CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-599/S-008

Trade Name: Rilutek

Generic Name: riluzole

Sponsor: Covis Pharma Sarl

Approval Date: September 21, 2004

Indication: For the treatment of patients with amyotrophic lateral sclerosis (ALS).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-599/SLR-008

Aventis Pharmaceuticals Inc.
Attention: Jay Kraker
1023 Marion Park Drive
Kansas City, MO 64134-0720

Dear Mr. Kraker:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilutek® (riluzole) 50 mg tablets.

We acknowledge receipt of your submissions dated March 23, 2004 and August 12, 2004.

Your submission of March 23, 2004 constituted a complete response to our February 6, 2004 action letter.

This supplemental new drug application provides for changes to the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the package insert to include information based on mutagenicity studies completed with the active metabolite.

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

The final printed labeling (FPL) must be identical to the submitted label (contained in your submission dated August 12, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-599/S-008" Approval of this submission by FDA is not required before the labeling is used.

In addition, you must submit the content of labeling in electronic format as described in 21 CFR 314.50(l)(5). Current guidance for industry specifies that the content of labeling should be provided in PDF or SPL file format. This new submission requirement was published on December 11, 2003 (68 FR 69009) and was effective June 8, 2004. For additional information, consult the following guidance for industry: *Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004).
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Melina Griffis, R.Ph., Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I

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/s/

Russell Katz
9/21/04 09:52:51 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-008

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-599/SLR-008

Aventis Pharmaceuticals Inc.
Attention: Kerry Rothschild, J.D.
200 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Mr. Rothschild:

Please refer to your supplemental new drug application dated August 5, 2003, received August 6, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilutek® (riluzole) Tablets.

This supplemental new drug application provides for changes in the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the package insert to include information based on mutagenicity studies completed with the active metabolite.

We completed our review of this application and it is approvable. Before this application may be approved, however, you must submit draft or final printed labeling revised as follows (edits below are based on your proposed draft labeling):

(b) (4)

[redacted]

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We

will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Melina Griffis, R.Ph., Senior Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
2/6/04 01:36:14 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-008

PHARMACOLOGY REVIEW(S)

Memo

NDA NUMBER:	**20-599**
SERIAL NUMBER:	**008**
DATE RECEIVED BY Division:	**August 12th 2004**
PRODUCT:	**Rilutek® (riluzole) tablets**
Code name:	**PK 26124/RP54274**
INTENDED CLINICAL POPULATION:	**ALS**
SPONSOR:	**Aventis Pharmaceuticals**
	Bridgewater, NJ
DOCUMENTS REVIEWED:	**eNDA**
REVIEW DIVISION:	**Division of Neuropharmacological Drug Products (HFD-120)**
PHARM/TOX REVIEWER:	**Aisar H. Atrakchi, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barry Rosloff, Ph.D.**
DIVISION DIRECTOR:	**Russell Katz, Ph.D.**
PROJECT MANAGER:	**Melina Griffis**

Date of review submission to Division File System (DFS): June 14th 2004

Information to sponsor:	**No (x)**
Memo date:	**June 13th 2004**

This is a note to the NDA file to acknowledge and accept the final wording to the section on "Carcinogenesis, Mutagenesis, and Impairment of Fertility" of the label. The following wording has been accepted and agreed to by both the sponsor and the Division (2nd paragraph of the section):

"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 etc…"

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/s/

Aisar Atrakchi
9/13/04 04:10:18 PM
PHARMACOLOGIST

Barry Rosloff
9/16/04 05:39:06 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20-599**
SERIAL NUMBER:	**005**
DATE RECEIVED BY CENTER:	**August 18 1999**
PRODUCT:	**Rilutek® (riluzole) tablets**
INTENDED CLINICAL POPULATION:	**ALS**
SPONSOR:	**RPR previously/Aventis Pharmaceuticals Bridgewater, NJ**
DOCUMENTS REVIEWED:	**Label changes**
REVIEW DIVISION:	**Division of Neuropharmacological Drug Products (HFD-120)**
PHARM/TOX REVIEWER:	**Aisar H. Atrakchi, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barry Rosloff, Ph.D.**
DIVISION DIRECTOR:	**Russell Katz, Ph.D.**
PROJECT MANAGER:	**Melina Griffis**

Date of review submission to Division File System (DFS): July 7th 2004

NDA number: 20-599
Sequence number/date/type of submission: S-005/Aug 18 1999
Information to sponsor: Yes
Sponsor and/or agent: Aventis
Manufacturer for drug substance: see chemistry review

Reviewer name: **Aisar H. Atrakchi, Ph.D.**
Division name: **Neuropharmacological Drug Products**
HFD #: **120**
Review completion date: **July 7th 1999**

Drug:
Trade name: Rilutek®
Generic name: Riluzole
Code name: PK 26124/RP54274

Relevant INDs/NDAs/DMFs: 20-599

Drug class: Excitatory amino acid antagonist

Intended clinical population: ALS

Clinical formulation and Route: oral tablets

This is a draft labeling supplement that included proposed changes to Carcinogenesis, Mutagenesis, Impairment of Fertility section of the package insert for Rilutek®. Reports for the carcinogenicity studies have been previously submitted in 1998 serial#s 147 and 148. The changes made were acceptable to the Division.

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/s/

Aisar Atrakchi
7/7/04 01:38:41 PM
PHARMACOLOGIST

Barry Rosloff
7/21/04 03:34:55 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20-599**
SERIAL NUMBER:	**8**
DATE RECEIVED BY CENTER:	**March 23rd 2004**
PRODUCT:	**Rilutek® (riluzole) tablets**
INTENDED CLINICAL POPULATION:	**ALS**
SPONSOR:	**Aventis Pharmaceuticals** **Bridgewater, NJ**
DOCUMENTS REVIEWED:	**eNDA and Vol. 1-3 desk copies of requested genetic tox reports submitted previously June 29th 1995.**
REVIEW DIVISION:	**Division of Neuropharmacological Drug Products (HFD-120)**
PHARM/TOX REVIEWER:	**Aisar H. Atrakchi, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barry Rosloff, Ph.D.**
DIVISION DIRECTOR:	**Russell Katz, Ph.D.**
PROJECT MANAGER:	**Melina Griffis**

Date of review submission to Division File System (DFS): June 14th 2004

NDA number: 20-599
Sequence number/date/type of submission: S-008/Mar 23rd and Jan 29th 2004
Information to sponsor: Yes (x)
Sponsor and/or agent: Aventis
Manufacturer for drug substance: see chemistry review

Reviewer name: **Aisar H. Atrakchi, Ph.D.**
Division name: **Neuropharmacological Drug Products**
HFD #: **120**
Review completion date: **June 10th 2004**

Drug:

Trade name: Rilutek®
Generic name: Riluzole
Code name: PK 26124/RP54274

Relevant INDs/NDAs/DMFs:

Drug class: Excitatory amino acid antagonist

Intended clinical population: ALS

Clinical formulation and Route: oral tablets

This is a response to the Approvable letter dated February 6th 2004 where the Division made additional labeling revisions to the proposed label. The sponsor also referenced Supplement 008 dated August 5th 2003 that made changes to the section on "Carcinogenesis, Mutagenesis, and Impairment of Fertility" and added new statements on mutagenesis. In the current amendment the sponsor accepts the revisions made by the Division (b) (4) the words "chromosomal aberration" (see below). The following is detailed review of the 3 mutagenicity studies previously submitted and the Division's comments on the sponsor's changes.

Recommendations:

This reviewer believes the words "chromosomal aberration" (b) (4) This is for the purpose of consistency in writing the label for this section, it is the general rule to define the test as a gene mutation or chromosomal aberration test. The sponsor's justification is that these words are only descriptive for that particular test and their (b) (4) will not change the intended meaning of the paragraph.

"N-hydroxriluzole, the major active metabolite of riluzole, (b) (4)

Study title: in vitro assessment of clastogenic activity of PK 26124 in cultured human peripheral lymphocytes.

Key findings: statistically significant increase in aberrations at the highest concentration tested. The sponsor stated that additional study is needed to clarify this finding.

Study no.: (b) (4) 84/PHA/128/257
Volume #, and page #: 1/1
Conducting laboratory and location: (b) (4)
Date of study initiation: Dec 1983
GLP compliance: Yes FDA, OECD, Japanese
QA reports: yes (x) no ( )
Drug, lot #, and % purity: C1100/100% pure

Methods
Strains/species/cell line: peripheral blood was obtained from a single healthy, non-smoking male volunteer via veinpuncture.
Doses used in definitive study: 0.4, 2, 10ug/ml in -/+S9

Basis of dose selection: preliminary cytotoxicity study, 5 concentrations: 6.1, 30.6, 153, 765, and 3825ug/ml; solubility limited the use of higher concentrations; solvent used was ethanol, tests done in duplicate in both -/+S9. Table from sponsor presents the cytotox results, from this table, concentrations ≥153ug/ml were toxic, remaining cultures were prepared and 1000 lymphocytes per culture were examined and mitotic index calculated.

Preliminary toxicity test - mitotic indices

Group	:	1	2	3	4	5	6
Compound	:	Ethanol	---------- PK 26124 ----------				
Concentration (µg/ml)	:	0	6.1	30.6	153	765	3825

Group	1				2				3				4				5				6			
Culture number	1	2	13	14	3	4	15	16	5	6	17	18	7	8	19	20	9	10	21	22	11	12	23	24
S-9 mix	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+
Lymphocytes	1007	1003	1013	1009	1016	1019	1009	1037	1016	1005	1015	1006	a	c	a	a	b	b	b	b	b	b	b	b
Metaphases	39	45	60	37	84	68	81	84	42	60	19	21												
Mitotic index*	3.9	4.5	5.9	3.7	8.3	6.7	8.0	8.1	4.1	6.0	1.9	2.1												
Group mean mitotic index		4.5				7.8				3.5														

* Mitotic index = $\frac{\text{number of metaphases}}{\text{number of lymphocytes}}$ x 100

a = Very few lymphocytes and no metaphases present; not scored.
b = Not harvested due to extreme toxicity.
c = No cells, no metaphases present.

Negative controls: ethanol was the solvent as well as the negative control.
Positive controls: CP at 6ug/ml used in -/+S9. Another positive control should have been tested in –S9 since CP is used commonly only in +S9.
Incubation and sampling times: only 3 concentrations of PK 26124 were tested: 0.4, 2.0, and 10.0ug/ml in -/+S9 in triplicate. Colcemid 10ug/ml was added 3hr before end of

incubation to arrest cell division. Total incubation time was 24hr. Standard procedures were followed and slides were prepared. Slides were coded and blindly evaluated, 100 metaphases per culture were evaluated per concentration, MI was assessed in 1000 cells.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): inadequate number of concentrations were tested in the main assay (at least 5 as stated in the OECD guidelines). 30ug/ml was initially tested in the main assay since little toxicity was observed at this concentration in the cytotoxicity assay (table 1 above). However, the sponsor stated that when 30ug/ml was tested in the main assay, though toxicity was low (no inhibition of MI), there were few cells in the cultures and adequate number of metaphases could not be obtained. The sponsor thus proposed that the drug is killing cells without an effect on "rate of proliferation of surviving cells". Such an effect was also seen at the 6ug/ml therefore, the sponsor repeated the main assay using 10ug/ml as the maximum concentration.

The following were considered inappropriate analyses of the data:

- combined the MI results from – and + S9 because of low variability in the data for the drug,
- 1 of 3 cultures in +S9 of 0.4ug/ml rilutek was contaminated with bacteria but still included in data analysis because the incidence of abs were similar to those in other cultures.

Table from sponsor presents the data from the main study:

Lymphocyte cytogenetic test - number and types of chromosomal aberrations

Group	:	1			2			3						4			5		
Compound	:	Ethanol			---------- PK 26124 ---------												Cyclophosphamide		
Concentration (µg/ml)	:	0			0.4			2						10			6		
Group		1						2							3				
Culture number		1	2	3	16	17	18	4	5	6	19	20*	21		7	8	9	22	23	24
S-9 mix		-	-	-	+	+	+	-	-	-	+	+	+		-	-	-	+	+	+
Number of cells scored		100	100	100	100	100	100	100	100	100	100	100	100		100	100	100	100	100	100
% cells with aberrations		1	1	1	2	6	2	1	2	5	3	3	0		3	2	2	4	3	2
% cells with aberrations other than gaps		0	0	0	2	5	1	0	2	1	2	1	0		1	1	1	2	0	2
Number and specific types of chromosomal aberration	SSG		1	1		1	1	1		3	1	2			2	1	1	2	3	
	DSG	1								1										
	SSB					3				1		1						1		
	DSB																			
	E																			
	F				1	2	1		1		3				1		1	1		1
	OA				1α				1α							1α				1α

Group		4						5					
Culture number		10	11	12	25	26	27	13	14	15*	28	29	30
S-9 mix		-	-	-	+	+	+	-	-	-	+	+	+
Number of cells scored		100	100	100	100	100	100	100	100	100	100	100	100
% cells with aberrations		3	4	1	11	2	8	3	3	8	17	18	14
% cells with aberrations other than gaps		3	2	1	5	2	5	1	2	4	8	12	10
Number and specific types of chromosomal aberration	SSG		2		7		3	2	1	4	8	6	3
	DSG										2		1
	SSB				2		1			1	1	2	2
	DSB												1
	E									1			
	F	2	1		3	2	4	1		6	7	9	7
	OA	1α	1b	1α			1c		2α			2α	

SSG Single strand (chromatid) gap.
DSG Double strand (chromosome) gap.
SSB Single strand (chromatid) break.
DSB Double strand (chromosome) break.
c Pulverised metaphase.
E Exchange.
F Fragment.
OA Other aberrations.
α Endoriduplication.
* In addition, one severely damaged metaphase noted - chromosome count impossible due to damage.
b Multiple aberrations.

Study outcome: statistically significant increase in % of cells with abs in +S9 was seen in high concentration compared to solvent in absence of toxicity. It is noted and as indicated by the sponsor that 1 of the 3 cultures of the solvent control had an unusually high number of abs and there were no abs in any of the 3 cultures in –S9. The sponsor concluded that rilutek at 10ug/ml statistically significantly increased the incidence of abs in +S9 (with 1 completely pulverized metaphase), relative to the control however, suggested the study be repeated due the “weak positive response”.

Study title: In vitro assessment of clastogenic activity of PK 26124 in cultured human peripheral lymphocytes.

Key findings: negative up to 20ug/ml in either -/+S9

Study no.: (b) (4) 85/PHA137/159
Volume #, and page #: 2/1
Conducting laboratory and location: (b) (4)
Date of study initiation: Dec 1984
GLP compliance: Yes FDA, OECD, Japanese
QA reports: yes (x) no ( )
Drug, lot #, and % purity: C1100/100% pure

Methods
Strains/species/cell line: peripheral blood was obtained from a single healthy, non-smoking male volunteer via veinpuncture.
Doses used in definitive study: 10 and 20ug/ml in -/+S9

Basis of dose selection: preliminary cytotoxicity assay. There was 45% inhibition of MI at 20ug/ml and minimal to no reduction at 10ug/ml.
Negative controls: solvent, ethanol
Positive controls: CP 6ug/ml in -/+S9; similar to the above study, it is inappropriate to use CP in –S9 as the positive control.

Incubation and sampling times: total incubation with drug was 24hrs. 3hr before termination, colcemid 10ug/ml was added to all cells to arrest cell division, SOPs were followed thereafter and through slide preparation. Triplicate cultures were tested per concentration and slides were scored blindly; cytotoxicity assessed in 1000 cells and MI calculated as percent of cells in metaphase; 100 metaphases per culture were examined.

Note: data from the 10ug/ml and solvent control were combined with those from the above previous study to "allow comparison of larger population" as stated by the sponsor, and used in the statistical analyses; this is not considered appropriate approach. Also the S9 fraction was prepared by the CRO.

Results
Study validity (comment on replicates, counting method, criteria for positive results, etc.): see above. Neither concentration, 10 or 20ug/ml caused an increase in % of cells with abs when gaps were either included or excluded and in either -/+S9 (table from sponsor); the positive control CP produced the expected response. However, when data were pooled for the 10ug/ml, statistical significance was observed in +S9 relative to the control but only *when gaps were included*.

Number and types of chromosomal aberrations

Group	:	1						2						3					
Compound	:	Ethanol						---------- PK26124 ----------						Cyclophosphamide					
Concentration (µg/ml)	:	-						10						20					
Group		1						2						3					
Culture number		1	2	3	19	20	21	10	11	12	22	23	24	13	14	15	25	26	27
S-9 mix		-	-	-	+	+	+	-	-	-	+	+	+	-	-	-	+	+	+
Number of cells scored		100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
% cells with aberrations		2	6	1	1	1	2	1	0	1	3	4	2	0	3	1	3	0	2
% cells with aberrations other than gaps		0	3	1	1	1	1	0	0	0	1	2	2	0	3	0	2	0	1
Number and specific types of chromosomal aberration	SSG	2	3				1	1		1	2	2				1	1		1
	DSG																		
	SSB												1		1		2		
	DSB																		
	E											1							
	F		3	1	1	1	1				1		1		2				1
	OA											1a							

Group		4					
Culture number		16	17	18	28	29	30
S-9 mix		-	-	-	+	+	+
Number of cells scored		100	100	100	100	100	100
% cells with aberrations		4	0	0	45	29	18
% cells with aberrations other than gaps		2	0	0	36	21	16
Number and specific types of chromosomal aberration	SSG	2			13	15	4
	DSG				3	1	1
	SSB				24	7	5
	DSB				4	1	1
	E				6	6	2
	F	2			19	8	9
	OA						

SSG Single strand (chromatid) gap. E Exchange. SSB Single strand (chromatid) break. OA Other aberrations.
DSG Double strand (chromosome) gap. F Fragment. DSB Double strand (chromosome) break.

Study outcome: negative clastogenicity; cytotoxicity was adequate at the 20ug/ml but minimal at the lower concentration of 10ug/ml.

Study title: in vitro micronucleus test in mouse lymphoma cells L5178Y

Key findings: positive clastogen in vitro MN both in -/+S9

Study no.: RPR/RD/SA/CRVA 00-504
Volume #, and page #: 3/1
Conducting laboratory and location: Aventis Pharma, France
Date of study initiation: Nov 2000
GLP compliance: Yes; French GLP
QA reports: yes (x) no ( )
Drug, lot #, and % purity: MRT2237/93.8%

Methods
Strains/species/cell line: mouse lymphoma LY5178Y cell line.
Doses used in definitive study: see tables below

Basis of dose selection: based on previous results from MLA tk locus (RPR/RD/SA/CRVA 00-367, 2001), and preliminary MN assay in MLA L5178Y cells where the highest concentration tested in the current main assay is expected to induce a reasonable level of cytotoxicity.

Negative controls: DMSO diluted in culture medium at final concentration of 1% with or without S9; DMSO was also the solvent.

Positive controls: MMC 20ug/ml in –S9 and benzo(a)pyrene 100ug/ml in +S9

Incubation and sampling times: cells were treated for 3hrs followed by incubation for 24hr and harvested. Slides were prepared, stained, and scored blindly; micronuclei were scored from 1000 cells.

Results
Study validity (comment on replicates, counting method, criteria for positive results, etc.): duplicate cultures were tested for each condition and concentration for drug, negative control, and positive control. There were 2 assays each in -/+S9, in the 1st assay, cells were treated for 3hr with the drug and harvested 24hr later; because results were positive in this assay, a 2nd assay was conducted under the exact same conditions of the 1st one. The S9 fraction was purchased commercially from (b) (4). Cytotoxicity was assessed in parallel to the assay using RCG (relative cell growth). Assessment criteria included: RCG at the highest concentration should be between 40-50%, positive controls should induce a statistically significant increase in number of MN. A positive finding should encompass all of the following: statistically significant, dose response (or highest concentration), and reproducible increase in MN, and the number of MN should be out of the historical negative control data. If any of these criteria is not met, the response is considered negative.

Study outcome: Statistically significant increase in MN at ≥3ug/ml in + S9 and ≥2ug/ml in –S9 (tables from sponsor), that were reproducible in the 2nd assay.

Table 1 - First micronucleus assay without metabolic activation
Cytotoxicity and micronucleus incidence

Compound	Cytotoxicity		Micronuclei			
	Cells 1.00E+05	% survival cells	Replicate /2000 cells	Number	Ratio	Statistical Significance (a)
Solvent	6.53	100	A	23	-	-
			B	27	-	-
Control			**Totals/4000**	**50**	**1.0**	-
RPR112512A	8.95	137	A	20	-	-
			B	26	-	-
1 µg/ml			**Totals/4000**	**46**	**0.9**	NS
RPR112512A	5.62	86	A	47	-	-
			B	44	-	-
2 µg/ml			**Totals/4000**	**91**	**1.8**	**
RPR112512A	5.00	77	A	41	-	-
			B	38	-	-
3 µg/ml			**Totals/4000**	**79**	**1.6**	*
RPR112512A	5.08	78	A	55	-	-
			B	54	-	-
4 µg/ml			**Totals/4000**	**109**	**2.2**	**
RPR112512A	5.10	78	A	52	-	-
			B	82	-	-
5 µg/ml			**Totals/4000**	**134**	**2.7**	**
RPR112512A	5.29	81	A	71	-	-
			B	86	-	-
7.5 µg/ml			**Totals/4000**	**157**	**3.1**	**
RPR112512A	4.66	71	A	83	-	-
			B	61	-	-
10 µg/ml			**Totals/4000**	**144**	**2.9**	**
MMC	6.60	101	A	99	-	-
			B	120	-	-
0.2 µg/ml			**Totals/4000**	**219**	**4.4**	**

A. B Replicate cultures
(a) Statistical analysis on 4000 cells

NS Not significant
* Significant p≤0.05
** Significant p≤0.01

Table 2 - Second micronucleus assay without metabolic activation
Cytotoxicity and micronucleus incidence

Compound	Cytotoxicity		Micronuclei			
	Cells 1.00E+05	% survival cells	Replicate /2000	Number	Ratio	Statistical Significance (a)
Solvent	8.98	100	A	23	-	-
			B	25	-	-
Control			**Totals/4000**	**48**	**1.0**	-
RPR112512A	7.26	81	A	44	-	-
			B	58	-	-
2 µg/ml			**Totals/4000**	**102**	**2.1**	**
RPR112512A	5.56	62	A	51	-	-
			B	54	-	-
4 µg/ml			**Totals/4000**	**105**	**2.2**	**
RPR112512A	5.11	57	A	80	-	-
			B	108	-	-
8 µg/ml			**Totals/4000**	**188**	**3.9**	**
RPR112512A	4.94	55	A	91	-	-
			B	81	-	-
12 µg/ml			**Totals/4000**	**172**	**3.6**	**
RPR112512A	4.65	52	A	74	-	-
			B	100	-	-
16 µg/ml			**Totals/4000**	**174**	**3.6**	**
RPR112512A	3.71	41	A	63	-	-
			B	55	-	-
20 µg/ml			**Totals/4000**	**118**	**2.5**	**
MMC	6.50	72	A	155	-	-
			B	172	-	-
0.2 µg/ml			**Totals/4000**	**327**	**6.8**	**

Table 3 - First micronucleus assay with metabolic activation
Cytotoxicity and micronucleus incidence

Compound	Cytotoxicity		Micronuclei			
	Cells 1.00E+05	% survival cells	Replicate /2000	Number	Ratio	Statistical Significance (a)
Solvent	12.61	100	A	11	-	-
			B	19	-	-
Control			**Totals/4000**	**30**	**1.0**	-
RPR112512A	14.44	115	A	10	-	-
			B	11	-	-
1 µg/ml			**Totals/4000**	**21**	**0.7**	NS
RPR112512A	8.63	68	A	64	-	-
			B	53	-	-
3 µg/ml			**Totals/4000**	**117**	**3.9**	**
RPR112512A	6.50	52	A	49	-	-
			B	34	-	-
5 µg/ml			**Totals/4000**	**83**	**2.8**	**
RPR112512A	5.53	44	A	61	-	-
			B	68	-	-
7.5 µg/ml			**Totals/4000**	**129**	**4.3**	**
B(a)P	11.75	93	A	72	-	-
			B	61	-	-
1 µg/ml			**Totals/4000**	**133**	**4.4**	**

Table 4 - Second micronucleus assay with metabolic activation
Cytotoxicity and micronucleus incidence

Compound	Cytotoxicity		Micronuclei			
	Cells 1.00E+05	% survival cells	Replicate /2000	Number	Ratio	Statistical Significance (a)
Solvent	15.63	100	A	15	-	-
			B	15	-	-
Control			**Totals/4000**	**30**	**1.0**	-
RPR112512A	15.75	101	A	15	-	-
			B	9	-	-
1 µg/ml			**Totals/4000**	**24**	**0.8**	NS
RPR112512A	12.12	78	A	46	-	-
			B	45	-	-
3 µg/ml			**Totals/4000**	**91**	**3.0**	**
RPR112512A	7.22	46	A	41	-	-
			B	53	-	-
4 µg/ml			**Totals/4000**	**94**	**3.1**	**
RPR112512A	6.75	43	A	57	-	-
			B	28	-	-
5 µg/ml			**Totals/4000**	**85**	**2.8**	**
B(a)P	12.77	82	A	75	-	-
			B	75	-	-
1 µg/ml			**Totals/4000**	**150**	**5.0**	**

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Aisar Atrakchi
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PHARMACOLOGIST

Barry Rosloff
7/21/04 03:33:17 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-008

OTHER REVIEW(S)

Division of Neuropharmacological Drug Products
PROJECT MANAGER REVIEW

Application Number: NDA 20-599/SLR-008
Name of Drug: Rilutek® (riluzole) Tablet
Sponsor: Aventis Pharmaceuticals

Materials Reviewed:
Last approved product labeling for Rilutek® (dated May 19, 2003; serial # 50069093)
SLR-008 (dated March 23, 2004 and amended August 12, 2004)

Review and Evaluation:
SLR-008: This supplement provides for the addition of following language to the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of labeling to read as follows:

> 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.

In the submission dated March 22, 2004 (which was a response to the February 6, 2004 approvable letter), the sponsor adopted the proposed FDA language with the (b) (4) "chromosomal aberration" (describing the in vitro mammalian mouse lymphoma assay). Subsequent labeling negotiations between the FDA and Aventis resulted in the proposed labeling mentioned above (amendment dated August 12, 2004).

This labeling supplement was submitted as "Prior Approval Supplement".

Recommendation:
In a line by line comparison between the last approved labeling and the current proposed labeling only those changes indicated by the sponsor were made. All changes have been approved by the pharmacology/toxicology reviewer. I recommend approval of the above listed supplements.

Melina Griffis, R.Ph., Project Manager

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Melina Griffis
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CSO