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APPLICATION NUMBER: 020936

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-936
Paxil CR © (Paroxetine hydrochloride)
(12.5 and 25 mg controlled-release tablets)

Type of submission: NDA (supplement)
Submission Date: Dec, 18, 1998

Sponsor: Smithkline Beecham

INDICATION: Antidepressant agent

REVIEWER: Rae Yuan, Ph.D.

Draft Review Date: 1/5/99

This submission responds to the approvable letter for Paxil CR 12.5 and 25 mg products manufactured in . It contains the revised labeling and response to the recommended dissolution methods and specifications.

In the approvable letter, the agency requested that the sponsor adopt the following dissolution methods. The agency requested method was similar to the method proposed by the sponsor with the exception of specifications, which were modified based on the submitted individual dissolution data.

Apparatus: USP II (paddles) 150 rpm.

| Dissolution Media | Time | Limit (% dissolved) |
|--|------|---------------------|
| Step 1: 0.1 M HCl (750 mL) for 2 hr | 2 hr | Not more than |
| Step 2: pH 7.5 Tris buffer containing 60 mmol Tris, 90 mmol NaCl (1000 mL) for 7 hr. | 1 hr | |
| | 2 hr | |
| | 4 hr | |
| | 6 hr | |

at room temperature.

In this submission, the sponsor requested to include a provision in the original dissolution methods to reduce the ionic strength. They noted that they have "encountered analytical problems with the original methodology which resulted in artefactually fast release which was attributable to the high ionic strength of the method using "salt out" of the matrix." The new methodology (as follows), will provide an equivalent release rate to the old method, but prevents the artefactually fast release. The proposed method is being routinely utilized within SkB for release and stability testing.

In addition, the sponsor also considers the proposed specification at 2 and 4 hours being to tight. In view of their plan to transfer the manufacturing site from _____, the sponsor has suggested the following specifications in order to accommodate the dissolution data obtained from _____ tablets. It should be noted that bioequivalence between _____ tablets and _____ tablets has not been established.

Apparatus: USP II (paddles) 150 rpm.

| Dissolution Media | Time | Limit (% dissolved) |
|---|------|---------------------|
| Step 1: 0.1 M HCl (750 mL) for 2 hr | 2 hr | Not more than _____ |
| Step 2: pH 7.5 Tris buffer containing 50 mmol Tris (1000 mL) for 7 hrs. | 1 hr | _____ |
| | 2 hr | _____ |
| | 4 hr | _____ |
| | 6 hr | _____ |

at room temperature. In the submission, the sponsor wrote that "specifications _____ are generally acceptable only when the sponsor submits evidence that lots with mean dissolution profiles that are allowed by the upper and lower dissolution specifications are bio-equivalent".

Comments:

1. The revised labeling is acceptable to OCPB.
2. The FDA recommended dissolution methods and specification were based on the available dissolution data in the original submission. Although sponsor claims to have developed and cross-validated the new methods, no additional information has been submitted to the agency to support the proposed new dissolution methodology. Therefore, in order to change the dissolution media, the sponsor needs to submit cross-validation report containing individual dissolution data on 12 tablets from the clinical/biobatch of the approvable products.
3. The new dissolution specification will be based on the new dissolution methods conducted on the approvable product. Since _____ tablets have not been shown bioequivalent to the approvable _____ tablets, the dissolution specification will be set based on the data of _____ tablets.

RECOMMENDATION:

The revised labeling is acceptable. Until additional data are submitted to support the requested changes in dissolution method and specifications, the method and specifications change request can not be granted.

Please convey comments 2 and 3 to the sponsor.

Rae Yuan, Ph.D.

/S/

1/7/99
Team Leader: Chandra Sahajwalla, Ph.D.

/S/
1/7/99

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

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SEP 30 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-936

Paxil CR ® (Paroxetine hydrochloride)
(12.5, 25

RECEIVED SEP 30 1998

Type of submission: Original NDA
Submission Date: Dec, 19, 1997

Sponsor: Smithkline Beecham

INDICATION: Antidepressant agent

REVIEWER: Rae Yuan, Ph.D.

The sponsor seeks an approval for controlled-release formulation (CR tablets) of the already-approved immediate release product (IR) paroxetine at 12.5, 25, for the treatment of depression. Two randomized, double-blind, placebo controlled clinical studies were conducted on 12.5 and 25 mg CR tablets to demonstrate the efficacy and safety of the drug. Seven pharmacokinetic studies were performed on healthy volunteers to assess bioequivalence between CR and IR forms, and between the two manufacture sites ; to assess the effect of food on CR formulations; and to compare the bioavailability of a series of prototype formulations. The studies which are pertinent to the labeling and approval of the final product are included in this review.

1. Study 472: Dose proportional study of CR tablets.

This was a randomized, single dose 4-way crossover study(18 male and 5 female) to investigate the dose proportionality of CR tablets of 12.5, 25. Each strength was administered under fasting condition and was separated by a washout interval of at least 10 days. Safety measurements were taken throughout the study. Plasma samples was obtained at time zero, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 36, 48, 72, 96, and 120 hours post dose. The concentrations of the drug in plasma samples were detected by a validated Please refer to the Attachment I for the details of the study.

Results:

The CR tablets of paroxetine demonstrated non-linear kinetics in the study. The trend of the nonlinearity is similar to that found in the IR formulations, which is believed to be due to the saturation on CYP2D6 enzyme that is responsible for paroxetine metabolism.

Among the serious non-fatal events among paroxetine CR patients, only two are considered to represent clinically important occurrences possibly related to drug: acute pancreatitis and intestinal obstruction.

Patient 449.21.658 was a 46 y.o. male with a past history of alcohol abuse and pancreatitis who experienced multiple symptoms during the study: abdominal bloating from day 22 for 37 days, nausea and vomiting from day 29 for 27 days, and diarrhea and severe abdominal pain on day 48 which resulted in discontinuation of paroxetine CR 50 mg/day, hospitalization, and subsequent diagnosis of acute pancreatitis felt to be secondary to alcohol abuse. Symptoms resolved over the next week.

Patient 487.7.1562 was a 73 y.o. male with a history of an appendectomy, colon cancer surgery, hernia surgery, and basal cell carcinoma who was hospitalized after 46 days of treatment with paroxetine CR (to 37.5 mg/day) for a moderate small bowel blockage. Drug was discontinued and his condition resolved without surgery. The investigator opined that this event was attributable to abdominal adhesions from colon surgery 13 years ago.

There are no known cases of overdose with paroxetine CR.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

Table 8.1.3.1.1 displays the numbers (percentages) of patients in the pool of studies 448 and 449 who completed the study and who dropped out for various reasons. Table 8.1.3.1.2 depicts similar data for patients in study 487.

In the pool of 448 and 449, about two-thirds of the patients randomized completed the studies. As expected, more active drug patients events than placebo patients dropped out for adverse experiences, the opposite being true for lack of efficacy. A substantial number of patients (6-8%) were lost to follow-up.

| Table 8.1.3.1.1: Enumeration (Percentages of Randomized) of Premature Terminations by Reason (Studies 448 & 449) | | | |
|---|-----------|-----------|-----------|
| | Par CR | Placebo | Par IR |
| Randomized | 212 | 211 | 217 |
| Completed | 153 (72%) | 150 (71%) | 145 (67%) |
| Dropout due to: | | | |
| Adverse Event | 22 (10%) | 13 (6%) | 34 (16%) |
| Lack of Efficacy | 6 (3%) | 19 (9%) | 8 (4%) |
| Protocol Deviation | 8 (4%) | 7 (3%) | 12 (6%) |
| Lost to F/U | 17 (8%) | 13 (6%) | 12 (6%) |
| Other | 6 (3%) | 9 (4%) | 6 (3%) |

Completion rates in the study in elderly patients were slightly higher (72-78%) and smaller proportions of patients were lost to follow-up. Otherwise, the pattern of dropouts was similar to that in the younger patient pool.

| Table 8.1.3.1.2: Enumeration (Percentages of Randomized) of Premature Terminations by Reason (Study 487) | | | |
|---|----------|----------|----------|
| | Par CR | Placebo | Par IR |
| Randomized | 104 | 109 | 106 |
| Completed | 81 (78%) | 84 (77%) | 76 (72%) |
| Dropout due to: | | | |
| Adverse Event | 13 (13%) | 9 (8%) | 17 (16%) |
| Lack of Efficacy | 4 (4%) | 5 (5%) | 2 (2%) |
| Protocol Deviation | 3 (3%) | 3 (3%) | 8 (8%) |
| Lost to F/U | 1 (1%) | 3 (3%) | 1 (1%) |
| Other | 2 (2%) | 5 (5%) | 2 (2%) |

8.1.3.2 Dropouts due to Adverse Experiences

Tables 8.1.3.2.1 and 8.1.3.2.2 contains the proportions of patients who dropped out due to adverse experiences that led to dropout in at least 1% of the paroxetine CR patients.

| TABLE 8.1.3.2.1: ADVERSE EVENTS LEADING TO DROPOUT IN AT LEAST 1% OF PAROXETINE CR PATIENTS (STUDIES 448 & 449) | | | |
|--|--------|------|--------|
| Body System/Event | Par CR | Plac | Par IR |
| Body as a Whole | | | |
| Asthenia | 2% | <1% | 1% |
| Headache | 2% | 1% | 1% |
| Digestive | | | |
| Nausea | 3% | <1% | 4% |
| Nervous | | | |
| Dizziness | 1% | 0% | <1% |
| Somnolence | 1% | 0% | 4% |
| Urogenital | | | |
| Impotence ¹ | 1% | 1% | 0% |

| TABLE 8.1.3.2.2: ADVERSE EVENTS LEADING TO DROPOUT IN AT LEAST 1% OF PAROXETINE CR PATIENTS (STUDY 487) | | | |
|--|--------|------|--------|
| Body System/Event | Par CR | Plac | Par IR |
| Body as a Whole | | | |
| Headache | 2% | <1% | 0% |
| Digestive | | | |
| Nausea | 3% | 0% | <1% |
| LFT's Abnormal | 2% | 0% | 0% |
| Nervous | | | |
| Depression | 2% | 0% | 0% |
| Urogenital | | | |
| Testes Disorder ² | 2% | 0% | 0% |

These observations are typical for SSRI's in similar studies with the exception of two dropouts due to abnormal liver function tests in study 487 (none in 448/449). These two cases will be discussed in section 8.1.5.3.1.

A review of all adverse events leading to dropout among paroxetine CR subjects in the entire safety database revealed only two which were not expected by this reviewer based on experience with paroxetine IR, acute pancreatitis

¹ Denominator = the number of male patients.

² This term represents a case of "heavy testicles." Rate has been adjusted for the number of male patients.

and intestinal obstruction. Both cases were described under Other Serious Adverse Events (section 8.1.2).

Nine paroxetine CR subjects in clinical pharmacology studies dropped out due to adverse events. Most of these events were typical of SSRI's (e.g., nausea, diarrhea); only two were considered unusual:

Patient 495 in study 452 dropped out due to the emergence of rash and pruritus after the first dose. These experiences resolved with drug discontinuation and symptomatic treatment.

Patient 563.001.00004 experienced syncope 28 hours after a 50mg dose of paroxetine CR. The subject fully recovered after 30 minutes.

8.1.4 Adverse Events

8.1.4.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse experiences were coded using the World Health Organization (WHO) disease codelist, and were then mapped to the ADECS (COSTART based) classification to give a body system and preferred term.

The thesaurus used to code verbatim adverse event terms to preferred terms in studies 448 and 449 was examined to assess the accuracy and usefulness of this coding process. A thesaurus for study 487 was not available so coding in this study was assessed using the adverse event line listing.

Coding appeared to be reasonable except in two instances:

- 1) Female experiences of anorgasmia or delayed orgasm were coded to the preferred term "Female Genital Disorders," which is felt to be too vague to adequately convey the nature of these events.
- 2) Suicide gestures and suicide attempts were coded to the preferred term "Emotional Lability," which is not considered to be an accurate representation of these events.

8.1.4.2 Common, Drug-Related Adverse Events

Treatment emergent adverse events were those events reported for the first time on or after the first day of double-blind medication and up to the last dose of medication in the

treatment phase, i.e., prior to taper. This definition also encompasses non-serious events during this phase that were rated as more severe relative to baseline.

Table 8.1.4.2.1 in Appendix 8.1 presents the proportions of paroxetine CR and placebo patients who experienced treatment emergent adverse events for those events occurring in at least 1% of paroxetine CR patients in the pool of studies 448 and 449.

Within the pool of studies 448 and 449, the adverse events that were common and probably drug-related (i.e., occurring in at least 5% of the paroxetine CR patients at an incidence at least twice that in the placebo group) are summarized in Table 8.1.4.2.2.

| Table 8.1.4.2.2: Common and Probably Drug-Related Adverse Events (Studies 448 & 449) | | |
|---|--------------------------------|----------------------------|
| | % Reporting³ | |
| | Par CR (N=212) | Placebo (N=211) |
| Abnormal Ejaculation ^{4,5} | 26% | 1% |
| Nausea | 22% | 10% |
| Somnolence | 22% | 8% |
| Diarrhea | 18% | 7% |
| Dizziness | 14% | 4% |
| Constipation | 10% | 4% |
| Female Genital Disorder ^{6,7} | 10% | <1% |
| Libido Decreased | 7% | 3% |
| Tremor | 7% | 1% |
| Sweating | 6% | 2% |
| Abnormal Vision ⁸ | 5% | 1% |
| Trauma ⁹ | 5% | 1% |
| Yawning | 5% | 0% |

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³ <1% means greater than zero but less than 1%.

⁴ Based on the number of male patients.

⁵ Mostly anorgasmia or delayed orgasm.

⁶ Based on the number of female patients.

⁷ Mostly anorgasmia or delayed orgasm.

⁸ Mostly blurred vision.

⁹ A wide variety of injuries with no obvious pattern.

8.1.4.3 Effects of Age, Gender, and Race on Adverse Event Reporting Incidence

Study 487 provides useful safety data from a sample of elderly patients with which to assess any major effect of age on the safety profile of paroxetine CR. Table 8.1.4.3 in Appendix 8.1 displays the proportions of paroxetine CR and placebo patients who experienced treatment emergent adverse events for those events occurring in at least 5% of paroxetine CR patients in study 487.

Common and probably drug-related events from study 487, using the above criteria, overlapped with those from the above pool to a considerable degree. These events (with the associated paroxetine CR and placebo incidence) were: dry mouth (18%,7%), abnormal ejaculation (17%,3%), constipation (13%,5%), decreased appetite (12%,5%), sweating (10%,<1%), impotence (9%,3%), libido decreased (8%,<1%), tremor (7%,0%), and infection (6%,2%). Thus, it appears that there are no major differences in the common adverse event profiles between younger and older patients.

The sponsor further explored the effect of demographics on adverse experience incidence by statistical testing of the odds ratios for most of these events between gender subgroups (male vs. female) and race subgroups (white vs. non-white).¹⁰ Results of this analysis, which were submitted to the NDA on 2/18/98, did not reveal any significant effect of these demographic variables on event reporting rates ($\alpha=0.10$).

8.1.4.4 Dose-Relatedness

The potential relationship between adverse event incidence and dose could not be reasonably evaluated from these three flexible dose studies. Study PAR 09, submitted in support of the original paroxetine (IR) NDA, used fixed doses the immediate release formulation (10, 20, 30, and 40 mg/day) and did reveal evidence of dose-dependency for some of the more common adverse events with paroxetine IR, such as nausea, somnolence, sweating, and abnormal ejaculation.

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¹⁰ Events evaluated were: trauma, constipation, diarrhoea, nausea, dizziness, libido decreased, somnolence, tremor, sweating, female genital disorders, abnormal ejaculation, and impotence.

8.1.4.5 Other Events Observed During Premarketing Depression Studies with Paroxetine CR

Events other than those listed in Table 8.1.4.2.1 or 8.1.4.2.2 that were reported during studies 448, 449, or 487 are depicted in Table 8.1.4.5 in Appendix 8.1 by body system and preferred term.

8.1.5 Laboratory, Vital Sign, and ECG Data

8.1.5.1 Laboratory, Vital Sign, and ECG Assessments

Table 8.1.5.1.1 below summarizes the timing of laboratory, vital sign, and ECG assessments during studies 448, 449, and 487. For dropouts, these assessments were done at the time of termination. Laboratory testing in all three studies consisted of the following: hematology (H/H, WBC/diff, platelets), chemistry (alkaline phosphatase, BUN/creatinine, AST/ALT, total bilirubin, electrolytes, TSH/T3/T4), and urinalysis (dipstick for blood, protein, and glucose). For studies 448 and 449, vital sign measures were sitting blood pressure and pulse; for study 487, blood pressure and pulse were measured after sitting for 5 minutes and blood pressure was assessed after standing for 2 minutes also.

| TABLE 8.1.5.1.1: TIMING OF LABORATORY, VITAL SIGN, AND ECG ASSESSMENTS (STUDIES 448, 449, & 487) | | | |
|---|--|--|---|
| | Study 448 | Study 449 | Study 487 |
| Laboratory Tests | Screening, weeks 6, 12 | Screening, weeks 6, 12 | Screening, weeks 6, 12 |
| Vital Signs | Screening, baseline, weeks 1,2,3,4,6,8, 12, end of taper | Screening, baseline, weeks 1,2,3,4,6,8, 12, end of taper | Screening, baseline, weeks 1,2,3,4,6,8, 10,12, end of taper |
| 12-lead ECG | Screening only. | Screening only. | Screening, week 12. |

8.1.5.2 Analyses of Laboratory, Vital Sign, and ECG Data

For purposes of the Integrated Summary of Safety, the sponsor pooled data from studies 448 and 449. Data from study 487, which was submitted as an Information Amendment to this NDA, was not pooled; as previously mentioned, given that the patients in study 487 were generally older than patients in 448 and 449, this strategy is not objectionable.

For both the pool of studies (448 and 449) and study 487, this review will focus on an analysis of outliers (i.e., patients who met predetermined criteria for findings of potential clinical concern) for laboratory and vital sign parameters as well as dropouts due to abnormalities in laboratory, vital sign, or ECG measurements.^{11,12}

8.1.5.3 Results of Analyses

8.1.5.3.1 Laboratory Data

Tables 8.1.5.3.1.1 and 8.1.5.3.1.2 in Appendix 8.1 displays the proportions of patients in the paroxetine CR and placebo groups who experienced a laboratory value of potential clinical concern (post-baseline up to 14 days after drug discontinuation in the pool of studies 448 and 449 and during treatment in study 487). Only those variables for which at least one paroxetine CR patient had a flagged value and for which the drug incidence is higher than the placebo incidence are presented.

The fractions of patients with laboratory values of potential concern were compared between the paroxetine CR and placebo groups: there were no statistically significant differences between the two groups.¹³

No paroxetine CR patient from any clinical pharmacology study or from study 448 or 449 dropped out due to an abnormality in laboratory values but two patients from study 487 dropped out for this reason, both for elevated liver enzymes:

Patient 487.5.1308 was a 68 y.o. female with a past history of hepatitis A and jaundice who experienced a moderate increase in liver function tests after 44 days of paroxetine CR (to 37.5 mg/day): SGPT=455 U/L (nl to 48), SGOT=292 U/L (nl to 55), and total bilirubin=1.7 mg/dl (nl to 1.3); screening values were normal. Treatment was tapered and labs remained abnormal following taper but had normalized by 77 days after discontinuing drug.

¹¹ Tables 8.1.5.2.1 and 8.1.5.2.2 in Appendix 8.1 display criteria for lab values of potential clinical concern. These tables were electronically copied from the sponsor's CANDA. Criteria for vital sign values are provided in the footnotes to tables in Table Series 8.1.5.3.2 in Appendix 8.1.

¹² Please note that the sponsor provided no systematic analysis of urinalysis information any study and, from study 487, no analysis of ECG data.

¹³ Two-tailed Fishers exact test ($\alpha=0.100$).

Patient 487.6.1236 was a 64 y.o. female with a history of small cell lung cancer who experienced moderate liver enzyme elevation after 41 days of treatment with paroxetine CR (to 25 mg/day): SGPT=59 U/L (nl to 48), SGOT=129 U/L (nl to 42) with normal total bilirubin; at screening, SGOT was elevated (89 U/L) and SGPT was normal. Abnormalities increased following taper (SGPT=79, SGOT=210) but had decreased almost to screening values by 20 days after drug discontinuation.

Thus, neither patient experienced jaundice or severe liver damage and, in both cases, transaminases normalized after drug discontinuation.

Mean change from baseline data from study 487 for LFT variables (alkaline phosphatase, total bilirubin, AST, and ALT) revealed no marked differences between paroxetine CR and placebo.¹⁴

No placebo or paroxetine IR patients withdrew from study 487 due to elevated transaminases.

Additionally, one other paroxetine CR patient from study 487 experienced an elevation in SGPT that met the criterion for clinical concern (>165 U/L). Patient 487.26.1360 experienced an increase in SGPT from 12 at baseline to 226 U/L at day 55 with a similar increase in SGOT. Treatment was continued and the patient completed the study, with normalization of this finding by the end of the study.

Coincidentally, however, Patient 448.10.211, who had been treated with paroxetine IR during the study, continued this formulation after completing the study and experienced hepatocellular jaundice 17 days post-study. Work-up revealed a distended gallbladder with numerous echogenic nodules consistent with cholelithiasis, which was felt to be a chronic condition due to gallbladder wall thickening. Paroxetine was stopped and bilirubin and liver enzymes decreased considerably over the next three weeks.

If paroxetine CR had a hepatotoxic effect, then one would expect that the immediate release formulation would exhibit a similar effect. According to current Paxil labeling, clinical trial experience showed no differences between Paxil and placebo in the percentage of patients with marked abnormalities for SGPT, SGOT, alkaline phosphatase, or bilirubin.

¹⁴ See Table 47 in the study report for study 487.

On the other hand, there have been several postmarketing reports of significant liver function test elevations with paroxetine IR, to include cases of fatal hepatic necrosis. As a result of this reports, the Division Safety Group was consulted in April 1996 to evaluate the risk of liver failure with SSRI's. This examination did not suggest a unique hepatotoxic effect of the SSRI's and no significant difference between the SSRI's with respect to crude reporting rates of serious hepatic events.¹⁵

In sum, the data in this NDA provide no evidence that paroxetine carries a risk of significant hepatotoxicity.

8.1.5.3.2 Vital Sign Data

Table Series 8.1.5.3.2 in Appendix 8.1 displays the proportions of patients in the paroxetine CR and placebo groups who experienced a vital sign reading of potential clinical concern observed post-baseline in the pool of studies 448 and 449 and in study 487.¹⁶ Statistical comparison of the paroxetine CR and placebo groups revealed significant differences for only two variables, both in study 487: low sitting diastolic blood pressure ($p=0.055$) and a significant increase in standing diastolic blood pressure ($p=0.057$).¹²

With respect to low sitting diastolic BP, 4/104 paroxetine CR had a reading <50 mmHg at some time.¹⁷ However, these were isolated findings for all four patients, none of whom had related symptoms, dropped out, or had a serious adverse experience.

With respect to the significant increase in standing diastolic BP, 4/104 paroxetine CR patients had an increase of 30 mmHg or more in this measure. In two patients, these were isolated findings.¹⁸ In one patient, readings fluctuated considerably and high readings were consistent with the screening BP, although higher than the baseline BP.¹⁹ In the fourth patient, increases in BP were sustained but diastolic values never exceeded 96 mmHg.²⁰ None of

¹⁵ Drugs examined were paroxetine, sertraline, fluvoxamine, fluoxetine, and venlafaxine. This evaluation was performed by James Knudsen, M.D., Ph.D. on July 23, 1996, under the supervision of the Safety Group Leader, Greg Burkhart, M.D., M.S.

¹⁶ This series of tables was electronically copied from the sponsor's CANDA.

¹⁷ Patients 487.5.1306, 487.11.1496, 487.11.1644, and 487.24.1213.

¹⁸ Patients 487.6.1236 and 487.11.1644.

¹⁹ 487.21.1251.

²⁰ 487.26.1355.

these patients dropped out for a vital sign change or cardiovascular event and none had a serious adverse event.

No paroxetine CR patient dropped out due to an abnormal vital sign observation. Also, examination of mean change from baseline data for blood pressure, pulse, and body weight for both the pool of studies 448/449 and for study 487 revealed no remarkable differences relative to placebo.²¹

8.1.5.3.3 ECG Data

No paroxetine CR patient dropped out due to an abnormal ECG finding. As mentioned above, no systematic examination of ECG data from study 487 was performed.

8.1.6 Special Studies

Study 452 was a multicenter, randomized, double-blind, placebo-controlled study designed to investigate the incidence of nausea in healthy adult volunteers after 3 days of treatment with placebo or paroxetine 30 mg/day given as one of three formulations (immediate-release, controlled-release enteric coated, or controlled-release non-enteric coated); about 120 subjects were treated in each group. Diary cards were used to record nausea and vomiting.

The proportion of subjects with nausea and/or vomiting was lower in subjects who received the controlled-release formulations compared to the immediate-release product; all were higher than placebo:

| | Proportion Reporting Nausea and/or Vomiting |
|---------------------------|--|
| Controlled-release EC | 40% |
| Controlled-release non-EC | 49% |
| Immediate-release | 59% |
| Placebo | 13% |

From these data, the sponsor concluded that gastrointestinal tolerability may be enhanced with the controlled-release preparations.

²¹ These data may be found in Tables 30 and 31 of the ISS for studies 448/449 and in Table 43 of the study report for study 487. Data were examined by visual inspection since the sponsor provided no formal statistical comparisons between treatment groups.

8.2 Adequacy of Patient Exposure and Safety Assessments

Paroxetine (IR) has been the subject of three previous NDA submissions²² and has accumulated substantial postmarketing experience both in the U.S. and abroad, which have permitted extensive assessment of the safety profile of the active ingredient. The relatively small size of this safety database cannot be expected to reveal previously unknown risks associated with paroxetine. Nevertheless, there exist three potential sources of new safety problems with this formulation:

- 1) Safety of excipients in paroxetine CR.
- 2) As with any controlled release product, the possibility of dose-dumping (i.e., immediate release of the total amount of drug).
- 3) Given the delayed absorption characteristics of this formulation, potential risks associated with drug absorption in a lower part of the gastrointestinal tract.

The first issue has been addressed by the reviewing chemist, Mona Zarifa, Ph.D., in her 4/27/98 review in which she states that all excipients are USP/NF except for _____ which is supplied by _____ (DMF _____) and corresponds to the description and specifications

Regarding the second issue, the highest strength of paroxetine CR will be 50mg and the maximum dose will be 62.5mg. Since immediate release paroxetine is considered safe for use in doses up to 60mg and since paroxetine has a wide therapeutic index, the risk associated with any dose-dumping should be minimal.

It is difficult to predict what adverse effects might be associated with absorption in a lower segment of the gastrointestinal tract. There is no clear data from this safety database to suggest any unusual effects related to this process (e.g., GI bleeding).

Although this safety database is limited in terms of the number of exposed patients (316 in Phase 3 trials) and safety assessments (e.g., no systematically analyzed ECG data), in view of the above considerations, it is felt to be sufficient to reasonably assess the safety of this formulation.

²² NDA 20-031 (depression), 20-031 (S-007) (OCD), and 20-031 (S-009) (panic disorder).

8.3 Assessment of Data Quality and Completeness

Case report forms for the five randomly selected patients were reviewed to audit the completeness and accuracy of data contained in corresponding narrative summaries and line listings. No discrepancies were found.

As discussed in section 8.1.4.1 above, the coding of two groups of adverse events was not deemed to be sufficiently specific or accurate.

Also, Tables 38 and 39 in the ISS, which depict the proportions of patients with laboratory values of potential clinical concern in the pool of studies 448 and 449, including marked abnormalities observed at screening and baseline, i.e., before study drug exposure. To enhance my ability to interpret this data, I revised this information to exclude pre-drug abnormalities.

Additionally, the sponsor did not provide any systematic analysis of ECG data from study 487 or urinalysis data from any study. Adequate information on these variables from other clinical trials has been previously submitted and reviewed.

However, these issues are not felt to substantially impact on the safety conclusions derived from this review.

8.4 Conclusions Regarding Safety

This safety review revealed no major safety concerns that would preclude approval of this drug product or warrant substantial modification of labeling vis-a-vis that of the already approved product, Paxil. Based on the pool of studies 448 and 449, the common adverse event profile for paroxetine CR is very similar to that of other SSRI's.

9.0 Labeling

The clinical sections of product labeling proposed by the sponsor in the original 12/19/97 submission and revised in the 4/21/98 information amendment, to incorporate data from study 487, were examined. The following comments, organized by section, pertain.

Clinical Trials

For reasons expressed above, I feel that the analysis of study 448 which excludes center group 2/4 more accurately portrays the efficacy of paroxetine CR in that trial. Given

that approved paroxetine IR was used as a comparator in this study and performed no better than paroxetine CR (i.e., both formulations failed to show a statistically significant effect), I consider study 448 as lacking assay sensitivity and a failed study. Accordingly, this section of labeling should focus on the two studies that adequately demonstrated efficacy, 449 and 487.

Also, since the proportion of patients achieving remission (HDRS total score ≤ 8) is not generally considered a primary efficacy variable in our assessment of antidepressant efficacy and was not in this case, the description of findings on this measure should be deleted.

Likewise, mention of improvement of the HDRS anxiety factor score was not a key variable and is potentially misleading in that it suggests that paroxetine CR may have distinct anxiolytic effects. This information should be deleted as well.

A description of the data supporting long-term (1 year) therapy with paroxetine IR is acceptable.

In view of the above recommendations, the following revision for this section is offered:

"The efficacy of Paxil CR controlled-release tablets as a treatment for depression has been established in two 12-week, flexible dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. In one study of patients generally in the age range 18-65 years, Paxil CR was shown to be significantly more effective than placebo in treating depression as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness score. In the second study, Paxil CR was shown to be effective in the treatment of elderly patients (ages 60 to 88) with depression. In this study, Paxil CR was significantly more effective than placebo in treating depression as measured by the Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness score.

A study of depressed outpatients who had responded to immediate-release paroxetine tablets (HDRS total score < 8) during an initial 8-week open-treatment phase and were then randomized to continuation on immediate-release paroxetine tablets or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking immediate-release

paroxetine tablets (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients."

INDICATIONS AND USAGE

The sponsor should be requested to update the description of a major depressive episode for consistency with DSM-IV.

ADVERSE REACTIONS

Information under the "Incidence in Controlled Trials with Paxil CR" subsection should include not only data from the pool of studies 448 and 449 but also, separately, data from study 487 in the elderly. Specifically, it is recommended that corresponding data from study 487 be presented under "Adverse Events Associated with Discontinuation of Treatment:"

"In a placebo-controlled study of depressed, elderly patients, 13% (13/104) of Paxil CR patients discontinued due to an adverse event. Events meeting the above criteria included the following:

| | Paxil CR | Placebo |
|-----------------|----------|---------|
| Nausea | 2.9% | 0.0% |
| Headache | 1.9% | 0.9% |
| Depression | 1.9% | 0.0% |
| LFT's abnormal | 1.9% | 0.0% |
| Testes disorder | 1.9% | 0.0% |

Under "Commonly Observed Adverse Events," the listing has omitted two events from the pool of studies 448 and 449 which appear to meet the stated criteria: abnormal vision and yawning. These events should be added. Also, as in the last subsection, events meeting the stated criteria from study 487 should be mentioned (i.e., dry mouth, abnormal ejaculation, constipation, decreased appetite, sweating, impotence, libido decreased, tremor, and infection).

Under "Incidence in Controlled Clinical Trials," it is suggested that Table 8.1.4.2.1 from Appendix 8.1 of this review be used for Table 1, which was proposed by the sponsor. There are no substantial differences between the sponsor's table and Table 8.1.4.2.1, but the latter is preferred due to the following minor differences: a) my table lists events within each body system in order of decreasing frequency, the more customary fashion, whereas the sponsor lists events alphabetically; b) my table provides footnotes to help clarify vague adverse event

terms; and c) it appears that some of the placebo rates in the sponsor's table are slightly inaccurate (i.e., abnormal vision should be 1% not 2%, and both female genital disorders and menstrual disorder should be <1% not 1%).

Likewise, it is suggested that Table 8.1.4.3 in Appendix 8.1 replace the sponsor's Table 3, which depicts adverse events from study 487. The sponsor has designated this as Table 3 to reserve Table 2 for the table of ADR's from studies in their pending NDA for the use of paroxetine CR in panic disorder; since this NDA will likely gain approval before the panic disorder NDA, I would suggest that this table be designated as Table 2 for the time being.

The subsection "Adaptation to Certain Adverse Events" should be deleted. Although the sponsor did attempt to examine this phenomenon by tracking the proportions of patients reporting common adverse events within cohorts of completers who reported events at week 1 for both drug and placebo treatment groups, this methodology is not entirely acceptable because of selection bias and failure to account for variables such as adverse event severity and duration over time. No satisfactory approach to this question is known at this time.

Regarding "Liver Function Tests," it is true that there were no differences between Paxil CR and placebo in the proportions of patients with increases of potential clinical concern in alkaline phosphatase, total bilirubin, AST, or ALT in the pool of studies 448 and 449 (i.e., 0% for all variables in both groups). However, no mention is made of the data from study 487, where the picture is somewhat different. In 487, greater proportions of paroxetine CR than placebo patients experienced increased LFT's of potential clinical concern for AST and ALT (equal proportions for total bilirubin and alkaline phosphatase):

| | Paroxetine CR | Placebo |
|-----|---------------|---------|
| AST | 2.9% | 0.0% |
| ALT | 1.9% | 0.0% |

Admittedly, neither comparison is statistically significant²³ and this finding could be a chance occurrence as opposed to a signal of an increased risk of LFT elevation in elderly patients. Mean change from baseline data from study 487 for these four variables revealed no marked differences between paroxetine CR and placebo. However, it

²³ $\alpha=0.10$, 2-tailed Fishers exact test.

is remarkable that 2% of paroxetine CR patients in study 487 dropped out due to abnormal LFT's versus 0% of placebo patients, although this cannot be construed as independent evidence of an increased risk. Nevertheless, for purposes of completeness and accuracy in labeling, these findings from study 487 (% with values of clinical concern and dropouts) should be added to this subsection.

The subsection "Other Events: Infrequent Adverse Events Observed with Paxil CR" apparently has not been revised to incorporate adverse events seen in study 487. A comparison of this table with Table 8.1.4.5 in Appendix 8.1, which lists "other events" reported in the pool of studies 448, 449, and 487, indicates that such a revision should include the following events:

cellulitis, angina pectoris, bradycardia, bundle branch block, eructation, gastroenteritis, glossitis, hepatosplenomegaly, intestinal obstruction, melena, peptic ulcer, stomach ulcer, tooth caries, ulcerative stomatitis, chronic lymphocytic leukemia, eosinophilia, hyperglycemia, depression, neuropathy, paralysis, dyspnea, pruritus, seborrhea, tinnitus, albuminuria, hematuria, kidney function abnormal, prostate disorder, testes disorder, and urinary incontinence.

In addition, the size of the patient sample from which these data were derived and the primary diagnoses of the relevant patients should be stated

paroxetine CR. Some way of specifying the proportion of patients experiencing these events should be provided, too.

The subsection "Other Events Observed with the Immediate-Release Formulation of Paroxetine Hydrochloride" appears to be based on the cumulative experience with immediate-release paroxetine, to include the active control arms of the Paxil CR depression. It is noted that mention of the proportions of patients experiencing these events has been deleted. It is suggested that this information be included in this listing.

OVERDOSAGE

The "Overdosage Management" subsection states that gastric evacuation either by induction of emesis or lavage or both should be performed. According to a consultation response from Dan Spyker, M.D., dated 4/15/98 which addresses induction of vomiting and which was prepared in consultation

with _____, induction of emesis in the management of overdoses with recently approved antidepressants, including the SSRI's, is not recommended. This seems to be based on the possibility that such patients may abruptly become sedated and aspirate as well as demonstrated effectiveness of gastric lavage in the emergency room. Hence, the recommendation to induce emesis should be deleted.

10.0 Conclusions

This application presents adequate data to support the sponsor's claim of the effectiveness of paroxetine CR in the treatment of depression. While the clinical experience with Paxil CR is too limited to rule out infrequently or rarely occurring safety problems, the safety record of Paxil (IR) is reassuring and the clinical trials data with Paxil CR do not suggest any problems unique to this formulation. Thus, paroxetine CR is expected to be reasonably safe for use as labeled.

11.0 Recommendations

From a clinical perspective, it is recommended that Paxil CR be approved for the treatment of depression after agreement is reached on the labeling issues raised in section 9.0.

As noted in section 3.0, a number of CMC deficiencies should be addressed by the sponsor prior to final approval.

Also, if the sponsor proceeds with the plan to shift manufacturing from the _____ site to _____, bioequivalence between the products from these two sites must be adequately established.

/S/

Gregory M. Dubitsky, M.D.
July 17, 1998

9-30-98

We have developed a draft of labeling and I agree that we can proceed with an approvable version. See memo to file for more detailed comments.

cc: NDA 20-936
HFD-120 (Division File)
HFD-120/TLaughren
/GDubitsky
/PDavid

/S/

-1 PDD

APPENDIX 5.0
CLINICAL DATA SOURCES

Table 5.1.1.1: Table of Studies

| Phase 1 Studies (healthy volunteers) | |
|---|---|
| 452/Europe | Multicenter, randomized, DB, PC, parallel group study of the incidence of nausea after 3 days of treatment with paroxetine 30mg daily given as one of two modified release formulations or standard Paxil or placebo; n=488 healthy volunteers. |
| 472/Germany | Randomized, open label, four period crossover study of single dose PK of 4 strengths of the CR tablets: 12.5, 25, 37.5, and 50mg); n=23. |
| 473/UK | Randomized, open label, two period crossover study of single dose bioavailability of the 50mg CR tablet in fasted vs. High fat meal state; n=22. |
| 474/Germany | Randomized, open label, two period crossover study of multiple dose PK (14 days/period) of the 50mg CR tablet vs. Paxil 50mg; n=23. |
| 480/Germany | Randomized, open label, two period crossover study to show bioequivalence between paroxetine CR 50mg (Cidra) and paroxetine CR (2x25mg) (Crawley) given as single doses; n=50. |
| 485/ UK, Belgium | Randomized, open label, three part crossover study to evaluate bioavailability of two modified release formulations of paroxetine (10mg+20mg tablets) and Paxil 30mg given as single doses; n=15. |
| 505/Europe | Randomized, open label, four part single dose crossover study comparing an enteric-coated modified release tablet (25mg), two uncoated modified release tablets (20mg), and Paxil 20mg; n=16. |
| 539/UK | Randomized, open label, two period crossover study to show bioequivalence between paroxetine CR 25mg (Cidra) and paroxetine CR 25mg (Crawley) given as single doses; n=47. |
| 563/UK | Randomized, open label, five period, single dose crossover study to evaluate bioavailability of paroxetine CR 50mg in four different fed states vs. fasted; n=23. |
| 564/Germany | Open label study of steady state PK of paroxetine CR 25mg/day given for 21 days under two dietary states (fasted days 1-14, high fat meal days 15-21; n=21. |

| Table 5.1.1.1: Table of Studies (continued) | |
|--|---|
| Phase 3 Studies (Depression) | |
| 448/US | Multicenter, 12 week, randomized, DB, PC, parallel group study; n=310 outpatients; flexible, once daily dosing: paroxetine CR (25-62.5mg/d), paroxetine IR (20-50mg/d). |
| 449/US,Canada | Multicenter, 12 week, randomized, DB, PC, parallel group study; n=330 outpatients; flexible, once daily dosing: paroxetine CR (25-62.5mg/d), paroxetine IR (20-50mg/d). |
| 487/US,Canada | Multicenter, 12 week, randomized, DB, PC, parallel group study; n=319 elderly outpatients; flexible, once daily dosing: paroxetine CR (12.5-50mg/d), paroxetine IR (10-40mg/d). |

| TABLE 5.1.1.2: PATIENT ENUMERATION BY STUDY TYPE | | | | |
|---|----------------------|---|----------------------|----------------|
| | Paroxetine CR | Paroxetine Modified Release Prototypes | Paroxetine IR | Placebo |
| Phase 1 | | | | |
| Single Dose | 202 | 30 | 30 | 0 |
| Multiple Dose | 169 | 122 | 144 | 120 |
| Subtotal | 371 | 152 | 174 | 120 |
| Phase 3 (depression only) | | | | |
| Short-term, placebo-controlled, flexible dose: | | | | |
| 448 + 449 | 212 | 0 | 217 | 211 |
| 487 | 104 | 0 | 106 | 109 |
| Subtotal | 316 | 0 | 323 | 320 |
| Phase 1 + Phase 3 Combined | | | | |
| Single-Dose Total | 202 | 30 | 30 | 0 |
| Multiple Dose Total | 485 | 122 | 467 | 440 |
| Grand Total | 687 | 152 | 497 | 440 |

| TABLE 5.1.2.1 | | | |
|--|----------------------------------|----------------------------------|----------------------------|
| DEMOGRAPHIC CHARACTERISTICS (STUDIES 448 + 449) | | | |
| | Paroxetine CR (n=212) | Paroxetine IR (n=217) | Placebo (n=211) |
| Enumeration (%) | | | |
| by Age Group | | | |
| 18-34 | 67 (32%) | 76 (35%) | 79 (37%) |
| 35-54 | 120 (57%) | 111 (51%) | 108 (51%) |
| 55-59 | 17 (8%) | 21 (10%) | 19 (9%) |
| 60-65 | 8 (4%) | 8 (4%) | 5 (2%) |
| 66-74 | 0 (0%) | 1 (0%) | 0 (0%) |
| Age | | | |
| Mean | 40.70 | 39.98 | 39.75 |
| Range | 18-64 | 18-71 | 19-64 |
| Gender | | | |
| Male | 78 (37%) | 67 (31%) | 78 (37%) |
| Female | 134 (63%) | 150 (69%) | 133 (63%) |
| Race | | | |
| White | 187 (88%) | 188 (87%) | 180 (85%) |
| Non-White | 25 (12%) | 29 (13%) | 31 (15%) |

| TABLE 5.1.2.2 | | | |
|--|----------------------------------|----------------------------------|----------------------------|
| DEMOGRAPHIC CHARACTERISTICS (STUDY 487) | | | |
| | Paroxetine CR (n=104) | Paroxetine IR (n=106) | Placebo (n=109) |
| Enumeration (%) | | | |
| by Age Group | | | |
| 60-65 | 21 (20%) | 27 (25%) | 27 (25%) |
| 66-74 | 57 (55%) | 54 (51%) | 63 (58%) |
| 75-84 | 25 (24%) | 23 (22%) | 19 (17%) |
| ≥85 | 1 (1%) | 2 (2%) | 0 (0%) |
| Age | | | |
| Mean | 70.39 | 70.05 | 69.39 |
| Range | 60-88 | 60-88 | 60-82 |
| Gender | | | |
| Male | 54 (52%) | 46 (43%) | 40 (37%) |
| Female | 50 (48%) | 60 (57%) | 69 (63%) |
| Race | | | |
| White | 100 (96%) | 101 (95%) | 103 (95%) |
| Non-White | 4 (4%) | 5 (5%) | 6 (5%) |

Table 5.1.3.1: Number (Percent) of Patients by Daily Dosage Level and Duration of Exposure to Each Level (Pool of Studies 448 + 449)

| Days Exposure: | 1-7 | | 8-14 | | 15-21 | | 22-28 | | 29-42 | | 43-56 | | 57-70 | | 71-84 | | >84 | | Total | |
|---------------------|----------------------|------|------|------|-------|------|-------|-----|-------|------|-------|------|-------|------|-------|-----|-----|-----|-------|-------|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Daily Dosage | Paroxetine CR | | | | | | | | | | | | | | | | | | | |
| Level (mg/d) | Paroxetine CR | | | | | | | | | | | | | | | | | | | |
| 1 (25.0) | 87 | 41.0 | 62 | 29.2 | 22 | 10.4 | 9 | 4.2 | 6 | 2.8 | 4 | 1.9 | 1 | 0.5 | 7 | 3.3 | 14 | 6.6 | 212 | 100.0 |
| 2 (37.5) | 65 | 37.4 | 42 | 24.1 | 18 | 10.3 | 8 | 4.6 | 9 | 5.2 | 6 | 3.4 | 10 | 5.7 | 14 | 8.0 | 2 | 1.1 | 174 | 100.0 |
| 3 (50.0) | 42 | 32.6 | 26 | 20.2 | 11 | 8.5 | 5 | 3.9 | 9 | 7.0 | 13 | 10.1 | 21 | 16.3 | 2 | 1.6 | 0 | 0 | 129 | 100.0 |
| 4 (62.5) | 5 | 6.4 | 3 | 3.8 | 4 | 5.1 | 2 | 2.6 | 20 | 25.6 | 14 | 17.9 | 30 | 38.5 | 0 | 0 | 0 | 0 | 78 | 100.0 |
| | Paroxetine IR | | | | | | | | | | | | | | | | | | | |
| 1 (20) | 86 | 39.6 | 69 | 31.8 | 17 | 7.8 | 7 | 3.2 | 9 | 4.1 | 6 | 2.8 | 3 | 1.4 | 9 | 4.1 | 11 | 5.1 | 217 | 100.0 |
| 2 (30) | 60 | 34.7 | 54 | 31.2 | 14 | 8.1 | 7 | 4.0 | 9 | 5.2 | 6 | 3.5 | 11 | 6.4 | 11 | 6.4 | 1 | 0.6 | 173 | 100.0 |
| 3 (40) | 38 | 29.2 | 23 | 17.7 | 13 | 10.0 | 5 | 3.8 | 18 | 13.8 | 6 | 4.6 | 22 | 16.9 | 5 | 3.8 | 0 | 0 | 130 | 100.0 |
| 4 (50) | 7 | 10.1 | 3 | 4.3 | 5 | 7.2 | 5 | 7.2 | 13 | 18.8 | 13 | 18.8 | 21 | 30.4 | 2 | 2.9 | 0 | 0 | 69 | 100.0 |
| | Placebo | | | | | | | | | | | | | | | | | | | |
| 1 | 105 | 49.8 | 57 | 27.0 | 24 | 11.4 | 4 | 1.9 | 6 | 2.8 | 1 | 0.5 | 2 | 0.9 | 6 | 2.8 | 6 | 2.8 | 211 | 100.0 |
| 2 | 87 | 45.1 | 54 | 28.0 | 13 | 6.7 | 7 | 3.6 | 7 | 3.6 | 4 | 2.1 | 11 | 5.7 | 10 | 5.2 | 0 | 0 | 193 | 100.0 |
| 3 | 59 | 38.8 | 39 | 25.7 | 12 | 7.9 | 6 | 3.9 | 12 | 7.9 | 11 | 7.2 | 9 | 5.9 | 4 | 2.6 | 0 | 0 | 152 | 100.0 |
| 4 | 4 | 3.6 | 4 | 3.6 | 4 | 3.6 | 9 | 8.0 | 13 | 11.6 | 21 | 18.8 | 52 | 46.4 | 5 | 4.5 | 0 | 0 | 112 | 100.0 |

Data Source: Table 4.3.1 in Section 21.1

Table 5.1.3.2: Number (Percent) of Patients by Daily Dosage Level and Duration of Exposure to Each Level (Study 487)

| Number of Patients Exposed | Paroxetine CR 12.5 mg | | Paroxetine CR 25 mg | | Paroxetine CR 37.5 mg | | Paroxetine CR 50 mg | |
|----------------------------|-----------------------|------|---------------------|------|-----------------------|------|---------------------|------|
| | No. | % | No. | % | No. | % | No. | % |
| Total Duration of Exposure | | | | | | | | |
| < 3 days | 2 | 1.9 | 0 | 0.0 | 0 | 0.0 | 1 | 3.6 |
| 3-7 days | 47 | 44.3 | 29 | 33.3 | 15 | 25.9 | 0 | 0.0 |
| 8-21 days | 25 | 23.6 | 28 | 32.2 | 17 | 29.3 | 4 | 14.3 |
| 22-42 days | 9 | 8.5 | 12 | 13.8 | 10 | 17.2 | 6 | 21.4 |
| 43-56 days | 1 | 0.9 | 6 | 6.9 | 5 | 8.6 | 7 | 25 |
| 57-84 days | 19 | 17.9 | 12 | 13.8 | 11 | 19 | 10 | 35.7 |
| >84 days | 3 | 2.8 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Mean (SEM) (days) | 25.52 (2.857) | | 24.60 (2.421) | | 28.12 (3.074) | | 43.89 (3.765) | |
| Median | 8 | | 14 | | 16 | | 49.5 | |
| Range | | | | | | | | |
| Number of Patients Exposed | Paroxetine IR 10 mg | | Paroxetine IR 20 mg | | Paroxetine IR 30 mg | | Paroxetine IR 40 mg | |
| | No. | % | No. | % | No. | % | No. | % |
| Total Duration of Exposure | | | | | | | | |
| < 3 days | 3 | 2.8 | 0 | 0.0 | 0 | 0.0 | 1 | 2.4 |
| 3-7 days | 48 | 44.4 | 32 | 36 | 25 | 39.7 | 1 | 2.4 |
| 8-21 days | 32 | 29.6 | 30 | 33.7 | 15 | 23.8 | 10 | 24.4 |
| 22-42 days | 5 | 4.6 | 11 | 12.4 | 10 | 15.9 | 8 | 19.5 |
| 43-56 days | 6 | 5.6 | 2 | 2.2 | 3 | 4.8 | 6 | 14.6 |
| 57-84 days | 12 | 11.1 | 13 | 14.6 | 10 | 15.9 | 15 | 36.6 |
| >84 days | 2 | 1.9 | 1 | 1.1 | 0 | 0.0 | 0 | 0.0 |
| Mean (SEM) (days) | 21.27 (2.432) | | 22.69 (2.319) | | 24.59 (2.779) | | 40.61 (3.392) | |
| Median | 8 | | 14 | | 14 | | 44 | |
| Range | | | | | | | | |
| Number of Patients Exposed | Placebo Level 1 | | Placebo Level 2 | | Placebo Level 3 | | Placebo Level 4 | |
| | No. | % | No. | % | No. | % | No. | % |
| Total Duration of Exposure | | | | | | | | |
| < 3 days | 4 | 3.7 | 3 | 3.2 | 0 | 0.0 | 1 | 2.3 |
| 3-7 days | 52 | 47.7 | 36 | 37.9 | 25 | 33.8 | 0 | 0.0 |
| 8-21 days | 34 | 31.2 | 25 | 26.3 | 20 | 27 | 5 | 11.4 |
| 22-42 days | 7 | 6.4 | 14 | 14.7 | 15 | 20.3 | 8 | 18.2 |
| 43-56 days | 1 | 0.9 | 5 | 5.3 | 4 | 5.4 | 6 | 13.6 |
| 57-84 days | 7 | 6.4 | 12 | 12.6 | 10 | 13.5 | 24 | 54.5 |
| >84 days | 4 | 3.7 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Mean (SEM) (days) | 17.51 (2.110) | | 21.89 (2.236) | | 24.51 (2.498) | | 49.02 (2.744) | |
| Median | 7 | | 9 | | 14 | | 59 | |
| Range | | | | | | | | |

Data Source: Data Source Table, 13.11.3, Appendix B Listing 13.11

APPENDIX 7.2.1

EFFICACY DATA: STUDY 448

Table 7.2.1.1
Study 448: Investigators/Sites

| Investigators and Their Hospital or University Affiliation | | |
|---|--|-------------------|
| Investigator | Affiliated Institution | Location |
| James Bremner, MD | Bremner Research Institute | Olympia, WA |
| Larry Davis, MD | The Davis Clinic PC | Indianapolis, IN |
| Eugene DuBoff, MD | Center for Behavioral Medicine | Denver, CO |
| David Dunner, MD | University Washington | Seattle, WA |
| James M. Ferguson, MD | Pharmacology Research Corporation | Murray, UT |
| Saul H. Helfing, MD | Hill Top Research, Inc. | Portland, OR |
| Marc Hertzman, MD | Private Practice | Glen Burnie, MD |
| Carl Houck, MD and Karen E. Callahan, MD | University of Alabama, Birmingham | Birmingham, AL |
| Richard Kavoussi, MD | Medical College of PA | Philadelphia, PA |
| Barbara L. Kennedy, MD | University of Louisville | Louisville, KY |
| Arifulla Khan, MD. | Northwest Psychiatric Institute, Inc | Kirkland, WA |
| R. Bruce Lydiard, MD | Medical University of South Carolina | Charleston, SC |
| John J. Murphy, MD and Dennis J. Munjack, MD | Southwestern Research | Beverly Hills, CA |
| Raj Nakra, MD | Washington University School of Medicine | Chesterfield, MO |
| Mark H. Rapaport, MD | USCD Psychopharmacology Research Program | La Jolla, CA |
| Edward Schweizer, MD | University of PA | Philadelphia, PA |
| Ram K. Shrivastava, MD | Eastside Comprehensive Medical Services | New York, NY |
| Peter M. Thompson, MD | University of New Mexico Health Sciences Center | Albuquerque, NM |
| Madhukar H. Trivedi, MD | UT SW Medical Center | Dallas, TX |
| Harold Udelman, MD | Psychiatric Research Network | Phoenix, AZ |
| Source: CVs in Appendix A | | |

Table 7.2.1.2
Study 448: Baseline Characteristics

| Demographic Characteristics of all Randomized Patients Who Received Study Medication, ITT Population | | | | | | |
|---|---------------------|----------|---------------------|----------|--------------------------|----------|
| | CR N=104 | | IR N=105 | | Placebo N=101 | |
| | n | % | n | % | n | % |
| Age (years) | | | | | | |
| 18 - 24 | 10 | 9.62 | 8 | 7.62 | 6 | 5.94 |
| 25 - 34 | 26 | 25.0 | 28 | 26.67 | 31 | 30.69 |
| 35 - 44 | 37 | 35.58 | 35 | 33.33 | 33 | 32.67 |
| 45 - 54 | 22 | 21.15 | 25 | 23.81 | 26 | 25.74 |
| 55 - 65 | 9 | 8.65 | 9 | 8.57 | 5 | 4.95 |
| Mean ± SD | 38.95 ± 10.64 | | 39.37 ± 10.65 | | 38.7 ± 9.91 | |
| Range (min, max) | | | | | | |
| Mean Weight ± SD (lb) | 180.53 ± 50.35 | | 167.82 ± 37.27 | | 169.3 ± 37.95 | |
| Gender | | | | | | |
| Female | 62 | 59.62 | 67 | 63.81 | 67 | 66.34 |
| Male | 42 | 40.38 | 38 | 36.19 | 34 | 33.66 |
| Race | | | | | | |
| Black | 4 | 3.85 | 3 | 2.86 | 9 | 8.91 |
| Oriental | 1 | 0.96 | 1 | 0.95 | 1 | 0.99 |
| Other | 4 | 3.85 | 7 | 6.67 | 5 | 4.95 |
| White | 95 | 91.35 | 94 | 89.52 | 86 | 85.15 |

Source: Data Source Table 13.4b, Section 13, Appendix B Listing 13.4

Table 7.2.1.3
Study 448: Patients In-Study by Visit

| Number (%) of Patients Remaining at Each Visit | | | | | | | | |
|---|----------------------|----------|----------------------|----------|----------------|----------|--------------|----------|
| ITT Population | | | | | | | | |
| | Paroxetine CR | | Paroxetine IR | | Placebo | | Total | |
| | n | % | n | % | n | % | n | % |
| Baseline | 104 | 100.0 | 105 | 100.0 | 101 | 100.0 | 310 | 100.0 |
| Week 1 | 93 | 89.4 | 92 | 87.6 | 101 | 100 | 286 | 92.3 |
| Week 2 | 90 | 86.5 | 91 | 86.7 | 97 | 96.0 | 278 | 89.7 |
| Week 3 | 86 | 82.7 | 86 | 81.9 | 94 | 93.1 | 266 | 85.8 |
| Week 4 | 84 | 80.8 | 80 | 76.2 | 91 | 90.1 | 255 | 82.3 |
| Week 6 | 81 | 77.9 | 73 | 69.5 | 86 | 85.1 | 240 | 77.4 |
| Week 8 | 75 | 72.1 | 72 | 68.6 | 81 | 80.2 | 228 | 73.5 |
| Week 12 | 72 | 69.2 | 70 | 66.7 | 74 | 73.3 | 216 | 69.7 |

Source: Data Source Table 13.3.2b, Section 13, Appendix B, Listing 13.3b

Table 7.2.1.4 Study 448: HAM-D Total Score (LOCF)

Baseline and Change from Baseline in HAM-D Total Score
 Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAM-D Total Score and Duration of Current Episode of Depression
 Statistical Analysis Presented at LOCF Endpoints
 Intention to Treat Population

| | Paroxetine CR | | | Treatment Groups Paroxetine IR | | | Placebo | | | Pairwise Comparisons | | | | | |
|--------------|---------------|--------|-----|-----------------------------------|--------|-----|---------|--------|-----|----------------------|----------------|---------|------|---------------|---------|
| | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (95% C.I.) | p-value | Mean | (95% C.I.) | p-value |
| Baseline | 23.0 | (0.26) | 102 | 23.3 | (0.28) | 104 | 23.4 | (0.29) | 101 | | | | | | |
| Week 2 LOCF | -6.8 | (0.49) | 102 | -6.0 | (0.50) | 104 | -5.8 | (0.49) | 101 | -1.0 | (-2.31, 0.38) | 0.159 | -0.1 | (-1.48, 1.21) | 0.843 |
| Week 4 LOCF | -10.3 | (0.67) | 102 | -8.7 | (0.68) | 104 | -9.1 | (0.68) | 101 | -1.2 | (-3.04, 0.63) | 0.198 | 0.4 | (-1.40, 2.28) | 0.641 |
| Week 6 LOCF | -11.2 | (0.69) | 102 | -9.9 | (0.70) | 104 | -8.7 | (0.69) | 101 | -2.4 | (-4.30, -0.53) | 0.012 | -1.2 | (-3.07, 0.71) | 0.220 |
| Week 8 LOCF | -12.3 | (0.73) | 102 | -10.6 | (0.75) | 104 | -9.9 | (0.74) | 101 | -2.4 | (-4.37, -0.36) | 0.021 | -0.7 | (-2.69, 1.34) | 0.511 |
| Week 12 LOCF | -12.7 | (0.80) | 102 | -11.1 | (0.81) | 104 | -9.9 | (0.80) | 101 | -2.8 | (-4.94, -0.59) | 0.013 | -1.2 | (-3.40, 0.97) | 0.275 |

Table 7.2.1.5 Study 448: HAM-D Total Score (OC)

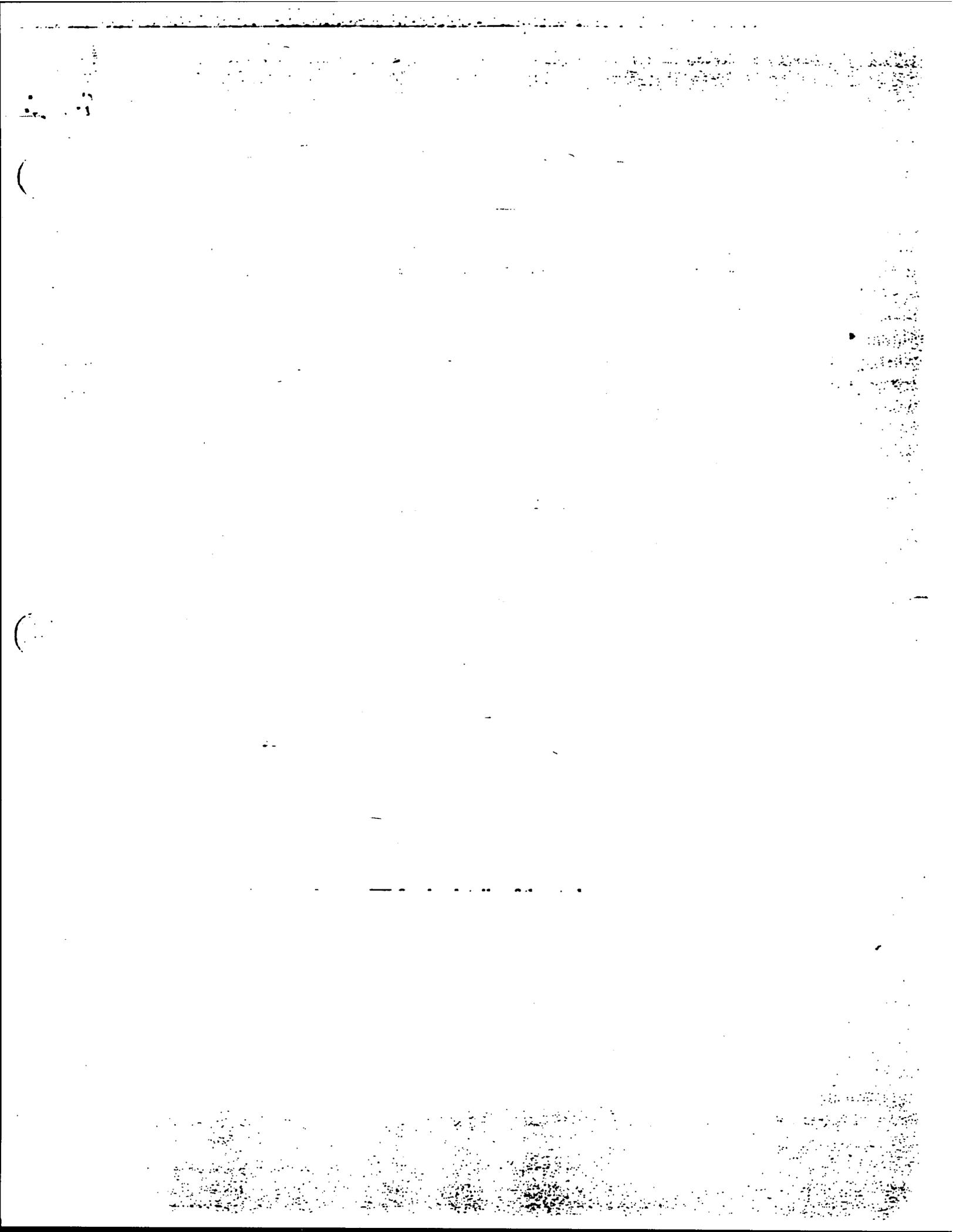
Baseline and Change from Baseline in HAM-D Total Score
 Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAM-D Total Score and Duration of Current Episode of Depression
 Statistical Analysis Presented at all Time Points
 Intention to Treat Population

| | Paroxetine CR | | | Treatment Groups Paroxetine IR | | | Placebo | | | Pairwise Comparisons | | | | | |
|----------|---------------|--------|-----|-----------------------------------|--------|-----|---------|--------|-----|----------------------|----------------|---------|------|----------------|---------|
| | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (95% C.I.) | p-value | Mean | (95% C.I.) | p-value |
| Baseline | 23.0 | (0.26) | 102 | 23.3 | (0.28) | 104 | 23.4 | (0.29) | 101 | | | | | | |
| Week 1 | -3.7 | (0.38) | 100 | -3.3 | (0.39) | 103 | -3.0 | (0.39) | 100 | -0.7 | (-1.71, 0.38) | 0.212 | -0.3 | (-1.38, 0.72) | 0.536 |
| Week 2 | -7.5 | (0.52) | 88 | -6.5 | (0.54) | 84 | -5.9 | (0.50) | 96 | -1.6 | (-3.02, -0.23) | 0.022 | -0.6 | (-1.99, 0.86) | 0.434 |
| Week 3 | -9.8 | (0.62) | 87 | -7.8 | (0.64) | 87 | -7.4 | (0.61) | 91 | -2.4 | (-4.13, -0.76) | 0.005 | -0.4 | (-2.13, 1.28) | 0.622 |
| Week 4 | -11.4 | (0.70) | 86 | -9.8 | (0.73) | 83 | -9.5 | (0.68) | 93 | -1.9 | (-3.79, -0.04) | 0.045 | -0.3 | (-2.22, 1.62) | 0.757 |
| Week 6 | -12.6 | (0.72) | 78 | -12.0 | (0.74) | 78 | -9.2 | (0.69) | 87 | -3.4 | (-5.33, -1.47) | <0.001 | -2.8 | (-4.75, -0.87) | 0.005 |
| Week 8 | -14.2 | (0.69) | 80 | -14.0 | (0.76) | 70 | -11.1 | (0.69) | 79 | -3.1 | (-4.98, -1.19) | 0.002 | -2.9 | (-4.84, -0.86) | 0.005 |
| Week 12 | -15.1 | (0.86) | 66 | -14.5 | (0.97) | 57 | -11.2 | (0.86) | 67 | -4.0 | (-6.33, -1.59) | 0.001 | -3.3 | (-5.78, -0.77) | 0.011 |

As with IR, the $t_{1/2}$ of CR did not increase with dose, indicating that the nonlinearity is confined mainly to the pre-systemic clearance. A large within subject variation in T_{max} and inter-subject variation in $AUC_{0-\infty}$ was observed at all dose strengths. Nevertheless, all the subjects at any given tablet strength had a lag-time of approximately 4 hr and reached C_{max} at an average of 6-10 hr after dosing (mean T_{max} for IR was 5.2 hr), indicating the reduced absorption rate as expected for the controlled-release tablet.

Comments:

- (1) The inter- and intra-individual variation of plasma concentration are pronounced. The inter-individual variation could be explained by the different enzyme levels among subjects. But the intra-individual variation could be related to the inconsistent CR absorption rate. For instance, the plasma concentration vs. time profile is completely different among subjects 9, 10 and 11 (see the Attachment I).
- (2) Though not substantial, there is a trend of increase in T_{max} with respect to increasing doses. Assuming that gut metabolism and absorption are not involved in determining PK characteristics of paroxetine, the increased T_{max} could indicate the possibility of non-uniform release rate in vivo.



4. Study 564: Food effect on 25 mg CR tablet at steady state.

The object of this study was to determine the effect of food on the steady-state pharmacokinetic profile of paroxetine-CR dosed repeatedly at a typical clinical dose (25 mg). The study was a open, non-randomized, steady state study design. Subjects (n=22) were dosed with 25 mg paroxetine CR qd for 21 days. Doses were administered after an overnight fast on D1-14, and immediately after a standard FDA high fat breakfast on D15-21. On days 1-10, the volunteers were required not to eat a proper lunch until 6 hr after dosing although 3 hr after dosing they were free to eat a light snack. Days 11-22, the volunteers were required to stay fasted until 6 hr after dosing. The blood samples were collected on days 12, 14, 15, 19 and 21.

Please refer to the Attachment IV for the details of the study.

Results:

Irrespective of dietary state, no significant changes in the primary bioavailability parameters (C_{max} or AUC) were evident in this study. Pharmacokinetic parameters of paroxetine CR on the first day of dosing in the fed state and repeated dosing in the fed state (Day 19 and 21) were each compared with repeated dosing in the fasted state (Day 12 and 14). By sampling on two separate occasions after repeated administration in each dietary state, within subject variability for C_{max} and AUC_{τ} were in the fasted state and lower in the fed state. Between subject variability is high (~90%), but is unaffected by the dietary state. After the first day of dosing in the fed condition, pharmacokinetic parameters (C_{max} , AUC_{τ} and C_{min}) were equivalent to those of the

fasted condition, indicating occasional change in dietary habits will have no significant effect on bioavailability of the drug.

5. Study 539: A single dose BE study to compare 25 mg CR tablets manufactured at and at

The sponsor applied for approval of 4 dosage strengths (12.5, 25, and of paroxetine -CR in this submission. The two lower strengths used in the pivotal Phase III trials (12.5 and 25 mg) were manufactured at the (the higher doses in the trials were reached by using multiples of the two lower strengths (12.5 + 25, 25 + 25 mg)). The sponsor intends to transfer the manufacturing site from in the future. This single dose 2-way crossover study was to demonstrate bioequivalence at 25 mg between site. Please refer to the Attachment V for the details of the study.

Results:

Forty five healthy subjects completed the study. The sample size was chosen based on a expected within-subject coefficient of variation for AUC and C_{max} of 30%, the variation that was previously seen in the single dose pilot study. It was calculated that a sample size of 40 would have enough power to show that the 90% confidence interval would be contained within the range of 0.8-1.25. However, the larger-than-expected (by one and half time) within-subject and between-subject variation lead to the failure of AUC comparison to meet the bioequivalence criteria (0.94-1.29), whereas C_{max} (0.92-1.21) fell within the boundary. The sponsor argued that the failure of AUC to meet the 90% C.I. criteria is due to the inadequate sample size which resulted from large variation, rather than the difference in the formulation. The residual plots of AUC indicate possible over-dispersion distribution. One subject (#004), who has an extremely low AUC for the Crawley formulation, was identified as an outlier. Excluding this subject resulted in passing 90% C.I. on AUC (0.91-1.22), but did not influence the statistical analysis-for C_{max}. No period or sequence effects were seen in any of the analysis.

Comments:

It is not acceptable to throw away any data for bioequivalence statistical analysis, unless it is confirmed that the data is truly an outlier. The result of the study shows that the product manufactured from the two sites are not bioequivalent.

6: Dissolution:

Apparatus: USP II (paddles) 150 rpm.

| <u>Dissolution Media</u> | <u>Time</u> | <u>Limit (% dissolved)</u> |
|--|-------------|----------------------------|
| Step 1: 0.1 M HCl (750 mL) for 2 hr | 2 hr | Not more than |
| Step 2: pH 7.5 Tris buffer containing 60 mmol Tris, 90 mmol NaCl (1000 mL) for 7 hr. | 1 hr | |
| | 2 hr | |
| | 4 hr | |
| | 6 hr | |

3D. Efficacy Results (Sponsor's Analyses)

The change from baseline to study in HAMD Total was the protocol-mentioned primary efficacy variable.

The protocol stated, "The change from baseline to study endpoint in the CGI severity of illness item and HAMD depressed mood item will be analyzed using the Wilcoxon rank sum test. No adjustment will be made for center or covariates." However, the NDA provided results for HAMD depressed mood item (as well as for HAMD total, as stated) adjusting for the effect of "Center Group Only" in one analysis and of "Center group, age, sex, baseline value, and duration of current episode of depression" in another analysis. Non-parametric analysis results for HAMD Depressed Mood Item were also provided.

Although the sponsor stated that these covariates were prospectively defined (may be in their internal document), this reviewer does not see them specifically cited in the protocol. The protocol stated, "The effect of suitable covariates will also be investigated e.g. baseline scores and demographic parameters."

The (1) Results with mean differences, 95% confidence intervals, and p-values (OC and LOCF) and (2) Graphs for cumulative distribution functions, for (adjusted) Mean Changes From Baseline are attached as Tables 3.3.1, 3.3.2, and Figure 3.3.3 (HAM-D Total); 3.4.1, 3.4.2, and 3.4.3 (HAM-D Depressed Mood Item), 3.5.1, 3.5.2, and 3.5.3 (CGI Severity of Illness).

LOCF results were not statistically significant for CGI Severity of Illness except at Week 12 and for HAMD Total except at Weeks 10 and 12. Other than that, all the results from, at least, Week 6 (and after) with respect to the efficacy variables mentioned, were clearly in favor of the efficacy of Paxil CR. Paxil IR results were slightly weaker but acceptable.

3E. Reviewer's Comments and Conclusions on Study 487

This study provided statistically significant evidence in favor of the efficacy of Paxil CR, in the treatment of major depression in elderly patients. Statistical evidence in favor of the efficacy of Paxil IR was also acceptable.

From the graphs of Change from Baseline for the dropouts (Stat. Vol. 5.6, pages 000127 to 000129; not attached to this report), we see that dropouts from the placebo group at Weeks 4 and 10 had better changes from baseline in HAMD Total and HAMD Depressed Mood Item than those of the dropouts from Paxil CR group at those weeks. (Week 1 dropouts are not important because of very small improvements anyway, in all treatment arms.)

Therefore, there is a possibility that Paxil CR was favored in OC analyses by the dropping out of some better responding placebo patients.

III. Overall Reviewer's Comments

Studies 449 and 487 (the latter in elderly patients) provided statistical evidence for the efficacy of Paxil CR. Study 448 provided statistical evidence by the all-centers-combined results. However, Center 002 in Study 448 produced outstandingly weak responses for placebo patients and outstandingly superior responses for Paxil CR patients. Excluding that center, Study 448 provided numerical evidence for the efficacy of Paxil CR. Paxil IR results were weaker than those of Paxil CR in some cases.

With the July 3, 1996 meeting in perspective, this reviewer concludes that the studies in this NDA have provided statistical evidence in favor of the efficacy of Paxil CR.

Daily Dosage Information

Number of patients exposed to each daily dose of study drug by visit is attached as Table 0.2.1a and mean and median daily dose of active medication by week are attached as Table 0.2.1b.

From Table 0.2.1a, we see that maximum daily doses for both paroxetine formulations were relatively evenly spread across the 4 dosing levels for both studies, with approximately 20% to 25% of patients remaining on the lowest dose in the Week 12 endpoint dataset. In sharp contrast, patients treated with placebo were more rapidly titrated through the 4 dosing levels and in each study a greater proportion of placebo patients had a maximum dose at level 4 than for either of the active treatment groups.

The mean daily doses (in mg/day) of both CR and IR Paxil were slightly lower in Study 449 (46.6 and 37.0 at Week 12) than those in Study 448 (50.0 and 39.5), although the results of Study

449 were stronger in favor of active drugs.

In Study 487, the proportion of patients with a maximum daily dose of the top dose level was greater in the placebo and Paxil IR groups than in the Paxil CR group (CR - 26.9%, IR - 38.7%, and placebo- 40.4%)

Consistency Across Sites

The center by treatment interaction in Study 448 and that the results were not statistically significant when the center 002 with 18 patients was excluded, has been discussed in details in the Section for that study.

For Study 449, the results across the sites were reasonably consistent.

In Study 487, there was not a single center where placebo performed better than any of Paxil CR and IR groups, with respect to the primary efficacy variable. The center group 002/020 produced the best results among all centers; however, it did not lead to a statistically significant center by treatment interaction. The overall efficacy of the Paxil groups was not driven by a few big centers.

Subgroup Analyses

The sponsor stated in "Conclusion," for studies 448 and 449 (this reviewer checked other details in ISE),

"The only significant covariate interaction demonstrated in the analyses of the variables of primary interest, was the baseline severity of illness. Interpretation of this interaction is difficult because of opposing effects of the baseline severity observed in these studies: in Study 449, patients with less severe disease appear to have a better response to study medication, whereas Study 448 patients who were more severely depressed responded better to study medication. The interpretation of this interaction was further complicated because of the small number of patients in each study who were severely depressed. ... , although age, gender, and duration of illness had been prospectively identified as potentially affecting the efficacy variables, none of these covariates were found to have a significant effect."