CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209080Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	August 20, 2018
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	209080
Applicant	Italfarmaco S.p.A.
Date of Submission	11/16/2017
PDUFA Goal Date	9/16/2018
Proprietary Name / Non-Proprietary Name	Tiglutik (riluzole oral suspension)
Dosage form(s) / Strength(s)	oral suspension 50 mg/10mL
Applicant Proposed Indication(s)/Population(s)	treatment of amyotrophic lateral sclerosis (ALS)
Recommendation on Regulatory Action	Approval

1. Background

The applicant has submitted a New Drug Application (NDA) for Tiglutik (riluzole oral suspension 5 mg/mL (50 mg/10 mL)). The applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on the findings of safety and effectiveness for the reference listed drug (RLD), Rilutek (riluzole 50 mg oral tablet), and on data from a relative bioavailability study for establishing a pharmacokinetic (PK) bridge between Tiglutik to the RLD. Additional nonclinical studies were required for the submission to assess a novel excipient, polyoxyl 20 cetostearyl ether.

Riluzole 50 mg oral tablet was approved for "the treatment of patients with amyotrophic lateral sclerosis (ALS)" on December 12, 1995 (NDA 020599). The applicant proposes the same indication as Rilutek. The recommended dosage for riluzole is 50 mg taken orally twice daily. A 10 ml volume of the oral suspension formulation of riluzole will provide an equivalent dose of the 50 mg tablet. The applicant suggests that an oral suspension formulation of riluzole may offer some benefit to patients with ALS who experience dysphagia. Tiglutik is marketed using the tradename, Teglutik, in several countries outside the United States.

Riluzole 50 mg/10 mL Oral Suspension was granted orphan drug designation by FDA on September 15, 2016.

2. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson-Lee. Dr. Wilson's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

According to the OPQ review, the drug substance is produced with adequate quality for use in the oral suspension formulation.

The drug product consists of a nonsterile, oral, aqueous suspension of riluzole at a single strength of 50 mg/10 mL supplied in an amber bottle with a child-proof screw cap. Once opened, an (b) (4) syringe/bottle adapter and a 10 mL oral dispenser (oral syringe, (b) (4)) are utilized to withdraw 10 mL suspension twice a day for 15 days.

Stability and release testing were found to be acceptable. The stability data provides adequate support for a shelf-life of 24 months at USP Controlled Room Temperature. In-use stability results and microbial quality assessment support the proposed 15-day in-use period once the bottle is opened. OPQ determined that the manufacturing process for the drug product appears to be satisfactory based on its process selection, in-process controls, final product release test, and executed submission batch records. All manufacturing facilities for this

product were found to be acceptable. There were no outstanding issues identified in the OPQ review.

OPQ recommends approval.

3. Nonclinical Pharmacology/Toxicology

The review of nonclinical data was performed by the nonclinical reviewer, Dr. David Carbone, and nonclinical supervisor, Dr. Lois Freed. Please refer to the nonclinical reviews for details of the nonclinical assessment.

Polyoxyl 20 cetostearyl ether is a novel excipient for riluzole oral suspension that is not present in orally-administered, FDA-approved drug products. At the pre-NDA meeting in October 2016, the applicant was advised that it would need *"to conduct a chronic toxicology study in one species (i.e., 6-month rodent or 9-month nonrodent) and a standard battery of reproductive and developmental toxicology studies for Polyoxyl 20 Cetostearyl Ether. The excipient will also need to be assessed in a carcinogenicity study in one species, but, considering the indication, that study may be conducted post-approval."*

The nonclinical studies of the excipient consisted of 2- and 26-week oral toxicity (GLP) studies and a standard battery of oral reproductive and developmental toxicity (GLP) studies in Wistar rat and New Zealand White rabbit. The following are the key findings from the nonclinical studies for polyoxyl 20 cetostearyl ether, as described in Dr. Carbone's review:

- There were no test article-related findings in a 2-week dose ranging toxicology study in rats at doses up to 750 mg/kg.
- In a 6-month toxicology study in rats (0, 100, 300, or 1000 mg/kg with 4-week recovery), there were 5 deaths. Two deaths were thought to be related to gastric toxicity in the high dose group. In surviving animals, histological findings of mild to marked epithelial hyperplasia of the nonglandular stomach were observed in some animals in the mid- and high-dose groups. The no-observed adverse effect level (NOAEL) for the 6-month study was 100 mg/kg based on gastric toxicity.
- There were no test article-related effects on fertility or embryofetal development in rats with doses up to 1200 mg/kg.
- In an embryofetal development in rabbits, increases in intrauterine death and postimplantation loss occurred at the high dose of 200 mg/kg. The NOAEL for the study was 100 mg/kg.
- There were no test article-related effects on offspring in a pre- and postnatal development study in rats administered up to 1000 mg/kg.

Safety margins for the maximum human daily oral dose of 20 mg/day polyoxyl 20 cetostearyl ether are calculated to be 49- and 98-fold (based on body surface area) at the NOAEL of 100 mg/kg in rats and rabbits, respectively.

Dr. Carbone recommends approval of the application from a nonclinical perspective but recommends that a carcinogencitiy study of polyoxyl 20 cetostearyl ether in one species be conducted as a postmarketing requirement (PMR).

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Bilal AbuAsal with Team Leader Dr. Sreedharan Sabarinath.

A Phase 1, open-label, pharmacokinetic study (DSC 15-2985-04) that compared the bioavailability of riluzole 50 mg/10 mL oral suspension to a Rilutek 50 mg tablet in healthy subjects served as the pivotal study for the application. The applicant also submitted three additional PK studies (Studies DSC 15-2985-01, DSC 15-2985-02, DSC 15-2985-03), that were used for the registration of this product in Europe. OCP considered these studies as supportive.

Study DSC 15-2985-04 was a single-center, open-label, single-dose, randomized, 3-period, 6-sequence, crossover, comparative bioavailability study, performed under fasting or fed conditions. Subjects were randomized to receive a single-dose of study medication or the reference formulation (under fasting or fed conditions) according to the randomization scheme. The study randomized 36 subjects and data from 34 subjects were available for PK analysis.

Bioavailability/Bioequivalence Assessment
The following table from the clinical study report for DSC 15-2985-04 provides a summary of the comparative bioavailability data from the bioequivalence studies. Test A refers to riluzole oral suspension under fasting conditions, Test C refers to riluzole oral suspension under fed conditions, and Reference B refers to the RLD.

Parameter	Treatment Comparisons	Geometric LS Mean (A)	Geometric LS Mean (B)	Ratio[1]	90% Geometric C.I.[2] Lower	90% Geometric C.I.[2] Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test(A) - Reference(B)	570722.85	601508.53	94.88%	90.15%	99.86%	12.48%	48.48%
AUC_{0-inf}	Test(A) - Reference(B)	621227.10	657540.08	94.48%	90.03%	99.15%	11.76%	48.94%
C_{max}	Test(A) - Reference(B)	153322.99	142055.49	107.93%	95.06%	122.54%	31.60%	39.98%
		Geometric LS Mean (C)	Geometric LS Mean (A)					
AUC_{0-t}	Test(C) - Test(A)	521146.78	570644.67	91.33%	87.58%	95.23%	10.19%	42.51%
AUC_{0-inf}	Test(C) - Test(A)	578946.88	621031.45	93.22%	89.30%	97.32%	10.48%	43.69%
C_{max}	Test(C) - Test(A)	70485.55	153397.06	45.95%	42.10%	50.15%	21.50%	36.43%

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.

[2] 90% Geometric Confidence Interval using ln-transformed data.

Data source: Tables 14.2.1-9, 14.2.1-10, 14.2.1-11, 14.2.1-12, 14.2.1-13, and 14.2.1-14.

The results show that the geometric means for AUC0-t, AUC0-inf, and for Cmax were approximately 95%, 95%, and 108%, respectively. OCP notes that this indicates a similar extent and rate of riluzole absorption after a single dose of the test and reference formulations. The criteria to demonstrate bioequivalence was satisfied for all primary endpoints (AUC0-t, AUC0-inf, and Cmax) with the 90% geometric confidence intervals (CI) for the ratio (A/B) of means within the acceptance limits of 80% to 125%.

Food Effects
The RLD, riluzole tablet, has significant food effects. As described in the prescribing information for the RLD, the Cmax decreases by approximately 45% and the AUC decreases by approximately 20% when administered with a high fat meal. The prescribing information (PI) for the RLD specifies that riluzole should be administered "at least 1 hour before or 2 hours after a meal".

Following the administration of riluzole 50 mg/10 mL oral suspension (total dose of 50 mg) to healthy subjects under fed conditions with a high-fat meal, Cmax decreased by approximately 55% and the AUC decreased by about 9% (b) (4) (b) (4) (b) (4) Although the 9% decrease in AUC is not predicted to be clinically relevant, OCP believes the observed food effects with the proposed product (oral suspension) are comparable to the RLD, riluzole tablets (45% vs 55% reduction in Cmax and 20% vs 9% reduction in AUC for RLD and proposed product, respectively). Therefore, OCP recommends that the dosing instructions for Tiglutik should (b) (4) the same as the RLD.

OCP Recommendation:
OCP recommends approval based on the bioequivalence demonstrated between the proposed oral suspension and the RLD. Based on the food effects observed with the oral suspension that are comparable to the RLD, OCP recommends that (b) (4) the dosing recommendations contained in the PI for the RLD that Tiglutik be taken at least 1 hour before or 2 hours after a meal.

5. Clinical- Efficacy

The effectiveness of Tiglutik is based on the demonstration of bioequivalence to the RLD.

6. Clinical- Safety

The safety of Tiglutik is based on the demonstration of bioequivalence to the RLD. Dr. Veneeta Tandon, the clinical reviewer for this application, reviewed the new safety data in this submission. The safety review focused on the pivotal US bioequivalence study; however, Dr. Tandon also reviewed safety data from the supportive European studies and data from the published literature and FDA Adverse Event Reporting System (FAERS) database.

There were no deaths or serious adverse events in Study DSC 15-2985-04. There were two discontinuations in the study but they were not related to adverse events.

A new safety signal of oral hypoesthesia was identified for the oral suspension formulation of riluzole. Oral hypoesthesia was observed in 29% of subjects taking riluzole oral suspension compared to 6% with riluzole tablet in fasting conditions. Under fed conditions, oral hypoesthesia was observed in 43% of subjects taking riluzole oral suspension. The hypoesthesia was transient and resolved during the study. Circumoral paresthesia is described in the label for the RLD. The rates of hypoesthesia observed with the riluzole oral suspension may be potentially be related to greater contact with the oral mucosa than with the tablet formulation. All other adverse events were generally consistent with the established safety profile of riluzole.

Clinical recommendation: Dr. Tandon identified oral hypoesthesia as a new safety signal observed with this oral suspension formulation of riluzole. This will be described in Section 6 of the PI. She recommends approval of this supplement and I agree with her recommendation.

7. Advisory Committee Meeting

None required as drug is not a new molecular entity.

8. Pediatrics

The submission did not include any pediatric data. Because the product has orphan drug designation, Pediatric Research Equity Act (PREA) requirements were not triggered.

9. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

The Division of Medication Error and Prevention Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP) provided consultations on the product labeling, including the proposed instructions for use (IFU).

10. Recommendations/Risk-Benefit Assessment

The applicant has provided substantial evidence of the effectiveness and safey of Tiglutik (riluzole oral suspension 5 mg/mL (50 mg/10 mL) based on bioequivalence to the RLD.

Oral hypoesthesia was identified as a new safety signal observed with this oral suspension formulation of riluzole in the Phase 1 bioavailability study and will be described in labeling. This new safety finding does not impact the risk-benefit assessment of riluzole.

There are no outstanding unresolved issues.

Specific postmarketing risk management activities are not needed.

A PMR will be issued for a nonclinical oral carcinogencitiy study of the excipient polyoxyl 20 cetostearly ether in a single species.

Agreement has been reached with the applicant on product labeling.

I agree with the review team that this NDA should be approved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
09/04/2018

ERIC P BASTINGS
09/04/2018
I concur.