have been packaged in a PVC blister as well as a HDPE bottle and stored for six months at 40°C/ 75% RH. No trends or changes are observed.

Manufacturing process
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches (lower range). The product is manufactured using conventional manufacturing techniques. Process validation for full-scaled, upper range, production batches will be performed post authorisation.

Excipients
Except for Opadry the excipients comply with the Ph.Eur. Adequate specifications for Opadry are included. The individual components of Opadry are in accordance with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, uniformity of dosage units, water content, dissolution and microbiological quality.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site has been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product have been provided three production-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-Alu blister and HDPE bottle. An in-use stability study for the HDPE bottle has been performed.
A photo stability study has been performed during validation of the analytical methods. The drug product is photo stable. The claimed storage condition "*No special storage conditions required*" is justified.
The claimed shelf-life of 24 months is acceptable. The need for the proposed in-use shelf-life of one month for the product packed in the HDPE tablet container was questioned and the MAH has removed the claim from the product information.

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.

** 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.*

II.2 Non clinical aspects

This product is a generic formulation of Rilutek which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 riluzole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Riluzole is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Riluzol Hexal 50 mg film-coated tablets (Hexal AG, Germany) is compared with the pharmacokinetic profile of the reference product Rilutek 50 mg tablets (Aventis Intercontinental, France).

The choice of the reference product
Rilutek tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A randomized, open label, two treatment, two period, two sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 80 healthy, non-smoking South-asian male volunteers, aged 18-45 years. Each subject received a single dose 50 mg of one of the 2 riluzole formulations. The order of receiving the test and reference product for each subject during the two periods of the study was determined according to SAS® (version 9.1) generated randomization schedule. The randomization was balanced. After a supervised overnight fast of at least 10 hours, a single oral dose of the investigational product was administered with 240 ml of water. There were 2 dosing periods, separated by a washout period of 7 days.

The pre-dose blood sample was collected within 1 hour before dosing. Post dose blood samples were collected at 0.167, 0.333, 0.500, 0.667, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 3.500, 4.000, 4.500, 5.000, 6.000, 8.000, 12.000, 16.000, 24.000 and 36.000 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Riluzole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of riluzole. 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.

Results
Eight adverse events were recorded in the study of which 4 (headache, sore throat, rhinitis, pyrexia) occurred in test treatment group and 4 (vomiting, diarrhea, rhinitis, pyrexia) occurred in reference treatment group. In both the treatment groups 3 adverse events were related to the medication administered and 1 adverse event (pyrexia) was unlikely due to the study medication.
Increase in blood pressure was noted for one subject before drug administration and the subject was withdrawn from the study and was referred to the physician for further follow up. There were no SAEs (Serious Adverse Events) in the study.
Five subjects (Group I) were withdrawn from the study. Seventy-five subjects completed the study and were included in PK and statistical analysis.

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

Treatment N = 75	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	609.9 ± 284.8	650.0 ± 288.7	134.9 ± 60.7	1.0 (0.5 – 4.0)	8.3 ± 1.94
Reference	598.9 ± 293.6	638.3 ± 306.7	127.4 ± 57.6	1.25 (0.33 – 5.0)	7.9 ± 1.55
***Ratio (90% CI)**	1.02 (0.97 - 1.07)	1.02 (0.97 - 1.07)	1.06 (0.96 - 1.17)	---	---
CV (%)	19.0	17.6	37.7	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. A statistically significant period effect was detected for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of riluzole. However, since there was no detectable pre-dose concentration at any of the study periods and there was no sequence effect, there is no indication of carryover effect.
Based on the pharmacokinetic parameters of riluzole under fasted conditions, it can be concluded that Riluzol Hexal 50 mg film-coated tablets and the Rilutek 50 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.

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
Riluzole was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of riluzole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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 text is identical to the innovator product with the exception of the product specific sections.

Readability test
No user testing has been performed. The content of the proposed PIL is identical to the innovator leaflet. The MAH submitted a bridging report which indicates that the design and lay-out (type size, fonts, headings, print colour, syntax, writing style, and paper weight) is used for the leaflets of a variety of other products, which have all successfully passed a readability test. This bridging report is considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Riluzol Hexal 50 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Rilutek 50 mg talbets. Rilutek 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Riluzol Hexal 50 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 November 2010. Riluzol Hexal 50 mg film-coated tablets is authorised in the Netherlands on 26 January 2011.

The innovator product Rilutek is registered through a central procedure. The PSUR cycle of Rilutek is currently 2-yearly with the next Data Lock Point in June 2011. The MAH committed to adhere to the PSUR cycle of Rilutek and to submit the first PSUR with a DLP in June 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be 22 March 2014

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

Quality - medicinal product

- The MAH has committed to validate batches of production-scale in the upper range of the batch formula, whenever they are manufactured. - The MAH has committed to continue and complete the on-going stability studies in support of the proposed shelf-life.
- The MAH has committed for stability studies to be performed on the first three industrial batches of the drug product.

Pharmacovigilance

- The MAH has committed to adhere to the PSUR cycle of Rilutek and to submit the first PSUR with a DLP in June 2011 (22 March 2014 will be the common renewal date).

List of abbreviations

ALS	Amyotrophic Lateral Sclerosis
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached