CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20-972

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW

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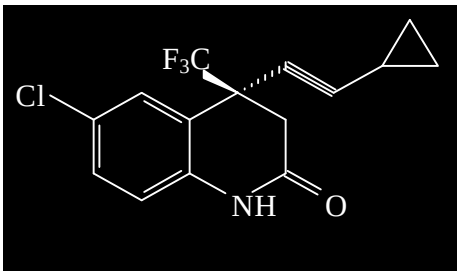

SPONSOR Dupont Merck Co.
Wilmington, DE

DRUG Sustiva®; Efavirenz; DMP 266; L-743,726; (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4(trifluoromethyl)-2H-3,1-benzoxazin-2-one; $C_{14}H_9ClF_3NO_2$; MW: 315.7

FORMULATION (b)(4)----------

INDICATION Treatment of HIV

INTRODUCTION

DMP 266 is a non-nucleosid(b)(4)--------scriptase inhibitor for use in the treatment of AIDS. The NDA is originated from ----------that was initially submitted on 12/30/95. The preclinical program of this NDA consisted of more than 50 animal toxicity studies conducted in rodents, cynolmogus monkeys, dogs, and rabbits in supp(b)(4)---------nded human uses. Portion of the toxicity studies have been reviewed under----------This review document summarizes and comments on the up-to-date preclinical safety information and the proposed labeling on DMP 266.

SUMMARY OF PRECLINICAL SAFETY INFORMATION: DMP 266

Animal toxicity studies conducted with DMP 266 include

- Single-dose toxicity studies in rats and mice
- Repeat-dose toxicity studies in rats and cynomolgus monkeys
- Pre-carcinogenicity rangefinding studies in rats and mice
- Reproductive toxicity studies in rats, rabbits, and cynomolgus monkeys
- Neonatal toxicity studies in rhesus monkeys, and toxicokinetics in weanling cynomolgus monkeys
- *In vitro* and *in vivo* mutagenicity assays
- Special toxicity studies on nephrotoxicity and thyroid toxicity caused by DMP 266 in rats

(b)(4)--------d evaluation on the animal toxicology studies that were not reviewed under -----------please refer to the APPENDIX of this document. Key preclinical safety information is recapitulated and issues discussed below.

(1) TARGET ORGAN/SYSTEM AND PROFILE OF TOXICITY OF DMP 266

Major toxicity findings and key target organ/system of toxicity were identified in a series of repeat-dose toxicity studies conducted in rodents, monkeys, and rabbits, as highlighted below.

KIDNEY: ***Renal tubule necrosis in rats.*** DMP 266-induced nephrotoxicity occurred in rats. Treatment with doses ≥500 mg/kg bid of DMP 266 in rats resulted in death due to acute tubular necrosis. Renal cortical epithelial cell necrosis, associated with intraluminal casts, proteinaceous debris, and tubular dilatation, was observed at doses ≥250 mg/kg bid. Clinical pathology findings of nephrotoxicity include drug-related crystals (glucuronide conjugate of 8-OH DMP 266), renal epithelial cells, and casts in the urine sediment. Serum BUN and creatinine, fractional sodium excretion, and renal cell-histochemical labeling indices, were found not to be sensitive indicators of DMP 266-induced renal toxicity in rats. NOAELs for this toxicity were: 50 mg/kg bid for 3 months or 100 mg/kg bid for 6 months (female rats); 30 mg/kg bid for 3 months or 15 mg/kg bid for 6 months (male rats). The renal toxicity caused by DMP 266 in rats is due to the formation of a nephrotoxic glutathione conjugate (not formed in primates or man.) There has been no parallel evidence of DMP 266-related nephrotoxicity reported in mice, monkeys, rabbits and humans given this drug.

LIVER P450 ENZYME SYSTEM: ***Hepatocellular hypertrophy in rats, mice and monkeys.*** DMP 266 induces hepatic drug metabolizing enzymes in rats, mice, rhesus and cynomolgus monkeys. A marked increase in the metabolic clearance of DMP 266 was also seen as a result of enzyme induction. In rats, increases in liver weight and hepatocellular hypertrophy could be seen at doses of ≥30 mg/kg/day. The hepatic enzymes involved are CYP 2B1 and 3A1 in rats and rhesus monkeys; and CYP3A and UDP-glucuronyl transferase in cynomolgus monkeys. Autoinduction of hepatic enzymes increased metabolic clearance of DMP 266 in the rats and rhesus monkeys and resulted in low AUC values (lower than human exposure in the rat). Toxicity studies conducted in these two species often suffered the drawback of insufficient systemic drug exposure.

LIVER CELLS: ***ALT elevations in monkeys and hepatocellular necrosis in mice.*** Increases in serum alanine aminotransferase (ALT; 1.5-3 fold) activity were observed in cynomolgus monkeys given doses ≥45 mg/kg bid for ≤1 year. No histological evidence of a hepatocellular injury was observed after ≤1 year of dosing in cynomolgus monkeys. In mice, ALT and AST were increased in males (2-5 fold) and female (2-3 fold, ALT) at 300 mg/kg/day. Hepatocellular necrosis was observed in the liver of males at 100 mg/kg/day and of females at 300 mg/kg/day. No drug-related transaminase elevations have been observed in patients given DMP 266 during clinical trials.

BILIARY SYSTEM: ***Fibrosis and hyperplasia in rats, mice and monkeys.***

Multifocal biliary fibrosis and dilatation of smaller bile ductules could be induced by DMP 266 in female rats given ≥250 mg/kg bid, and in male rats given ≥350 mg/kg bid in the 3-month oral toxicity study. The severity of this toxicity after oral gavage involved relatively isolated bile ducts. Biliary fibrosis was also observed in the liver of rats after 3 months of dietary administration of doses ≥500 mg/kg/day. The lesions were more severe after dietary dosing, obliterating the ductular lumen, and were accompanied by biliary hyperplasia. Biliary lesions were not observed in rats given 100 mg/kg bid by oral gavage for 6 months or 100 mg/kg/day in the diet for 3 months. In mice, occlusion of bile ducts by globular masses of pigment and biliary hyperplasia and pericholangitis were also reported in a 3-month study (450 mg/kg). Biliary hyperplasia (increase in the number of small caliber bile ducts) was observed in the liver of cynomolgus monkeys (75 mg/kg bid; AUC 5X > AUC in humans at 600 mg/day). NOAELs for biliary toxicity were about 90 mg/kg/day bid in both rats and cynomolgus monkeys.

Biliary fibrosis and hyperplasia are cross-species phenomena and can not be easily monitored clinically. Its relevance to humans is not known. The sponsor indicated that they are conducting a 2-year study (with a 6-month recovery period) to further evaluate the development and reversibility of biliary hyperplasia in DMP 266-treated cynomolgus monkeys.

BLOOD COAGULATION SYSTEM: ***Prolongation of APTT and PT in rats and monkeys.***

At the end of the 6-month oral toxicity study in rats, increases in prothrombin time (PT) and activated partial thromboplastin times (APTT) were observed in several male rats given ≥50 mg/kg bid. These prolongations were not associated with any gross or microscopic evidence of bleeding. Prolonged APTT (≤approximately 10 seconds longer than the highest concurrent control) were also observed in cynomolgus monkeys given ≥45 mg/kg bid of DMP 266 in the 6-month and 1-year studies. Further investigation of this change revealed a slight decrease in the activities of Factor XII in affected animals, and a slight decrease in the activity of Factor XI in the animals with the longest APTT. Apart from decreased coagulation factor activities, no alterations in coagulation parameters, fibrinogen concentration, prothrombin time, or platelet count were noted and no evidence of bleeding was observed upon postmortem examination. The cause of the decreased activities of Factor XII and or XI is not known. No increases in APTT have been reported from clinical trials on DMP 266

THYROID GLAND: ***Follicular cell hypertrophy in monkeys.***

Thyroid follicular cell hypertrophy occurred in one mid-dose male cynomolgus monkey (45 mg/kg bid), all of the high-dose male cynomolgus monkeys (75 mg/kg bid), and half of the high-dose females at the end of the 1-year oral toxicity study. The sponsor considered the toxicity seen in the thyroid of cynomolgus monkeys an adaptive change related to the hepatic induction of UDP-glucuronyl transferase in this species (UDP-glucuronyl transferase is a rate limiting Phase II enzyme involved in the clearance of thyroxine). The enzyme induction results in an increased clearance of thyroxine causing a compensatory increase in TSH. An increased clearance of ^{125}I-derived radioactivity in monkeys given ^{125}I-thyroxine and elevations

in serum TSH were demonstrated in cynomolgus monkeys given 75 mg/kg bid of DMP 266 for 1 month. It is not known whether this thyroid toxicity would pose a risk to patients given DMP 266. Chronic treatment with other known enzyme inducers such as phenobarbital, carbamazepine, phenytoin, and rifampicin may not be associated with clinical hypothyroidism, goiter, or thyroid neoplasia in humans.

TOXICO-KINETICS Plasma DMP 266 concentrations achieved at the maximally tolerated doses given during chronic rat toxicology studies were lower than those achieved in humans given therapeutic doses of DMP 266. Thus, the exposures to DMP 266 in the rat in various studies are considered insufficient and the toxicity profile of the drug in this species could not be fully explored. DMP 266 has a very short plasma half-life in rats (between approximately 0.8 and 1.9 hours) compared to a substantially longer half-life in humans (>40 hours). Plasma DMP 266 AUC values in male and female rats given 500 mg/kg/day (250 mg/kg bid) during the 3-month oral rat study were only 20% (male) and 45% (female), respectively, of the plasma AUC values achieved in patients given 600 mg/day of DMP 266 (38 μM-h and 84 μM-h in male and female rats given 250 mg/kg bid respectively, versus 186 μM-h in humans given 600 mg/day). Renal toxicity precluded the testing of higher DMP 266 doses in chronic rat studies. While plasma DMP 266 concentrations are low in DMP 266-treated rats due to the rapid metabolic clearance of DMP 266, plasma Cmax concentrations and AUC values of the 8-OH DMP 266 glucuronide (the principal metabolite of DMP 266) are 50- to 75-fold higher in rats given 250 mg/kg bid than in humans given therapeutic doses of DMP 266).

The plasma AUC values of DMP 266 in cynomolgus monkeys given 45 and 75 mg/kg bid during chronic toxicology studies were approximately 1.5- and 5-fold higher than those attained in humans given 600 mg/day of DMP 266. Mean plasma DMP 266 Cmax and AUC values achieved in cynomolgus monkeys are summarized in the table below.

TABLE 1.
MEAN PLASMA DMP 266 CMAX AND AUC VALUES ACHIEVED IN CYNOMOLGUS MONKEYS AND HUMANS

Cynomolgus Monkey	DMP 266 Mean Cmax (uM)	DMP 266 Mean AUC (uM-h)
15 mg/kg bid	5.9	65
45 mg/kg bid	20.4	283
75 mg/kg bid	53.5	907
Human - 600 mg/day	13.1	186

REPRO-DUCTIVE SYSTEM: ***Fetal malformations in monkeys.*** In the cynomolgus monkeys, significant teratologic effects were reported. Fetal malformations in 3 of 20 fetuses from the DMP 266-treated group upon Cesarean sectioning were reported at 30 mg/kg bid (dosed from gestational day 20 through day 150). Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. In the sponsor's historic control database, anencephaly has only been

observed 1/300 fetuses, microophthalmia, anophthalmia, and cleft palate have never been observed in approximately 300 control fetuses at the laboratory where the study is being conducted. Thus, these teratogenic findings are considered drug-induced. It should be mentioned that DMP 266 crosses the placenta, and has a similar metabolic profile between monkeys and humans (glucuronide conjugate of 8-OH DMP 266 as the major plasma and urinary metabolite in both species). Further details and comments on the cynomolgus monkey teratogenicity study are not available because the final report has not been submitted by the sponsor (will be available 12/98).

Other Maternal, embryonic and fetal toxicities in rats and rabbits. No significant teratologic, maternal, embryonic and fetal toxicity findings were reported from studies on pregnant rats or rabbits treated with DMP 266. The lack of effects might have been due to insufficient exposures of the drug to the animals (high drug clearance resulted from autoinduction of hepatic enzymes, see above). The plasma AUC values achieved in pregnant female rats given 100 mg/kg bid of DMP 266 only equated to those achieved in humans given 600 mg/day of DMP 266 (188 μM-h versus 186 μM-h in humans). Average fetal blood concentrations in fetal rats were 25% - 49% lower than the corresponding maternal concentrations. In pregnant rabbits (75 mg/kg/day DMP 266), the plasma AUC values were 60% lower than those achieved in humans given therapeutic doses of DMP 266. Fetal plasma AUC concentrations in rabbits (148 μM-h) μM were also lower than the plasma AUC attained in humans (186 μM-h).

INFANT AND NEONATAL TOXICOLOGY*: For future pediatric formulation.* In the 5-week oral infant rhesus toxicity study, dosing with DMP 266 was initiated on Day 2 of life. Groups of four monkeys/sex/dose were given doses of 0, 30, and 45 mg/kg/day for the first 3 days of the study; thereafter, doses of 0, 30, and 45 mg/kg bid were given. A decrease in body weight gain and decreases in food intake were reported in infant rhesus monkeys (females) given 30 mg/kg bid were. Doses of 45 mg/kg bid produced vomiting, lethargy, dehydration, poor appetite, and/or weakness in infant rhesus monkeys and decreases in the average amount of body weight gain. Histologic examination of a complete set of tissues revealed no DMP 266-related changes in any DMP 266-treated infant rhesus monkeys. The Cmax and AUC average values in males given 30 mg/kg bid were similar to those in humans given 600 mg/day of DMP 266, and the average Cmax and AUC values in females given 30 mg/kg bid were 2-fold higher than those in humans given 600 mg/day of DMP 266. Average Cmax and AUC values in male and female infant rhesus monkeys given 45 mg/kg bid were 2.5-fold higher than those in humans given 600 mg/day of DMP 266.

DNA AND CHROMOSOME SYSTEMS DMP 266 tested negative in the Ames assay, mammalian cell mutation assay, in vitro chromosome aberration assay in human peripheral lymphocytes, and micronucleus assay in mouse bone marrow.

CARCINO-GENICITY The two-year carcinogenicity studies are being conducted in the rat and mouse. The final phase of the in-life dosing is in progress. Currently no interim reports on gross tumor findings have been submitted by the sponsor.

METABOLISM: DMP 266 undergoes extensive metabolism in rats and cynomolgus monkeys leading to a diverse array of metabolites and higher concentrations of the primary metabolite (8-OH glucuronide) in rats than in monkeys or humans. Plasma DMP 266 concentrations and AUC values were substantially higher in female compared to male rats. Plasma AUC values in male and female rats were markedly lower than those attained in cynomolgus monkeys given 75 mg/kg bid and in humans given 600 mg/day of DMP 266 (see table below).

Plasma DMP 266

TABLE 2.
MEAN PLASMA DMP 266 CONCENTRATIONS IN RATS, CYNOMOLGUS MONKEYS AND HUMANS

DMP 266	Cmax (μM)	AUC (μM-h)
Rat 250 mg/kg bid	1.0 (5.4) (Males/Females)	9.7 (38.8) (Males/Females)
Cynomolgus Monkey 75 mg/kg bid	53.5	907
Human 600 mg/day	13.1	186

Plasma 8-OH Glucuronide

The concentrations of the 8-OH glucuronide were markedly higher in rats than in cynomolgus monkeys or humans (see table below). Plasma Cmax concentrations and AUC values for the 8-OH glucuronide in rats were approximately 51 and 31 times greater, respectively, than in cynomolgus monkeys given 75 mg/kg bid of DMP 266, and 75 and 49 times greater, respectively, than in humans given 400-800 mg/day of DMP 266. The markedly higher plasma concentrations of the 8-OH glucuronide found in rats are indicative of the rapid biotransformation of DMP 266 in this species.

TABLE 3.
MEAN PLASMA 8-OH DMP 266 GLUCURONIDE CONCENTRATIONS IN RATS, CYNOMOLGUS MONKEYS AND HUMANS

	8-OH DMP 266 Glucuronide
Rat 250 mg/kg bid Cmax (μM)	1093.3/1515.7 (male/female)
AUC (μM-h)	13878.5/16947.0(male/female)
Cynomolgus Monkey 75 mg/kg bid Cmax (μM)	25.6
AUC (μM-h)	497.7
Human 400-800 mg/day Cmax (μM)	17.5
AUC (μM-h)	314.1

Urinary 8-OH Glucuronide

The average 24-hour urinary concentrations of the 8-OH glucuronide in rats (250 mg/kg bid) were approximately 4- to 9-fold greater than in cynomolgus monkeys given 75 mg/kg bid and approximately 23-fold greater than in humans given 400-800 mg/day of DMP 266 (see table below).

TABLE 4.
MEAN URINARY DMP 266 AND 8-OH GLUCURONIDE METABOLITE CONCENTRATIONS IN RATS, CYNOMOLGUS MONKEYS AND HUMANS

Urinary Concentrations (μM)	DMP 266 Male	DMP 266 Female	8-OH DMP 266 Male	8-OH DMP 266 Female	8-OH Glucuronide DMP 266 Male	8-OH Glucuronide DMP 266 Female
Rat 250 mg/kg bid	<3	<3	442.4	569.5	5075.7	4730.2
Cynomolgus Monkey 75 mg/kg bid	<3	<3	283.3	364	1128.1	547.3
Human 400-800 mg/day	<3		<3		210.8	

Glutathione conjugate of 8-OH sulfate cyclopropanol The glutathione conjugate of 8-OH sulfate DMP 266 cyclopropanol was suggested to be directly involved in the genesis of DMP 266-induced nephrotoxicity in rats because inhibition of renal glutathione catabolism by acivicin resulted in (1) a 3-fold decrease in the total amount of cysteinyl-glycine conjugate in the urine of DMP 266-treated rats, (2) a significantly less severe renal tubular epithelial cell necrosis than those given DMP 266 alone with fewer rats affected.

RISK ASSESSMENT OF DMP 266 BASED ON NON-CLINICAL TOXICOLOGY STUDIES

LIMITATIONS OF PRECLINICAL TOXICITY STUDIES CONDUCTED ON DMP 266

- The sponsor had conducted at least 5 acute toxicity studies in rats and mice, 14 repeat-dose toxicity studies in rats and cynomolgus monkeys and rhesus monkeys, 2 pre-carcinogenicity rangefinding studies in rats and mice, 8 reproductive toxicity studies in rats, rabbits, and cynomolgus monkeys, 2 neonatal toxicity studies in rhesus monkeys, 4 *In vitro* and *in vivo* mutagenicity assays, and other special toxicity studies on nephrotoxicity and thyroid toxicity in support of this NDA.

- The use of rat as the major animal species for identifying target organ of toxicity, reprodcutive toxicity and carcinogenicity of DMP 266 was handicapped by the limitation of drug exposure. Plasma drug levels could not be effectively escalated because of the highly inductive nature of DMP 266 on the hepatic P450 enzyme system. The resulting P450 enzyme autoinduction led to a very quick clearance of DMP 266, a short plasma drug half-life and low drug exposure levels. Thus, in the rat toxicity studies, the plasma AUC only equates to humans AUC (≅186 uM-hr). The dose exaggeration schemes in rats were also restricted by the life-threatening nephrotoxicity. Because of insufficient drug exposure, one should be cautioned when interpreting information derived from rat studies regarding general target organ/system of toxicity, reprotoxicity and carcinogenic potential of DMP 266.

- While plasma DMP 266 concentrations are low in rats, plasma Cmax concentrations and AUC values of the 8-OH DMP 266 glucuronide (the principal metabolite of DMP 266) are 50- to 75-fold higher in rats given 250 mg/kg bid than in humans given therapeutic doses of DMP 266. The utility of the rat toxicity studies can be highlighted here in regard to concerns on the safety profile of 8-OH DMP 266 glucuronide presented in humans upon which information gained from the rat studies could be used.

- Although DMP 266 induced the hepatic P450 enzyme system in cynomolgus monkeys, plasma drug levels could be escalated 1.5- and 5-fold higher than those attained in humans given 600 mg/day of DMP 266. Toxicity information derived from cynomolgus monkey studies is considered comparably more significant than that obtained form the rat studies.

COMMENTS ON TOXICITY PROFILE OF DMP 266

- DMP 266 produced a spectrum of toxicities in animals that involved primarily liver (hepatic enzyme P450 system and biliary secretary system), kidney, thyroid and the blood coagulation system. These toxicities, so far, were only observed in the animals, and have not been reported in humans from the clinical trials. Therefore it had not impeded the clinical development of this drug.

- Among the toxicities explored, nephrotoxicity in the rat has caused attention. The sponsor conducted special studies suggesting that it is a species-specific toxic phenomena. The studies showed that DMP 266-induced nephrotoxicity in rats resulted from the formation of a unique DMP 266 glutathione conjugate not formed in cynomolgus monkeys or humans.

- Biliary fibrosis and hyperplasia were also observed in rats and monkeys chronically given DMP 266. Clinical relevance of this animal toxicity is not known. Although the sponsor indicated that they has been conducting a 2-year study (with a 6-month recovery period) to further evaluate the development and reversibility of biliary hyperplasia in DMP 266-treated cynomolgus monkeys, the difficulty to monitor biliary fibrosis and hyperplasia should be recognized.

- DMP 266-induced thyroid follicular cell hypertrophy in cynomolgus monkey was explained by the sponsor as an adaptive change (compensatory increase in TSH) related to the hepatic induction of UDP-glucuronyl transferase, an enzyme involved in the clearance of thyroxine, in this species. It is not known whether thyroid toxicity would pose a risk to patients given DMP 266. Although other known enzyme inducers such as phenobarbital, carbamazepine, phenytoin, and rifampicin have not been associated with clinical hypothyroidism, goiter, or thyroid neoplasm, the potential risk to thyroid toxicity during DMP 266 therapy exists. The sponsor should monitor hypothalamus-pituitary-thyroid axis function by measuring thyroxine, TSH and T^3 levels in future human trials (b)(4)----------

- The drug is teratogenic. Fetal malformations (anencephaly, unilateral anophthalmia, microophthalmia, and cleft palate) were observed in 3 of 20 fetuses from the DMP 266-treated cynolmogus monkeys. The drug will be categorized into the *Pregnancy Category C*. Detailed teratogenicity information will be given in the labeling. The potential for carcinogenicity is not known and is currently under evaluation.

CONCLUSION

This NDA in its present form has provided adequate preclinical safety information in support of its approval. The sponsor has employed feasible levels of dosage and number of animals of both sexes in their studies. The sponsor has explored the toxicity of the drug and adequately addressed issues regarding the modes and mechanisms of each toxicity uncovered. While the toxicity testing on DMP 266 is still ongoing (b)(4)---------- (b)(4) it is concluded that the NDA has provided sufficient preclinical safety information to allow for prediction of potential toxicity in humans with the judicious use of this drug in humans. The following regulatory request is proposed as follows.

REGULATORY REQUEST:

The sponsor should consider monitoring the effects of DMP 266 on the hypothalamus-pituitary-thyroid function by measuring thyroxine, TSH and T_3 levels in future human trials.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/DepDir/WDempsey
DAVDP/HFD-530/PTL/JFarrelly
Wu/Pharm/6/12/98

Disk: JFarrelly

HFD-530 NDA 20-972 (000)
HFD-530/Division File
HFN-340
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