COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Emylif 50 mg orodispersible film (riluzole)

NL/H/5494/001/DC

Date: 20 January 2023

This module reflects the scientific discussion for the approval of Emylif 50 mg orodispersible film. The procedure was finalised at 25 October 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ALS	Amyotrophic lateral sclerosis
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PAS	Penetration Aspiration Scale
Ph.Eur.	European Pharmacopoeia
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
VFSS	Videofluoroscopic Swallowing Study

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Emylif 50 mg orodispersible film, from Zambon S.p.A.

The product is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults. Emylif has not been shown to be effective in the late stages of ALS.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Rilutek 50 mg film-coated tablets which has been registered in the EEA by Sanofi Mature IP since June 1996 by centralised procedure (EU/1/96/010).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Luxembourg, Norway, Portugal, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. The pharmaceutical form of the new product Emylif is an orodispersible film, which is different from the pharmaceutical form of the reference product (film-coated tablets).

II. QUALITY ASPECTS

II.1 Introduction

Emylif is an orange, rectangular, orally dissolvable, thin film with “R50” printed in white on one side. Each orodispersible film contains as active substance 50 mg riluzole.

Each film is packed in a sachet consisting of two identical layers of polyester-/laminate foil which is heat sealed. These sachets are packed in cardboard boxes.

The excipients are:

- *Orodispersible film* – polacrilex resin, pullulan (E1204), hypromellose (E464), glycerol (E422), glycerol mono-oleate, sucralose (E955), fructose, macrogol, natural honey flavour, xanthan gum, lemon flavour (“juicy lemon”) and sunset yellow FCF (E110)
- *White ink* – purified water, titanium dioxide (E171), propylene glycol (E1520), hypromellose (E464), isopropyl alcohol and SDA 3A alcohol (ethanol and methanol).
- Traces of the antioxidant butylated hydroxytoluene (BHT, E321)

II.2 Drug Substance

The active substance is riluzole, an established active substance described in the United States Pharmacopoeia (USP). No European Pharmacopoeia (Ph.Eur.) monograph is available

for this substance. Riluzole is a white to pale yellow powder, very slightly soluble or insoluble in water. Riluzole does not exhibit isomerism and is not polymorphic.

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/EMA 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.

Manufacturing process

Riluzole is manufactured in three stages followed by milling and/or micronisation and, when applicable, blending of individual batches to increase the batch size. The blending operation is performed as per ICH Q7 recommendations. The drug substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents. The specification of a substance is the total of quality tests, analytical procedures and acceptance criteria (limits) this substance has to adhere to. Most manufacturing information which has been evaluated by the member states during the procedure is considered confidential.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is in line with the USP monograph as well as the in-house specification of the drug substance manufacturer. Additional requirements for particle size have been set by the MAH. The acceptance limit for particle size has been adequately justified; validated tests and limits for the control of microbiological quality of the drug substance have been implemented by the MAH. Batch analytical data demonstrating compliance with this specification have been provided for three batches. Most quality control tests and results submitted by the MAH are considered confidential.

Stability of drug substance

Stability data on the active substance have been provided for three commercial batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 5 years. Based on the data submitted, a retest period could be granted of 2 years.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The aim of the development was to develop a product similar to the reference product. The MAH has provided a thorough justification discussing the excipients' characteristics and their influence on product quality and performance as well as manufacturability. This includes the film-forming polymers, which are key components in creating orodispersible film. Critical process

parameters, their target values and the overall control strategy of the process have been adequately justified.

Detecting any differences in dissolution for this product might not be possible. This was acceptable because the overall product control strategy was considered adequate to ensure product quality and consistency.

The comparative dissolution profiles between the new product and the reference product (complementary to the bioequivalence study), at three pH levels, were not statistically identical. However, the *in vivo* results of the bioequivalence study show sufficient similarity between the two products and the observed differences can be explained by the pharmaceutical forms (film-coated tablets versus orodispersible film). Therefore, this was acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The process consists of three phases: (1) preparation of the coating mix, which includes adding the excipients; (2) formation of the bulk film, including the coating, drying and collection of dried film; (3) creation of the final unit dose, which includes printing and cutting the bulk film into the individual dosage units and sealing each dose within the primary packaging. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. and, where applicable, with in-house requirements. These specifications were acceptable.

Quality control of drug product

The finished product specifications were adequate to control the relevant parameters for the dosage form. The specification included tests for appearance, physical description of the film, identification, water content, assay, related substances, uniformity of dosage units, dissolution and microbiological quality. Limits in the specification have been justified and were considered appropriate for adequate quality control of the product. A risk evaluation on nitrosamines was provided, which addressed all known possible sources of contamination as stated in relevant guidance. Background documentation was also included. No additional control on nitrosamines was necessary.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data has been provided on six commercial scale batches, packaged as proposed for marketing. The batches were stored at long-term conditions (25°C/60% RH) for 36 months, intermediate conditions (30°C/65% RH) for 24 months and accelerated conditions (40°C/75% RH) for 6 months. Significant changes in dissolution and assay were observed at accelerated storage conditions at 3 and 6 months, but stability of the product has been demonstrated at

long term and intermediate conditions for the periods mentioned above. The conditions used in the stability studies were according to the ICH stability guideline. Photostability and lack of sensitivity to moisture were adequately demonstrated. Based on the test data, a shelf-life was granted of 24 months, with the storage condition “Store below 30°C”.

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 could be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Emylif has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Emylif is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Rilutek, which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there was no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies were required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Riluzole is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states

agreed that no further clinical studies were required, besides the three bioequivalence studies and the safety study discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Emylif 50 mg orodispersible film (Zambon S.p.A., Italy) was compared with the pharmacokinetic profile of Rilutek reference products (either EU or US sourced). This was deemed acceptable.

Bioequivalence studies

Bioequivalence study 1 – pilot study under fasting conditions

Study 1 was a pilot study which compared Emylif to Rilutek 50 mg film-coated tablets (from the EU) under fasting conditions. Bioequivalence was not shown in this study, possibly due to the low number of subjects in this study (n=10 and n=13, dependent on the treatment) and the high variability.

Bioequivalence study 2 – study under fasting and fed conditions

Study 2 was performed using US sourced Rilutek as reference product, both under fasting and fed conditions. Under fasting conditions, bioequivalence was shown. The food effect was comparable between Emylif and the reference product. Because the EU-registered Rilutek was not used as reference product in this study, the study was considered supportive only.

Study 3 was the pivotal bioequivalence study in which Emylif was compared to Rilutek 50 mg film-coated tablets as registered in the EU, under fasting conditions, in a larger number of subjects. The choice of reference product was justified by comparison of dissolution results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. This study is discussed here in detail.

Bioequivalence Study 3 – pivotal single dose, 50 mg, fasted

Design

A single dose, open-label, randomised, 2-sequence, 4-period replicate cross-over bioequivalence study was carried out under fasted conditions in 54 healthy (21 male and 33 female) subjects, aged 18-55 years. Each subject received a single dose (50 mg) of one of the two riluzole formulations after an overnight fast of at least 10 hours. The tablets were orally administered with 150 mL water. The orodispersible film was orally administered after the subjects drank 20 mL water in order to wet their mouth, without further water. There were four dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 15, 30, 45 minutes, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24 and 36 hours after administration of the products.

The design of the study was acceptable.

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

Results
Three subjects discontinued the study (one on their own accord, one due to a protocol deviation and one due to an adverse event). This left 51 subjects eligible for pharmacokinetic analysis and because there were four dosing periods (two for each formulation), this resulted in twice as many measurements being included in the analysis (N=102).

The area under the curve (AUC) value, presented in the table below, is a measure of the concentration of riluzole in the plasma of test subjects after oral administration. The new (test) product and the reference product should be comparable in AUC values, as well as in the maximum plasma concentration reached (C_{max}). The time at which this is reached (t_{max}) is also compared. The ratio (90% confidence interval) represents the similarity between the two products, with an acceptance range of 0.80 to 1.25.

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

Treatment N=102	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1263.40 ± 571.58	1348.31 ± 630.80**	315.62 ± 124.95	0.75 (0.25-2.00)
Reference	1135.98 ± 514.98	1207.79 ± 566.13	278.81 ± 123.32	0.75 (0.25-4.00)
***Ratio (90% CI)**	1.11 (1.08-1.16)	1.11 (1.08-1,15)**	1.17 (1.10-1.24)	--

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Ln-transformed values
**	N=101

Conclusion on bioequivalence studies
Study 2 supported that food influence on absorption (bioavailability) is similar between the test and reference products. No additional food influence study was deemed necessary. The SmPC of Emylif discourages eating after administration of the product in case of the possible side effect of oral hypesthesia (decreased tactile sensibility in the mouth) which may impact chewing and swallowing, but eating before administration is not limited.

In Study 3, the 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the bioequivalence acceptance range of 0.80 – 1.25. Based on this study, Emylif is considered bioequivalent with Rilutek.

The MEB has been assured that the bioequivalence studies have 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).

IV.3 Pharmacodynamics

Considering that bioequivalence between Emylif and reference product Rilutek has been shown, the MAH can bridge pharmacodynamic data from the reference product to Emylif. No pharmacodynamic data specific for Emylif 50 mg orodispersible film were deemed necessary.

IV.4 Clinical efficacy

As bioequivalence between Emylif and reference product Rilutek has been shown, efficacy data obtained with Rilutek can be bridged to Emylif. No additional efficacy data was considered necessary to support the indication.

In case of sialorrhea (excessive salivation or drooling) there is a risk the film would not stay in the patient's mouth when it is left to dissolve. Therefore, the following warning was added in section 4.4 of the Emylif SmPC,: "The swallowing safety of Emylif has not been evaluated in patients with (severe) sialorrhea or dysphagia. Caution should be exercised when administering Emylif to these patients."

The indication of reference product Rilutek was approved in 1996 and has not been changed since. In that time period, there was not much guidance available with respect to wording of an indication. Currently, certain changes were considered appropriate, given that this is a 10(3) hybrid application and therefore the new SmPC does not need to be identical to that of the reference product. The indication of Emylif was formulated as: "Emylif is indicated for the treatment of amyotrophic lateral sclerosis (ALS)" with the additional statement "Emylif has not been shown to be effective in the late stages of ALS".

IV.5 Clinical safety

The MAH has shown that Emylif and Rilutek are bioequivalent, hence the overall safety profile can be extrapolated. Additionally, safety data have been provided from the four studies in which Emylif was evaluated: the three bioequivalence studies mentioned above, plus Study 4, an open-label, swallowing safety study conducted in patients with ALS. Across the four studies, a total of 101 subjects (including 9 patients with ALS) were exposed to (at least one dose of) Emylif.

In Studies 1 to 3, the most commonly reported adverse events related to Emylif were somnolence, oral hypoesthesia and headache. (No adverse events were reported by ALS

patients in Study 4.) All events were considered mild to moderate in severity. These events were consistent with the safety profile stated in Rilutek's SmPC, but oral hypoesthesia was reported far more frequently with Emylif. In Study 3, all subjects on Emylif reported oral hypoesthesia (n=52, 100%) compared to none in the Rilutek group. Given the high incidence, oral hypoesthesia has been added as a very common side-effect into section 4.8 of the SmPC of Emylif. Overall, the event had a median time to onset of 1 minute and a median duration of 40 minutes. This has been adequately reflected in the SmPC.

Furthermore, qualitative properties of Emylif and possible oromucosal absorption were discussed by the MAH. Based on the provided data, it was agreed by the member states that no oromucosal absorption of Emylif was suggested, and there would be no subsequent impact on safety.

Study 4 - Swallowing safety study, single dose, 50 mg

Swallowing safety in ALS patients was evaluated in this Videofluoroscopic Swallowing Study (VFSS), which is an established method to evaluate swallowing. The Penetration Aspiration Scale (PAS) score was used. The PAS is an 8-point validated scale of swallowing safety that takes into account both the level of airway invasion during swallowing and the patient's response to the penetration or aspiration episode. A PAS score of 1 or 2 indicates a safe swallow, 3-5 indicates penetration and 6-8 indicates aspiration.

Design

The study included 9 subjects with ALS who had no perceived swallowing impairment or eating restriction. The PAS score was measured before and after a single dose of 50 mg Emylif. The study was initially planned for 25 subjects, however it was terminated after an interim analysis, when 9 subjects had completed it. As a consequence, no formal testing was performed.

Results

Around half of the subjects (55.6%) had a score of 1 or 2 (indicating safe swallow) as their single worst score and remained on the same score pre- and post-dose. There was only one subject whose worst score worsened post-dose, from 2 (safe swallow) to 3 ("material enters the airway, remains above vocal folds and is not ejected from airway") indicating penetration. None of the subjects in this study reported oral hypoesthesia or other adverse events.

Conclusion

Based on these results, it appeared that Emylif can be swallowed safely in ALS patients without a swallowing impairment, who have normal eating behaviour without restriction, who do not experience oral hypoesthesia. However, it remained unclear what the swallowing safety would be for ALS patients with dysphagia or oral hypoesthesia. The result analyses of Study 4 were repeated, but as no subject in Study 4 had dysphagia, this did not yield new pivotal information. Post-marketing data from the US were provided (as the product was marketed there since July 2021, as Exservan), but they were considered too limited to draw conclusions. Therefore, a warning in section 4.4 of the SmPC was added.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, 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 Emylif.

Table 2. Summary of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Rilutek. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. A swallowing safety study was performed and showed that Emylif can be swallowed safely in ALS patients without a swallowing impairment. Risk management was adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 PL was English. The test consisted of a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Emylif 50 mg orodispersible film has a proven chemical-pharmaceutical quality and is a hybrid form of Rilutek 50 mg film-coated tablets. 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 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Emylif with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A