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APPLICATION NUMBER:

209080Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(2)
Application Number(s)	209080
Priority or Standard	Standard
Submit Date(s)	11/16/17
Received Date(s)	11/16/17
PDUFA Goal Date	8/16/18
Division/Office	Division of Neurology Products
Reviewer Name(s)	Veneeta Tandon
Review Completion Date	7/24/18
Established Name	Riluzole Oral Suspension
(Proposed) Trade Name	TIGLUTEK
Applicant	Italpharmaco S.p.A
Formulation(s)	Oral Suspension, 5 mg/mL
Dosing Regimen	50 mg/10 mL every 12 hours
Applicant Proposed Indication(s)/Population(s)	Amyotrophic lateral sclerosis (ALS)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Amyotrophic lateral sclerosis (ALS)

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1 Executive Summary

1.1. Product Introduction

This application is for a new oral liquid formulation of riluzole (ITF2985), Riluzole 5mg/mL (50 mg/10 mL) Oral Suspension (TILGLUTIK®). Riluzole (RILUTEK®, 50 mg tablets) was approved for the treatment of patients with amyotrophic lateral sclerosis (ALS) in 1995. The indication for Riluzole Oral Suspension is proposed to be the same as RILUTEK®, treatment of patients with ALS. This application is a 505 (b)(2) application based on a bioequivalence study to bridge the safety and efficacy of the new oral suspension formulation to the approved tablet dosage form.

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. Oral administration of the new formulation is by graduated dosing syringe. Dilution with liquids is not necessary. The applicant asserts that this dosage form will be advantageous for ALS patients that have oropharyngeal dysphagia as an early onset symptom as it will eliminate the need to crush the RILUTEK®, tablets to powder and combine it with liquid.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505 (b)(2) application based on a pivotal bioequivalence study to bridge the safety and efficacy of the new oral suspension formulation to the approved tablet dosage form of riluzole.

The Office of Clinical Pharmacology review team has reviewed the results of this pivotal bioequivalence study (DSC/15/2985/04) and concluded that the test formulation Riluzole 50 mg/10 mL Oral Suspension is bioequivalent to the reference RILUTEK ® 50 mg film-coated tablet following a 50-mg dose under fasting conditions (refer to Clinical Pharmacology Review).

1.3. Benefit-Risk Assessment

The overall benefit - risk assessment of new oral suspension formulation of riluzole is unchanged from the approved tablets, however, a higher incidence of oral hypoesthesia was observed after the administration of riluzole oral suspension (TILGLUTIK®) compared to the approved tablets (RILUTEK ®)

Therapeutic Context

2.1. Analysis of Condition

ALS is a neurodegenerative disease characterized by progressive muscular paralysis reflecting degeneration of motor neurons. The incidence is 2 per 100,000 (in the US, 6,000) per year. ALS generally strikes people between 40 and 60 years of age (median age 55). Approximately 50% of patients with ALS die within 3 years from the onset of symptoms and approximately 90% die within 5 years. Shorter survival is associated with older age at onset, bulbar onset, shorter time from first symptoms to presentation, and greater severity of clinical disability or faster rate of respiratory dysfunction.

2.2. Analysis of Current Treatment Options

Riluzole tablets (RILUTEK®) was approved for use in ALS in 1995 after studies showed that it extended survival by 2-3 months. Recently in 2017 edaravone (RADICAVA) was approved for the treatment of ALS based on slowing the decline in physical function by 33% in ALS patients.

3 Regulatory Background

3.1. Summary of Presubmission/Submission Regulatory Activity

Riluzole oral suspension was granted orphan drug designation on September 15, 2016.

The following key meetings were held for the new dosage form Riluzole Oral Suspension:

Pre-IND (WRO)	November 25, 2014
May Proceed letter	December 23, 2015
Pre-NDA (WRO)	May 26, 2016

3.2. Foreign Regulatory Actions and Marketing History

The riluzole oral suspension formulation is approved and marketed using the tradename TEGLUTIK® in several countries outside the United States: Italy, Greece, Spain, France, Portugal, Austria, Belgium, Germany, United Kingdom, Israel and Turkey. The dossier is under review process in two countries: Switzerland and Australia.

4 Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

Type of Study	Study ID	Study objective	Study design	Study drug, dose, route of administration	No. of subjects	Healthy subjects or diagnosis of patients	Treatment duration
BA **Pivotal US**	DSC/15/2985/04	To compare Cmax and AUC Riluzole 50 mg/10 mL oral suspension (Test) versus Rilutek® 50 mg film-coated tablet (Reference), under fasting conditions.	single-center, open-label, randomized, 3- period, 6- sequence, crossover Comparative bioavailability study	Oral suspension; 10 ml of Riluzole 50mg/10mL; PO	36	Healthy subjects	Single dose
BE EU Pilot	DSC/08/2985/01	To compare the pharmacokinetic profiles and the bioavailability of riluzole after administration of a single dose of a new riluzole 50 mg/10mL oral suspension formulation (Italfarmaco S.A., Spain) vs. the marketed reference Rilutek® 50 mg film-coated tablet	Single center, , randomized, two-way, cross-over bioequivalence pilot study	Oral suspension; 10 ml of Riluzole 50mg/10mL; PO **Reference product not sourced from US**	10	Healthy subjects	Single dose

BE EU	DSC/09/2985/02	To assess the bioequivalence of riluzole, after replicate single dose administration of a new riluzole 50 mg/10mL oral suspension formulation (Italfarmaco S.A., Spain; test) vs. the marketed reference Rilutek® 50 mg film-coated tablet	Single center, open label, randomized, 2-sequence, 4- period, replicate two-stage cross- over design, bioequivalence study.	Oral suspension; 10 ml of Riluzole 50mg/10mL; PO **Reference product not sourced from US**	14	Healthy subjects	Replicate Single dose
BE EU	DSC-09-2985-03	To assess the bioequivalence of riluzole 50 mg/10 mL oral suspension (Italfarmaco S.A., Spain) vs. the marketed reference Rilutek® 50 mg riluzole film- coated tablet (Aventis Pharma S.A., France)	open- label, randomized, two-way crossover study.	Oral suspension; 10 ml of Riluzole 50mg/10mL; PO **Reference product not sourced from US**		Healthy subjects	

4.2. Review Strategy

This review only includes the safety review of the new riluzole oral suspension formulation.

5 Review of Relevant Individual Trials Used to Support Efficacy

This section is not applicable as this application is a 505 (b)(2) application based on a bioequivalence study to bridge the safety and efficacy of the new Oral Suspension formulation to the approved tablet dosage form.

6 Review of Safety

Review of the safety included safety data from the US pivotal study (DSC/15/2985/04), the supportive safety data from the three European studies, as well as information from the published literature, and the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

6.1. Safety Review Approach

The review particularly attempted to identify new safety signals, if any from the pivotal and supportive study with the new formulation, the literature (August 2015-June 2017) and the FAERS database (Q4 1997 and Q1 2017) that could change the current safety profile of riluzole.

6.2. Review of the Safety Database

6.2.1. Overall Exposure

In the US pivotal study DSC/15/2985/04, 36 subjects were exposed to single doses of Riluzole Oral Suspension and RILUTEK®, 34 subjects completed the study. All 36 subjects completed period 1 of the study. One subject on test drug discontinued the study in Period 2 due to protocol deviation. Another subject discontinued in the Period 3 due to a positive alcohol test at check in. An additional 54 subjects were exposed in the European bioequivalence studies to single doses of Riluzole Oral Suspension and RILUTEK®.

A total of 957 cases were identified in the US FAERS database between Q4 1997 and Q1 2017.

6.3. Adequacy of Applicant's Clinical Safety Assessments

Applicant's safety assessments for this 505(b)(2) application appeared adequate.

The clinical safety assessments included treatment-emergent adverse events, vitals and laboratory assessments.

6.4. Safety Results

6.4.1. Deaths, Serious Adverse Events and Significant Adverse Events

None

6.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

There were no discontinuations in the Pivotal US study. There was one discontinuation on test drug due to an adverse event (migraine headache) in the EU study DSC/09/2985/02, which started approximately 14 hours after the first administration of Riluzole Oral Suspension and lasted for approximately 12 hours. The investigator considered the event to be related to treatment. (b) (4).

6.4.3. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events (TEAEs) from Study DSC/15/2985/04 are shown is Table 1. The frequency of TEAEs that appeared to be more in the Riluzole Oral Suspension formulation compared to the approved tablets were: oral hypoesthesia, soft feces, headache and somnolence. The frequency of hypoesthesia was the same under fasted or fed conditional with the oral suspension formulation.

Table 1 Most Frequently Reported Treatment-Emergent Adverse Events

MedDRA System Organ Class MedDRA Preferred Term	Riluzole 50 mg/10 mL Oral Suspension Fasting Conditions (N=35) n(%)E	Riluzole 50 mg Film-coated Tablet Fasting Conditions (N=36)	Riluzole 50 mg/10 mL Oral Suspension Fed Conditions (N=35)	Overall (N=36)
Number of TEAEs (E) Number of Subjects with TEAEs n(%)	21 16 (45.7)	13 9 (25.0)	19 15 (42.9)	53 20 (55.6)
Gastrointestinal disorders Hypoesthesia oral Feces soft	10 (28.6) 10 2 (5.7) 2	2 (5.6) 2 0	15 (42.9) 15 0	16 (44.4) 27 2 (5.6) 2
Nervous system disorders Headache Dizziness Somnolence	4 (11.4) 4 1 (2.9) 1 2 (5.7) 2	3 (8.3) 3 0 0	0 1 (2.9) 1 0	6 (16.7) 7 2 (5.6) 2 2 (5.6) 2
Injury, poisoning and procedural complications Procedural nausea Procedural dizziness	0 0	1 (2.8) 2 1 (2.8) 1	1 (2.9) 1 1 (2.9) 1	2 (5.6) 3 2 (5.6) 2

Vascular disorders Hot flush	1 (2.9) 1	0	1 (2.9) 1	2 (5.6) 2

N: Number of Subjects Dosed
MedDRA®: Medical Dictionary for Regulatory Activities, Version 18.1; TEAEs: Treatment-emergent adverse events.
Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences

The intensity of the TEAEs were mostly mild and moderate as shown in Table 2.

Table 2 Number of Treatment-Emergent Adverse Events by intensity

Treatment	Severity		
	Mild	Moderate	Severe
Riluzole Oral Suspension (Fasted)	19	2	0
Riluzole Tablet (Fasted)	12	1	0
Riluzole Oral Suspension (Fed)	18	1	0
Overall	49	4	0

No new safety signals were observed in the EU bioequivalence studies and the literature review.

6.4.4. Laboratory Findings

There were no clinically significant shifts in any clinical chemistry or hematology parameters in any of the three studies.

6.4.5. Vital Signs

No relevant differences in mean values and changes from baseline were observed for vital signs. An abnormal value if occurred post dose, was due to low or high values at baseline.

6.5. Safety in the Postmarket Setting

Based on the Periodic Safety Update (PSUR) for RILUTEK® between 1/12/15 and 3/8/17, no new safety concern or risk was identified.

A total of 957 cases were identified in the US FDA Adverse Event Reporting System between Q4 1997 and Q1 2017. The most frequently reported (≥ 40 cases, approximately 5%) adverse drug reactions aside from death (n = 127) or ALS (n = 66) were nausea (71 cases), pyrexia (50 cases), asthenia (46 cases), and dyspnea (n = 41 cases). Notable adverse events included increased ALT (30 cases), drug interaction (30 cases), fatigue (30 cases), AST increase (29 cases), pneumonia (27 cases) and dysphagia (25 cases). The majority of all cases occurred in patients between 50

and 79 years of age. These adverse drug reactions are (b) (4) expected in the patient population.

Post marketing reports on TIGLUTIK in Europe between the period of 1/12/2015-31/8/2107, also show mouth and throat paresthesia, pharyngeal hypothesia, numbness of tongue, swollen tongue, mouth swelling, throat swelling as reported events. These reports are consistent with the finding of oral hypoesthesia observed in the pivotal study.

6.6. Integrated Assessment of Safety

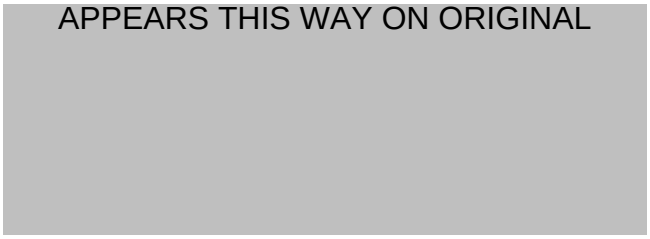
Other than oral hypothesia seen with the oral suspension formulation, there are no new safety findings for riluzole.

7 Labeling Recommendations

The applicant has proposed the following paragraph to the "Adverse Reactions" Section 6 of the approved riluzole label.

(b) (4)

Please refer to the final label for the negotiated language for the "Adverse Reactions" Section 6.


APPEARS THIS WAY ON ORIGINAL

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/

VENEETA TANDON
07/24/2018

TERESA J BURACCHIO
08/24/2018