CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209080Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: August 23, 2018
From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 209-080 (Tiglutik, riluzole oral suspension)

NDA 209-080 was submitted by the sponsor (Italfarmco S.p.A.) on November 16, 2017, for riluzole oral suspension for the treatment of patients with Amyotrophic Lateral Sclerosis. The NDA is a 505(b)(2) application, with Rilutek (NDA 20-599) as the Reference Listed Drug (RLD). Clinical development was conducted under IND 123532. To support clinical development and an NDA for this product, the sponsor conducted nonclinical studies to assess the potential toxicity of an excipient, Polyoxyl 20 Cetostearyl Ether, present in the to-be-marketed drug product but not in any FDA-approved oral drug product. Nonclinical studies of riluzole oral suspension were not required, based on the Agency's previous finding of safety for the RLD and the sponsor's bridging studies.

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. Under the IND, the sponsor was told it would be acceptable for a carcinogenicity study in one species to be conducted post-approval because of the seriousness of the indication (*IND 123532 Advice letter, October 27, 2016)*. The nonclinical data have been reviewed by Dr. Carbone (*Pharmacology/Toxicology NDA Review and Evaluation, NDA 209080, David L. Carbone, Ph.D., April 23, 2018*). Dr. Carbone has concluded that the data are adequate to support approval, with a post-marketing requirement (PMR) for a carcinogenicity study of the excipient.

I concur with this conclusion and recommendation.

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/s/

LOIS M FREED
08/23/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209080
Supporting document/s:	1
Applicant's letter date:	November 16, 2017
CDER stamp date:	November 16, 2017
Product:	Tiglutik® (riluzole oral suspension)
Indication:	Amyotrophic Lateral Sclerosis
Applicant:	Italfarmco S.p.A.
Review Division:	Neurology Products
Reviewer:	David L. Carbone, Ph.D.
Supervisor:	Lois M. Freed, Ph.D.
Division Director:	Billy Dunn, M.D.
Project Manager:	Brenda Reggetz

Disclaimer

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Any information or data necessary for approval of NDA 209080 that Italfarmco S.p.A. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 209080.

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1 Executive Summary

1.1 Introduction

Tiglutik is an oral suspension of riluzole, developed under the 505(b)(2) pathway by Italfarmco S.p.A. for the treatment of amyotrophic lateral sclerosis (ALS). The approved riluzole product (Rilutek) is the Reference Listed Drug. The proposed dose for tiglutik is 50 mg twice daily, which would result in a daily oral dose of 20 mg polyoxyl 20 cetostearyl ether. Because this excipient is not present in orally-administered, FDA-approved drug products, the sponsor conducted additional nonclinical studies to support the use of polyoxyl 20 cetostearyl ether in the tiglutik drug product.

1.2 Brief Discussion of Nonclinical Findings

See Integrated Summary.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data support approval of tiglutik.

1.3.2 Additional Nonclinical Recommendations

As a post-marketing requirement, the carcinogenic potential of polyoxyl 20 cetostearyl ether should be evaluated in a carcinogenicity study in one species.

1.3.3 Labeling

The proposed labeling includes a warning that administration of riluzole during gestation in rats resulted in increased embryofetal mortality and decreased postnatal offspring viability at clinically-relevant doses. Because of a 98-fold safety margin based on HED, no additional warning is required for similar embryofetal findings in rabbits administered polyoxyl 20 cetostearyl ether.

2 Drug Information

2.1 Drug

CAS Registry Number: 1744-22-5 (Riluzole)

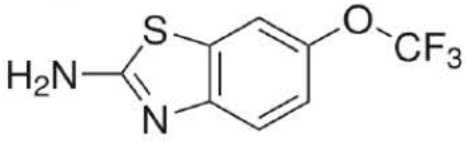
Generic Name: Tiglutik

Code Name: ITF2985

Chemical Name: 6-(trifluoromethoxy)-2-benzothiazolamine

Molecular Formula/Molecular Weight: $C_8H_5F_3N_2OS$, 234.2 g/mol (riluzole)

Structure or Biochemical Description:



(Riluzole; Sponsor's figure)

Pharmacologic Class (riluzole): Late sodium current (late I_{Na}) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs:

IND 123532: ITF2985 for ALS (active; DNP)
NDA 020599 (riluzole)

2.3 Drug Formulation

5 mg/mL riluzole suspension with the following excipients:

Ingredients	Function	Composition for 100 mL (% w/v)	Reference	FDA IIG Acceptable Limit and/or GRAS
Sorbitol (b) (4) (non-crystallising) (b) (4)	(b) (4)		USP	(b) (4)
Aluminum Magnesium Silicate (b) (4)			USP	
Xanthan Gum			USP	
Saccharin Sodium			USP	
Simethicone (emulsion (b) (4))			USP	
Sodium Laurylsulfate			USP	
Polyoxyl 20 Cetostearyl Ether (b) (4) (b) (4)			USP	
Purified Water			USP	

(Sponsor's Table)

2.4 Comments on Novel Excipients

Polyoxyl 20 cetostearyl ether is not present in orally-administered, FDA-approved drug products.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Tiglutik is intended to be used for the treatment ALS. Dosing is to be 50 mg (10 mL) taken orally twice daily (every 12 hours).

2.7 Regulatory Background

The following pre-NDA advice was issued October 27, 2016:

To support an NDA for Tiglutik, you will 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.

3 Studies Submitted

3.1 Studies Reviewed

PK (bioavailability) in beagle dogs; 2- and 26-week oral administration of polyoxyl 20 cetostearyl ether in rats; fertility (rat), embryofetal development (rat and rabbit), and pre/postnatal development (rat) studies with polyoxyl 20 cetostearyl ether. Method validation for measuring polyoxyl 20 cetostearyl ether in dosing solutions.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Nonclinical review of IND 123532 (David L. Carbone, Ph.D., December 30, 2015)

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Bioavailability (*from nonclinical review of 123532 by D. Carbone*):
Study TR#1195/I: This non-GLP study evaluated the bioavailability and PK profile of approximately 5 mg/kg riluzole following oral gavage of ITF2985 (tiglutik) or (b) (4) Rilutek tablets to male Sprague-Dawley rats (48/group; 6/timepoint). A comparison of the two formulations indicated similar riluzole bioavailability and pharmacokinetics.

RILUZOLE		
Compound	riluzole suspension	Rilutek® capsules
Dose (mg/kg)	4.85	5.90
C_{max} (ng/mL)	908	990
t_{max} (h)	4	6
C_{last} (ng/mL)	21	11
t_{last} (h)	16	16
$t_{1/2}$ (h)	1.75	1.45
AUC (h*ng/mL)	9375	9968
F_{rel} %	114.3	100

(Sponsor's Table)

(Study A2645) Polyoxyl 20 Cetostearyl Ether: Validation of the Analytical Method and Formulation Procedure in Water:
Polyoxyl 20 cetostearyl ether in dosing solutions was quantified by (b) (4) Accuracy was evaluated using standards ranging from (b) (4) mg/mL. Accuracy ranged from (b) (4) (b) (4)%.

6 General Toxicology

6.1 Single-Dose Toxicity

No single dose studies were submitted.

6.2 Repeat-Dose Toxicity

Study title: Polyoxyl 20 Cetostearyl Ether: 2 Week Preliminary Oral Toxicity Study in Rats

Study no.:	E0106
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 23, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 50, 125, 300, 750 mg/kg
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Water
Species/Strain:	Wistar Rats
Number/Sex/Group:	5/sex/group
Age:	41 to 43 days at initiation of dosing
Weight:	75 to 99 g on arrival (27 to 29 days old)
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No protocol deviations were reported

Observations and Results

Mortality, Clinical Signs, Body Weight, Food Consumption

All animals were evaluated twice daily for mortality or signs of morbidity. Clinical signs were evaluated daily. Body weights and food consumption were recorded weekly. There were no test article effects on mortality, clinical signs, body weights, or food consumption.

Ophthalmoscopy, ECG, Toxicokinetics

Not evaluated

Hematology, Clinical Chemistry, Urinalysis

Blood and urine were collected from fasted animals at scheduled necropsy. There were no test article effects on hematology, clinical chemistry, or urinalysis.

Gross Pathology, Organ Weights, and Histopathology

There were no test article effects on gross findings or organ weights. Histopathology was not evaluated.

Dosing Solution Analysis

Not provided

Study title: Polyoxyl 20 Cetostearyl Ether: 26 week Oral Toxicity Study in Rats Followed by a 4 week Recovery Period

Study no.:	A2357
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 13, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 100, 300, 1000 mg/kg (main); 0, 1000 mg/kg (recovery)
Frequency of dosing:	Once per day
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Water
Species/Strain:	Wistar rats
Number/Sex/Group:	15/sex/group (main); 6/sex/group (recovery)
Age:	39 to 41 days at initiation of dosing
Weight:	85 to 120 g at arrival (27 to 29 days old)
Satellite groups:	9/sex/group for TK
Unique study design:	None
Deviation from study protocol:	No significant deviations

Mortality

Animals were monitored twice daily for mortality or signs of morbidity. Seven animals were found dead during the study. COD was not determined in TK group deaths due to cannibalization or tissue autolysis; however, GI toxicity (erosion/ulceration of the nonglandular stomach) was thought to be the COD for 2/15 main study HDMs.

Dose (mg/kg)	Sex	Group	Animal No.	Day	COD
1000	M	TK	A2375200	88	Unknown
1000	F	TK	A2375191	147	Unknown
1000	M	Main	A2375120	135	GI toxicity
1000	M	Main	A2375106	157	GI toxicity
300	F	TK	A2375185	60	Unknown
300	F	TK	A2175183	61	Unknown
100	F	TK	A2375159	125	Gavage Error

Clinical Signs

Clinical signs were evaluated daily. Test article-related clinical signs during the dosing period included piloerection, swollen abdomen, rales, and salivation; there were no test article-related signs during the recovery period.

Finding	Sex	Dose (mg/kg)			
		0	100	300	1000
Piloerection	M	0/21	1/15	5/15	16/21
	F	0/21	0/15	4/15	17/21
Swollen abdomen	M	0/21	0/15	0/15	0/21
	F	0/21	0/15	4/15	10/21
Rales	M	0/21	0/15	0/15	2/21
	F	0/21	0/15	0/15	4/21
Salivation	M	0/21	0/15	0/15	1/21
	F	0/21	0/15	0/15	2/21

Body Weights and Food Consumption

Body weights and food consumption were evaluated weekly. Mean body weight gain relative to controls was decreased at Week 26 by 25 and 4% in HD males and females, respectively. Food consumption relative to controls during the dosing period was decreased by up to 17 and 15% in HDM and HDF, respectively.

Dose (mg/kg)	Sex	Mean Body Weight (g)			Δ Weight (g)	
		W1	W26	W30	Week 1-26	Week 26-30
0	M	276	540	519	264	-21
	F	185	282	299	97	17
100	M	280	543	N/A	263	N/A
	F	190	296	N/A	106	N/A
300	M	281	531	N/A	250	N/A
	F	190	292	N/A	102	N/A
1000	M	269	471	484	202	13
	F	190	274	286	84	12

Ophthalmoscopy

Main study animals were examined prestudy and during Weeks 12 and 25 by ophthalmoscope and slit lamp biomicroscope; there were no test article-related findings.

ECG

Not evaluated

Hematology, Clinical Chemistry, and Urinalysis

Blood and urine samples were collected during Weeks 13 and 27 from fasted animals; there were no test article-related findings.

Gross Pathology and Organ Weights

There were no test article-related findings.

Histopathology

Adequate Battery: Yes

Abnormalities	Larynx	Seminal Vesicles
Adrenal Glands	Liver	Skeletal Muscle
Aorta	Lungs	Skin
Bone Marrow	Lymph Nodes (cervical)	Spinal Column
Brain	Lymph Nodes (mesenteric)	Spinal Cord
Caecum	Mammary Ares	Spleen
Colon	Nasal Cavity	Stomach
Duodenum	Esophagus	Testes
Epididymides	Optic Nerves	Thymus
Eyes	Ovaries	Thyroid Gland
Harderian Glands	Oviducts	Tongue
Heart	Pancreas	Trachea
Ileum	Parathyroid Gland	Ureters
Jejunum	Rectum	Urinary Bladder
Femur	Salivary Glands	Uterus-cervix
Kidneys	Sciatic Nerve	Vagina

Signed Pathology Report: Yes

Peer Review: No

Histological Findings: In animals that survived to scheduled necropsy, mild to marked epithelial hyperplasia of the nonglandular stomach was observed in 1/15 MDM, 6/13

HDM, and 5/15 HDF. Sub mucosal edema of the non-glandular stomach was observed in 1/15 MDF. After recovery, minimal epithelial hyperplasia of the non-glandular stomach was observed in 1/6 HDM.

Special Evaluation

None

Toxicokinetics

Blood samples from the TK arm were collected and stored but were not analyzed.

Dosing Solution Analysis

Dosing solutions were within 10% of their respective target concentrations.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Polyoxyl 20 Cetostearyl Ether: Oral Fertility and Early Embryonic Development to Implantation Study in Rats

Study no.:	X0640
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 20, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 300, 600, 1200 mg/kg
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Water
Species/Strain:	Wistar rats
Number/Sex/Group:	24/sex/group
Satellite groups:	None
Study design:	Males were dose for at least 4 weeks prior to pairing. Females were dosed for at least 2 weeks prior to pairing, during pairing, and until GD7. Males were euthanized after mating. Females were euthanized on GD15.
Deviation from study protocol:	No significant deviations

Observations and Results

Mortality

Animals were checked twice daily for mortality or signs of morbidity. Five animals were found dead during the study. There were 3 deaths due to gavage error (1 LDM, 1 MDM, 1 HDF), and 2 deaths for which COD was not determined (1 HDM, 1 HDF).

Clinical Signs

Clinical signs were evaluated daily, and included salivation in males and females at all doses and soft feces MD and HD males and females. There were no test article effects on estrous cycle.

Body Weight and Food Consumption

Body weights and food consumption were evaluated in males and females twice weekly during dosing prior to mating. In females, body weights and food consumption were also recorded on GD 3, 6, 9, 12, and 15. Mean body weights were decreased by up to 8% relative to control in HDM; there were no test article effects on mean body weights in females. Decreases in food consumption up to 15 and 10% relative to control were observed in HDM and HDF, respectively.

Toxicokinetics

Not evaluated

Dosing Solution Analysis

All dosing solutions were within 10% of their respective target concentrations.

Necropsy (Fertility Parameters)

There were no test article effects on fertility, spermatogenic cycle or motility, uterine weights, or numbers of implantations, corporal lutea, implantation losses, intrauterine deaths, or viable embryos.

9.2 Embryofetal Development

Study title: Polyoxyl 20 Cetostearyl Ether: Preliminary Embryo-Foetal Development Study in Rats by Oral Administration

Study no.:	Y0130
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 12, 2016
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 125, 300, 750, 1000 mg/kg
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral Gavage
Formulation/Vehicle:	Water
Species/Strain:	Wistar rats
Number/Sex/Group:	6/group
Satellite groups:	None
Study design:	Rats were administered test article from GD 6 to 17. Cesarean section and necropsy were conducted on GD20.
Deviation from study protocol:	No significant deviations

Observations and Results

Mortality, Clinical Signs

Animals were monitored twice daily for mortality or signs of morbidity. Clinical signs were evaluated once daily. There were no deaths. Clinical signs included piloerection at 300 mg/kg (1/6) and 750 mg/kg (5/6) and 1000 mg/kg (4/6).

Body Weight and Food Consumption

Body weights were recorded on GD 0, 6, 9, 12, 15, 17, and 20; there were no test article-related effects. Food consumption was not evaluated.

Toxicokinetics

Not evaluated

Dosing Solution Analysis

Not provided

Necropsy

No test article-related gross findings were observed at necropsy.

Cesarean Section Data

Non dose-dependent increases in numbers of mean corpora lutea, implantations, and viable young were observed in all test article groups relative to control.

Group(s)		Corpora Lutea	Implan-tations	Uterine Deaths Early	Late	Total	Viable young Total	M	F	% Males	Implantation loss (%) Pre	Post	Total	Litter Weight (g)	Mean Foetal Weight (g)
1	Mean	9.00	9.00	0.60	0.00	0.60	8.40	5.80	2.60	73.16	0.00	4.28	4.29	31.06	3.66
	SD	4.69	4.69	1.34	0.00	1.34	4.04	2.77	1.52	16.44	0.00	9.57	9.58	15.16	0.31
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2	Mean	13.60	13.40	0.00	0.00	0.00	13.40*	6.00	7.40*	44.73*	1.42	0.00	1.43	49.91	3.72
	SD	0.55	0.55	0.00	0.00	0.00	0.55	1.58	1.52	11.70	3.18	0.00	3.19	2.86	0.11
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
3	Mean	13.00	12.67	0.17	0.17	0.33	12.33	6.17	6.17*	49.62*	2.47	2.90	5.27	46.22	3.75
	SD	1.67	1.63	0.41	0.41	0.52	1.97	1.83	1.47	11.54	3.83	4.50	6.38	7.14	0.16
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
4	Mean	14.00	14.00	0.33	0.00	0.33	13.67*	7.67	6.00*	56.59	0.00	2.30	2.30	50.62	3.70
	SD	1.41	1.41	0.52	0.00	0.52	1.37	1.37	2.00	11.52	0.00	3.57	3.57	5.51	0.11
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
5	Mean	12.83	12.83	0.17	0.17	0.33	12.50*	5.67	6.83*	44.70*	0.00	2.90	2.89	45.74	3.61
	SD	2.48	2.48	0.41	0.41	0.52	2.59	1.97	1.72	10.17	0.00	4.74	4.74	12.14	0.32
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6

= Body weight at necropsy minus gravid uterus weight, minus body weight at Day 0 of pregnancy
* = mean value of group is significantly different from control
Statistical analysis: Kruskall Wallis test
William's test if group differences are different from control at p < 0.05

(Sponsor's Table)

Offspring

There were no test article-related external findings.

Study title: Polyoxyl 20 Cetostearyl Ether: Oral Embryo-Foetal Development Study in Rats

Study no.:	X0660
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 21, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 300, 600, 1200 mg/kg
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Water
Species/Strain:	Female Wistar rats
Number/Sex/Group:	24/group
Satellite groups:	None
Study design:	Animals were dosed from GD 6 to 17. Cesarean section and necropsy was conducted on GD 20.
Deviation from study protocol:	No significant deviations

Observations and Results

Mortality and Clinical Signs

Animals were checked twice daily for mortality or signs of morbidity. Clinical signs were evaluated at least once daily. One LDF (X0660089) and one MDF (X0660121) were found dead on GD 14 and 11, respectively. COD in both cases was thought to be gavage error. Piloerection was observed in 1/24 MDF and 2/24 HDF; rales were observed in 1/24 MDF and 1/24 HDF.

Body Weight and Food Consumption

Body weights and food consumption were recorded on GD 0, 6, 9, 12, 17, and 20. There were no test article effects on body weights or food consumption.

Toxicokinetics

Not evaluated.

Dosing Solution Analysis

Dosing solutions were within 10% of their respective target concentrations.

Necropsy

There were no test article-related gross findings at necropsy.

Cesarean Section Data

There were no test article effects on uterus weight, numbers of implantations, corpora lutea, implantation loss, intrauterine deaths, viable fetuses, or male/female ratios.

Offspring

There were no test article-related external, skeletal, or visceral findings.

Study title: Polyoxyl 20 Cetostearyl Ether: Screening Study in Rabbits

Study no.:	E0113
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 2, 2016
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Findings

In the escalating phase, doses of 100, 300, or 750 mg/kg test article were administered once daily for 4 days by oral gavage to 3 female NZW rabbits; the MTD was defined as 300 mg/kg based on 1 death after 2 days of dosing at 750 mg/kg.

For the fixed phase of the study, 300 mg/kg was administered once daily by oral gavage to 3 female NZW rabbits for 14 days. One animal was euthanized *in extremis* on Day 5, with clinical signs including decreased activity, rales, pale appearance, and mucoid feces and diarrhea; gross findings at necropsy included darkening/reddening of the pyloric mucosa of the stomach. There were no abnormal clinical signs or gross findings (at necropsy) in the remaining two animals.

Study title: Polyoxyl 20 Cetostearyl Ether: Preliminary Oral Embryo-Foetal Development Study in Rabbits

Study no.:	Y0140
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 22, 2017
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 62.5, 125, 250 mg/kg
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Water
Species/Strain:	NNZW rabbit
Number/Sex/Group:	6 females/group
Satellite groups:	None
Study design:	Rabbits were dosed from GD 6 to 19. Cesarean sections were conducted on GD 29.
Deviation from study protocol:	No significant deviations

Observations and Results

Mortality and Clinical Signs

All animals were monitored twice daily for mortality or signs of morbidity. Clinical signs were evaluated once daily. One HDF was found dead on GD 11; necropsy revealed darkening/reddening of the fundic mucosa of the stomach, which, according to the sponsor, “may have contributed to its death.” One HDF was euthanized after aborting on GD24. One LDF and 1 HDF were found not pregnant on Day 29. Clinical signs included soft feces in the animal that was found dead.

Body Weight and Food Consumption

Body weights were recorded on GD 3, 6, 9, 12, 15, 19, 21, 23, 26, and 29. Food consumption was not evaluated. There were no test article effects on body weights.

Toxicokinetics

Not evaluated

Dosing Solution Analysis

Not provided

Necropsy

In animals that survived to scheduled necropsy, there were no test article-related gross findings or effects on uterus weight.

Cesarean Section Data

There were no test article effects on corporal lutea, implantations, early, late, or total intrauterine deaths, viable young, male/female ratios, pre- or post-implantation loss, or mean fetal weights.

Offspring

There were no test article-related malformations.

Study title: Polyoxyl 20 Cetostearyl Ether: Oral Embry-Foetal Development Study in Rabbits with Toxicokinetic Profile

Study no.:	X0630
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 22, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 50, 100, 200 mg/kg
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Water
Species/Strain:	NZW rabbits
Number/Sex/Group:	20 females/group (main); 4 females/group (tk)
Satellite groups:	50, 100, 200 mg/kg for TK
Study design:	Animals were dosed from GD 6 to 19. Cesarean sections were conducted on GD 29.
Deviation from study protocol:	TK samples were not analyzed.

Observations and Results

Mortality and Clinical Signs

All animals were evaluated twice daily for mortality or signs of morbidity. Clinical signs were evaluated once daily. One HDF was found dead on GD 23; COD was thought to be related to findings of thinned mucosa and an “abnormal open area” in the fundic mucosa of the stomach. The numbers of pregnant females on GD 29 were 20 (C), 18 (LDF), 17 (MDF), and 17 (HDF). Clinical signs included reduced feces in 14/20 HDF.

Body Weight and Food Consumption

Body weights were recorded on GD 3, 6, 9, 12, 15, 19, 21, 23, and 26. Food consumption was recorded on GD 3, 6, 9, 12, 15, 19, 23, and 29. Mean body weights in HDF were reduced 8 to 9% relative to controls from GD 12 to 29. Mean food consumption in HDF were reduced 27 to 40% relative to controls from GD 9 to 19.

Toxicokinetics

Blood samples for TK were collected on GD 6 and 19 but were not analyzed.

Dosing Solution Analysis

Dosing solutions were within 10% of their respective target concentrations

Necropsy

There were no test article-related gross findings in animals that survived until scheduled necropsy.

Cesarean Section Data

Increases in early uterine death and postimplantation loss were observed in HDF. There were no test article effects on uterine weight, corpora lutea, implantations, male/female ratios, or mean fetal weight.

Group(s)		Corpora Lutea	Implan-tations	Uterine Deaths Early	Uterine Deaths Late	Uterine Deaths Total	Viable young Total	Viable young m	Viable young f	% males	Implantation loss (%) Pre	Implantation loss (%) Post	Implantation loss (%) Total	Litter Weight (g)	Mean Foetal Weight (g)
1	Mean	9.65	9.20	0.10	0.15	0.25	8.95	4.60	4.35	50.34	4.78	2.38	7.07	364.4	40.97
	SD	1.50	1.64	0.31	0.49	0.55	1.47	2.11	1.63	18.88	7.14	4.98	8.12	51.42	3.36
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20
2	Mean	9.11	8.61	0.17	0.11	0.28	8.33	4.50	3.83	53.87	5.02	3.21	8.10	328.6	39.96
	SD	1.91	1.65	0.38	0.47	0.57	1.68	1.47	1.42	14.43	8.74	6.49	10.31	62.50	5.46
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	18
3	Mean	8.88	8.59	0.18	0.06	0.24	8.35	4.65	3.71	54.82	2.99	2.51	5.50	328.4	39.89
	SD	2.09	1.97	0.39	0.24	0.44	1.90	1.97	1.40	15.44	5.71	4.71	6.23	66.20	5.20
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17
4	Mean	9.00	8.76	0.94	0.24	1.18*	7.59	4.00	3.59	54.30	2.31	13.28*	14.82	295.4*	40.42
	SD	2.18	2.05	1.52	0.56	1.47	2.27	1.12	1.73	13.42	6.79	15.82	18.34	61.05	6.64
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17

* Statistically significant different from control group value at p < 0.05

(Sponsor’s Table)

Offspring

There were no test article-related external, visceral, or skeletal malformations.

9.3 Prenatal and Postnatal Development

Study title: Polyoxyl 20 Cetostearyl Ether: Oral Pre- and Postnatal Toxicity Study in Rats, Including Maternal Function

Study no.:	X0650
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 22, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Polyoxyl 20 cetostearyl ether, Batch Z000966372, purity not provided

Methods

Doses:	0, 100, 300, 1000 mg/kg
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Water
Species/Strain:	Wistar rats
Number/Sex/Group:	24 females/group (F0); 24/sex/group (F1)
Satellite groups:	None
Study design:	F0 animals were dosed from GD 6 to PND 20, and were allowed to deliver offspring. F1 offspring were mated, and F2 offspring were sacrificed on PND 21.
Deviation from study protocol:	No significant deviations.

Observations and Results

F_0 Dams

Survival:	Animals were monitored twice daily for mortality or signs of morbidity. One HDF was euthanized on PND 0 due to decreased activity, pale appearance, and reduced body temperature. A second HDF was euthanized on PND18 after cannibalizing its litter.
Clinical signs:	Clinical signs were evaluated once daily, and consisted of piloerection in MDF and HDF
Body weight:	Body weights were recorded on GD 0, 6, 9, 12, 15, and 20, and PND 1, 4, 7, 14, and 21; there was no test article effect
Food consumption:	Food consumption was recorded on GD 0, 6, 9, 12, 15, and 20, and PND 0, 7, 14, and 21; there was no test article effect
Uterine content:	No test article effect
Necropsy observation:	No test article-related gross findings or effects on corpora lutea, implantation sites, preimplantation loss, intrauterine loss, or total litter size.
Toxicokinetics:	Not evaluated
Dosing Solution Analysis	Dosing solutions were within 10% of their respective target concentrations.
Other:	N/A

F_1 Generation

Survival:	All offspring were evaluated twice daily for mortality or signs of morbidity; there were no test article effects
Clinical signs:	After weaning, clinical signs were evaluated once daily; there were no test article effects
Body weight:	Male body weights were recorded weekly from weaning until termination. Female body weights were recorded weekly from weaning until mating, and on GD 0, 6, 9, 12, 15, and 20, and PND 1, 4, 7, 14, and 21. There were no test article effects on body weights.
Food consumption:	Not evaluated
Physical development:	There were no test article-effects on pinna unfolding, hair growth, incisor eruption, startle response, eye opening, air righting reflex, or pupil reflex.
Neurological assessment:	Motor activity was evaluated by open field during Weeks 6 and 7. Learning and memory was evaluated by water-filled Y-maze during Weeks 7 and 8. There were no test article effects on motor activity or learning and memory.
Reproduction:	The onset of vaginal opening was monitored from weaning until occurrence. Testes descent and scrotal development were checked at 5 to 6 weeks of age. Animals were paired for mating at 11 weeks of age. There were no test article effects on reproduction.
Other:	N/A

F_2 Generation

Survival:	Pups were monitored until sacrifice at PND 21; there was no test article-related mortality.
Body weight:	Pups were weighed on PND 1, 4, 7, 14, and 21; there were no test article effect on body weights.
External evaluation:	There were no test article effects on external appearance, pinna detachment, hair growth, upper incisor eruption, startle response, eye opening, or air righting.
Male/Female ratio:	There were no test article effects on sex ratio.
Other:	N/A

11 Integrated Summary and Safety Evaluation

Tiglutik is an oral suspension of riluzole, developed under the 505(b)(2) pathway by Italfarmco S.p.A. for the treatment of amyotrophic lateral sclerosis (ALS). The approved riluzole product (Rilutek) is the Reference Listed Drug. The proposed dose for tiglutik is 50 mg twice daily, which would result in a daily oral dose of 20 mg polyoxyl 20 cetostearyl ether. Because this excipient is not present in orally-administered, FDA-approved drug products, the sponsor conducted general toxicity studies in rat and a complete battery of reproductive and developmental toxicity studies. Additionally, the sponsor conducted a non-GLP study in beagle dogs, demonstrating comparable PK (i.e., bioavailability, $t_{1/2}$, C_{max}, and AUC) for riluzole following administration of 5 mg/kg tiglutik or crushed Rilutek tablets. Carcinogenicity was not evaluated for polyoxyl 20 cetostearyl ether.

The general toxicity of polyoxyl 20 cetostearyl ether administered by daily oral gavage was evaluated in GLP-compliant 2-week (0, 50, 125, 300, and 750 mg/kg) and 6-month (0, 100, 300, or 1000 mg/kg with 4-week recovery) studies in male and female Wistar rats. There were no test article-related findings in the 2-week dose range-finding study. In the 6-month study, there were 5 deaths in TK animals for which COD was not determined due to cannibalization or tissue autolysis, with the exception of one LDF that died due to gavage error. However, 2/15 HDM from the main study were found dead, and COD was thought to be GI toxicity (erosion/ulceration of the nonglandular stomach). In surviving animals, clinical signs included decreases in food consumption and corresponding reductions in body weight gain in HDM and HDF. Histological findings included mild to marked epithelial hyperplasia of the nonglandular stomach in 1/15 MDM, 6/13 HDM, and 5/15 HDF. Minimal epithelial hyperplasia was still evident in 1/6 HDM after the 4-week recovery period. The NOAEL for the 6-month study was 100 mg/kg based on GI toxicity. Although blood samples were collected from satellite TK animals, no analysis was performed.

The reproductive and developmental toxicity of orally-administered polyoxyl 20 cetostearyl ether was evaluated by GLP-compliant fertility, embryofetal development, and pre- and postnatal development studies in Wistar rats and an embryofetal development study in New Zealand White (NZW) rabbits. There were no test article-related effects on fertility following oral administration of up to 1200 mg/kg/day for 4 or 2 weeks in males or females, respectively, prior to pairing. In the embryofetal development study in rats, doses up to 1200 mg/kg administered on GD 6-17 did not result in any test article-related fetal toxicity. In the embryofetal development study in rabbits (0, 50, 100, or 200 mg/kg), test article was administered from GD 6 to 19; increases in intrauterine death and postimplantation loss occurred at the HD. Additionally, 1 HDF was found dead, possibly due to test article toxicity to the stomach mucosa. There were no test article-related effects on offspring in a pre- and postnatal development study in rats administered up to 1000 mg/kg test article by oral gavage from GD 6 to PND 20.

In the sponsor's nonclinical studies, the primary toxicities associated with oral administration of polyoxyl 20 cetostearyl ether included irritation of the stomach mucosa

in rats and rabbits (NOAEL = 100 mg/kg), and increases in intrauterine death and postimplantation loss in rabbits (NOAEL = 100 mg/kg). No TK data were provided; however, safety margins for the maximum human daily oral dose of 20 mg/day polyoxyl 20 cetostearyl ether are 49- and 98-fold (based on body surface area) at the NOAEL in rats and rabbits, respectively.

12 Recommendations

Tiglutik is approvable from a nonclinical perspective; however, as a post-marketing requirement, the carcinogenic potential of polyoxyl 20 cetostearyl ether should be evaluated in a carcinogenicity study in one species.

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/s/

DAVID L CARBONE
04/23/2018

LOIS M FREED
04/23/2018

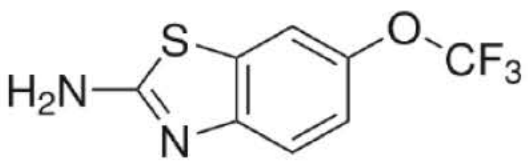
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Pharmacology/Toxicology 30-Day IND Safety Memorandum

Application Number:	IND 123532
Serial Number:	0000
Supporting Document Number:	5
Sponsor's Letter Date:	10/30/2015
Received Date:	10/30/2015
Product:	Teglutik® (riluzole oral suspension)
Indication:	Amyotrophic Lateral Sclerosis
Sponsor:	Italfarmco S.p.A.
Review Division:	Neurology Products
Reviewer:	David L. Carbone, Ph.D.
Supervisor:	Lois M. Freed, Ph.D.
Division Director:	Billy Dunn, M.D.
Project Manager:	Susan B. Daugherty, RN, BSN

Drug Information

Code Name: ITF2985
CAS No: 1744-22-5
Generic Name: Riluzole
Trade Name: Teglutik®
Molecular Formula: $C_8H_5F_3N_2OS$
Molecular Weight: 234.2 g/mol
Chemical Name: 6-(trifluoromethoxy)-2-benzothiazolamine
Pharmacologic class: Late sodium current (late I_{Na}) inhibitor
Structure:



Clinical Formulation: 5 mg/mL riluzole suspension with the following excipients:

Ingredients	Function	Composition for 100 mL (% w/v)	Reference	FDA IIG Acceptable Limit and/or GRAS
Sorbitol, (non-crystallising) (b) (4) (b) (4)	(b) (4)	(b) (4)	USP	(b) (4)
Aluminum Magnesium Silicate (b) (4)			USP	
Xanthan Gum			USP	
Saccharin Sodium			USP	
Simethicone (emulsion (b) (4))			USP	
Sodium Laurylsulfate			USP	
Polyoxyl 20 Cetostearyl Ether (b) (4) (b) (4)			USP	
Purified Water			USP	

(Sponsor's Table)

(b) (4)

Relevant INDs, NDAs, and DMFs:
A letter of authorization for MF-(b) (4) (riluzole) was provided. Riluzole is approved for ALS (NDA-020599).

Previous Reviews Referenced
None

Previous Clinical Experience
Riluzole is approved in the United States for ALS.

Proposed Clinical Protocols
DSC/155/2985/04: "A Phase 1, open-label, pharmacokinetic comparison of riluzole 50 mg/10 mL oral suspension vs. rilutek 50 mg tablet and an estimation of the food-effect on riluzole 50 mg/10 mL oral suspension after single dose in healthy volunteers." The primary objective of this study is to compare PK of the 50 mg riluzole oral suspension with Rilutek 50 mg tablets in 36 healthy male or female volunteers between 18 and 55 years of age. Three treatment periods are proposed, consisting of (A) the oral suspension under fasting conditions, (B) Rilutek under fasting conditions, and the (C) oral suspension under fed conditions. There will be a washout period of 5 days between doses.

Brief Discussion of Nonclinical Data
Bioavailability:
TR#1195/1: A non-GLP study evaluated the bioavailability and PK profile of approximately 5 mg/kg riluzole following oral gavage of ITF2985 or (b) (4) riluzole to male Sprague-Dawley rats (48/group; 6/timepoint). A comparison of the two formulations indicated similar bioavailability and pharmacokinetics of riluzole.

RILUZOLE		
Compound	riluzole suspension	Rilutek® capsules
Dose (mg/kg)	4.85	5.90
C_{max} (ng/mL)	908	990
t_{max} (h)	4	6
C_{last} (ng/mL)	21	11
t_{last} (h)	16	16
$t_{1/2}$ (h)	1.75	1.45
AUC (h*ng/mL)	9375	9968
F_{rel} %	114.3	100

(Sponsor's Table)

Excipients:
Polyoxyl 20 cetostearyl ether is used in Teglutik at a concentration of (b) (4)% w/v. Based on the proposed dose, the total daily intake of the excipient will be (b) (4)).

(b) (4)

Recommendations
This IND proposes a new formulation of riluzole for ALS. Although the safety profile for riluzole is well-established, the excipient, polyoxyl 20 cetostearyl ether, has not been qualified. According to the sponsor, no adverse effects have been reported for orally-administered products marketed in Europe that contain polyoxyl 20 cetostearyl ether; however, there are no nonclinical data supporting the safety of this excipient. Given the experience in humans, the proposed study may proceed at the discretion of the medical officer.

Key Points from 30-Day SRD Meeting
The following comment was added to the May Proceed Letter:

You have not documented that the excipient, polyoxyl 20 cetostearyl ether, is present in an FDA-approved oral drug product at a level resulting in a daily dose similar to or higher than that anticipated for ITF2985. Therefore, additional nonclinical data may be needed to support clinical development of ITF2985.

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/s/

DAVID L CARBONE
12/22/2015

LOIS M FREED
12/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DATE: June 8, 2015

TO: File, to serve as the review of SDN004, dated 12/16/2014

THROUGH: Lois M. Freed, PhD, Supervisory Pharmacologist, DNP

FROM: Rick A. Houghtling, PhD, Nonclinical Reviewer, DNP

SUBJECT: IND 123532 SDN 004, Request for clarification and feedback

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History
Italfarmaco S.p.A. is developing Teglutik (riluzole oral suspension) as a treatment for patients with Amyotrophic Lateral Sclerosis (ALS). A single dose PK study in humans was planned to generate the data needed for a 505(b)(2) submission. In response to a Pre-IND meeting package (received 10/14/2014), Meeting Minutes (WRO) were sent to the sponsor on 11/25/2014, that addressed questions related to development of Teglutik.

(b) (4)

[redacted]

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/s/

RICHARD A HOUGHTLING
06/09/2015

LOIS M FREED
06/09/2015