CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-235

PHARMACOLOGY REVIEW

DAVID

OCT - 6 2000

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10/2/00

PHARMACOLOGIST REVIEW OF NDA 21-235
ORIGINAL SUMMARY

SPONSOR: Eli Lilly and Co.

DRUG: Prozac ——— (fluoxetine ——— capsules for weekly dosing)

CATEGORY: Treatment of depression, obsessive compulsive disorder, and bulimia nervosa

RELATED IND: 53,079 (companion to present NDA)

RELATED NDA: 18-936 (Prozac)

SUMMARY:

No new preclinical studies of fluoxetine were submitted to this application. During the IND process, some concern was raised about the excipient ———, which, although marketed as an excipient abroad, is not so marketed in this country. (Hydroxypropylmethylcellulose [HPMC], is so marketed: ———

Preclinical studies of ——— were submitted to the IND and included 6 month toxicity in rats, segment I, II, and III reproduction in rats, and segment II reproduction in rabbits. These studies were not submitted in sufficient detail for independent review, and it is not known if they were GLP compliant. No significant adverse effects were seen at high oral doses of ———, this is not surprising since a study in rats indicated that it is likely that little or no drug was absorbed. (Rats were given oral ——— labelled in the succinate moiety; label was virtually entirely excreted in feces with little or no label found in urine, blood, or tissues).

We raised the question (meeting of 4/14/99) that it is not known that ———, is also not absorbed in humans. The sponsor responded that a study to determine this would be unethical and technically unfeasable (submission of 6/30/99). It was agreed (letter of 11/19/99) that the sponsor would perform a biliary excretion study in rats to be able to rule out the possibility that the high level of fecal excretion seen (see above) was due to biliary excretion of absorbed drug. This study is contained in the present application (volume 2.3, p. 60+) ——— was labelled in the ———moiety. Results are shown in the attached tables. Label was primarily excreted in feces. Little or no label was excreted in bile (Table 3). (Fecal excretion was delayed in time, and was slightly less in degree, in bile duct-cannulated rats [compare Tables 2 and 3]; the reason for this is not clear). Little or no label was seen in urine or (as measured in cannulated rats) plasma.

(The plasma levels in Table 4 were said to represent less than 0.003% of the dose). (The small amounts of label seen in plasma, urine, and bile may be due at least in part to the fact that the radiochemical purity of the [redacted] was [redacted], with the impurity "presumed" to be labelled [redacted]. The amount of label in carcass was greater in cannulated rats (9% of dose vs 0.2% in non-cannulated rats); the reason for this is not clear.

Table 1 **Mean (± SEM) Cumulative Percentage of Dose Recovered from Male F344 Rats Following a Single 1000-mg/kg Oral Dose of [^{14}C] ——**

Study 005R00 (n=4)

	Mean (± SEM) Percentage of ^{14}C Dose				
Hour	Feces	Urine	Cage Wash	Carcass	Total
24	88.47 ± 1.19	0.14 ± 0.01	0.74 ± 0.14		89.35 ± 1.28
48	92.78 ± 1.34	0.18 ± 0.03	0.85 ± 0.14		93.81 ± 1.45
72	93.07 ± 1.35	0.21 ± 0.03	0.91 ± 0.15		94.19 ± 1.47
96	93.18 ± 1.35	0.23 ± 0.03	0.95 ± 0.14	0.20 ± 0.03	94.55 ± 1.45

Table 2 **Percentage of Dose Recovered from Individual Male F344 Rats Following a Single 1000-mg/kg Oral Dose of [^{14}C] ——**

Study 005R00 (n=4)

	Time	Percentage of ^{14}C Dose					
	(Hour)	Rat 1	Rat 2	Rat 3	Rat 4	Mean	SEM
Urine	0 - 24					0.14	0.01
	24 - 48					0.05	0.01
	48 - 72					0.02	0.00
	72 - 96					0.02	0.01
	Total					0.23	0.03
Feces	0 - 24					88.47	1.19
	24 - 48					4.30	0.91
	48 - 72					0.30	0.03
	72 - 96					0.11	0.02
	Total					93.18	1.35
Cage Wash	0 - 24					0.74	0.14
	24 - 48					0.11	0.02
	48 - 72					0.06	0.02
	72 - 96					0.03	0.00
	Total					0.95	0.14
	Total Eliminated					94.35	1.48
Carcass						0.20	0.03
	Total Recovery					94.55	1.45

Table 3 **Percentage of Dose Recovered from Bile Duct-Cannulated Male F344 Rats Following a Single 1000-mg/kg Oral Dose of [^{14}C]**

Study 090R99

	Time (Hour)	Percentage of ^{14}C Dose							
		Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Mean	SEM
Bile	0 – 6							0.01	0.00
	6 – 12							0.00	0.00
	12 – 18							0.01	0.00
	18 – 24							0.01	0.00
	24 – 30							0.01	0.00
	30 – 36							0.00	0.00
	36 – 42							0.00	---
	42 – 48							0.00	---
	Total							0.03	0.01
Urine	0 – 24							0.09	0.02
	24 – 48							0.14	0.05
	Total							0.23	0.06
Feces	0 – 24							40.55	8.40
	24 – 48							43.52	7.04
	Total							84.07	3.26
Cage Wash	0 – 24							0.19	0.11
	24 – 48							0.65	0.21
	Total							0.85	0.28
Total Eliminated								85.18	3.01
Carcass								9.12	2.45
Total Recovery								94.29	0.70

[a]ND = No bile flow, not determined.

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Table 4 **Plasma Concentrations in Male F344 Rats Following a Single 1000-mg/kg Oral Dose of [^{14}C]**

Study 090R99

	Concentration (µg-equivalent/g plasma)					
Time (hr)	0.5	1	2	4	6	8
Rat ID						
7						
10						
13						
8						
11						
14						
9						
12						
15						
Mean	1.46	1.3	1.89	1.62	3.80	4.51
SEM	0.15	0.05	0.12	0.29	0.58	0.58

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EVALUATION:

Despite some anomalies in the results of the sponsor's study in bile duct-cannulated rats as noted above, it appears that little or no label is absorbed after oral administration of [redacted] labelled in the [redacted]. This would seem to indicate both that the [redacted] molecule is not absorbed whole, which is not surprising in view of its high molecular weight, and that the [redacted] is not de-esterified in the G.I. tract and subsequently absorbed. (The possibility of absorption of unlabelled moieties cannot be ruled out; e.g. lower molecular weight fragments of the HPMC backbone formed in the G.I. tract, although this would also occur after administration of HPMC, which is marketed in this country and considered safe, except in the unlikely case that the [redacted] somehow increased the formation or absorption of these fragments but were not themselves absorbed). It is not known if these findings would be the same in humans, although there is little reason to believe that [redacted] will not have a safety profile similar to that of HPMC.

RECOMMENDATION:

This NDA is approvable.

[/S/]

Barry N. Rosloff, Ph. D.

cc: NDA 21-235, original + division file

Rosloff, Fitzgerald, David

[/S/] 10/6/00

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