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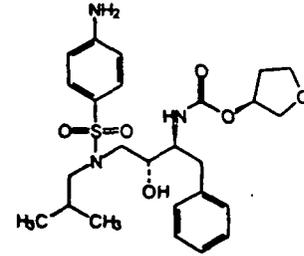
APPLICATION NUMBER

21-007/SE7-006

21-039/SE7-006

Pharmacology Review(s)

PHARMACOLOGIST'S REVIEW



NDA 21-007
NDA 21-039

Date Submitted: 4/4/2001
Date Assigned: 4/26/2001
Date review completed: 5/2/2001
Assigned reviewer: Hao Zhang

SPONSOR

GlaxoSmithKline., PO Box 13398., Five More Drive, Research Triangle Park, NC 27709; Tel.: 919-483-6972

DRUG

Agenerase®, amprenavir (141W94)

FORMULATION

Amprenavir (141W94): 50 mg, 150 mg Capsules (NDA 21-007); 15 mg/ml Oral Solution (NDA 21-039)

RELATED INDs and NDAs IND[]IND[]

INDICATION (S) Treatment of HIV infection

SUMMARY

NDA 21-007 and NDA 21-039 were granted accelerated approval by the agency on 15 April 1999. A Supplemental Application for traditional approval of these products was submitted on 13 July 2000. To revise the labeling to include information on Agenerase® when used in combination with ritonavir, the sponsor submitted a Supplemental New Application: Clinical Pharmacology and Labeling to NDA 21-007 (for Agenerase® Capsules) and NDA 21-039 (for Agenerase® oral solution) for review.

There are no new non-clinical pharmacology/toxicology data pertinent to this submission. The sponsor, however, summarized the preliminary histopathological findings from the carcinogenicity studies in rats and mice, which were submitted to the amprenavir IND[] on 27 October 2000 and 23 January 2001).

Preliminary carcinogenicity studies in rats showed hepatocellular adenoma in males at 750 mg/kg/day, and increased hepatocellular foci in males at 190 and 750 mg/kg/day and in females at 850 mg/kg/day. Uterine adenomyosis were seen in female rats at 750 mg/kg/day. Preliminary carcinogenicity studies in mice indicated an increased incidence of hepatocellular adenomas at 500 mg/kg/day, and an increased incidence of hepatocellular carcinoma and hepatocellular foci in males at 150, 270 and 500 mg/kg/day (Re: Pharmacologist's Review: IND [] Serial No.: 485; Appendix A).

Conclusion

There are no new nonclinical pharmacology/toxicology data pertinent to these submissions. There are no new data that would preclude approval of both.


Hao Zhang, M.D.
Pharmacologist

The summary of the preliminary histopathological findings from the rat oncogenicity study included in this submission was reviewed as follows.

The rat oncogenicity study was conducted at 50, 190 and 750 mg/kg/day. The study was initiated in June 1998 and the final necropsy was completed in June 2000. Increased incidences of hepatocellular adenoma in male rats at 750 mg/kg/day were seen. The incidence of altered hepatocellular foci was increased for male rats at 190 (1200 mg APV BID or 1200 mg APV: 200 mg ritonavir QD; AUC= 36 µg•hr/mL or 64.4 µg•hr/mL, respectively; multiples of rats to human exposure: 1 or 1.7, respectively) and 750 mg/kg/day (1200 mg APV BID or 1200 mg APV: 200 mg ritonavir QD; AUC= 36 µg•hr/mL or 64.4 µg•hr/mL, respectively; multiples of rats to human exposure: 1.9 to 3.3) and females at 750 mg/kg/day (1200 mg APV BID or 1200 mg APV: 200 mg ritonavir QD; AUC= 36 µg•hr/mL or 64.4 µg•hr/mL, respectively; multiples of rats to human exposure: 1.9 to 3.3). Histopathology for water control animals and females at 50 mg/kg/day is in progress.

Table 1. Preliminary neoplastic findings in the liver

Dose mg/kg/day	Males (n=60/group)				Females (n=60/group)			
	No. tested	Hepatocellular adenoma	Altered foci		No. tested	Hepatocellular adenoma	Altered foci	
			basophilic, clear cell, eosinophilic	Mixed			basophilic, clear cell, eosinophilic	Mixed
Water Control	14	1	3	0	24	0	9	0
Vehicle Control	60	1	14	0	61	0	37	0
50	58	0	17	3	24	0	12	0
50	60	0	13	3	18	0	12	0
190	60	3	33	7	60	1	34	4
750	59	7	25	14	60	0	44	3

Conclusion

No regulatory action is associated with this review.

/s/ 5/2/01

Hao Zhang, M.D.
Pharmacologist

Concurrences:

cc

HFD-530/JFarrelly
HFD-530/HZhang

5/8/01

HFD-530/IND
HFD-530/CSO
HFD-530/HZhang
HFD-530/MO
HFD-530/Chemist
HFD-530/Micro

Disk:
HFD-530/JFarrelly