

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20599 S-013

Trade Name: Rilutek

Generic Name: riluzole

Sponsor: Covis Pharma Sarl

Approval Date: Novembe 16, 2009

Indications: Treatment of patients with amyotrophic lateral sclerosis

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
NDA 20599 S-013**

CONTENTS

Reviews / Information Included in this NDA Review.

| | |
|---------------------------------------------------------|----------|
| Approval Letter | X |
| Approvable Letter | |
| Labeling | X |
| Summary Review | |
| Officer/Employee List | |
| Office Director Memo | |
| Cross Discipline Team Leader Review | |
| Medical Review(s) | X |
| Chemistry Review(s) | |
| Environmental Assessment | |
| Pharmacology Review(s) | |
| Statistical Review(s) | |
| Microbiology Review(s) | |
| Clinical Pharmacology/Biopharmaceutics Review(s) | |
| Risk Assessment and Risk Mitigation Review(s) | |
| Proprietary Name Review(s) | |
| Other Review(s) | X |
| Administrative/Correspondence Document(s) | X |

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20599 S-013

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-599/S-013

SUPPLEMENT APPROVAL

Sanofi Aventis U.S., L.L.C.
Attention: Jo Beth Crimmins, Specialist, Product Support
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Crimmins:

Please refer to your supplemental new drug application dated April 9, 2009, received April 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rilutek (riluzole) Tablets.

This "Changes Being Effected" supplemental new drug application provides for revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labeling to add information regarding interstitial lung disease and hypersensitivity pneumonitis.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 20-599/S-013.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

We request that you issue a Dear Health Care Professional letter communicating this new safety related information. Please submit a copy of the letter to this NDA for comment prior to issuance.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-20599

SUPPL-13

SANOFI AVENTIS
US LLC

RILUTEK (RILUZOLE) 50MG
TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
11/16/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

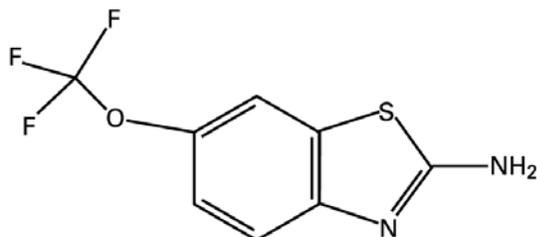
APPLICATION NUMBER:
NDA 20599 S-013

LABELING

RILUTEK®
(riluzole) Tablets
Rx only

DESCRIPTION

RILUTEK® (riluzole) is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-(trifluoromethoxy)benzothiazole. Its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2. Its structural formula is as follows:



Riluzole is a white to slightly yellow powder that is very soluble in dimethylformamide, dimethylsulfoxide and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1 N HCl and very slightly soluble in water and in 0.1 N NaOH. RILUTEK is available as a capsule-shaped, white, film-coated tablet for oral administration containing 50 mg of riluzole. Each tablet is engraved with “RPR 202” on one side.

Inactive Ingredients:

Core: anhydrous dibasic calcium phosphate, USP; microcrystalline cellulose, NF; anhydrous colloidal silica, NF; magnesium stearate, NF; croscarmellose sodium, NF.

Film coating: hypromellose, USP; polyethylene glycol 6000; titanium dioxide, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

The etiology and pathogenesis of amyotrophic lateral sclerosis (ALS) are not known, although a number of hypotheses have been advanced. One hypothesis is that motor neurons, made vulnerable through either genetic predisposition or environmental factors, are injured by glutamate. In some cases of familial ALS the enzyme superoxide dismutase has been found to be defective.

The mode of action of RILUTEK is unknown. Its pharmacological properties include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.

Riluzole has also been shown, in a single study, to delay median time to death in a transgenic mouse model of ALS. These mice express human superoxide dismutase bearing one of the mutations found in one of the familial forms of human ALS.

It is also neuroprotective in various *in vivo* experimental models of neuronal injury involving excitotoxic mechanisms. In *in vitro* tests, riluzole protected cultured rat motor neurons from the excitotoxic effects of glutamic acid and prevented the death of cortical neurons induced by anoxia.

Due to its blockade of glutamatergic neurotransmission, riluzole also exhibits myorelaxant and sedative properties in animal models at doses of 30 mg/kg (about 20 times the recommended human daily dose) and anticonvulsant properties at a dose of 2.5 mg/kg (about 2 times the recommended human daily dose).

Pharmacokinetics

Riluzole is well-absorbed (approximately 90%), with average absolute oral bioavailability of about 60% (CV=30%). Pharmacokinetics are linear over a dose range of 25 to 100 mg given every 12 hours. A high fat meal decreases absorption, reducing AUC by about 20% and peak blood levels by about 45%. The mean elimination half-life of riluzole is 12 hours (CV=35%) after repeated doses. With multiple-dose administration, riluzole accumulates in plasma by about twofold and steady-state is reached in less than 5 days. Riluzole is 96% bound to plasma proteins, mainly to albumin and lipoproteins over the clinical concentration range.

The 50 mg market tablet was equivalent, with respect to AUC, to the tablet used in the dose ranging clinical trials, while the C_{max} was approximately 30% higher. Both tablets have been used in clinical trials. However, if doses greater than those recommended are given, it is likely that higher plasma levels will be achieved, the safety of which has not been established (see DOSAGE AND ADMINISTRATION).

Metabolism and Elimination

Riluzole is extensively metabolized to six major and a number of minor metabolites, not all of which have been identified. Some metabolites appear pharmacologically active in *in vitro* assays. The metabolism of riluzole is mostly hepatic and consists of cytochrome P450-dependent hydroxylation and glucuronidation.

There is marked interindividual variability in the clearance of riluzole, probably attributable to variability of CYP 1A2 activity, the principal isozyme involved in N-hydroxylation.

In vitro studies using liver microsomes show that hydroxylation of the primary amine group producing N-hydroxyriluzole is the main metabolic pathway in human, monkey, dog and rabbit. In humans, cytochrome P450 1A2 is the principal isozyme involved in N-hydroxylation. *In vitro* studies predict that CYP 2D6, CYP 2C19, CYP 3A4 and CYP 2E1 are unlikely to contribute significantly to riluzole metabolism in humans. Whereas direct glucuroconjugation of riluzole (involving the glucurotransferase isoform UGT-HP4) is very slow in human liver microsomes, N-hydroxyriluzole is readily conjugated at the hydroxylamine group resulting in the formation of O- (>90%) and N-glucuronides.

Following a single 150 mg dose of ^{14}C -riluzole to 6 healthy males, 90% and 5% of the radioactivity was recovered in the urine and feces respectively over a period of 7 days. Glucuronides accounted for more than 85% of the metabolites in urine. Only 2% of a riluzole dose was recovered in the urine as unchanged drug.

Special Populations

Hepatic Impairment:

The area-under-the-curve (AUC) of riluzole, after a single 50 mg oral dose, increases by about 1.7-fold in patients with mild chronic liver insufficiency (n=6; Child-Pugh's score A) and by about 3-fold in patients with moderate chronic liver insufficiency (n=6; Child-Pugh's score B) compared to healthy volunteers (n=12) (see WARNINGS and PRECAUTIONS). The pharmacokinetics of riluzole have not been studied in patients with severe hepatic impairment.

Renal Impairment:

There is no significant difference in pharmacokinetic parameters between patients with moderate (n=5; creatinine clearance 30-50 ml.min⁻¹) and severe (n=7; creatinine clearance <30 ml.min⁻¹) renal insufficiency and healthy volunteers (n=12) after a single oral dose of 50 mg riluzole. The pharmacokinetics of riluzole have not been studied in patients undergoing hemodialysis.

Age:

The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole b.i.d.) are not affected in the elderly (≥ 70 years).

Gender:

No gender effect on riluzole pharmacokinetics has been found in young or elderly healthy subjects. However, in one placebo-controlled clinical trial with population pharmacokinetics, riluzole mean clearance was found to be 30% lower in female patients (corresponding to an approximate increase in AUC of 45%) as compared to male patients. No favorable or adverse effects of riluzole in relation to gender were seen in controlled trials, however.

Smoking:

Patients who smoke cigarettes eliminate riluzole 20% faster than non-smoking patients, based on a population pharmacokinetic analysis on data from 128 ALS patients, of whom 19 were smokers. However, there is no need for dosage adjustment in these patients.

Race:

A clinical study conducted to evaluate the pharmacokinetics of riluzole and its metabolite following repeated oral administration twice daily in healthy Japanese and Caucasian adult males showed that there were no significant racial differences in pharmacokinetic parameters between the Japanese and Caucasian subjects.

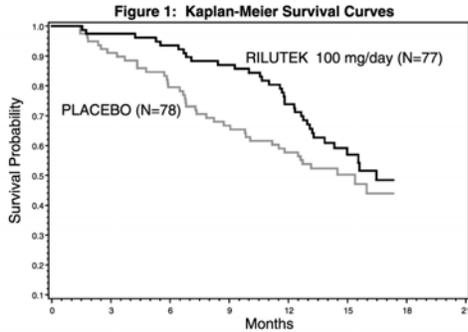
Clinical Trials

The efficacy of RILUTEK as a treatment of ALS was established in two adequate and well-controlled trials in which the time to tracheostomy or death was longer for patients randomized to RILUTEK than for those randomized to placebo.

These studies admitted patients with either familial or sporadic ALS, a disease duration of less than 5 years, and a baseline forced vital capacity greater than or equal to 60%.

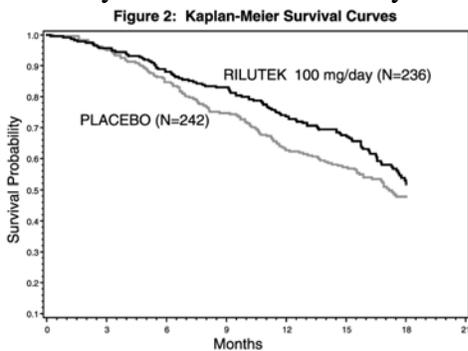
In one study, performed in France and Belgium, 155 ALS patients were followed for at least 13 months (maximum duration 18 months) after being randomized to either 100 mg/day (given 50 mg BID) of RILUTEK or placebo.

Figure 1, which follows, displays the survival curves for time to death or tracheostomy. The vertical axis represents the proportion of individuals alive without tracheostomy at various times following treatment initiation (horizontal axis). Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p=0.12), the difference was found to be significant by another appropriate analysis (Wilcoxon test p=0.05). As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of approximately 90 days. There was no statistically significant difference in mortality at the end of the study.



In the second study, performed in both Europe and North America, 959 ALS patients were followed for at least 1 year (North American centers) and up to 18 months (European centers) after being randomized to either 50, 100, 200 mg/day of RILUTEK or placebo.

Figure 2, which follows, displays the survival curves for time to death or tracheostomy for patients randomized to either 100 mg/day of RILUTEK or placebo. Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test $p = 0.076$), the difference was found to be significant by another appropriate analysis (Wilcoxon test $p = 0.05$). Not displayed in Figure 2 are the results of 50 mg/day of RILUTEK which could not be statistically distinguished from placebo and the results of 200 mg/day which are essentially identical to 100 mg/day. As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of approximately 60 days. There was no statistically significant difference in mortality at the end of the study.



Although riluzole improved early survival in both studies, measures of muscle strength and neurological function did not show a benefit.

INDICATIONS AND USAGE

RILUTEK is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy.

CONTRAINDICATIONS

RILUTEK is contraindicated in patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components.

WARNINGS

Liver Injury / Monitoring Liver Chemistries

RILUTEK should be prescribed with care in patients with current evidence or history of abnormal liver function indicated by significant abnormalities in serum transaminase (ALT/SGPT; AST/SGOT), bilirubin, and/or gamma-glutamyl transferase (GGT) levels (see PRECAUTIONS and DOSAGE AND ADMINISTRATION sections). Baseline elevations of several LFTs (especially elevated bilirubin) should preclude the use of RILUTEK.

RILUTEK, even in patients without a prior history of liver disease, causes serum aminotransferase elevations. Treatment should be discontinued if ALT levels are ≥ 5 X ULN or if clinical jaundice develops.

Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevations > 5 X ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzymes with jaundice (ALT 26 X ULN, AST 17 X ULN, and bilirubin 11 X ULN) four months after starting RILUTEK; these returned to normal 7 weeks after treatment discontinuation.

Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when < 5 times ULN. In trials, if ALT levels were < 5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2 to 6 months. Treatment in studies was discontinued, however, if ALT levels exceeded 5 X ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN. There were rare instances of jaundice. There is limited experience with rechallenge of patients who have had RILUTEK discontinued for ALT > 5 X ULN, but there is the possibility of increased ALT values reoccurring (see PRECAUTIONS: Laboratory Tests). Therefore, rechallenge is not recommended.

In postmarketing experience, cases of clinical hepatitis associated with riluzole have been reported, including with fatal outcome.

Neutropenia

Among approximately 4000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than $500/\text{mm}^3$), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was more complex, with marked anemia as well as neutropenia and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check white blood cell counts.

Interstitial Lung Disease

Cases of interstitial lung disease (see ADVERSE REACTIONS) have been reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

PRECAUTIONS

Use in Patients with Concomitant Disease

RILUTEK should be used with caution in patients with concomitant liver insufficiency (see WARNINGS, CLINICAL PHARMACOLOGY). In particular, in cases of RILUTEK-induced hepatic injury manifested by elevated liver enzymes, the effect of the hepatic injury on RILUTEK metabolism is unknown.

Special Populations

Riluzole should be used with caution in elderly patients whose hepatic function may be compromised due to age. Also, female patients may possess a lower metabolic capacity to eliminate riluzole compared to males (see CLINICAL PHARMACOLOGY: Special Populations).

Information for the Patient

Patients should be advised to report any febrile illness to their physicians (see WARNINGS: Neutropenia).

Patients should be advised to report any cough or difficulties in breathing to their physicians (see WARNINGS: Interstitial Lung Disease).

Patients and caregivers should be advised that RILUTEK should be taken on a regular basis and at the same time of the day (e.g., in the morning and evening) each day. If a dose is missed, take the next tablet as originally planned (see DOSAGE AND ADMINISTRATION).

Patients should be warned about the potential for dizziness, vertigo, or somnolence and advised not to drive or operate machinery until they have gained sufficient experience on RILUTEK to gauge whether or not it affects their mental and/or motor performance adversely.

Whether alcohol increases the risk of serious hepatotoxicity with RILUTEK is unknown; therefore, patients being treated with RILUTEK should be discouraged from drinking excessive amounts of alcohol.

Patients should also be made aware that RILUTEK should be stored at temperatures between 20°-25°C (68°-77°F) and protected from bright light.

RILUTEK must be kept out of the reach of children.

Laboratory Tests

Serum aminotransferases including ALT levels should be measured before and during riluzole therapy. Serum ALT levels should be evaluated every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter.

Serum ALT levels should be evaluated more frequently in patients who develop elevations (see WARNINGS).

As noted in the WARNINGS Section, there is no experience with continued treatment of patients once ALT exceeds 5 X ULN. Treatment should be discontinued if ALT levels are ≥ 5 X ULN or if clinical jaundice develops. There is limited experience with rechallenge of patients who have had RILUTEK discontinued for ALT > 5 X ULN, but there is the possibility of increased ALT values reoccurring. Therefore, rechallenge is not recommended.

In the two controlled trials in patients with ALS, the frequency with which values for hemoglobin, hematocrit, and erythrocyte counts fell below the lower limit of normal was greater in RILUTEK-treated patients than in placebo-treated patients; however, these changes were mild and transient. The proportions of patients observed with abnormally low values for these parameters showed a dose-response relationship. Only one patient was discontinued from treatment because of severe anemia. The significance of this finding is unknown.

Drug Interactions

There have been no clinical studies designed to evaluate the interaction of riluzole with other drugs.

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Hepatotoxic Drugs:

The clinical trials in ALS excluded patients on concomitant medications which were potentially hepatotoxic, (e.g., allopurinol, methyldopa, sulfasalazine). Accordingly, there is no information about the safety of administering RILUTEK in conjunction with such medications. If the practitioner chooses to prescribe such a combination, caution should be exercised.

Drugs Highly Bound To Plasma Proteins:

Riluzole is highly bound (96%) to plasma proteins, binding mainly to serum albumin and to lipoproteins. The effect of riluzole (up to 5 mcg/mL) on warfarin (5 mcg/mL) binding did not show any displacement of warfarin. Conversely, riluzole binding was unaffected by the addition of warfarin, digoxin, imipramine and quinine at high therapeutic concentrations.

Effect of Other Drugs On Riluzole Metabolism:

In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when riluzole is given concurrently with agents that affect CYP 1A2 activity. Potential inhibitors of CYP 1A2 (e.g., caffeine, phenacetin, theophylline, amitriptyline, and quinolones) could decrease the rate of riluzole elimination, while inducers of CYP 1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

Effect of Riluzole On the Metabolism of Other Drugs:

CYP 1A2 is the principal isoenzyme involved in the initial oxidative metabolism of riluzole; potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP 1A2 (e.g., theophylline, caffeine, and tacrine). Currently, it is not known whether riluzole has any potential for enzyme induction in humans.

Drug Laboratory Test Interactions: None known

Carcinogenesis, Mutagenesis, Impairment of Fertility

Riluzole was not carcinogenic in mice or rats when administered for 2 years at daily oral doses up to 20 mg/kg and 10 mg/kg, respectively, which are approximately equivalent to the maximum human dose on a mg/m² basis.

The genotoxic potential of riluzole was evaluated in the bacterial mutagenicity (Ames) test, the mouse lymphoma mutation assay in L5178Y cells, the *in vitro* chromosomal aberration assay in human lymphocytes and the *in vivo* rat cytogenetic assay and *in vivo* mouse micronucleus assay in bone marrow. There was no evidence of mutagenic or clastogenic potential in the Ames test, the mouse lymphoma assay, or the *in vivo* assays in the mouse and rat. There was an equivocal clastogenic response in the *in vitro* human lymphocyte chromosomal aberration assay, which was not reproduced in a second assay performed at equal or higher concentrations; riluzole was therefore considered non-clastogenic in the human lymphocyte assay.

N-hydroxyriluzole, the major active metabolite of riluzole, caused chromosomal damage in the *in vitro* mammalian mouse lymphoma assay and in the *in vitro* micronucleus assay that used the same mouse lymphoma cell line, L5178Y. N-hydroxyriluzole was not mutagenic in this cell line when tested in the HPRT gene mutation assay, and was negative in the Ames bacterial gene mutation assay (with and without rat or hamster S9), the *in vitro* UDS assay in rat hepatocytes, the chromosomal aberration test in human lymphocytes, and the *in vivo* mouse bone marrow micronucleus test.

Riluzole impaired fertility when administered to male and female rats prior to and during mating at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m² basis (see PRECAUTIONS: “Pregnancy” for effects on fertility).

Pregnancy

Pregnancy category C:

Oral administration of riluzole to pregnant animals during the period of organogenesis caused embryotoxicity in rats and rabbits at doses of 27 mg/kg and 60 mg/kg, respectively, or 2.6 and 11.5 times, respectively, the recommended maximum human daily dose on a mg/m² basis. Evidence of maternal toxicity was also observed at these doses.

When administered to rats prior to and during mating (males and females) and throughout gestation and lactation (females), riluzole produced adverse effects on pregnancy (decreased implantations, increased intrauterine death) and offspring viability and growth at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m² basis.

There are no adequate and well-controlled studies in pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

In rat studies, ¹⁴C-riluzole was detected in maternal milk. It is not known whether riluzole is excreted in human breast milk. Because many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants from RILUTEK® is unknown, women should be advised not to breast-feed during treatment with RILUTEK.

Geriatric Use

Age-related compromised renal and hepatic function may cause a decrease in clearance of riluzole (see CLINICAL PHARMACOLOGY: Special Populations). In controlled clinical trials,

about 30% of patients were over 65. There were no differences in adverse effects between younger and older patients.

Pediatric Use

The safety and the effectiveness of RILUTEK in pediatric patients have not been established.

ADVERSE REACTIONS

The most commonly observed AEs associated with the use of RILUTEK more frequently than placebo treated patients were: asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, circumoral paresthesia, anorexia, and somnolence. Asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related.

Approximately 14% (n = 141) of the 982 individuals with ALS who received RILUTEK in pre-marketing clinical trials discontinued treatment because of an adverse experience. Of those patients who discontinued due to adverse events, the most commonly reported were: nausea, abdominal pain, constipation, and ALT elevations. In a dose response study in ALS patients, the rates of discontinuation of RILUTEK for asthenia, nausea, abdominal pain, and ALT elevation were dose related.

Incidence in Controlled ALS Clinical Studies

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with ALS treated with RILUTEK (n=794) participating in placebo-controlled trials and were numerically greater in the patients treated with RILUTEK 100 mg/day than with placebo or for which a dose response relationship is suggested.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the AE incidences in the population studied.

Table 1
Adverse Events Occurring in Placebo-Controlled Clinical Trials

| Body System / Adverse Event† | ‡Percentage of patients reporting events | | | |
|---------------------------------|------------------------------------------|-----------------------------------|-----------------------------------|--------------------|
| | Riluzole 50 mg/day (N=237) | Riluzole 100 mg/day (N=313) | Riluzole 200 mg/day (N=244) | Placebo (N=320) |
| Body as a Whole | | | | |
| Asthenia | 14.8 | 19.2 | 20.1 | 12.2 |
| Headache | 8.0 | 7.3 | 7.0 | 6.6 |
| Abdominal pain | 6.8 | 5.1 | 7.8 | 3.8 |
| Back pain | 1.7 | 3.2 | 4.1 | 2.5 |
| Aggravation reaction | 0.4 | 1.3 | 2.0 | 0.9 |
| Malaise | 0.4 | 0.6 | 1.2 | 0.0 |
| Digestive | | | | |
| Nausea | 12.2 | 16.3 | 20.5 | 10.6 |
| Vomiting | 4.2 | 4.2 | 4.5 | 1.6 |
| Dyspepsia | 2.5 | 3.8 | 6.1 | 5.0 |
| Anorexia | 3.8 | 3.2 | 8.6 | 3.8 |
| Diarrhea | 5.5 | 2.9 | 9.0 | 3.1 |
| Flatulence | 2.5 | 2.6 | 2.0 | 1.9 |

| Body System / Adverse Event† | Riluzole 50 mg/day (N=237) | Riluzole 100 mg/day (N=313) | Riluzole 200 mg/day (N=244) | Placebo (N=320) |
|--------------------------------------------|-------------------------------------------|--------------------------------------------|--------------------------------------------|----------------------------|
| Stomatitis | 0.8 | 1.0 | 1.2 | 0.0 |
| Tooth disorder | 0.0 | 1.0 | 1.2 | 0.3 |
| Oral Moniliasis | 0.4 | 0.6 | 1.2 | 0.3 |
| Nervous | | | | |
| Hypertonia | 5.9 | 6.1 | 5.3 | 5.9 |
| Depression | 4.2 | 4.5 | 6.1 | 5.0 |
| Dizziness | 5.1 | 3.8 | 12.7 | 2.5 |
| Dry mouth | 3.0 | 3.5 | 2.0 | 3.4 |
| Insomnia | 2.1 | 3.5 | 2.9 | 3.4 |
| Somnolence | 0.8 | 1.9 | 4.1 | 1.3 |
| Vertigo | 2.5 | 1.9 | 4.5 | 0.9 |
| Circumoral paresthesia | 1.3 | 1.6 | 3.3 | 0.0 |
| Skin and Appendages | | | | |
| Pruritus | 3.8 | 3.8 | 2.5 | 3.1 |
| Eczema | 0.8 | 1.6 | 1.6 | 0.6 |
| Alopecia | 0.0 | 1.0 | 1.2 | 0.6 |
| Exfoliative dermatitis | 0.0 | 0.6 | 1.2 | 0.0 |
| Respiratory | | | | |
| Decreased lung function | 13.1 | 10.2 | 16.0 | 9.4 |
| Rhinitis | 8.9 | 6.4 | 7.8 | 6.3 |
| Increased cough | 2.1 | 2.6 | 3.7 | 1.6 |
| Sinusitis | 0.4 | 1.0 | 1.6 | 0.9 |
| Cardiovascular | | | | |
| Hypertension | 6.8 | 5.1 | 3.3 | 4.1 |
| Tachycardia | 1.3 | 2.6 | 2.0 | 1.3 |
| Phlebitis | 0.4 | 1.0 | 0.8 | 0.3 |
| Palpitation | 0.4 | 0.6 | 1.2 | 0.9 |
| Postural hypotension | 0.8 | 0.0 | 1.6 | 0.6 |
| Metabolic and Nutritional Disorders | | | | |
| Weight loss | 4.6 | 4.8 | 3.7 | 4.7 |
| Peripheral edema | 4.2 | 2.9 | 3.3 | 2.2 |
| Musculoskeletal System | | | | |
| Arthralgia | 5.1 | 3.5 | 1.6 | 3.4 |
| Urogenital System | | | | |
| Urinary tract infection | 2.5 | 2.6 | 4.5 | 2.2 |
| Dysuria | 0.0 | 1.0 | 1.2 | 0.3 |

Other Adverse Events Observed

Other events which occurred in more than 2% of patients treated with RILUTEK 100 mg/day but equally or more frequently in the placebo group included: accidental injury, apnea, bronchitis, constipation, death, dysphagia, dyspnea, flu syndrome, heart arrest, increased sputum, pneumonia, and respiratory disorder.

The overall adverse event profile for RILUTEK was similar between females and males, and was independent of age. Because the largest non-white racial subgroup was only 2% of patients exposed to RILUTEK (18/794) in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. In ALS studies, dizziness did occur more commonly in females (11%) than in males (4%). There was not a difference between females and males in the rates of discontinuation of RILUTEK for individual adverse experiences.

Other Adverse Events Observed During All Clinical Trials

RILUTEK has been administered to 1713 individuals during all clinical trials, some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 1713 individuals exposed to RILUTEK who experienced an event of the type cited on at least one occasion while receiving RILUTEK. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

* = AE frequency \leq to placebo

Body as a Whole:

Frequent: Hostility*. *Infrequent:* Abscess*, sepsis*, photosensitivity reaction*, cellulitis, face edema*, hernia, peritonitis, attempted suicide, injection site reaction, chills*, flu syndrome, intentional injury, enlarged abdomen, neoplasm. *Rare:* Acrodynia, hypothermia, moniliasis*, rheumatoid arthritis.

Digestive System: *Infrequent:* Increased appetite, intestinal obstruction*, fecal impaction, gastrointestinal hemorrhage, gastrointestinal ulceration, gastritis*, fecal incontinence, jaundice, hepatitis, glossitis, gum hemorrhage*, pancreatitis, tenesmus, esophageal stenosis. *Rare:* Cheilitis*, cholecystitis, hematemesis, melena*, biliary pain, proctitis, pseudomembranous enterocolitis, enlarged salivary gland, tongue discoloration, tooth caries.

Immune System Disorders: *Infrequent:* Anaphylactoid reaction and anaphylaxis.

Nervous System: *Frequent:* Agitation*, tremor. *Infrequent:* Hallucinations, personality disorder*, abnormal thinking*, coma, paranoid reaction*, manic reaction, ataxia, extrapyramidal syndrome, hypokinesia, urinary retention, emotional lability, delusions, apathy, hypesthesia, incoordination, confusion*, convulsion, leg cramps, amnesia, dysarthria, increased libido, stupor, subdural hematoma, abnormal gait, delirium, depersonalization, facial paralysis, hemiplegia, decreased libido, myoclonus. *Rare:* Abnormal dreams, acute brain syndrome, CNS depression, dementia, cerebral embolism, euphoria*, hypotonia, ileus*, peripheral neuritis, psychosis*, psychotic depression, schizophrenic reaction, trismus, wristdrop.

Skin and Appendages: *Infrequent:* Skin ulceration, urticaria, psoriasis, seborrhea*, skin disorder, fungal dermatitis*. *Rare:* Angioedema, contact dermatitis, erythema multiforme, furunculosis*, skin moniliasis, skin granuloma, skin nodule.

Respiratory System: *Infrequent:* Hiccup, pleural disorder*, asthma, epistaxis, hemoptysis, yawn, hyperventilation*, lung edema*, hypoventilation*, lung carcinoma, hypoxia, laryngitis, pleural effusion, pneumothorax*, respiratory moniliasis, stridor, interstitial lung disease, hypersensitivity pneumonitis.

Cardiovascular System: *Infrequent:* Syncope*, hypotension, heart failure, migraine, peripheral vascular disease, angina pectoris*, myocardial infarction*, ventricular extrasystoles, cerebral hemorrhage, atrial fibrillation*, bundle branch block, congestive heart failure, pericarditis, lower extremity embolus, myocardial ischemia*, shock*. *Rare:* Bradycardia, cerebral ischemia,

hemorrhage, mesenteric artery occlusion, subarachnoid hemorrhage, supraventricular tachycardia*, thrombosis, ventricular fibrillation, ventricular tachycardia.

Metabolic and Nutritional Disorders: *Infrequent:* Gout*, respiratory acidosis, edema, thirst*, hypokalemia, hyponatremia, weight gain*. *Rare:* Generalized edema, hypercalcemia, hypercholesteremia.

Endocrine System: *Infrequent:* Diabetes mellitus, thyroid neoplasia. *Rare:* Diabetes insipidus, parathyroid disorder.

Hemic and Lymphatic System: *Infrequent:* Anemia*, leukocytosis, leukopenia, ecchymosis. *Rare:* Neutropenia, aplastic anemia, cyanosis, hypochromic anemia, iron deficiency anemia, lymphadenopathy, petechiae*, purpura.

Musculoskeletal System: *Infrequent:* Arthrosis, myasthenia*, bone neoplasm. *Rare:* Bone necrosis, osteoporosis, tetany.

Special Senses: *Infrequent:* Amblyopia, ophthalmitis. *Rare:* Blepharitis, cataract, deafness, diplopia*, ear pain, glaucoma, hyperacusis, photophobia, taste loss, vestibular disorder.

Urogenital System: *Infrequent:* Urinary urgency, urine abnormality, urinary incontinence, kidney calculus, hematuria, impotence, prostate carcinoma, kidney pain, metrorrhagia, priapism. *Rare:* Amenorrhea, breast abscess, breast pain, nephritis*, nocturia, pyelonephritis, enlarged uterine fibroids, uterine hemorrhage, vaginal moniliasis.

Laboratory Tests: *Infrequent:* Increased gamma glutamyl transferase, abnormal liver function/tests, increased alkaline phosphatase, positive direct Coombs test, increased gamma globulins. *Rare:* increased lactic dehydrogenase.

OVERDOSAGE

No specific antidote or information on treatment of overdose with RILUTEK is available. In the event of overdose, RILUTEK therapy should be discontinued immediately. Experience with riluzole overdose in humans is limited. Neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma, and methemoglobinemia have been observed in isolated cases. Treatment should be supportive and directed toward alleviating symptoms.

Severe methemoglobinemia may be rapidly reversible after treatment with methylene blue.

The estimated oral median lethal dose is 94 mg/kg and 39 mg/kg for male mice and rats, respectively.

DOSAGE AND ADMINISTRATION

The recommended dose for RILUTEK is 50 mg every 12 hours. No increased benefit can be expected from higher daily doses, but adverse events are increased.

RILUTEK tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability.

Special Populations

Patients with Impaired Hepatic Function: see WARNINGS, PRECAUTIONS, CLINICAL PHARMACOLOGY.

HOW SUPPLIED

RILUTEK 50 mg tablets are white, film-coated, capsule-shaped and engraved with “RPR 202” on one side. RILUTEK is supplied in bottles of 60 tablets, NDC 0075-7700-60.

**STORE AT CONTROLLED ROOM TEMPERATURE 20°-25°C (68°-77°F) AND
PROTECT FROM BRIGHT LIGHT.
KEEP OUT OF THE REACH OF CHILDREN.**

Revised March 2009

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

© 2009 sanofi-aventis U.S. LLC

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20599 S-013

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

| | |
|--------------------------------|----------------------------------------------------------------------------|
| NDA (Serial Number) | 20,599 |
| Sponsor: | Sanofi-Aventis |
| Drug: | Rilutek[®] (riluzole) |
| Proposed Indication: | Amyotrophic Lateral Sclerosis |
| Material Submitted: | Proposed Labeling, Literature |
| Correspondence Date: | April 09, 2009 |
| Date Received / Agency: | April 09, 2009 |
| Date Review Completed | October 09, 2009 |
| Reviewer: | Christopher D. Breder, M.D., Ph.D. Medical Reviewer, DNP, ODE I |

1. Introduction

Riluzole is a chemical entity of the benzothiazole class. Riluzole appears to have several mechanisms of action, including an indirect blockade of excitatory amino-acid receptor mediated responses, inhibition of glutamic acid release, inactivation of voltage dependent sodium channels and stimulation of a G-protein dependent signal transduction pathway. It is approved for use in the following indications: extension of lifetime or the time to mechanical ventilation for patients with ALS. The FDA granted approval to Sanofi-Aventis to market riluzole (Rilutek) on December 12, 1995 (NDA# 20-599).

2. Proposed labeling Changes

On April 09, 2009, in accordance with 21 CFR §314.70 (c)(6)(iii) Sanofi-Aventis U.S. submitted a Change Being Effected (CBE) Supplement to advise the agency of changes made to the package insert for Rilutek[®].

Under the WARNINGS section, the following new header and paragraph have been added:

"Interstitial Lung Disease

Cases of interstitial lung disease (see ADVERSE REACTIONS) have been reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment."

Under PRECAUTIONS, Information for the Patient, the following statement has been added:

"Patients should be advised to report any cough or difficulties in breathing to their physicians (see WARNINGS: Interstitial Lung Disease)."

Under ADVERSE REACTIONS, Other Adverse Events Observed During All Clinical Trials, Respiratory System, the following have been added: "interstitial lung disease, hypersensitivity pneumonitis".

This was reportedly predicated by their observation of 8 cases of interstitial lung disease were identified in the clinical trials (observational and phase III studies irrespective of the indications). Of them, 1 case report was identified in the four pivotal phase III ALS studies. Following the above-described methodology, for the determination of frequency in the ALS population, 1 out of 493 (0.2%) ALS patients treated with Riluzole 100 mg/day in phase III placebo controlled studies reported an adverse reaction of "interstitial lung disease". (b) (4)

Evaluation of these cases by this medical reviewer into causality including the temporal relationship and discontinuation effect and alternative therapeutic explanations were suggestive of a role for riluzole in most of these cases, although given the occurrence of pneumonia and the natural history of ALS, a definitive relationship could not be firmly established. This medical reviewer wanted to independently evaluate the strength of the ILD signal in patients taking Rilutek. The Division therefore consulted OSE to develop an AERS search strategy for interstitial lung disease/hypersensitivity pneumonitis related to riluzole to assess a) the strength of any signal, b) if there are particular populations or associated previous medical history, concomitant medications, or similar associated factors, and c) the evolution and outcome of these cases.

3. Summary of the OSE Consult

On September 15, 2009, Empirica was searched to identify data mining scores related to interstitial lung disease using the following criteria:

Adverse event term: MedDRA1 preferred term with hierarchy level:

- HLT - Lower respiratory tract inflammatory and immunologic conditions
 - Includes the following PTs: alveolitis, alveolitis fibrosing, pneumonitis
- HLT - Parenchymal lung disorders NEC
 - Includes the following PTs: interstitial lung disease, lung infiltration, pulmonary fibrosis, pulmonary toxicity
- PT - Acute respiratory distress syndrome
- PT - Obliterative bronchiolitis

¹ MedDRA = the Medical Dictionary for Regulatory Activities

Drug Product criteria:

- Riluzole

A search of AERS identified 540 reports of any event ever reported to riluzole. A second search to identify cases of ILD revealed 46 reports including five duplicates. Twenty-four were excluded from further review for the following reasons:

Table 1 Reasons for Excluded Cases

| Reason for elimination | Count of eliminated cases |
|-------------------------------------|----------------------------------|
| Atelectasis | 9 |
| Aspiration pneumonia | 5 |
| Not temporal | 4 |
| Unspecified pneumonia | 2 |
| Viral infection and not temporal | 1 |
| Confounded by drug – bromocriptine* | 1 |
| Unrelated | 1 |
| Not enough detail | 1 |

*labeled for pulmonary fibrosis and pulmonary infiltrates

The remaining 17 cases of interstitial lung disease (15), eosinophilic pneumonia (1), and pulmonary fibrosis (1) were included in this review. All 17 patients were hospitalized and one patient died from progression of amyotrophic lateral sclerosis (ALS). ALS (13) comprised the most frequently reported indication followed by off-label use in study patients to treat Parkinson's disease (2) and neuropathic pain (1). Treatment indication in one case was not reported. The time from the start of therapy to the onset of symptoms (such as respiratory difficulty) averaged 108 days with a median of 46 days, but one occurred as early as seven days. Nearly all cases reported radiographic changes on chest x-ray, two performed bronchoalveolar lavage (BAL), and several foreign cases used drug induced lymphocyte stimulation test (DLST). Time to recovery from symptoms or improvement noted on radiographic images was as early as three days after drug discontinuation.

In this case series, drug-related attributes included a strong temporal drug relationship and a correlation between inadequate responses to an antibiotic challenge and in turn a favorable response to riluzole withdrawal and steroid pulse therapy. Based on this correlation of events, 14 healthcare professionals reported and assessed the drug-event relationship as probable or likely.

OSE concurred with the sponsor's labeling changes to include warnings of ILD/hypersensitivity pneumonitis. In addition, due to the severity of the event, OSE recommended the sponsor distribute a Dear Healthcare Provider Letter.

Reviewer's Comment: *This reviewer finds the association of the alleviation of symptoms and the discontinuation of drug most compelling with respect to a causal relationship of the Drug to ILD. The findings of immune- or hypersensitivity findings are suggestive but nonspecific. The value of the Drug Induced Lymphocyte Stimulation Test findings is uncertain given the low sensitivity (and possibly specificity) of the test (1) .*

4. Comments

This Medical Reviewer agrees with the wording provided by the Sponsor for the CBE. This Medical Reviewer also agrees with the evaluation, findings, and recommendations from OSE.

5. Recommendation

Pursuant to 21 CFR §314.70 (c)(6)(iii)(A), this Medical Reviewer concurs with the CBE. A Dear Healthcare Provider Letter should be sent given the seriousness of this type of event.

6. Comments to Sponsor

The Division concurs with the CBE. Given the seriousness of Interstitial Lung Disease/Hypersensitivity pneumonitis, a Dear Healthcare Provider Letter should be sent.

References

1. Matsuno O, Okubo T, Hiroshige S, Takenaka R, Ono E, Ueno T, Nureki S, Ando M, Miyazaki E, Kumamoto T. Drug-induced lymphocyte stimulation test is not useful for the diagnosis of drug-induced pneumonia. *Tohoku J Exp Med* 2007 May;212(1):49-53.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|--------------------------|---------------------------------|
| NDA-20599 | SUPPL-13 | SANOFI AVENTIS US LLC | RILUTEK (RILUZOLE) 50MG TABS |

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER D BREDER
10/20/2009

RONALD H FARKAS
11/03/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20599 S-013

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 7, 2009

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Mark Avigan, MD, CM, Director
and
Cindy Kortepeter, Pharm. D., Team Leader
Division of Pharmacovigilance I (DPV-I)

From: Charlene Flowers, R.Ph., Safety Evaluator
Office of Surveillance and Epidemiology, DPV-I

Subject: Interstitial Lung Disease (ILD)/Hypersensitivity pneumonitis

Drug Name(s): Rilutek™, riluzole

**Application Type/
Number:** NDA# 20-599

Applicant/sponsor: Sanofi-Aventis

OSE RCM #: 2009-791

Table of Contents

| | |
|---------------------------------------------------------------------------------|-------|
| EXECUTIVE SUMMARY | p. 2 |
| 1.0 INTRODUCTION | p. 3 |
| 1.1 Regulatory History..... | p. 3 |
| 1.2 Product Labeling | p. 4 |
| 1.3 Background and Case Definition | p. 4 |
| 2.0 METHODS and MATERIALS | p. 5 |
| 2.1 Data mining Search Strategy..... | p. 5 |
| 2.2 AERS Strategy and Case Selection..... | p. 6 |
| 3.0 RESULTS | p. 6 |
| 3.1 Data mining Results | p. 6 |
| 3.2 AERS Search Results/Selection of Cases | p. 7 |
| 4.0 DISCUSSION | p. 9 |
| 5.0 CONCLUSIONS | p. 10 |
| 6.0 RECOMMENDATIONS | p. 10 |
| Appendix- 1 Empirica Data Mining Tool | p. 11 |
| Appendix- 2. Table 4. AERS cases of ILD associated with riluzole use (n=17) ... | p. 13 |

EXECUTIVE SUMMARY

Rilutek™ was approved in December 1995. We evaluated 17 relatively unconfounded and well documented cases of ILD associated with riluzole from primarily foreign sources (14). All the patients were hospitalized and one patient died from progression of amyotrophic lateral sclerosis (ALS). ALS (13) comprised the most frequently reported indication followed by off-label use in study patients to treat Parkinson’s disease (2) and neuropathic pain (1). Treatment indication in one case was not reported. The time from the start of therapy to the onset of symptoms (such as respiratory difficulty) averaged 108 days with a median of 46 days, but one occurred as early as seven days. Nearly all cases reported radiographic changes on chest x-ray, two performed bronchoalveolar lavage (BAL) and several foreign cases used drug induced lymphocyte stimulation test (DLST). Time to recovery from symptoms or improvement noted on radiographic images was as early as three days after drug discontinuation.

ALS patients commonly require chronic ventilator support and are therefore predisposed to pulmonary disorders (such as aspiration pneumonia and atelectasis); consequently, shadowing appearances on radiographic examinations may be readily mistaken for pulmonary interstitial infiltrates thereby potentially confounding the diagnosis of ILD. Although none of our cases reported the patient’s clinical ALS course, our relatively unconfounded cases describing pulmonary shadowing were likely drug-related because of other collectively supportive clinical attributes. In this case series, drug-related attributes included a strong temporal drug relationship and a correlation between inadequate responses to an antibiotic challenge and in turn a favorable response to riluzole

withdrawal and steroid pulse therapy. Based on this correlation of events, 14 healthcare professionals reported and assessed the drug-event relationship as probable or likely. In our case series, two cases reported a constellation of adverse events including features of or a diagnosis of ILD. The first¹ case reported a constellation of pulmonary infiltrates, constrictive pericarditis, skin rash, and hypercellular marrow. The second² patient experienced serum sickness/drug-related hypersensitivity describing rash, polyarthralgia, and ILD.

In conclusion, this case series supports an association between riluzole and ILD. We concur with the sponsor's labeling changes to include warnings of ILD/hypersensitivity pneumonitis. An excerpt from the sponsor's current Rilutek labeling follows:

Warnings section: . . . Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

Adverse Event Section: Respiratory System: . . . interstitial lung disease, hypersensitivity pneumonitis.

In addition, due to the severity of the event, we recommend the sponsor distribute a Dear Healthcare Provider Letter.

1.0 INTRODUCTION

The Division of Neurology is reviewing a changes being effected (CBE) for interstitial lung disease (ILD) with Rilutek. We have been requested to assist with this review. We searched AERS on 15Sept09 for cases of ILD with riluzole. This document provides a summary of our findings and evaluation.

1.1 Regulatory History

The FDA granted approval to Sanofi-Aventis to market riluzole (Rilutek), a benzothiazole, on December 12, 1995 (NDA# 20-599). The results from 2 randomized double-blind placebo-controlled trials in patients with amyotrophic lateral sclerosis (ALS; a motor neuron disease) demonstrated that riluzole can extend survival and/or time to tracheostomy.³

¹ ISR# 5802162 a literature report: Sorenson, Eric, An acute, life-threatening reaction to riluzole. Neurology. 2006. Dec26;67 (12) 2260-1.

² ISR#3106115

³ Bryson, HM, et. al., Riluzole. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in amyotrophic lateral sclerosis, Drugs [DRUGS]. Vol. 52, no. 4, pp. 549-563. 1996.

1.2 Product Labeling (excerpt)

The sponsor of Rilutek, Sanofi-Aventis, submitted to the Agency a changes being effected (CBE), and provides the following language for inclusion to the warnings section of labeling: Liver injury/ Monitoring Liver Chemistries . . . Neutropenia . . . Interstitial Lung Disease: *Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.*

1.3 Background and Case Definition^{4,5,6}

Amyotrophic lateral sclerosis (ALS), often referred to as Lou Gehrig's disease causes rapidly progressive muscle atrophy and weakness resulting from the degeneration of both lower and upper motor neurons. ALS causes varying degrees of spasticity, hyperreflexia, and muscle paralysis, eventually leading to pulmonary complications and the need for mechanical ventilatory support. Because there is no curative therapy for this disease, symptomatic management is directed at preventing pulmonary infections and forestalling terminal respiratory failure.

As a result of pulmonary complications from underlying ALS in patients treated with Rilutek (riluzole), a diagnosis of drug-induced interstitial lung disease (ILD) may be challenging. ALS can cause respiratory muscle paralysis and increase the potential for pulmonary/respiratory complications. The need for an indwelling tracheostomy, and long-term use of ventilators to support paralysis of respiratory muscles accompanied by increased pulmonary secretions, and dysphagia may foster environments promoting respiratory infections, aspiration pneumonias, or respiratory atelectasis, which could further confound the diagnosis of ILD. Thus we utilized the following case definition in our case series:

The diagnosis of drug-induced lung disease is largely dependent on finding a temporal association between exposure to a drug and the development of signs or symptoms. Exclusion of other potential etiologies is also important, because drugs induce lung diseases that can closely resemble ILDs from other causes; the differential diagnosis might include lung disease related to infection; hemodynamics; radiation; collagen vascular disease; cancer; or occupational and environmental exposures.

⁴ OSE interstitial lung disease (ILD) cases definition: DPV electronic L-drive: Case definition working group, ILD

⁵ Web version: Isselbacher, BrownR, et. al.: Harrison's Principles of Internal Medicine – 17th Ed. (2008): ch. 369. Amyotrophic Lateral Sclerosis (ALS) and Other Motor Neuron Diseases - BrownR.

⁶ Web version: TintinalliJ, et. al., Emergency Medicine: A comprehensive Study guide – 6th Ed. (2004): Ch. 234. Chronic Neurologic Disorders – ALS, SloanE.

Some patients with ILD may present with symptoms but have a normal chest radiograph, whereas others have an abnormal chest radiograph but have not yet developed symptoms. Also, removal of a drug is followed by improvement in the majority of patients, though cases that have progressed to pulmonary fibrosis may be poorly reversible.

The following satisfies the inclusion criteria for Diffuse Parenchymal Lung Diseases (DPLD) also called **interstitial lung disease**:

- A clinical diagnosis⁷ of interstitial lung disease or interstitial pneumonia or diffuse parenchymal lung disease or alveolitis or similar terminology. Respiratory symptoms and radiologic evidence of bilateral diffuse parenchymal opacities are considered supporting information. There is usually improvement in symptoms and imaging after the drug is discontinued.

2.0 METHODS AND MATERIALS

2.1 DATA MINING SEARCH STRATEGY

On September 15, 2009, Empirica was searched to identify data mining scores related to interstitial lung disease using the following criteria:

Adverse event term: MedDRA⁸ preferred term with hierarchy level:

- HLT - Lower respiratory tract inflammatory and immunologic conditions
 - Includes the following PTs: alveolitis, alveolitis fibrosing, pneumonitis
- HLT - Parenchymal lung disorders NEC
 - Includes the following PTs: interstitial lung disease, lung infiltration, pulmonary fibrosis, pulmonary toxicity
- PT - Acute respiratory distress syndrome
- PT - Obliterative bronchiolitis

⁷ It is important to emphasize the challenging nature of making a *specific ILD clinical diagnosis*. This was illustrated in a prospective, single-center study of 59 patients consecutively referred for further diagnostic evaluation of new-onset ILD. The study compared the accuracy of a clinical diagnosis by an ILD expert with the histopathologic diagnosis. The diagnosis made on clinical grounds alone was correct in only 60% of confirmed cases of ILD other than IPF. (Raghu G, et al. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease. *CHEST* 1999; 116:1168-1174.) The findings of that study complement a comparison of the specific clinical diagnoses made by three pulmonologists with the histopathologic diagnosis for 91 patients with suspected IPF. Overall, IPF was present in 54 cases and not present in 37 cases. The probability of interobserver agreement regarding a specific ILD diagnosis was only 0.49. (Hunninghake GW, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001; 164:193-196.)

⁸ MedDRA = the Medical Dictionary for Regulatory Activities

Drug Product criteria:

- Riluzole

2.2 AERS Search Strategy and Case Selection

An AERS search was conducted on September 15, 2009 to capture cases of interstitial lung disease (ILD). We used the following search criteria:

Product criteria: Rilutek™ (T), riluzole (AI)

MedDRA coded terms:

- HLT - Lower respiratory tract inflammatory and immunologic conditions
 - Includes the following PTs: alveolitis, alveolitis fibrosing, pneumonitis
- HLT - Parenchymal lung disorders NEC
 - Includes the following PTs: interstitial lung disease, lung infiltration, pulmonary fibrosis, pulmonary toxicity
- PT - Acute respiratory distress syndrome
- PT - Obliterative bronchiolitis

3.0 RESULTS

3.1 Data mining Results

An Empirica data mining search identified the following EB05 values of > 2 for MedDRA preferred terms possibly related to ILD.

Table 1. Empirica data mining scores for riluzole and related Interstitial Lung Disease MedDRA preferred terms as of September 15, 2009

| Generic name | PT* | SOC | N | EB05 |
|--------------|-------------------------------------|------|----|-------|
| Riluzole | Atelectasis ⁹ | Resp | 10 | 4.132 |
| Riluzole | Interstitial lung disease | Resp | 15 | 3.868 |
| Riluzole | Pneumonia aspiration | Resp | 7 | 1.94 |
| Riluzole | Lung infiltration | Resp | 7 | 1.666 |
| Riluzole | Pneumonitis | Resp | 4 | 0.95 |
| Riluzole | Pulmonary fibrosis | Resp | 4 | 0.899 |
| Riluzole | Restrictive pulmonary disease | Resp | 2 | 0.724 |
| Riluzole | Alveolitis allergic | Resp | 5 | 0.665 |
| Riluzole | Pulmonary toxicity | Resp | 2 | 0.646 |
| Riluzole | Acute respiratory distress syndrome | Resp | 2 | 0.35 |
| Riluzole | Alveolitis | Resp | 2 | 0.281 |
| Riluzole | Eosinophilic pneumonia | Resp | 2 | 0.28 |
| Riluzole | Chest X-ray abnormal | Inv | 1 | 0.214 |

*One report may have more than one term

⁹ Atelectasis/alveolar collapse may be caused by hypoventilation. AERS cases reported atelectasis resulting possibly from ALS, mechanical ventilation, situations of hypoventilation, and coexistence with pulmonary diseases.

OSE routinely uses an EB05>2.0 as the “suspicious level” for a signal. An EB05 score of 2.0 indicates, with 95% confidence that the drug-event combination in question occurs at least at twice the expected rate when considering all other drugs and events in the AERS database. Data mining does not determine causality or degree of risk, but quantifies potential drug-event associations by producing a ranked set of scores which indicate varying strengths of reporting relationships between drugs and events. (see Appendix-1 for further information on data mining)

3.2 AERS Search Results/Selection of Cases

A search of AERS identified 540 reports of any event ever reported to riluzole. A second search to identify cases of ILD revealed 46 reports including 5 duplicates. Twenty-four were excluded from further review for the following reasons:

Table 2. AERS reports excluded from final cases series (n=24)

| Reason for elimination | Count of eliminated cases |
|-------------------------------------|---------------------------|
| Atelectasis | 9 |
| Aspiration pneumonia | 5 |
| Not temporal | 4 |
| Unspecified pneumonia | 2 |
| Viral infection and not temporal | 1 |
| Confounded by drug – bromocriptine* | 1 |
| Unrelated | 1 |
| Not enough detail | 1 |

*labeled for pulmonary fibrosis and pulmonary infiltrates

The remaining 17 cases of interstitial lung disease (15), eosinophilic pneumonia (1), and pulmonary fibrosis (1) were included in this review.

Table 3. Summary of AERS cases of interstitial lung disease (ILD) associated with riluzole™ use as of 15Sept09 (n = 17)

| | |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Age | Range: 50 – 74 years; Mean/Median = 66 years |
| Gender | Female (6); Males (11) |
| Indication (n= 16) | ALS (13) Parkinson’s disease (2) Idiopathic peripheral neuropathy (1) |
| Dose (n=12) | 100 mg/day (7) (U.S. recommended dose is 50 mg every 12 hours) 200 mg/day (4) 50 mg/day (1) |
| Time to onset of symptoms (n= 16) | Range: 7 – 630 days Mean – 108 days; Median – 46 days |
| Symptoms (Patients experienced) | Respiratory distress/shortness of breath - cough, malaise, fever, chills, sweats, polyarthralgia, and flu-like syndrome |

| | |
|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| one or more) (n= 16) | |
| ILD Diagnoses | Interstitial pneumonia (8 ^a) alveolitis (2 ^b) ‘hypersensitivity pneumonitis’ (1), pulmonary fibrosis (1), serum sickness/hypersensitivity reaction (1), ‘drug related pneumonia’ (1), ‘drug induced pulmonary disease’ (1), eosinophilic pneumonia (1), NR (1) |
| Diagnostic findings (may have more than one) | Chest X-Ray (n=16): pulmonary interstitium changes described as shadowing (6), interstitial changes (5), ground glass opacities (2), interstitial pneumopathy (2), and pulmonary fibrosis (1) Bronchoalveolar Lavage [BAL] (n =2) |
| Time to improvement in symptoms or chest x-ray after drug withdrawal (n=8) | Days 3, 4, 6, 17, 21, and 90 days (n=6) 7 days (n=2) |
| Reporting Source | U.S. (3) Foreign (14): Japan (9 ^c), Germany (2), Belgium (1), Canada (1), and Spain (1) |
| FDA receive date | 1998-1, 2000-1, 2001-1, 2002-2, 2003-3, 2005-4, 2006-2, 2007-1, 2008 -2 |
| Outcome | Death (1 ^d), Hospitalized (12), Life threatening event (2), Other (2) |
| Reporters assessment of drug related ILD (n=15) | Probable (12) Likely (2) Unlikely (1) |

^a Interstitial pneumonia: 3 of 8 reported the following specific diagnosis: ‘interstitial pneumonitis, interstitial pneumopathy, or pneumonitis’

^b alveolitis: two cases reported specifically: ‘bilateral alveolar infiltrates or drug induced alveolitis’

^c One case may be a duplicate, but this could not be reconciled due to a lack of details.

^d Death was due to the progression of ALS

A representative case of ILD with riluzole follows:

ISR#4454417/MFR#200413969JP/2005

A 62 year old male patient had been on riluzole 100 mg daily for the treatment of amyotrophic lateral sclerosis (ALS) since 20Oct03. On 10Nov03, cough and pyrexia developed. The symptoms didn’t improve with antibiotics and dyspnea developed. The patient was hospitalized on 18Nov03. Chest x-ray and CT scans found abnormal shadows in both lungs and decreasing oxygenation. Riluzole was discontinued because there was no improvement on antibiotic therapy and significant clinical improvement ensued. Drug induced pneumonia caused by riluzole was suspected. Drug Induced Lymphocytic Stimulation Test (DLST) was positive. The physician assessed the causal relationship between riluzole and drug-induced pulmonary disorder as highly probable.

4.0 DISCUSSION

In AERS, 17 cases of ILD appeared related to riluzole use. FDA received reports from U.S. (3) and Foreign (14) sources; Japan (9) was the primary reporting source. One Japanese case was likely a duplicate; however, lack of details precluded definitive case reconciliation. There were more males than females. Ages ranged from 50 to 74 years; mean/median age was 66 years. The patients were prescribed riluzole for on and off-label uses. ALS (13) comprised the most frequently reported indication followed by off-label use in study patients to treat Parkinson's disease (2) and neuropathic pain (1). Indication in one case was not reported. The duration from start of therapy to onset of symptoms (such as respiratory difficulty) averaged 108 days with a median of 46 days, one had an onset as early as seven days. Treatment of 100 mg daily was prescribed for ALS patients (7); 200 mg daily for one ALS patient and three study patients. One patient received 50 mg daily.

In our case series, two cases reported a constellation of adverse events including features of or a diagnosis of ILD. The first¹⁰ case reported a constellation of pulmonary infiltrates, constrictive pericarditis, skin rash, and hypercellular marrow. The second¹¹ patient experienced serum sickness/drug-related hypersensitivity describing rash, polyarthralgia, and ILD. Of 17 cases, 16 reported objective pulmonary changes primarily on Chest x-ray (16) and two reported concomitant bronchoalveolar lavage (BAL). In several of the non-U.S. cases, drug induced lymphocyte stimulation tests (DLST) were utilized as a diagnostic tool for ILD. Three of five DLST test results were negative despite a definitive diagnosis of drug-related ILD. One case¹² reported increased immunoglobulin levels that suggested a hypersensitivity reaction.

Five patients with interstitial changes on their chest x-ray received empiric use of antibiotic therapy, but did not improve. In all cases, riluzole therapy was discontinued and the patients recovered: including 16 patients receiving steroid treatment. Eight cases reported the time to first signs of recovery (such as the patient's symptoms subsided or objective changes noted on the chest x-ray) and recovery occurred as early as three days. Although three cases reported other suspect medications including zolpidem, bisoprolol, lansoprazole, and Tamiflu™, none are labeled for ILD.

ALS patients commonly require chronic ventilator support which may predispose them to pulmonary disorders (such as aspiration pneumonia and atelectasis) on which a shadowing appearance may be readily mistaken for pulmonary interstitial infiltrates thereby potentially confounding the diagnosis of ILD. Although none of our cases reported the patient's ALS course, our potentially un-confounded cases describing pulmonary shadowing were likely drug-related because of other clinical attributes

¹⁰ ISR# 5802162 a literature report: Sorenson, Eric, An acute, life-threatening reaction to riluzole. *Neurology*. 2006. Dec26;67 (12) 2260-1.

¹¹ ISR#3106115

¹² ISR# 4903679

including a strong temporal drug relationship and a correlation between inadequate responses to an antibiotic challenge and in turn a favorable response to riluzole withdrawal and steroid pulse therapy. Based on this correlation of events, 14 health professionals reported the event and assessed the drug-event relationship as probable or likely. All the patients required hospital admission for a potential life threatening event. One patient died eight months later of progressive ALS.

5.0 CONCLUSION

We reviewed 17 cases of ILD associated with riluzole use. The temporal relationship (one case reported the onset of the event as early as seven days after drug exposure) with supporting diagnostic data including chest x-rays revealing pulmonary interstitial findings and improvement upon withdrawal of the drug¹³ all suggest a probable association of ILD with riluzole use.

6.0 RECOMMENDATIONS

Based on our findings including the seriousness of the event, we concur with the sponsor's proposed labeling change in the Warnings section (excerpt):

Warnings section: . . . Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

Adverse Event Section: Respiratory System: . . . interstitial lung disease, hypersensitivity pneumonitis.

In addition, due to the severity of the event, we recommend the sponsor distribute a Dear Healthcare Provider Letter.

¹³ Including patient improvement in one case (ISR#4208079) that elected drug withdrawal and observation without medical intervention.

APPENDICES

Appendix -1

Empirica Data Mining Tool

A data mining search of the AERS database was performed for this analysis using Empirica version 7.0. This method uses the Multi-item Gamma Poisson Shrinker (MGPS)^{14[1]-15[2]} algorithm which analyzes the records contained in the AERS database. The algorithm then quantifies reported drug-event associations by producing a set of values or scores, which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted as EB05 and EB95 respectively.

Appendix-2

Table 4. As of 15Sept09: AERS cases of ILD associated with Riluzole use (n=17)

| ISRNUM | indicati on | Source | AGE/ SEX | symptoms | Radiograph | diagnosis | TTO: sxs | Infect ion | recovery time | allergy test | dose | reporters drug asses | treatment of ILD |
|--------------------------------------------------|----------------|--------|-------------|------------------------------------------------|----------------------------------------------------|--------------------------------------|------------|---------------|------------------|---------------------------------------------------------------------|----------|----------------------------|--------------------------------------|
| 5802162 literature ¹⁶ | ALS | USA | 50/M | malaise, fever | c X-ray showed interstitial lung infiltrates | not reported (NR) | 14 days | No | NR | nr | 100 mg/d | probable | nr |
| 4851901 | ALS | Japan | 58/M | cough | interstitial shadowing | interstitial pneumonia | 72 days | NR | 6 days | nr | 100 mg/d | NR | none recovered |
| 4197769 | ALS | Japan | 61/F | dec oxy sat. ($< 90\%$) | ground glass shadow | interstitial pneumonia | 49 days | none | | drug induced lymphoc yte stimulati on test (DLST) | 100 mg/d | probable | steroids |
| 4554417/ 4575461 ¹⁷ Case-report | ALS | Japan | 62/M | cough, fever, SOB | bilateral shadowing | drug induced pulmonary disease | 22 days | nr | 3 months | DLST - positive | 100 mg/d | probable | antibiotics and stopped the drug. |
| 3705866 study | Parkins ons | USA | 62/F | flu-like, SOB, joint and muscle aches | bilateral infiltrated | interstitial pneumonia | 7 days | none | | nr | 200 mg/d | probable | steroids and antibiotics |
| 3583039 | ALS | Japan | 63/M | wet cough, SOB | bilateral reticulo- nodular shadow | pneumonitis | 5 months | nr | 4 days | DLST - negative | 200 mg/d | probable | antibiotics and stopped drug |
| 4850776 | ALS | Japan | 63/M | fever, cough, SOB | bilateral infiltrate shadow | drug-related pneumonia' | 67 DAYS | NR | | nr | 100 mg/d | related | steroids and antibiotics |

¹⁶ ISR# 5802162 a literature report: Sorenson, Eric, An acute, life-threatening reaction to riluzole. Neurology. 2006. Dec26;67 (12) 2260-1

¹⁷ ISR#4554417: case-report: 149th annual meeting of the Japanese Society of Internal Medicine; October 2004.

| ISRNUM | indicati on | Source | AGE/ SEX | symptoms | Radiograph | diagnosis | TTO: sxs | Infect ion | recovery time | allergy test | dose | reporters drug asses | treatment of ILD |
|----------------------------------|----------------------------------|---------|----------|--------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------|-----------|------------|---------------|-----------------|----------|----------------------|-----------------------------|
| 3854826 | ALS | Germany | 66/F | SOB | changes in pulmonary interstitium | drug-induced alveolitis | 13days | nr | 7 days | nr | 50 mg/d | probable | steroids: improved |
| 4828213 | ALS | Japan | 66/M | SOB, fever | interstitial shadowing | interstitial pneumonia | 32 days | nr | 7 days | DLST - negative | NR | probable | steroids and antibiotics |
| 4927450 | NR | Japan | 67/F | nr | nr | interstitial pneumonia | nr | nr | nr | nr | NR | probable | nr |
| 3106115 study | idiopathic peripheral neuropathy | USA | 68/F | SOB, genl rash, fever, polyarthritis | bilateral interstitial ; atelectasis w/ r-sided fluid accumulation | (serum sickness/ hypersensitivity RXN) with rash, polyarthralgia , and ILD | 12 days | | | nr | 200 mg/d | likely | steroids and antibiotics |
| 5290162 literature ¹⁸ | ALS | Belgium | 69/M | SOB, cough, | interstitial pneumonitis, | hypersensitivity pneumonitis | 21 months | nr | 3 weeks | nr | 100 mg/d | probable | steroids and antibiotics |
| 4208079 | ALS | Japan | 71/M | SOB, | ground glass opacity | interstitial pneumonitis, | 81 days | nr | | nr | 100 mg/d | probable | tx decision was to observe. |
| 5798845 | ALS | Germany | 72/M | fever, acute respiratory distress, chills. | bilater interstitial pneumopathy | interstitial pneumopathy | 20 days | nr | | nr | nr | unlikely | steroids/abx and antifungal |
| 3910984/ study | Parkinsons | Canada | 73/F | SOB/ dyspnea | pulmonary fibrosis | pulmonary fibrosis | 61 days | nr | 17 days | nr | 200 mg/d | NR | nr |
| 4847564 ¹⁹ | ALS | Japan | 74/M | flu-like sxs, dysarthria, dysphagia | bilateral ground glass appearance | eosinophilic pneumonia/ drug-induced pneumonia | 30 days | nr | nr | DLST - negative | nr | probable | steroids. |

¹⁸ CassimanD, et.al., Hypersensitivity pneumonitis possibly caused by riluzole therapy in ALS. Neurology (61), October (2003) 1150-1.

¹⁹ ISR#4554417: case-report provided at the 57th Annual Meeting of the Japanese Society for Tuberculosis; November 2005.

| ISRNUM | indicati on | Source | AGE/ SEX | symptoms | Radiograph | diagnosis | TTO: sxs | Infect ion | recovery time | allergy test | dose | reporters drug asses | treatment of ILD |
|--------------------------------------------------|----------------|--------|-------------|----------------------------|------------|-------------------------------------------------------|----------|---------------|------------------|-------------------------------|------|----------------------------|--------------------------------------|
| 4903679/ 4970929/ literature ²⁰ | ALS | Spain | 74/M | cough, sweating, SOB | | bilateral alveolar- interstitial infiltrates | 105 days | | 3 days | Mantoux test - negative | | probable | abx - no relief; steroids + recvy |

²⁰ Borderias-ClauL, et.al., Strong Suspicion of Lung Toxicity due to Riluzole. Arch Bronchopneumonia. 2006; 42 (1): 42-4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLENE M FLOWERS
10/08/2009

CINDY M KORTEPETER
10/08/2009

MARK I AVIGAN
10/14/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20599 S-13

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

| | | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Mail: OSE Attn: Daniel Brounstein | | FROM: Division of Neurology Products | | |
| DATE 4-28-09 | IND NO. | NDA NO. 20-599/SLR-013 | TYPE OF DOCUMENT CBE Labeling supplement | DATE OF DOCUMENT 4/9/09 |
| NAME OF DRUG Rilutek (riluzole) | | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG ALS | DESIRED COMPLETION DATE 6/30/09 |
| NAME OF FIRM: Sanofi-Aventis | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | <input type="checkbox"/> PRECLINICAL | | |
| <p>COMMENTS/SPECIAL INSTRUCTIONS: The sponsor for riluzole submitted a Changes Being Effected (eCTD Sequence No. 0002, 09 APR 2009) stating a change in the WARNINGS, PRECAUTIONS and ADVERSE REACTIONS sections to add Interstitial Lung Disease or Hypersensitivity Pneumonitis. This was reportedly predicated by their observation of 8 cases from observational or Phase 3 studies within their clinical database based on related terms. Investigations into causality including the temporal relationship and discontinuation effect and alternative therapeutic explanations were suggestive of a role for riluzole in most of these cases. We would like to consult you about developing an AERS search strategy for interstitial lung disease/hypersensitivity pneumonitis related to riluzole, and for assessing a) the strength of any signal, b) if there are particular populations or associated previous medical history, concomitant medications, or similar associated factors, and c) the evolution and outcome of these cases?</p> | | | | |
| The Clinical reviewer for this submission is Chris Breder @ 6-1365 If you wish to view the submission, it may be accessed @ \\CDSESUB1\EVSPROD\NDA020599\0002 | | | | |
| SIGNATURE OF REQUESTER Susan Daugherty 6-0878 | | METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Susan B. Daugherty
4/28/2009 01:33:26 PM



NDA 20-599/S-013

CBE-30/CBE-0 SUPPLEMENT

Sanofi Aventis U.S., L.L.C.
Attention: Jo Beth Crimmins, Specialist, Product Support
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Crimmins:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Rilutek (riluzole) Tablets
NDA Number: 20-599
Supplement number: 013
Date of supplement: April 9, 2009
Date of receipt: April 9, 2009

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labeling to add information regarding interstitial lung disease and hypersensitivity pneumonitis.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 8, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 9, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 20-599/S-013

Page 2

If you have questions, call me, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Susan B. Daugherty
4/28/2009 02:12:39 PM