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PHARMACOLOGY REVIEW

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Griffin, RPM

Review of Pharmacology and Toxicology Data 1

Keywords: PRIFTIN®, rifapentine, nasal cavity neoplasia, adenoma, Wistar rat

Reviewer name: Owen McMaster
Division name: Division of Special Pathogen and Immunologic Drug Products
HFD-590
Review completion date: October 7, 1999
Sponsor: Hoechst Marion Roussel Inc.
Drug: PRIFTIN® (rifapentine)

OCT 25 1999

PRIFTIN® (rifapentine) is indicated for the treatment of pulmonary tuberculosis. It is administered twice weekly for two months followed by once weekly treatment for four months and must always be used in conjunction with another antituberculosis drug to which the isolate is susceptible.

The sponsor has completed a rat carcinogenicity study and has submitted the following preliminary results, which show an increase in nasal cavity adenomas in both sexes (See Table 1, Below).

Table 1. Incidences (%) of nasal cavity neoplasia (NCN*) in Wistar rats treated with rifapentine for two years.

Rifapentine Dose (mg/kg)	% with NCN* (MALES)	% with NCN* (FEMALES)
0 (control)	0	0
0 (control)	2	0
2.5	0	0
10	2	2
40	22	8

There was no difference in survival between the doses or the sexes but number of deaths did increase with the number of doses administered (see Table 2 below).

Table 2. Mortality in Wistar rats treated with rifapentine for two years.

Sex	Total deaths	Male					Female				
Priftin dose (mg/kg)		0	0	2.5	10	40	0	0	2.5	10	40
Weeks 1- 52	9	0	0	1	1	2	2	2	1	0	0
Weeks 53-78	44	3	5	2	3	3	5	9	1	7	6
Weeks 78-107	94	14	7	12	3	5	13	9	10	11	16
Total deaths		17	12	15	7	10	20	20	12	18	16

The tumors did not seem to affect the survival of the rats since most animals with nasal adenomas survived until the end of the study. Three animals with adenomas died during the study: one control male, one high dose male and one high dose female.

The plasma AUC for rifapentine in the high dose was 40 times the AUC in humans given the 600mg dose every 72 hours. The metabolite, 25-desacetyl rifapentine, was only found in trace amounts in rat plasma. Thus, although the metabolite, 25-desacetyl rifapentine was positive in the chromosome aberration assay, the low amounts of the metabolite in rat plasma may imply that the tumors were due to some other cause (probably rifapentine itself).

Discussion

It is unclear if the nasal cavity neoplasia seen in these rats imply that patients on rifapentine are at increased risk for nasal adenomas. Firstly, the rats showing these changes were exposed to 40 times more rifapentine than patients in the clinic. In addition, animals were dosed daily, while humans are dosed every 72 hours. Also, although the metabolite, 25-desacetyl rifapentine was positive in the chromosome aberration assay, the low amounts of the metabolite in rat plasma may imply that the tumors were due to rifapentine. The pattern of rifapentine metabolism seems to be different in man. In man, the plasma AUC (0-∞) value of the metabolite (25-desacetyl rifapentine) was two-thirds that of rifapentine and the Cmax value was four-tenths of the rifapentine value when a 600 mg dose was administered. As mentioned above, the metabolite was only present in trace amounts in rat plasma.

The sponsor also cites two examples of compounds (formaldehyde and phenacetin) which produce nasal tumors in rats, but which do not seem to pose a risk to humans. Nasal tumors only seem to be prevalent in a few occupational areas, where workers produce items such as shoes, chromate, nickel, wood furniture, mustard gas and isopropyl alcohol.

This submission represents a preliminary report of these findings. When the complete report is submitted, a decision will be made about whether or not a "Dear doctor" letter needs to be circulated but these results will be reflected in the labelling for PRIFTIN®.

/S/

Owen McMaster, Ph.D.

Concurrences:
/S/ 10/27/99
HFD-590/Ralbrecht
HFD-590/KHastings /S/ 10/25/99
Disk:
HFD-590/KHastings
cc:
HFD-590 Original IND

Div. File

Keywords: PRIFTIN®, rifapentine, carcinogenicity study, hepatocellular carcinoma, mice, male mice, tumor, adenoma.

DEC 15 [illegible]

Reviewer name: Owen McMaster
Division name: Division of Special Pathogen and Immunologic Drug Products
HFD-590
Review completion date: December 7, 1999
Sponsor: Hoechst Marion Roussel Inc.
Drug: PRIFTIN® (rifapentine)

Background

PRIFTIN® (rifapentine) is indicated for the treatment of pulmonary tuberculosis. It is administered twice-weekly for two months followed by once-weekly treatment for four months and must always be used in conjunction with another anti tuberculosis drug to which the isolate is susceptible.

A carcinogenicity study of mice treated with rifapentine has just been completed. This submission discussed tumor findings detected from a preliminary examination of the study animals. The study was conducted according to the following protocol:

Table 1: Carcinogenicity study of rifapentine in mice: Study Protocol.

Group #	Main study mice		Pk study mice		Dose levels (mg/kg/day)
	Male	Female	Male	Female	
1	50	50	15	15	0
2	50	50	15	15	0
3	50	50	15	15	5
4	50	50	15	15	20
5	50	50	15	15	80

Mortality during the study was as shown on Table 2 (below):

Table 2: Mortality data in mice treated for two years with rifapentine

Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
Weeks 1-52	2	2	0	1	8	3	8	7	4	6
Weeks 53-78	7	6	5	8	7	15	18	18	19	22
Weeks 79-105	13	20	24	18	18	8	11	8	12	10
Total deaths	22	28	29	27	33	26	37	33	35	38
Terminal sac.	28	22	21	23	17	24	13	17	15	12
Total	50	50	50	50	50	50	50	50	50	50

Comment

There were no striking differences in mortality between controls and drug-treated animals, with the exception of an excess of early deaths (weeks 1-52) in group 5 males compared to controls.

There was however, a clear increase in the percentage of male mice with adenomas and carcinomas at all doses (see Table 3, below)

Table 3: Incidences of hepatocellular neoplasia (%)

Sex	Males					Females				
Group number	1	2	3	4	5	1	2	3	4	5
Number examined	50	50	50	50	50	50	50	50	50	50
Adenoma	4	4	10	10	10	0	0	0	0	0
Carcinoma	16	18	34	52	40	0	0	0	6	2

While male mice are clearly more susceptible to tumors than female mice in this study, there is a clear increase in tumor-formation when drug-treated mice are compared to control animals. Drug-treated male mice have over twice the incidence of adenomas as control mice and up to three times the incidence of carcinoma.

The sponsor has argued that the increase in hepatic tumors in male mice does not alter the risk-benefit ratio for rifapentine. They argue that the mouse is not a good model of human carcinogenic potential since other rifamycins have not been reported to cause human liver tumors despite having positive findings in mouse studies (increased hepatomas were observed in female mice treated with rifampin). They also argue that because rifapentine was negative in the standard battery of genotoxicity tests, the mechanism of action is probably related to enzyme–induction or through a modulation of hormonal balance. They also make the point that the tumors are seen at doses higher than those seen in the clinic.

Comment

– Any tumor finding must be reported in the label, whether or not the findings are judged relevant to humans. Knowledge of the mechanism involved in the tumor induction is useful, but will not necessarily change the risk-benefit ratio for rifapentine. Also, the exposure data for the mid dose (20 mg/kg/day), shows that these mice are exposed to 11 times the AUC observed in humans, but tumors were also increased in mice exposed to one fourth of that dose (5 mg/kg/day). As such, tumors are being produced in mice at AUC values only slightly higher than those seen in man.

The final report of this study has been requested from the sponsor. Once the final study reports have been submitted to the agency, a decision will be made regarding the need for a "Dear Doctor" letter and labeling changes.

/S/

Owen G. McMaster, Ph.D.
Pharmacology/Toxicology Reviewer DSPIDP

Concurrences:
HFD-590/RAlbrecht /S/ 12/15/99
HFD-590/KHastings /S/ 12/15/99
Disk:
HFD-590/KHastings
cc:
HFD-590 Original IND
HFD-590/PM/LBernato
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HFD-590/Micro/LGosey
HFD-340
HFD-590/MO/JKorvick
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