

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-299

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom
 Division Name: Neuropharmacological Drug Products
 HFD# 120
 Review Completion Date: May 2, 2001.

Review number: 1.

NDA number: 21-299.

Serial number/date/type of submission: N-000 / July 26, 2000 / NDA 505 (b)(2) [Paxil, SmithKline Beecham, Innovator].

Information to sponsor: Yes (X) No ()

Sponsor: Synthron Pharmaceuticals.

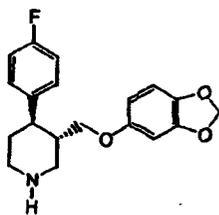
Manufacturer for drug substance: _____

Drug:

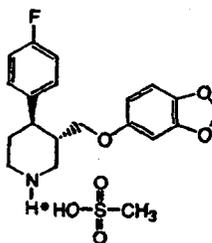
Code Name: not provided.

Generic Name: paroxetine mesylate.

Trade Name: not provided.

Structural Formula:

Paroxetine



Paroxetine mesylate

Molecular Formula:

Paroxetine: $C_{19}H_{20}FNO_3$
 Paroxetine mesylate: $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$

Molecular Weight

Paroxetine: $M_r = 329.37$
 Paroxetine mesylate: $M_r = \text{---}$

Relevant INDs/NDAs/DMFs: IND 57,407 (Synthron, mesylate); IND _____
 NDA 20-031 (SmithKline Beecham, HCl, approved for depression); NDA 20-710 (SB, HCl, 10 mg, oral suspension, approved for depression); NDA 20-885 (SmithKline Beecham, HCl, 10, 20, 30, 40 mg caps, approved for depression, OCD, panic disorder); NDA 20-936 and NDA 20-982 (SmithKline Beecham, HCl, 12.5, 25 mg CR tabs, approved for depression and approvable for panic disorder, respectively).

Drug Class: selective serotonin reuptake inhibitor (SSRI).

Indication: Depressive illness, obsessive compulsive disorder, and panic disorder.

Clinical formulation: tablets, 10, 20, 30, 40 mg; maximum daily doses recommended in the proposed labeling (volume 1, p 33) are 50 mg/d for depression and 60 mg/d for OCD and panic disorder.

Route of administration: oral.

Proposed clinical protocol or Use: Depression, Obsessive-Compulsive Disorder, Panic disorder.

Previous clinical experience: Paroxetine hydrochloride (Paxil, marketed by SmithKline Beecham) is approved for depression, obsessive compulsive disorder (OCD), panic disorder (PD), and social anxiety disorder (SAD) at doses up to 50 mg/day for depression, 60 mg/day for OCD and PD, and 20 mg/day for SAD.

Disclaimer -- use of sponsor's material: Where feasible, the Sponsor's figures and tables were incorporated directly into this review and noted as such.

Introduction and drug history: Paroxetine as the HCl salt (Paxil) is currently marketed by SmithKline Beecham (Innovator, NDA 20-031, P/T reviewed by Gary Evoniuk, 8/30/90). In the current NDA, Synthon is seeking to market the mesylate salt of paroxetine under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

Under IND 57,407, Synthon conducted bioequivalence studies comparing their mesylate salt with the HCl salt. Under that IND Synthon also submitted comparative acute toxicity studies in rats and mice, comparative 14-day dose ranging studies in rats, comparative 28-day repeated dose studies in rats, and comparative Ames tests (reviewed by Nuoyo Huang, 12/14/1998). The Agency has had considerable experience with mesylate salts and does not consider them *a priori* to pose a hazard. Consequently, the Agency accepted the submitted additional preclinical testing, including comparative 4-week repeated dose toxicology studies in rats and *in vitro* bacterial mutation assays, with the understanding that other studies might be required based upon chemistry, kinetics or toxicology study results. In the initial submission of this NDA, specifications for —impurities in the clinical drug substance and/or drug product exceeded the thresholds for qualification. These impurities would have required additional preclinical testing to be qualified, however, the Sponsor chose to lower its specifications for these impurities to levels not requiring qualification (submission N-B2, stamp-dated 12/11/00).

Studies within this submission: all comparing mesylate and HCl salts of paroxetine.

- Acute (iv and po) toxicity in mice and rats
 - po to rats (report no. 10764/97 vol 1.15 pp 5076-5115; 10765/97 pp 5116-5155)
 - iv to rats (report no. 10766/97 vol 1. pp 5156-5189; 10767/97 pp 5190-5222)
 - po to mice (report no. 10768/97 vol 1. pp 5223-5261; 10769/97 pp 5262-5295)
 - iv to mice (report no. 10770/97 vol 1. pp 5296-5326; 10771/97 pp 5327-5356)
- Repeated dose toxicity in rats (14-day ranging and 4-week, vs HCl salt)
 - 4-week study (report no. 10773/97 vol 1.16 pp 5413-6084 (vol.1.18))

- Ames' test (report no. 10774/97, vol 18:6085-6114 and report no. 11292/98 vol 19:6435-6464)
- Pharmacokinetic animal studies (ADME in non-pregnant and AD in pregnant rats)

Studies not reviewed within this submission: none.

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OVERALL SUMMARY AND EVALUATION:

Introduction: This NDA is for a new salt formulation of an already approved drug, paroxetine (currently marketed as the HCl salt, Paxil, by SmithKline Beecham). Since the new salt form, the mesylate, is a common salt and not expected to introduce toxicity, the Agency accepted minimal preclinical studies comparing the mesylate salt form to the HCl salt form submitted for the IND 57,047: 1) acute toxicology in rats and mice; 2) 4-week, repeated dose toxicology in rats; and 2) an *in vitro* bacterial test for mutagenicity. These same studies were submitted for the current NDA. Additionally, although the original submission of this NDA revealed impurities present in the drug product or substance at levels that would require additional preclinical studies for qualification, the Sponsor subsequently lowered the specifications for these impurities below the threshold for qualification.

Safety evaluation: No new preclinical toxicity issues have arisen from the studies submitted for this NDA. Toxicities or lack thereof seem to be the same as for the HCl salt; this is true for the comparisons between the salts presented in this NDA and in comparison to studies for the HCl salt previously submitted by the Innovator and reviewed under NDA 20-031.

Safety issues relevant to clinical use: No new clinical issues have arisen from the preclinical studies submitted for this NDA.

Other clinically relevant issues: none.

Conclusions: The Sponsor has submitted adequate preclinical studies, as previously accepted by the Agency, which do not present any new preclinical issues for the mesylate formulation of paroxetine that have not already been addressed in the Innovator's NDA 21-031 for the hydrochloride salt formulation of paroxetine. There are no preclinical issues that would preclude approval of this NDA.

Communication review:

Labeling review: The preclinical sections of the labeling that the Sponsor is proposing appear to be identical to the original Paxil labeling. This is consistent with the lack of differences between the 2 salt forms in preclinical studies; any alterations in the labeling would seem to be unwarranted.

RECOMMENDATIONS: From a pharmacology/toxicology perspective, there are no objections to the approval of this NDA.

Internal comments: None.

External recommendations (to sponsor): The study reports submitted here were very well organized and easy to review.

Addendum to review: Histopathology Inventory for NDA # 21-299; 4-week study in rats.

Appendix: List of relevant P/T reviews consulted.

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1 PHARMACOLOGY:

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and is presumed to exert its antidepressant activity through this mechanism. Paroxetine as the hydrochloride salt is currently marketed for therapy of major depression, obsessive compulsive disorder (OCD), panic disorder (PD), and social anxiety disorder (SAD). The pharmacology of the mesylate salt is presumed to be the same as for the hydrochloride salt. No new pharmacology studies were submitted with this NDA.

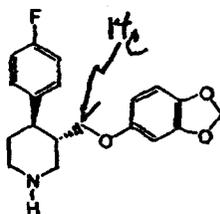
2 SAFETY PHARMACOLOGY:

The pharmacology of the mesylate salt is presumed to be the same as for the hydrochloride salt. No new safety pharmacology studies were submitted with this NDA.

3 PHARMACOKINETICS/TOXICOKINETICS:

The Sponsor submitted studies comparing ^{14}C -labeled (see position of label in structure below) paroxetine as the mesylate salt to the hydrochloride salt after a single intravenous or oral (by gavage) administration (5 mg/kg of the base) to rats:

- Study of the absorption, distribution, metabolism and excretion following oral and intravenous administration of ^{14}C -labelled POT.mes to Sprague-Dawley rats — Report No. 10775/97; volume 18: 6115-6241.
- Study of the absorption, distribution, metabolism and excretion following oral and intravenous administration of ^{14}C -labelled POT.HCl.H₂O to Sprague-Dawley rats. — Report No. 10779/97; volume 19: 6242-6368.



Paroxetine

PK parameters: Plasma levels of total radioactivity expressed as ng-equivalents of paroxetine were measured up to 96 hr after a single iv (5 mg/kg) or po (5 mg/kg) dose of paroxetine as mesylate or hydrochloride salt; plasma curves looked fairly smooth and levels were essentially down to background after 24 hr and undetectable after 48 hr. Systemic exposures (both AUC and C_{max}) for total radioactivity (i.e., parent plus metabolites) were similar after oral administration of either salt formulation; there was an apparent sex difference, with exposures for total radioactivity (i.e., parent plus metabolites) higher in females than males. The $t_{1/2}$ for elimination was ~ 6 (4-8) hr after

iv administration of either salt to males and females and for females after oral administration. The $t_{1/2}$ for males after oral administration of either salt was shorter, ~2-3 hr.

Table 1. PK parameters for total radioactivity (paroxetine plus metabolites) from ^{14}C -paroxetine as the mesylate salt (left panel) or HCl salt (right panel) administered po or iv to rats. These are the Sponsor's tables from volume 18:6123 and 19:6250.

Route	Sex	n	AUC	$t_{1/2}$	$t_{1/2}$	AUC
oral	male	5	182.7 ± 56.5	2.04 ± 0.34	2.34 ± 0.32	1280.0 ± 130.0
oral	female	5	290.7 ± 84.0	1.10 ± 0.25	6.18 ± 3.50	2586.7 ± 955.5
intra-venous	male	5	685.3 ± 144.1	-	4.42 ± 0.56	1980.0 ± 252.4
intra-venous	female	5	1158.7 ± 661.5	-	5.87 ± 6.15	3044.3 ± 2065.1
oral	male	5	175.0 ± 44.5	1.97 ± 0.68	3.26 ± 0.42	1606.7 ± 185.6
oral	female	5	329.0 ± 102.1	1.14 ± 0.11	5.10 ± 2.77	2663.3 ± 560.8
intra-venous	male	5	864.0 ± 296.0	-	6.10 ± 1.37	2220.0 ± 329.2
intra-venous	female	5	1084.7 ± 358.7	-	8.15 ± 0.84	3300.0 ± 320.8

Absorption: Oral bioavailability from the mesylate salt appeared to be lower for males (65%) than females (85%), however, oral bioavailability from the hydrochloride salt was comparable for males (72%) and females (77%).

Distribution: Tissue distribution was determined 96 hr after dosing; tissue levels were low. No clear differences between salt formulations were evident, except for possibly higher amounts of radioactivity in the gastric and intestinal contents following oral administration of the HCl salt.

Metabolism: Values presented in these studies were for total radioactivity (i.e., parent plus metabolites). "Semiquantitative" (or qualitative) HPLC determination of paroxetine and 2 metabolites (MET I: 4-hydroxymetaproxetine; MET III: desmethylparoxol) in plasma (1 hr after dosing) and urine (24 hr) was submitted in a separate report (Report NO. 11842/98; volume 19:6465-6500). No metabolites were detected in plasma 1 hr after administration. Most excreted test substance found in urine was glucuronide of sulfate conjugates of parent or metabolites. There was no apparent difference between patterns following administration of the 2 salt forms.

Excretion: There were no clear differences in excretion patterns between the 2 salt forms. Approximately 15 % of the administered dose (regardless of route or sex) was excreted in urine and ~70% in feces within 96 hr of dosing, mostly within the first 24 hr. Less than 1% of the administered radioactivity could be found in the carcass after 96 hr.

Other studies:

- Study of the absorption and distribution of ^{14}C -POT.HCl and ^{14}C -POT.mes following oral administration to pregnant Sprague-Dawley rats. Report No. 10802/97; volume 19:6369-6434.

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Pregnant rats were dosed daily on gestation days 6-18 with 5 mg/kg paroxetine as mesylate or hydrochloride salt labeled as above. Tissue levels were determined 1 hr after the last dose and, to quote the study report, "only little radioactivity could be found." Levels of total radioactivity (paroxetine plus metabolites) were quantifiable in brain, heart, kidney, liver, spleen and plasma of dams and in whole fetuses and fetal blood; however, there were no differences in disposition from the 2 salts (except a small increase in liver after the HCl salt compared with the mesylate).

PK/TK conclusions: In the studies reported here, the mesylate salt gave essentially identical results to those obtained with an equivalent dose of the hydrochloride salt, with regard to kinetic parameters, absorption, distribution, excretion, and metabolism. The results from this study also agree with those previously submitted by the Innovator for the hydrochloride salt (see review cited in Appendix).

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4 TOXICOLOGY:

4.1 Acute (iv and po) toxicity studies of paroxetine as mesylate and hydrochloride hemihydrate salts in mice and rats:

- Acute toxicity of POT.HCl.1/2H₂O by oral administration to Sprague-Dawley rats (— report no. 10764/97 vol 15 pp 5076-5115);
- Acute toxicity of POT.mes by oral administration to Sprague-Dawley rats — report no. 10765/97 vol 15 pp 5116-5155);
- Acute toxicity of POT.HCl.1/2H₂O by intravenous administration to Sprague-Dawley rats (— report no. 10766/97 vol 16 pp 5156-5189);
- Acute toxicity of POT.mes by intravenous administration to Sprague-Dawley rats — report no. 10767/97 vol 16 pp 5190-5222);
- Acute toxicity of POT.HCl.1/2H₂O by oral administration to NMRI mice — report no. 10768/97 vol 16 pp 5223-5261);
- Acute toxicity of POT.mes by oral administration to NMRI mice (— report no. 10769/97 vol 15 pp 5262-5295);
- Acute toxicity of POT.HCl.1/2H₂O by intravenous administration to NMRI mice (— report no. 10770/97 vol 16 pp 5296-5326);
- Acute toxicity of POT.mes by intravenous administration to NMRI mice — report no. 10771/97 vol 15 pp 5327-5356).

Acute LD₅₀'s for the 2 salt forms were essentially identical (see Table 2, below). There were no sex-related differences. The acute LD₅₀ for iv administration was the same for rats and mice. The acute LD₅₀ for po administration was ~40% lower for mice than rats; and 6- to 10-times higher than that for iv administration.

Table 2. Acute LD₅₀'s (mg/kg) for paroxetine by iv and po administration as mesylate or HCl salt to rats and mice. These LD₅₀'s are for deaths within 24 h of a single dose. All studies used 5 animals/sex/dose.

SPECIES	SEX	IV ADMINISTRATION		PO ADMINISTRATION	
		As mesylate	As HCl	As mesylate	As HCl
rat	M	46.7	46.7	474	466
	F	47.4	47.4	474	474
mouse	M	46.7	46.7	323	282
	F	46.7	46.7	261	287

- 4.2 Study title: 14-Day dose-range-finding study for a 4-week subchronic study of POT.mes and POT.HCl.1/2H₂O by oral administration to Sprague-Dawley rats. — Report No. 10772/97. See volume 16:5357-5412.

Key study findings: Doses of 0, 5, 50, 125 mg/kg/day as mesylate (batch # POT.mes.01Y1 (R&D batch)), 125 mg/kg/day as HCl (batch # POT.hcl.hhy.01Y1 (R&D

batch)) were administered by oral gavage to rats (Sprague-Dawley/Crl:CD®BR, 30-31 days old at start of dosing, 5/sex/group) daily for 14 days. Only clinical signs, mortality, body weight, food consumption, and gross pathology were observed/measured (not e.g., clinical chemistry, hematology, histology). The HD of paroxetine, 125 mg/kg/day, was in the lethal range for both salts: 3-4/5 male and female rats died during the 2-week period in each group. HD rats (either salt) showed sensitiveness to touch and rough fur from day 5 or 6 onward, decreases in body weights and food consumption and hemorrhagic lungs (decedents only). No deaths nor clinical signs were found at lower doses of paroxetine (as the mesylate), 5 and 50 mg/kg/d, however, there were decreases in body weights and food consumption and slight diffuse reddening of the lungs at the MD of 50 mg/kg/d. The LD of 5 mg/kg/d was a NOEL in this 14-day study (no clinical chemistry, hematology or histopathology performed). Doses chosen for the subsequent 4-week study were 0, 5, 15 and 50 mg/kg/d paroxetine as mesylate and 50 mg/kg/d as HCl hemihydrate; the proposed HD is ~half a lethal dose in the 14-day study and the proposed LD was a NOEL in the 14-day study.

4.3 Study title: 4-week subchronic study of POT.mes and POT.HCl.1/2H₂O by oral administration to Sprague-Dawley rats.

Key study findings: Although lower doses (5 and 15 mg/kg paroxetine as the mesylate salt) were well tolerated, the HD (50 mg/kg paroxetine as either mesylate or HCl salt) showed evidence of some toxicity. This included mortality (with mesylate salt only) and clinical signs such as sensitiveness to touch, salivation, respiratory sounds, and emaciation. Body weights were decreased throughout the 4-week study, with only a transient decrease in food consumption. Clinical chemistry and hematology showed few, slight changes. Possible targets of toxicity were lung and mesenteric lymph nodes, with histopathological changes showing increased histiocytosis with vacuolation, and several organs that weighed less, namely spleen, heart, liver and thymus, without histopathological sequelae. All these findings were approximately the same at the HD for both of the salts. Toxicokinetics showed that for at least the first 2 hours after dosing (on the last day of the study), the systemic exposure to the parent drug was the same for the 2 salt forms.

Study no: — Report No. 10773/97

Volume #, and page #: 16:5413-18:6084 (672 pages).

Conducting laboratory and location: _____

Date of study initiation: April 16, 1998.

GLP compliance: yes, see vol 16:5417.

QA report: yes, see vol 16:5418.

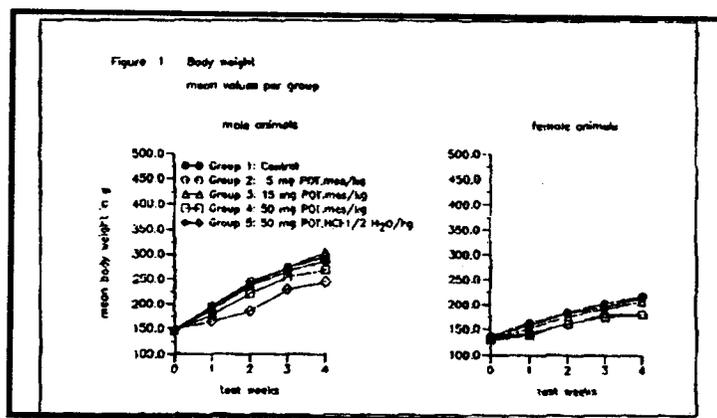
Drug, lot #, radiolabel, and % purity: paroxetine mesylate, POT.mes.01Y1 (R&D batch), 99.6% pure (with at least — total impurities: _____ not determined), by HPLC, see vol 18:6074 for certificate of analysis; paroxetine hydrochloride hemihydrate: batch # POT.hcl.hhy.01Y1 (R&D batch); 100.4% pure (with

Mortality: 2/10 HDF (mesylate) died on day 28; Sponsor suggests the cause of death is "...probably related to the general poor condition of the animals, intensified by the physical stress which was caused by the terminal examinations of the animals" (see volume 18:5447).

Clinical signs: LD and MD (mesylate) animals showed normal behavior and appearance. At HD (both mesylate and HCl) animals showed sensitiveness to touch and slightly increased salivation from day 10 onward; respiratory sounds were noted in ~half males and females from days 10-12 onward; were emaciated throughout week 4 of dosing.

Body weights: No effects of LD or MD. At HD as HCl, weights of both males and females were decreased ~15% compared with controls at each weekly weighing during dosing. At HD as mesylate, weights of females were decreased ~15%, but males only ~6%, compared with controls at each weekly weighing during dosing. See Sponsor's graph in Figure 1, below.

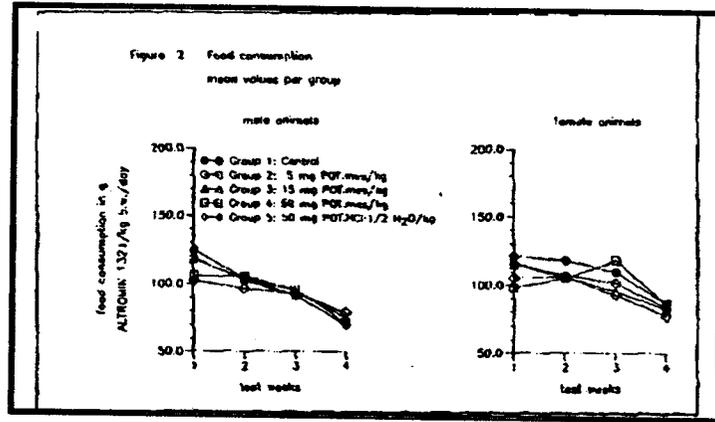
Figure 1. Paroxetine (as mesylate or HCl) decreases body weight gain in Sprague-Dawley rats. Sponsor's table from volume 16:5449.



Food consumption: Individual weekly food consumption was reported as g food/kg body weight/day (not g food/day). There were no effects at LD and MD. In males, the HD as mesylate or HCl resulted in a transient decrease in food consumption (normalized to body weight) compared with controls during the first week only; in females the decrease in food consumption was possibly more protracted into the 3rd week, at least for the HCl group (see Sponsor's graph in Figure 2, below).

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Figure 2. Paroxetine (as mesylate or HCl) transiently decreases food consumption (normalized to body weights) in Sprague-Dawley rats. Sponsor's table from volume 16:5450.



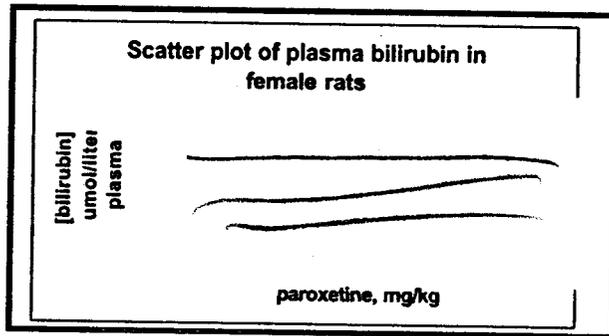
Ophthalmoscopy: No effects noted; all animals were normal when tested on day 0 and day 29 (excepting 2 HDF that died prematurely).

Hearing: No effects noted; all animals were normal when tested on day 0 and day 29 (excepting 2 HDF that died prematurely).

Electrocardiography: Not performed.

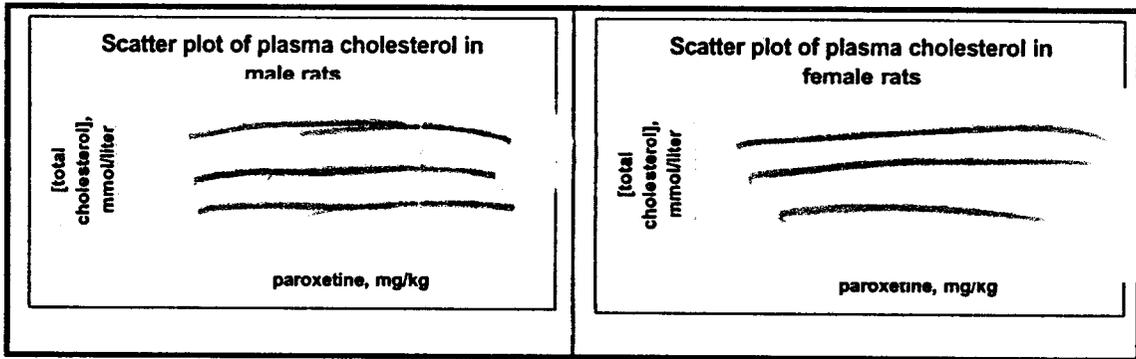
Hematology: Effects were slight and confined to HD groups. A slight, apparently dose-related decrease in thromboplastin time, which was only significant at HD (7% less than controls), was observed in males (both salt forms), with no effect on PTT or activated PTT. Reticulocyte count was decreased (35% less than controls) in females treated with the HCl form of the HD only.

Clinical chemistry: Effects were slight and largely confined to the HD groups. At HD, bilirubin was increased (~25%) in females (not males) with both salts; see my graph of the data below.

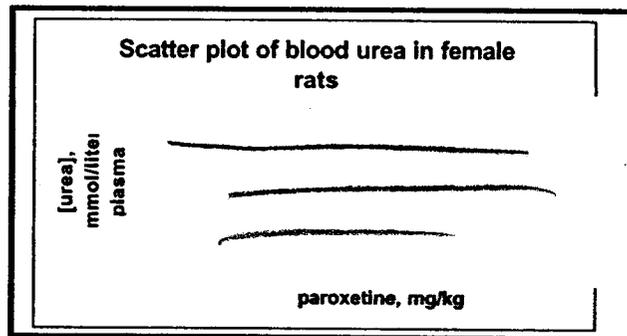


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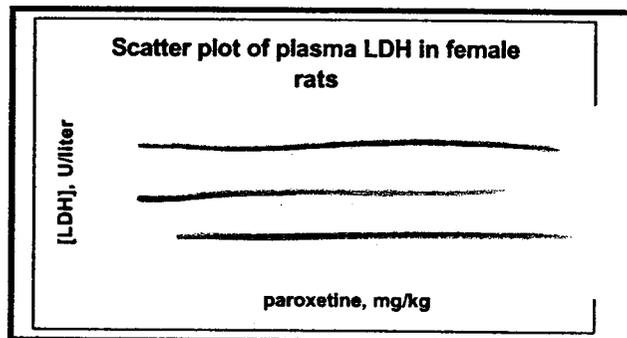
The Sponsor noted a dose-related increase in cholesterol in males (up to 26% over controls with HD as mesylate, 40% with HD as HCl); see my graph of the data below.



The Sponsor also noted increased urea, especially in females (20% over controls), with HCl salt only; however, the mesylate salt showed a similar increase, see my graph of the data below.



Although not noted by the Sponsor, variability in LDH was elevated in dosed females, suggesting that LDH may have been elevated, especially at the HD with either salt (see my graph of the data below).



Urinalysis: No effects of any doses or either salt.

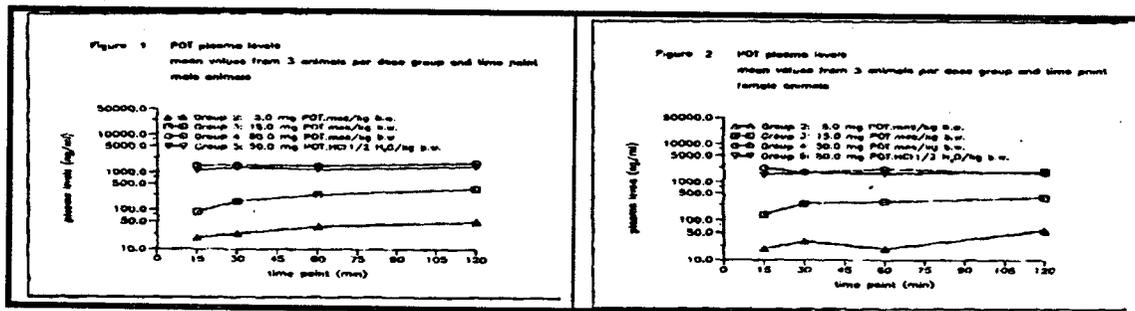
Organ weights: *Spleen:* dose-related decrease in absolute (~25% in HDM, both salts, ~20% in MDF, ~35% in HDF, both salts) and relative weights; *heart:* 15% decrease in absolute wt at HD (in females with mesylate salt, both sexes with HCl salt); *liver:* decrease in absolute wt at HD (~10% in males and females with mesylate salt, ~15% in males and females with HCl salt, only statistically significant at $p < 0.01$ for females given HCl form); *thymus:* decreased ~30% in females (only statistically significant at $p < 0.01$ for females given HCl form).

Gross pathology: The pathologist concluded that there were "no macroscopic findings considered to be related to treatment with the test articles" and review of the individual animal results supports this conclusion. The Sponsor noted diffuse reddening of lungs at MD and HD, however, this was seen for only 1/10 MDM, 2/10 HDM (mesylate salt), 1/10 HDM (HCl salt) and the 2 HDF (mesylate salt) that died spontaneously compared with 0/10 controls/sex and 0/10 LD/sex.

Histopathology: Findings were limited to lungs and nearby lymph glands. In lung, accumulations of foamy macrophages were seen at the HD for both salts (with the mesylate salt, 6/10 males and 8/10 females had minimal to slight incidence; with the HCl salt, 8/10 males and 9/10 females had minimal to slight incidence, and 2/10 males and 1/10 females had moderate incidence; incidence was 0 for controls, LD and MD groups). In mesenteric lymph nodes severity of histiocytosis was increased by the HD of both salts (slightly more rats were moderately affected rather than just slightly affected as for controls and lower doses), with increased incidence of vacuolation of histiocytes (with the mesylate salt, 10/10/sex had minimal vacuolation; with HCl salt, 10/10/sex had slight vacuolation; there was 0 incidence in other groups). The Sponsor also notes that there was increased histiocytosis with vacuolation in the cervical lymph node of a few HD rats (both salts), but this is less clear from the data.

Toxicokinetics: Although plasma concentrations of paroxetine were only measured for 2 hr after the last administration, systemic exposure clearly increased with the dose of the mesylate salt, though it is not clear whether this increase was dose-proportional. Over this short time interval, the systemic exposure to paroxetine appears to be the same for the 2 salt formulations. See the Sponsor's graphs of this data below.

Figure 3. Plasma curves for paroxetine during the 2 hours after the last administration (4 weeks of daily dosing). Sponsor's graphs from volume 18:6061.



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Toxicology summary: Acute testing determined LD₅₀'s for paroxetine (as mesylate or HCl salt) by oral gavage of ~470 mg/kg for rats and ~290 mg/kg for mice, with no apparent differences between sexes or between the 2 salt formulations. In a preliminary study, repeated dosing of rats for 2 weeks showed that 125 mg/kg/day killed at least half the rats (both sexes, both salts). After 4 weeks of dosing, 50 mg/kg/day showed some mortality (2/10 females with mesylate salt, only), decreased body weights, with only transiently decreased food consumption, clinical signs, including sensitivity to touch, salivation, and respiratory sounds. Targets of organ toxicity appeared to be the lungs and mesenteric lymph nodes, where histiocytosis, with vacuolation, was observed. Decreased weights of spleen, heart, and liver suggest possible toxicity, however, these decreases in weights were not accompanied by obvious changes in clinical chemistry, hematology or histopathology. In general, the toxicity of paroxetine as the mesylate salt (the formulation under consideration for this NDA) was the same as that for the equivalent amount of the hydrochloride salt (the formulation marketed by the innovator).

Toxicology conclusions: The Sponsor has performed a 4-week repeated dose toxicology study in rats as requested by the Agency. The results within this study show similar effects of paroxetine as the mesylate or hydrochloride salt. The results in this study also agree well with a similar 4-week study of the hydrochloride salt reviewed for the innovator NDA (see review in cited in Appendix).

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5 GENETIC TOXICOLOGY:

5.1 Study title: Mutagenicity study of POT.mes in the *Salmonella typhimurium* reverse mutation assay (*in vitro*).

Key findings: Negative: no mutagenic effect was observed for paroxetine (as the mesylate) tested up to a cytotoxic concentration of 1000 µg/plate in any of the 5 tester strains (TA 98, TA 100, TA 102, TA 1535, and TA 1537) in 2 independent experiments without and with metabolic activation. NB Although not explicitly stated, the testing of the mesylate salt of paroxetine appears to have been done in parallel with that of the hydrochloride salt reviewed below, using the same negative and positive control values.

Study no: — Report No. 10774/97.

Study type (if not reflected in title): Ames test.

Volume #, and page #: 18: 6085-6114.

Conducting laboratory and location: _____

Date of study initiation: May 8, 1998 (preliminary test), May 25, 1998 (main test); protocol submitted October 22, 1997.

GLP compliance: yes, see page 6087.

QA reports: yes, see page 6088.

Drug, lot #, radiolabel, and % purity: paroxetine mesylate, POT.mes.01Y1 (R&D batch), 99.6% pure (with at least — total impurities: _____ not determined), by HPLC, see page 6111 for certificate of analysis.

Formulation/vehicle: dissolved in DMSO, 100 µl/plate.

Methods:

Strains/species/cell line: *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, and TA 1537; genotypes were regularly confirmed by: a) histidine and biotin requirement, b) (rfa⁻) deep rough character (i.e., inhibition by crystal violet), c) uv-sensitivity, and d) ampicillin resistance.

Dose selection criteria:

Basis of dose selection: cytotoxicity in TA 100.

Range finding studies: 6 (half-log) doses from 31.6 to 5000 µg/plate, in duplicate in strain TA 100; complete growth inhibition in both replicates at the 3 doses ≥ 1000 µg/plate; normal lawns at doses ≤ 316 µg/plate.

Test agent stability: test solutions were freshly prepared before use; test substance was stored at room temperature, protected from light.

Metabolic activation system: Post-mitochondrial (S9) fraction from (20-30) rats treated with Aroclor 1254; assayed at protein content of 34.12 mg/ml and P450 activity of 0.19 nmol/mg protein.

Controls:

Vehicle: the lab's historical range of spontaneous reversion frequencies were presented and are acceptable.

Negative controls: DMSO, 100 µl/plate.

Positive controls: See Sponsor's table below.

Table 3. Positive controls used in Ames test (Sponsor's table, volume 18:6095).

a) without metabolic activation	
1. sodium azide ² in H ₂ O (10 µg/plate)	TA 1535, TA 100
2. 2-nitro-9H-fluorene ² in DMSO (10 µg/plate)	TA 98
3. 9-amino-acridine ² in ethanol (100 µg/plate)	TA 1537
4. methyl methane sulfonate ² (1300 µg/plate)	TA 102
b) with metabolic activation	
2-aminoanthracene ² in DMSO (2 µg/plate)	TA 98, TA 100, TA 102 TA 1535, TA 1537

Comments:

Exposure conditions:

Incubation and sampling times: revertant colonies were counted after 48 hr incubation at 37 degrees C in the dark.

Doses used in definitive study: 0, 3.16, 10, 31.6, 100, 316, and 1000 µg/plate.

Study design: plate incorporation assay.

Analysis:

No. of replicates: 2 independent experiments with triplicates.

Counting method: revertants were counted and presence of background lawn was confirmed on all plates; thin lawns were noted.

Criteria for positive results: Positive if all of the following hold: 1) significant ($p \leq 0.05$, by non-parametric Mann-Whitney U-test) increase versus solvent control to at least 2-fold the solvent control for TA 98, TA 100, and TA 102 and to at least 3-fold the solvent control for TA 1535 and TA 1537 in both independent experiments; and 2) a significant ($p \leq 0.05$, by non-parametric Spearman's rank correlation coefficient test) log dose-response effect is observed; and 3) positive results have to be reproducible and the histidine-independence of the revertants has to be confirmed by streaking random samples on histidine-free agar plates.

Summary of individual study findings:

Study validity: The study was valid: 1) strains that detect GC mutations (TA 98, TA 100, TA 1535, and TA 1537), AT-mutations (TA 102) and cross-linking (TA 102) were used, 2) negative controls were within normal limits, 3) positive controls were robust, 4) each strain was tested to a dose that was completely cytotoxic, and 4) 3-4 non-cytotoxic doses were tested for each strain.

Study outcome: Negative: there was no evidence of increased incidence of revertants at any dose tested, without or with metabolic activation, in any strain.

5.2 Study title: Mutagenicity study of POT.HCl.1/2H₂O in the *Salmonella typhimurium* reverse mutation assay (*in vitro*).

Key findings: Negative: no mutagenic effect was observed for paroxetine (as the hydrochloride) tested up to a cytotoxic concentration of 1000 µg/plate in any of the 5 tester strains (TA 98, TA 100, TA 102, TA 1535, and TA 1537) in 2 independent experiments without and with metabolic activation. NB Though not explicitly stated, the testing of the HCl salt of paroxetine appears to have been done in parallel with that of the mesylate salt reviewed above, using the same negative and positive control values.

Study no: — Report No. 11292/98.

Study type (if not reflected in title): Ames test.

Volume #, and page #: 19:6435-6464.

Conducting laboratory and location:

Date of study initiation: May 8, 1998 (preliminary test), May 25, 1998 (main test); protocol submitted April 22, 1998.

GLP compliance: yes, see page 6437.

QA reports: yes, see page 6438.

Drug, lot #, radiolabel, and % purity: paroxetine hydrochloride hemihydrate: batch # POT.hcl.hhy.01Y1 (R&D batch); 100.4% pure (with at least — impurities: —) by HPLC; see page 6461 for certificate of analysis.

Formulation/vehicle: DMSO, 100 µl/plate.

Methods: Although this is a separate report from the one testing the mesylate salt (above), apparently the 2 salts were tested in the same experiments, because the values for negative and positive controls are identical in the 2 reports. The same methods were used as for the test of the mesylate salt above. Dose-selection was based on cytotoxicity of background revertants in TA 100 strain; 6 (half-log) doses from 31.6 to 5000 µg/plate, in duplicate, resulted in complete growth inhibition in both replicates at the 3 doses ≥ 1000 µg/plate; scarce lawn at 316 µg/plate; normal lawns at doses ≤ 100 µg/plate. For the definitive study, the same doses of paroxetine (as the HCl) were chosen as were used for paroxetine as the mesylate salt above.

Summary of individual study findings:

Study validity: valid, as for the mesylate salt above.

Study outcome: negative.

Genetic toxicology summary: Paroxetine mesylate was not mutagenic in a valid Ames test. Paroxetine hydrochloride was similarly not mutagenic in a valid Ames test. Both salts showed similar cytotoxic potencies in this assay.

Genetic toxicology conclusions: The Sponsor was asked to test the mutagenicity of the mesylate salt of paroxetine in an *in vitro* bacterial mutagenicity assay. The mesylate and hydrochloride salts were determined not to be mutagenic in a valid Ames test. This agrees with the negative findings in the Ames test previously performed by the innovator on the hydrochloride salt (see review in cited in Appendix).

Labeling recommendations: The Sponsor is not proposing any changes in the mutagenicity section from the innovator's label; the results reviewed here support that labeling.

- 6 CARCINOGENICITY: NO STUDIES PROVIDED.**
- 7 REPRODUCTIVE TOXICOLOGY: NO STUDIES PROVIDED.**
- 8 SPECIAL TOXICOLOGY STUDIES: NO STUDIES PROVIDED.**

9 ADDENDUM TO REVIEW:

Table 4. Histopathology Inventory for NDA # 21-299; 4-week study in rats.

Study: 4-week	mg/kg/d Paroxetine as Mesylate or HCl salt				
Species: rat	0	5 mes	15 mes	50 mes	50 HCl
Adrenals	X*	x*	x*	X*	X*
Aorta	x	x	x	x	x
Bone Marrow smear	X	x	x	X	X
Bone (femur)	X	x	x	X	X
Brain	X*	x*	x*	X*	X*
Cecum	x	x	x	x	x
Cervix					
Colon	X	x	x	X	X
Duodenum	X	x	x	X	X
Epididymis	X	x	x	X	X
Esophagus	X	x	x	X	X
Eye	X	x	x	X	X
Fallopian tube					
Gall bladder					
Gross lesions	X	x	x	X	X
Harderian gland	X	x	x	X	X
Heart	X*	x*	x*	X*	X*
Ileum	X	x	x	X	X
Injection site					
Jejunum	X	x	x	X	X
Kidneys	X*	x*	x*	X*	X*
Lachrymal gland					
Larynx					
Liver	X*	x*	x*	X*	X*
Lungs	X*	x*	x*	X*	X*
Lymph nodes, cervical	X	x	x	X	X
Lymph nodes mandibular					
Lymph nodes, mesenteric	X	x	x	X	X
Mammary Gland	X	x	x	X	X
Nasal cavity					
Optic nerves	X	x	x	X	X
Ovaries	X*	x*	x*	X*	X*
Pancreas	X	x	x	X	X
Parathyroid	X	x	x	X	X
Peripheral nerve, sciatic	x	x	x	x	x
Pharynx	x	x	x	x	x
Pituitary	X*	x*	x*	X*	X*

Study: 4-week	mg/kg/d Paroxetine as Mesylate or HCl salt				
Species: rat	0	5 mes	15 mes	50 mes	50 HCl
Prostate	X	x	x	X	X
Rectum	X	x	x	X	X
Salivary gland	X	x	x	X	X
Sciatic nerve	x	x	x	x	x
Seminal vesicles	x	x	x	x	x
Skeletal muscle, leg	x	x	x	x	x
Skin	x	x	x	x	x
Spinal cord	X	x	x	X	X
Spleen	X*	x*	x*	X*	X*
Sternum					
Stomach	X	x	x	X	X
Teeth	x	x	x	x	x
Testes	X*	x*	x*	X*	X*
Thymus	X*	x*	x*	X*	X*
Thyroid	X*	x*	x*	X*	X*
Tongue	x	x	x	x	x
Trachea	X	x	x	X	X
Urinary bladder	X	x	x	X	X
Uterus	X	x	x	X	X
Vagina	x	x	x	x	x
Zymbal gland					
Standard List					

X, x: organs collected/fixd.
X, histopathology performed
*, organ weight obtained

10 APPENDIX:

In the preparation of the current review of NDA 21-299, the following reviews were consulted:

- Review and evaluation of pharmacology and toxicology data for NDA 20-031, by Garry Evoniuk, August 30, 1990; 77 pages.
- Review and evaluation of pharmacology and toxicology data for IND 57,407, by Nuoyu Huang, December 14, 1998; 8 pages.

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/s/

Linda Fossom
5/7/01 11:57:48 AM
PHARMACOLOGIST

I made the changes we talked about...thanks for the suggestions.

Barry Rosloff
5/8/01 11:54:26 AM
PHARMACOLOGIST