Treatment Phase Emergent Adverse Experiences Occurring in 5% (rounded off) or More of the Paroxetine Group and Twice that of Placebo subjects– Studies 637, 641 and 642 (ITT Population)				
Body System Preferred Term	**Placebo N = 529**		**Paroxetine N = 735**	
	n	(%)	n	(%)
Body As a Whole				
Asthenia	34	(6.4)	105	(14.3)
Infection	18	(3.4)	41	(5.6)
Digestive System				
Constipation	9	(1. 7)	77	(10. 5)
Decreased Appetite	6	(1. 1)	38	(5. 2)
Dry Mouth	25	(4.7)	80	(10.9)
Nausea	28	(5.3)	148	(20.1)
Nervous System				
Libido Decreased	8	(1.5)	69	(9.4)
Somnolence	24	(4.5)	113	(15.4)
Tremor	4	(0.8)	34	(4.6)
Skin and Appendages				
Sweating	8	(1.5)	46	(6.3)
Urogenital				
*Abnormal Ejaculation	4	(2. 0)	70	(24. 7)

* Percentage corrected for gender

When only considering the US/Canadian studies (Studies 641 and 642) the following additional TP AE's met criteria for being considered as "commonly occurring": female genital disorders (incidence of 6.4% and 1.0%, in paroxetine and placebo groups, respectively) and yawning (incidence of 5.5% and 0.3%, respectively). In contrast to these studies, the European study (637) had no additional TP AE's that were reported at a rate meeting the "commonly occurring" AE criteria. However, the sample size of this study was smaller than that of the two US/Canadian studies, combined.

Visual inspection of Table 8.1.3 in the appendix (the enumeration of TP AE's in US/Canadian or European study populations, as provided by the sponsor) reveals that the percentage of TP AE's among treatment groups of the European study were generally less than that observed in the North American study. The placebo groups compared to the paroxetine groups of the European versus the combined US/Canadian study populations generally show a similar pattern of TP AE's. Therefore, the sponsor indicates that "the attributable risk which takes into account incidences of an event in the paroxetine groups relative to that of placebo group supports that most of the common AE's are similar in the North American and European studies". However, the magnitude of the difference in the incidence of each TP AE between the placebo and paroxetine groups, generally appears to be greater in the Northern American population compared to that observed in the European study population (based on visual inspection of Table 8.1.3, as provided by the sponsor).

A coding error is noted in the submission for one of the reported AE's in Study 642 regarding a female patient with history of anorgasmia, reported anorgasmia on day 9 of

paroxetine treatment. Because this AE was incorrectly coded as a male AE and the ADECS dictionary term "produced the preferred term of abnormal ejaculation". Hence, this event was not included in the summary tables provided by the sponsor and in this review.

Dose Dependent Relationship of Treatment Emergent Adverse Events. The table below shows the incidences of AE's that appeared to show a dose-dependent relationship between the 20 mg and 40 mg paroxetine groups in the fixed dose parallel group study (Study 641). These AE's were among AE's provided in Table 33 for Study 641 in the submission, with an incidence of at least 5% in paroxetine groups and of at least twice that of controls.

Incidence of Selected Adverse Events Occurring in at Least 5% of Paroxetine Subjects in Study 641

Adverse Event	Placebo Group	20 mg Paroxetine Group	40 mg Paroxetine Group
Asthenia	3.9	10.6	19.3
Constipation	3.3	8.5	14.2
Abnormal Ejaculation	2.5	17.4	36.0

Data Source: Table 33, page 000096 in the safety results section for Study 641 in the submission.

Similar results were revealed when examining incidences AE's considered to be severe that also occurred in at least 5% of either the paroxetine groups and with an incidence of at least twice that of placebo. The severe AE's that appeared to be dose dependent were asthenia (0%, 1.1%, and 2.5% in the placebo, 20 and 40 mg paroxetine groups, respectively) and constipation (0%, 0.5%, and 1.5% for each respective group).

The number of SAE's in the fixed dose study (Study 641) was insufficient to compare the low and high dose groups on the incidence of SAE's. The table below (derived from Table 42 in the safety results section for Study 641 of the submission) shows the incidence of those AE's associated with treatment cessation that at least revealed a trend for greater incidences in the high dose compared to the low dose groups. None of these AE's were common (occurred in ≥5% of a given paroxetine group).

Adverse Experiences Which Lead to Withdrawal in at Least Two Patients in Any Treatment Group and Showed at Least a Trend for a Greater Incidence in the High Dose Paroxetine Group compared to the Low Dose Paroxetine Group (see above text)

Adverse Experience+ by Preferred Term	Placebo N = 180		Paroxetine 20 mg N = 189		Paroxetine 40 mg N = 197	
	n	(%)	n	(%)	n	(%)
Asthenia	0	(0.0)	1	(0.5)	5	(2.5)
Insomnia	1	(0.6)	1	(0.5)	3	(1.5)
Amnesia	0	(0. 0)	0	(0. 0)	2	(1. 0)

+ "For three patients in the 20 mg paroxetine regimen and three in the 40 mg regimen, the AE leading to withdrawal was not identified. In addition, for one placebo patient and two paroxetine patients in the 20 mg regimen, the investigators reported that the AE leading to withdrawal occurred 1- 3 days after stopping medication. AE information from these nine patients is not included in Table 42 or Data Source Table 13.3.4, Section 13 (see Section 3.14 for details)."

Data source: "Tables 13.3.4 and 13.3.4x, Section 13; Listing D. 5 in Appendix D"

Gender, Age-group and Racial-group Analysis of AE's. An analysis of results on the incidence of AE's of the combined three studies by gender revealed results similar to that described in the product labeling. Interpretation of AE results analyzed by age-group or race is difficult, since the size of the subgroups were small and insufficient for an adequate analyses. The sample sizes of the placebo and paroxetine subgroups of subjects over 65 years old were 36 and 47 subjects, respectively. The number of non-Caucasian subjects was also small for each treatment group (N=65 and N=80 in the placebo and paroxetine groups, respectively.
AE's During Post-Marketing. A total of 5 SAE's and 24 non-serious AE's were described in the submission. No unlabeled SAE's were reported.

8.1.6 Laboratory Findings
8.1.6.1 Analysis of Central Tendency
The mean changes in various laboratory parameters were not clinically significant in magnitude. Upon visual inspection of Tables 8.1.5 and 8.1.6 in the appendix, as provided by the sponsor, the treatment groups showed similar mean changes in the various parameters. A list of the laboratory tests and the schedule of assessments that were performed may be found in Table 7.1.2 in the appendix. Tables 8.1.4 A in the appendix also provides a list of assessments, as well as the criteria for meeting "Potential Clinical Concern".

Tables 8.1.5 and 8.1.6 in the appendix summarize results on the mean laboratory values at baseline and the mean change from baseline to endpoint for the 3 completed studies (combined), as provided by the sponsor. The results summarized in these tables show that the paroxetine and placebo groups were similar in mean changes in the various laboratory parameters. The range of these mean changes was 0 to ± a few units and remained within the normal reference range for each parameter. However, the variance or standard deviations for the mean changes are generally several-fold to 10 fold larger in magnitude than the value for the mean change for each respective parameter.

The sponsor provides the following observations regarding the mean change in laboratory values when expressed as a percentage (the mean change at endpoint/mean baseline value x 100%). The percent change observed in each treatment group for each of the following blood chemistry values is less than 5%: BUN, Creatinine, potassium and sodium levels. The paroxetine and placebo groups showed 16 and 14% changes, respectively, in total bilirubin levels. The percent change in the liver function tests, alkaline phosphatase, AST and ALT ranged from 5 to 10% in the paroxetine group and from 0.4 to 1.6% in the placebo group.

8.1.6.2 Analysis of Outliers

Tables 8.1.4 A and B in the appendix provides the "potential clinical concern" (PCC) criteria for each laboratory measure monitored. The following table summarizes the number of subjects meeting criteria for PCC, as provided by the sponsor. With the exception of eosinophilia, the incidence of all other laboratory values meeting PCC criteria within each treatment group was less than 1%.

Clinical Laboratory Values Meeting Sponsor- Defined Potential Clinical Concern Criteria - Studies 637, 641 and 642 (ITT Population)						
			Placebo		Paroxetine	
			N = 529		N = 735	
Parameters	**Lab Units**		**n**	**(%)**	**n**	**(%)**
Aspartate Aminotransferase	IU/ L	H	0	(0.0)	2	(0.3)
Blood Urea Nitrogen	MMOL/ L	H	4	(0.8)	6	(0.8)
Creatinine	UMOL/ L	H	0	(0.0)	3	(0.4)
Potassium	MMOL/ L	H	0	(0.0)	2	(0.3)
Thyroid Stimulating	MU/ L	H	1	(0.2)	0	(0.0)
Hormone						
Total Bilirubin	MMOL/ L	H	1	(0. 2)	6	(0. 8)
Eosinophils	10^ 9/ L	H	5	(0.9)	14	(1.9)
Hematocrit	%	L	2	(0.4)	5	(0.7)
Hemoglobin	G/ L	L	1	(0.2)	1	(0.1)
Monocytes	10^ 9/ L	H	2	(0.4)	3	(0.4)
Platelets	10^ 9/ L	L	2	(0.4)	0	(0.0)
White Blood Cell Count	10^ 9/ L	L	0	(0.0)	2	(0.3)

Hematological results: There were no reported cases of agranulocytosis, but there were 2 reported cases of leukopenia in the paroxetine group. These two cases (subjects 637.099.03820, 641.115.00708) of leukopenia involved older patients (58 and 74 years old, respectively) with pre-existing disorders (Parkinson's disease and history of breast cancer, respectively) in which abnormally low white blood cell counts were found on the week 8 visit which met PCC criteria. These abnormal WBC values could have been associated with non drug related, pre-existing conditions/disorders given the subjects' medical histories and various abnormal values on other laboratory parameters observed at baseline, as described below.

Description of the Aforementioned Paroxetine Subjects (637.099.03820, 641.115.00708):

In the 58 y.o. subject with Parkinson's disease (subject 637.099.03820) the abnormal baseline laboratory value was a low TSH of 0.1 mU/l (normal reference range: 4.0-5.5mU/l). This subject's white blood cell count (WBC) dropped from 6.3 $x10^{9th}$ cells/l at baseline to 2.2$x10^{9th}$ cells/l after 54 treatment days (week 8 visit). At 54 days of treatment eosinophil and monocyte levels (17% and 15%, respectively) were high but reported to be within the normal range at baseline. These abnormal laboratory values met PCC criteria but were not reported to be associated with any AE's. The abnormal WBC and low neutrophils of 0.38 (normal range=1.8-8GI/L) reported on week 8 were considered "NCS" by the investigator. Given that the patient had Parkinson's disease and a low TSH level (not clear if evaluated and receiving thyroid hormone replacement therapy), the reason for the including this patient in the study remains unclear. Furthermore, it is not clear what the follow-up was for the abnormal laboratory results. A 14-day follow-up of labs was reportedly not conducted and marked on the CRF as "not required".

The 74 y.o. year old subject (subject 641.115.00708) with a history of breast cancer had low free T3 levels and thrombocytopenia (at screening platelet count was 96 $x10^{9th}$ cells/l with normal: 130-400 $x10^{9th}$ cells/l). Her low white cell blood cell count at both screening and on study visit week 8 were 3.0 $x10^{9th}$ cells/l and 2.0 $x10^{9th}$ cells/l, respectively which each met PCC criteria. According to the narratives of this subject, no AE's associated with low white cell counts were reported. A pre-existing low white count suggests that the low white cell count on

week 8 was not likely to be drug-related. In response to an inquiry made by this reviewer (a fax dated 8/7/0), the sponsor reported (in a fax dated 8/31/00) that the patients' physician considered her medical condition as "stable" and was "thought to have recovered well from her malignancy". Her blood dyscrasia was also reported as "stable" and that "no action was to be taken by the physician". The sponsor indicated that on 8/28/00 the patient was considered to be "stable and well" and was "taking Paxil® for her anxiety". A "follow-up bone marrow study" was also reported to be scheduled "in about two months". The patients abnormal laboratory values were not likely to be drug-related, given her pre-existing abnormal laboratory values and her continued treatment on Paxil® while remaining "stable and well".

There were no SAE's or adverse dropouts associated with white blood cell count or differential values meeting PCC criteria among paroxetine subjects, except for one subject. This one exception was an adverse dropout reported in subject 641.118.00851 who had a slightly elevated eosinophil at baseline (9% compared to 0-7% range for within normal limits) and on Day 56 of 13%, of which the latter met PCC criteria. This subject also had a mildly elevated alkaline phosphatase level on Day 56 (132.0IU/l). These abnormal laboratory values were "not of clinical concern" by the investigator and required no further laboratory evaluation, according to a fax from the sponsor (date 8/31/00) responding to this reviewers inquiries (a fax dated 8/7/00). The reported adverse events that led to cessation of paroxetine treatment on Day 11 were ataxia, dizziness, dyspepsia, palpitation and somnolence. This subject was a 63 y.o. Indian male with history of multiple fractures and removal of right patella . He had a current history of hyperlipidemia and hypertension for which he was receiving Lipitor and Zestril, respectively. The events resolved within at least 13 days and may have been drug-related. There was no indication of the duration of the abnormal laboratory values. These events are not unexpected and are included in the current labeling for Paxil®.

There were a total of 5 paroxetine treated subjects and 2 placebo treated subjects meeting PCC criteria on values for HgB and/or HCT. The paroxetine treated subjects had either low normal or abnormally low HgB and/or HCT levels at baseline or at screening and several subjects had pre-existing conditions that could potentially account for their anemia.

There were no reported serious adverse events or adverse dropouts among paroxetine patients due to HgB and/or HCT levels meeting PCC criteria, except for one subject. The one exception was subject 637.012.03615 who was a 57 y.o. white female with current history or menorrhagia and a low normal HCT level at baseline (35.2% with 35-46% within normal limits). The HCT decreased to 31.6% on Day 7. The study drug was stopped on Day 4 because of mild nausea, severe tinnitus and moderate tremor, which resolved with 4-8 days. These events may have been drug-related, but they are not unexpected and are described in various sections in the labeling for Paxil®. However, the anemia may be attributed to a pre-existing mild anemia associated with menorrhagia. Therefore, it is not likely that the low HCT levels were drug-related.

The reported percentage of paroxetine and placebo treated subjects having an AE "related to the hematological assessments" was 1.4% (10 subjects) and 1.1% (6 subjects) in each treatment group, respectively. These AE's included anemia, leukocytosis, leukopenia, lymphadenopathy, monocytosis, purpura, increase bleeding time, thrombocytopenia which occurred in 0 to 1 subjects in each treatment group with the exceptions of purpura (1 placebo and 2 paroxetine treated subjects) and anemia (1 placebo and 3 paroxetine subjects).

The sponsor provided laboratory transition tables. These summary tables provide results on the number of subjects showing a change (decrease or increase) or no change from baseline to

week 8 or study endpoint for each laboratory parameter. This enumeration is provided for each time-point during the study in which laboratory parameters for a given time-point are categorized as low, intermediate, or high relative to the normal reference range.

Based on visual inspection of the sponsor's transition tables, the Paroxetine and Placebo treatment groups showed similar percentages of subjects (ranging from 2 to 3%) transitioning from a higher category (high or intermediate level) to a lower category (intermediate or low) on various hematological parameters (HgB, HCT, RBC and WBC). The denominators for these percentages were the total number of subjects with transition results provided in each treatment group. Hence, these results show that treatment groups were similar in the frequency of subjects that showed a decrease (based on categorical data) in hematological parameters during treatment. Similar results were obtained for platelet counts in each treatment group in which 0.6% or less subjects decreased from baseline to week 8 or study endpoint. An increase in eosinophils (cells/l) was observed in 1.5% and 1.9% of placebo subjects at weeks 8 and study endpoint and in 2.5% and 2.0%, respectively of paroxetine subjects. One of these placebo subjects met PCC criteria, while 4 paroxetine subjects met PCC criteria. The maximum level of eosinophils among these 4 paroxetine subjects was 13% in subject 641.118.0085 who is described above.

Renal Function and Electrolyte Parameters: Potassium was the only electrolyte found to meet PCC criteria, which occurred in only 1 paroxetine subject (641.146.02209) in which the level increased from baseline to Day 59 by approximately 2-fold. Another paroxetine subject (637.062.03804) also had markedly elevated potassium, Cr and mildly elevated BUN. However, the sample from this subject was hemolyzed, according to the sponsor as indicated in a fax dated 8/31/00. A total of 6 Paroxetine treated subjects and 4 placebo treated subjects met PCC criteria for BUN and/or creatinine (these numbers include the paroxetine subject with the non-hemolyzed sample showing an elevated potassium level). The BUN levels in 2 of the 4 placebo treated subjects showed an increase from baseline to Week 8, upon visual inspection of the data, while Cr levels failed to show in any increase in any of these 4 subjects. These subjects failed to show BUN levels exceeding 12.5 umol/l, while 3 paroxetine treated subjects meeting PCC criteria showed marked elevations in either BUN or Cr (approximately a 3 to 4 fold increase from baseline). These paroxetine subjects are described in a separate subsection, below.

As determined from the transition laboratory tables (Table 7.6 in the submission), the paroxetine and placebo groups showed similar percentages of subjects (less that 1%) with an increase in Cr or potassium levels from baseline to week 8 or study endpoint. The percentages of subjects with an increase in BUN levels in the paroxetine and placebo groups were 2.4% and 1.6%, respectively, at week 8 and 2.5% and 1.7%, respectively, at study endpoint. Only 1 of these placebo subjects met high PCC criteria, while 4 of the paroxetine subjects met high PCC values, as indicated in the laboratory transition tables. **There were no SAE's or adverse dropouts associated with renal function and/or electrolyte parameters meeting PCC criteria.**

Description of Individual Paroxetine Subjects:

Subject 641.133.01610 was a 40 y.o. Hispanic male with history of enlarged prostate who also exhibited marked elevation of Cr levels from 88.4 umol/l (within normal limits) at baseline to 353.6 umol/l on Day 56 of treatment. The investigator reported the elevated Cr as an AE and the patient was described as having "completed the study as planned". The narrative did not provide any other pertinent information. It is not clear why this subject was included in the study given the abnormal baseline Cr level. Although, in response to an inquiry from this reviewer, the

sponsor reported (in a fax dated 8/31/00) that the creatinine level had normalized on a follow-up evaluation on Day 70. The investigator reported the mild elevation in ALT (noted above) "as not being clinically significant."

Subject 641.132.01559 is a 30 y.o white female which showed a marked increase in Cr and BUN from baseline levels (88.4 umol/l and 3.6 mmol/l, respectively which are within normal limits) to levels of 265.2 umol/l and 14.3 mmol/l, respectively on Day 60 of treatment. The potassium level of this patient was also increased from baseline (within normal limits: 3.5-5.3 mmol/l) to Day 60 of treatment (6.0 mmol/l). The narrative indicates that baseline WBC was elevated at $13x10^{9th}$ cells/l (3.8-10.8 within normal limits) and the subject had a history of bronchitis and was being treated with Biaxin for a "throat infection". Other concomitant medications included Percocet, Relafen, triple lesitan and Keflex (for carbuncles). The patient also has a history of gastritis, laparoscopy (exploratory), benign breast cyst and migraine. No other pertinent information was provided and the patient was reported to have completed the study as planned. However, in a fax dated 8/31/00 the sponsor indicated that all laboratory parameters that had been abnormal on Day 60, as described above, were within normal range on follow-up Day 63.

4 other paroxetine treated subjects (642.227.04466, 641.110.0045, 637.099.03861 and 126.01258) also showed an increase in their BUN levels from baseline (which were within normal limits ranging from 5.0 to 7.1 mmol/l) to a mildly elevated level (ranging from 11.1 to 11.8 mmol/l) after 42 to 59 days of treatment. These subjects are briefly described, as follows. The one subject completing only 42 days of treatment withdrew from the study because of a "lack of efficacy" and had no reported AE's. This subject was a 44 y.o. who also had mild anemia and a WBC of $3.0x10^{9th}$ cells/l on Day 42 of treatment. One of the other subjects who showed a 2-fold increase in BUN levels (5.0 mmol/l at baseline to 11.8 mmol/l on Day 67) was a 28 y.o. healthy female on Advil for headaches with an unremarkable medical history. The third subject was a 73 y.o with no concomitant medications and no reported AE's. The final subject was a 53 y.o. with history of skin cancer and sinus infection who had a slightly elevated AST level at screening that did not meet PCC criteria.

Subject 641.146.02209 was a 22 y.o. Asian female with no reported AE's. This subject showed a marked increase in potassium from baseline (4.0 mmol/l) to Day 59 of treatment (8.0 mmol/l). The narrative does not provide any other pertinent information and does not indicate if any AE's were associated with this laboratory finding or provide any follow-up status. In response to an inquiry about this subject, the sponsor reported (in a fax dated 8/31/00) that a follow-up laboratory evaluation conducted on Day 63 (14 days after treatment cessation) revealed a potassium level within normal limits (4.2 mmol/l). The sponsor also reports that the narrative indicates that "no adverse experiences were associated with these findings". There was no indication from the 8/31/00 fax from the sponsor that the Day 59 blood sample was hemolyzed.

Because of the above abnormalities regarding renal function, this reviewer examined reviews of previous supplemental NDA's and the initial NDA regarding any reports of renal impairment. However, this examination of previous clinical reviews failed to yield any remarkable findings that would merit changing the labeling of the Paxil®, regarding renal function, from that which already exists. Furthermore, a search was conducted on the AERS database on Paxil® for "renal failure", "renal impairment", and "hyperkalemia". This search revealed 27 cases since the time that the drug was approved for treatment of depression

(12/29/92). These results fail to provide any remarkable findings that would require a change in the labeling for Paxil®.

Liver function tests: 8 paroxetine treated subjects and 1 placebo treated subject met PCC criteria for at least one liver function parameter. 4 of subjects (subjects: 637.055.03668, 637.099.03849, 641.131.01517, 641.121.01002) from the paroxetine groups meeting PCC criteria for high bilirubin levels on Day 42 to 56 of treatment onset also had abnormal bilirubin levels at baseline, several of which met PCC criteria at baseline. It is not clear why these subjects were in the study, other than that the investigator(s) noted on the CRF's "that no clinically significant laboratory abnormalities were detected which would necessarily preclude the patient's entry into the study" (per fax from sponsor dated 8/31/00). In several subjects their bilirubin decreased during the treatment phase, although the levels met PCC criteria. Subject 641.131.0157 showed a bilirubin level within normal limits on a follow-up visit on Day 73 (per fax from sponsor dated 8/31/00). The bilirubin level of subject 641.121.01002 which increased to 51.3 umol/l at study endpoint was "comparable to the level at screening visit" and not considered to be clinically significant or to require further evaluations, as reported by the sponsor (fax dated 8/31/00). Two subjects (641.131.01503, 641.131.0150) receiving paroxetine showed a markedly elevated ASP on Day 21 or AST level on Day 56 of the treatment phase, respectively. However, the former subject reportedly consumed "a lot of alcohol" on the previous night according to the CRF, while the latter subject had a history of elevations in AST levels. Therefore, the observed liver function tests meeting PCC criteria among these 6 subjects are not likely to be drug-related but rather due to pre-existing conditions/disorders.

Two subjects (637.058.03692 and 637.058.03720) had elevated bilirubin levels (35 umol/l with 0-22 umol/l within normal limits) meeting PCC criteria on Days 10 and 58, respectively, after treatment onset of paroxetine. It is not certain if the bilirubinemia in these subjects were drug-related, since baseline levels were within normal limits (20 and 10 umol/l, respectively) and pre-existing conditions that could account for these abnormal laboratory parameters were not described in the narratives. These two subjects are described below. Subject 637.058.03692 had an AE leading to cessation of the study drug on Day 3 of the treatment phase in which the subject had experienced an "allergic reaction" for 2 days which was treated with Zyrtec®. The abnormal bilirubin level meeting PCC criteria was observed on Day 10 (7 days later) along with slightly elevated AST and ALT levels that did not meet PCC criteria. It is not clear if whether these abnormal laboratory values were associated with the allergic reaction experienced by the patient or some other potentially drug-related event. No pertinent details could be found in the narrative or the CRF of this subject. However, the patient is reported to have refused a follow-up evaluation (per sponsor in a fax dated 8/31/00)

The other above mentioned subject (637.058.03720) with the abnormal bilirubin level on Day 58, is a 42 y.o. WM with a current medical history that includes back pain and a past history of herniated disc who experienced "moderate back pain" on Day 54 of paroxetine treatment (4 days before his blood chemistries were drawn). The back pain was described as "acute lumbago" per a fax from the sponsor dated 8/31/00. The back pain lasted 3 days and was treated with myolastan® (a benzodiazapine) and voltarene® (an NSAID). According to a fax from the sponsor (dated 8/31/00), "follow-up laboratory studies were not required" according to the investigator.

There were two adverse dropouts and no SAE's reported in subjects with liver function tests meeting PCC criteria. One adverse drop out (subject 641.058.03692) had abnormal liver function test values and an AE "allergic reaction" that was reported to be the

reason for cessation of the study drug and is described above. The other adverse dropout (subject 641.131.01503) was reported to be due to impotence after 10 days of treatment, which continued for a period of 9 days. This subject also had elevated liver function tests revealed on Day 21 of treatment that was likely alcohol related, as described above. If the patient was consuming alcohol, impotence may also have not been drug-related. According to the submission there were 4 (0.5%) paroxetine patients and no placebo patients with AE's associated with abnormal laboratory values on liver function tests (elevations in bilirubin, SGOT, and/or SGPT among paroxetine patients.

Based on results from the transition laboratory tables 0.5% of placebo subjects and 2.1% of paroxetine subjects showed an increase in ALT levels at week 8 and 2.4% and 4.8% of placebo and paroxetine subjects, respectively, showed an increase in AST levels. Similar results were observed at study endpoint for these parameters. However, treatment groups were similar in the percentage of subjects with an increase in Alkaline phosphatase levels (approximately 0.5% of paroxetine subjects) and total bilirubin levels (approximately 1% in paroxetine subjects) at week 8 and study endpoint. Three of the paroxetine subjects and one placebo subject described in this paragraph met PCC criteria. Paxil® labeling includes "infrequent" increases in various liver enzyme levels, and "rare" increases in bilirubin levels based on results of the premarketing assessment of the drug.

8.1.7 Vital Signs

8.1.7.1 Analysis of Central Tendency

Table 8.1.7.A.(in the appendix) shows results on the mean baseline and mean change from baseline to endpoint on vital sign variables and weight for the paroxetine and placebo groups for the three studies combined. Treatment groups were similar in the mean change from baseline to endpoint on each vital sign parameter and on weight. The magnitude in the observed mean changes per treatment group was less than 2 units for each vital sign parameter. These mean changes were within the normal range and were not clinically significant. The mean changes in weight in the paroxetine and placebo groups (–0.1±2.3 kg and 0.2±1.9 kg, respectively) are not clinically significant.

8.1.7.2 Analysis of Outliers

Criteria for PCC for vital signs and weight changes are provided in Table 8.1.4.B. in the appendix. A summary table enumerating outliers based on PCC criteria is provided in Table 8.1.7.B. in the appendix. As shown in this table the percentage of outliers in each treatment group was no greater than 1% for each category except for weight in which the paroxetine group showed an incidence of 1.5% outliers in the high category and 1.7% in the low category. In the placebo group 1% of subjects were in each of the high and low categories for weight. There were no clinically significant group differences in the percentage of outliers.

There were 4 adverse dropouts and one SAE among subjects meeting PCC for vital signs and weight changes and are described in this section. One adverse dropout was on subject 637.018.03330 who met the criterion for low systolic blood pressure (89 mmHg after Day 7 from the start date of the study drug, with baseline sysBP of 100 mmHg). This 75 year old male had current history of diabetes mellitus, congestive heart disease among other illnesses, who developed "severe vomiting" on Day 1 of treatment which lasted 4 days resulting in withdrawal from the study. It is not clear if the low blood pressure was associated with dehydration, an exacerbation of the patient's underlying congestive heart disease or some other cause. The sponsor indicated (in a fax dated 8/31/00) that the heart rate obtained at the time the blood pressure was 89/65 mmHg (on Day 7 or 4 days after the vomiting ceased and while off

treatment), was unchanged from that observed at screening. The sponsor also indicated that the laboratory parameters at screening and at withdrawal were "all ok".

The adverse dropout that was also considered a SAE was a subject 641.150.02452 who was involved in a motor vehicle accident (hit by another driver) who also met PCC criterion for a decrease in weight. These events were not likely to be drug-related. The two other adverse dropouts were subjects (641.140.1959and 641.107.00314) meeting PCC criteria for decreased weight who experienced asthenia and tremor, respectively as adverse events resulting in their withdrawal from the study. The final adverse dropout occurred in subject 641.146.02207 who met PCC criteria for high systolic blood pressure, withdrew from the study because of gingivitis. These adverse events are included in the Paxil® labeling.

The percentages of post randomization AE's associated with hypertension, hypotension or syncope were no more than 0.5% in each treatment group. However, one cardiovascular event, vasodilatation was reported in paroxetine subjects at a rate of over twice that of controls (incidence of 2.7% compared to 0.8%). The percentages of AE's associated with arrhythmia, bradycardia, palpitations or tachycardia were no more than 1.1% in each treatment group. The incidences of weight gain or loss reported as AE's did not exceed 0.6% in each treatment group.

9.0 Labeling Review

The major proposed labeling changes regarding efficacy for Paxil® (tablets and oral suspension) include the following:

- An additional pharmacodynamic property of Paxil® is an "anxiolytic action" as follows (the proposed additions are indicated by underlined text):

- Under the "Clinical Trials" section of the proposed labeling the sponsor indicates "the

- Under the "Indications and Usage" se

Based on the sponsor's results described in the submission, Studies 641 and 642 support the efficacy claim of Paxil® for the treatment of GAD.

10.0 Conclusions

Two of three studies, Studies 641 and 642, revealed significant treatment group effects on the primary efficacy variable, based on the results provided in the submission. This conclusion was confirmed by a statistical analysis of the sponsor's raw data conducted by the Biometrics review Dr. Kallapa Koti.

11.0 Recommendations

Supplement SE 1-026 is approvable based on the support of Studies 641 and 642.

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

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K Brugge
A Homonnay
T Laughren

Appendix 1

Table 7.1.1.A. Investigators and Sites for Study 641, as provided by the sponsor.			
Center No.	**Investigator**	**Affiliation/ Address**	**State**
USA			
101	Mohammed Bari	MD Synergy Clinical Research	Chula Vista, CA
102	David Beck	MD University of Missouri - Columbia,	Columbia, MO
		Department of Psych/ Neuro	
103	Robert Birnbaum	MD Beth Israel Deaconess Medical Center, Boston, MA	
		Department of Psychiatry	
104	William Burke	MD University of Nebraska Medical	Omaha, NE
		Center, Psychopharmacology Research	
		Center	
105	Bruce Cohen	MD University of Virginia Health Sciences	Charlottesville,
		Center, Center for Psychiatric Clinical	VA
		Research	
106	Pedro Delgado	MD University of Arizona Health Sciences	Tucson, AZ
		Center, Department of Psychiatry,	
		70pc, Room 7402	
107	Eugene Du Boff	MD Denver Center for Medical Research	Denver, CO
108		James Mecham Ferguson MD Pharmacology Research Corporation	Salt Lake City,
			UT
109	William Gilmer	MD Northwestern University	Chicago, IL
110	Wayne Goodman	MD University of Florida College of	Gainesville, FL
		Medicine	
111	Laszlo Papp	MD Columbia University	New York, NY
112	Jon F. Heiser	MD Pharmacology Research Institute	Irvine, CA
113	Francis Haines	MD Clinical Studies Providence	East Providence,
			RI
114	Barbara Kennedy	MD University of Louisville, Department	Louisville, KY
		of Psychiatry and Behavioral Sciences,	
		Ambulatory Care Building	
115	Arifulla Khan	MD Northwest Clinical Research Center	Bellevue, WA
116	Lorrin Koran	MD Stanford University Medical Center,	Stanford, CA
		Department of Psychiatry	
117	Ronald Landbloom	MD Regions Hospital, Department of	St. Paul, MN
		Behavioral Health	
118	Sidney Lerfald	MD Suite 306, 415 Morris Street	Charleston, WV
119	Michael Liebowitz	MD The Medical Research Network, Llc	New York, NY
120	James Hartford	MD Cincinnati Medical Research Institute	Cincinnati, OH
121	Lucy Puryear	MD Baylor College of Medicine,	Houston, TX
		Department of Psychiatry	
122	Denis Mee - Lee	MD Hawaii Clinical Research Center	Honolulu, HI
123	Matthew Menza	MD Robert Wood Johnson Medical School, Piscataway, NJ	
		Department of Psychiatry	
124	Charles Merideth	MD Affiliated Research Institute	San Diego, CA
125	Kevin Miller	MD St. Louis University Health Sciences	St. Louis, MO

		Center	
126	Charles Nemeroff	MD Emory University School of Medicine	Atlanta, GA
127	Julie Oldroyd	MD The Irvine Clinical Research Center	Irvine, CA
128	Teresa Pigott	MD University of Texas Medical Branch at Galveston, TX	
129	Charles Ravaris	MD Darmouth Hitchcock Medical Center,	Lebanon, NH
		Department of Psychiatry	
130	Karl Rickels	MD Hospital of the University of	Philadelphia, PA
		Pennsylvania	
131	Robert Riesenberg	MD Biobehavioral Atlanta	Decatur, GA
132	Howard Schwartz	MD Miami Research Associates	Miami FL
133	Leslie Seiden	MD 133 East 91st Street	New York, NY
134	Hope Selamick	MD Temple University, Department of	Philadelphia, PA
		Psychology	
135	Anantha Shekhar	MD Indiana University School of Medicine Indianapolis, IN	
136	Jeffrey Simon	MD Northbrooke Research Center	Brown Deer, WI
137	Karen Weihs	MD George Washington University	Washington, DC
138	Richard Weisler	MD 900 Ridgefield Drive, Suite 320	Raleigh, NC
139	Kenneth Weiss	MD Delaware Valley Research Associates	King of Prussia,
		Inc.	PA
140	Andrew Winokur	MD Dartmouth- Hitchcock Medical Center	Labanon, NH
141	Dan Zimbroff	MD Pacific Clinical Research Medical	Upland, CA
		Group	
142	John Zwerneman	MD Health Advance Institute	South Bend, IN
143	David Brown	MD Community Clinical Research Inc.	Austin, TX
150	Rudolf Hoehn- Saric	MD 4303 North Charles Street	Baltimore, MD
Canada			
144	Jacques Bradwejn	MD Royal Ottawa Hospital	Ottawa, Ontario
145	Stanley Kutcher	MD Queen Elizabeth II Health Sciences	Halifax, Nova
		Centre	Scotia
146	Anthony Levitt	MD Sunnybrook Health Sciences Centre	Toronto, Ontario
147	Franscisco Jose Pinero-	MD Centre Universitaire en Sante de	Sherbrooke,
	Medina	l'Estrie	Quebec
148	Pierre Savard	MD Universite de Montreal	Montreal,
			Quebec
149	Richard Swinson	MD McMaster University, Dept. of	Hamilton,
		Psychiatry and Behavioral Neuro-	Ontario
		sciences	

Table 7.1.1.B. Study 642: Investigators, the SB Assigned Center Number and the Investigator Hospital or University Affiliation and Location (as provided by the sponsor)

Investigator	Center	Affiliated Institution	City	State
United States				
Apter, Jeffrey M. D.	201	Princeton Biomedical Research, P. A.	Princeton	NJ
Bakhtiar, Parvaneh M. D.	202	Lovelace Scientific Resources, Inc. (LSR) Albuquerque		NM
Carman, John M. D.	203	Carman Research	Smyrna	GA
Croft, Harry M. D.	204	The Croft Group Inc.	San Antonio	TX
Cunningham, Lynn M. D.	205	Vine Street Clinic	Springfield	IL
DePriest, Michael M. D.	206	Pharmacology Research Clinic	Las Vegas	NV
Taylor, Leslie M. D.	207	Dean Foundation for Health, Research & Education	Middleton	WI
Goddard, Andrew M. D.	208	Yale Anxiety Clinic	New Haven	CT
Holland, Peter M. D.	209	7280 W. Plametto Park Road, Ste. 203, N	Boca Raton	FL
Hollander, Eric M. D.	210	Mount Sinai School of Medicine	New York	NY
Houck, Carl M. D.	211	University of Alabama	Birmingham	AL
Kang, Jasbir M. D.	212	Western Pennsylvania Psychiatric Center	Center Township	PA
Kiev, Ari M. D.	213	Social Psychiatry Institute	New York	NY
Taylor, David M. D.	214	UCSF Langley Porter Psychiatric Institute		CA
Melchor, Pedro M. D.	215	Pharm Research, Inc.	Miami	FL
Murphy, John M. D.	216	Southwestern Research Institute	Beverly Hills	CA
Pollack, Mark M. D.	217	Massachusetts General Hospital- Psychiatry Boston		MA
Rosenthal, Murray M. D.	218	Behavioral Medicine Resources	San Diego	CA
Sheehan, David M. D.	220	University of South Florida	Tampa	FL
Stahl, Stephen M. D.	221	Clinical Neuroscience Research Center	San Diego	CA
Stein, Murray M. D.	222	University of California at San Diego	San Diego	CA
Stevens, Michael M. D.	223	Valley Mental Health	Salt Lake City	UT
Stewart, Rege M. D.	224	University of Texas Southwestern Medical Dallas School		TX
Tucker, Phebe M. D.	225	University of Oklahoma	Oklahoma City	OK
Lydiard, Bruce M. D.	230	Medical University of South Carolina	Charleston	SC
Maddock, Richard M. D.	234	University of California, Davis Medical Center	Sacramento	CA
Dietrich, Anthony M. D.	235	Five the Green	Woodstock	VT
Sambunaris, Angelo M. D.	236	Atlanta Institute of Medicine and Research Roswell		GA
Casat, Charles M. D.	237	Behavorial Health Center	Charlotte	NC
Canada				
Katzman, Martin M. D.	226	Clark Institute of Psychiatry	Toronto	Ont
Le Melledo, JM M. D.	227	University of Alberta, H Site	Edmonton	Alb
Reesal, Robin M. D.	228	Western Canada Behavioral Center	Calgary	Alb
Plamondon, Jacques M. D.	229	Centre Hospitalier U de Quebec	Laurier	Que
Saxena, Bishan M. D.	231	Hamilton Psychiatric Hospital	Hamilton	Ont
Goldner, Elliot M. D.	232	University of British Columbia	Vancouver	BC

Table 7.1.1.C. Study 637: Investigators, the SB Assigned Center Number and the Investigator Hospital or University Affiliation and Location (as provided by the sponsor)

Centre No.	Investigator	Affiliation/ Address	City
United Kingdom			
001	Dr Alun George	The Staploe Medical Centre	Ely
002	Dr Ian Parker	Comberton Surgery	Cambridge
003	Dr Katrina Young	St. Mary's Surgery	Ely
004	Dr Sally Barnard	Newnham Walk Surgery	Cambridge
006	Dr Andrew Smithers	The Surgery	Coventry
007	Dr Bhavesh Bodalia	Goodyers Lane End Surgery	Coventry
013	Dr Alun Jones	Talybont Surgery	Swansea
014	Dr Cosmo Hallstrom	Feighner Research Institute	London
016	Dr Martin Adler	Belmont Health Centre	Kenton
017	Dr Carol McKinnon	Castlemilk Health Centre	Glasgow
018	Dr William Carr	Leslie Surgery	Glenrothes
019	Dr William Aitchison	The surgery	Bridge of Weir
020	Dr Bryan Hopwood	The Burngreave Surgery	Sheffield
021	Dr Desmond Keating	Elm Lane Surgery 7	Sheffield
Ireland			
031	Dr Mary Belton	Town Hall Clinic, Town hall Centre	Co. Wicklow
032	Dr Donal O'Brien	Wilmer Road	Co. Offaly
033	Dr Paul Armstrong	Lifford Health Centre	Co. Donegal
035	Dr Christopher MacNamara	43 Harrington Street	Dublin
036	Dr Eamonn Kelly	The Surgery	Co. Wicklow
038	Dr Kevin Kelly	Emmet House Medical Centre	Co. Tipperary
040	Dr Stephen Murphy	The Park Clinic	Dublin
042	Dr Padraig McGarry	40 Ballymahon Street	Co. Longford,
043	Dr Charles Bourke	Health Centre	Co. Donegal
044	Dr Bernadette	O'Leary Medical Centre	Clonmel
045	Dr Alan Byrne	Scholarstown Family Practice	Dublin
France			
051	Dr Fabrice Buton	153 route de Vannes	Saint Herblain
052	Dr Jean- Marie Letzelter	7 quai Saint Jean	Strasbourg
054	Dr Nathan Abenhaim	35 Boulevard Tauler	Strasbourg
055	Dr Francois- Xavier Poudat	3 rue Marceau	Nantes
057	Dr Sami Atallah	6 rue Denave	Tarare
058	Dr Alain Campagne	81 rue Blaise Pascal	Tours
059	Dr Loic Boucher	25 rue V. Desormeaux	Murs Erigne
062	Dr Joel Gailledreau	Centre Medical Claude Bernard	Elancourt
Austria			
072	Dr Siegfried Kasper	Department of General Psychiatry, University Wahringer of Vienna	Gurtel
Germany			
071	Dr Frank Godemann	Psychiatrische Intensiv und Krisenintervention sstation	Berlin
074	Dr Bernhard Stahr	Felnbelliner Str. 28	Falkensee
075	Dr E. Geschke	Woltersdorfer Landstrasse 19	Eckner
076	Dr Otmar Desch	Steinstrasse 31	Berlin
077	Dr Hartmut Dorn	Grabenstrasse 41	Berlin
078	Dr Martin Schumann	Schonhauser Allee 83	Berlin

Table 7.1.1.C., continued.

Centre No.	Investigator	Affiliation/ Address	City
079	Dr Marion Gille	Fachargton Fur Innere Medigin Prenzlaver Allee 189	Berlin
080	Dr Ingrid Berndt	Muggelstrasse 28	Berlin
081	Dr Friedemann Cramer	Gross Ziethener Chaussee 16	Berlin
086	Dr Silvia Ost	Greifswalder Str 112	Berlin
088	Dr Peter Franz	Orankestrasse 84	Berlin
089	Dr Muzaffer Dilmac	Muskauer Strasse 24	Berlin
091	Dr Helmut Peter	Klinik fur Psychiatrie und Psychotherapie	Hamburg
092	Dr Katrin Bornkessel	Mandelstrasse 2	Berlin
097	Dr Ilona Weisshuhn	Bornholmerstrasse 2	**Berlin**
Italy			
099	Dr Giampietro	Casa Di Cura Villa Margherita Neurologia	Vicenza
	Nordera		

Table 7.1.2 Assessment Schedule for Studies 641, 642*, 637**

	Scrn Visit Day -1	Base-Line Visit Day 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Early W/D	Taper Interim Visit	Taper End Visit	14-Day Study F/U[c]	28-day Study F/U[g]
Screen/Baseline Evaluations													
General Patient Information	X												
MINI	X												
Psychoactive Med. History	X												
Psych Inter./Mental Status	X												
Medical/Surgical History	X												
GAD Criteria (DSM-IV)	X												
ECG Record	X	X[d]											
Inclusion/Exclusion Criteria	X	X											
Patient Randomization		X											
Informed Consent	X												
Efficacy Parameters													
HAM-A	X	X	X	X	X	X	X	X	X				
CGI (Severity of Illness)		X	X	X	X	X	X	X	X				
CGI (Global Improvement)			X	X	X	X	X	X	X				
HAD		X	X	X	X	X	X	X	X				
COVI Anxiety Scale		X				X		X	X				
Sheehan Disability Scale (SDS)		X				X		X	X				
MADRS	X	X						X	X				
Job Employment Status		X											
Job Attendance			X	X	X	X	X	X	X				
Quality of Life (EuroQol)		X						X	X				
Safety Evaluations													
Vital Signs	X	X[b]						X	X	X[b]	X[b]	X[b]	X[b]
Body Weight	X[h]							X	X				
Adverse Experience Monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluation	X	X[a]						X	X	X[a]	X[a]	X[a]	X[a]
Urine Benzodiazepine Screen	X							X	X				
Physical Examination	X												
Serum Pregnancy Test	X[e]												
Miscellaneous Records													
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication	X	X	X	X	X	X	X	X[f]	X[f]	X[f]			
Study Medication Record		X	X	X	X	X	X	X	X	X	X		
Study Termination Record								X	X				

a Laboratory Evaluation to be performed if clinically significant values are noted at a previous visit. Laboratory evaluations were: Hematology (hemoglobin, hematocrit, WBC with differential, RBC, and platelet count); blood chemistry (creatinine, BUN, total bilirubin, alkaline phosphatase, SGPT[ALT], SGOT[AST], electrolytes, TSH, T_3, T_4 [thyroid tests at Screening Visit only]; dipstick urinalysis (if positive for blood or protein, full microscopy was performed).

b Repeat vital signs were done if results at previous visit are clinically significant.

c Follow-up Visit was completed 14 days following last dose of study medication for all patients.

d ECG to be done if results at Screening Visit were abnormal. Results of repeat evaluation were to be interpreted before patient randomization.

e For women of child-bearing potential only

f Taper medication dispensed for all eligible patients.

g F/U Visit to be scheduled within 28 days of last study medication dose for all patients with adverse experiences at 14-Day F/U Visit.

h Height was measured also.

Data source: Protocol, Appendix A.

* An additional visit was included in the protocol for Study 642, which occurred on Week 5 of Treatment. Assessments on this visit were the same as those conducted on Week 6 of Treatment. A Taper Interim Visit was not included in the protocol for this study.

** In Study 637, an alcohol breath test was not performed at screening. While body weight and height were obtained at screening, these parameters were not monitored over time.

Table 7.1.3 A Study 641: Summary of Baseline and Change from Baseline (Least Square Means) at Weekly Intervals HAM-A Total, by Treatment Group (ITT Efficacy Population)†

	Placebo			Paroxetine					
				20 mg			40 mg		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Baseline	180	23.9	0. 3	188	23.8	0. 3	197	23.3	0. 3
LOCF									
Wk 1	178	-4. 9	0.4	187	-4. 6	0.4	195	-4. 7	0.4
Wk 2	180	-7. 9	0.5	188	-7. 8	0.5	197	-7. 3	0.5
Wk 3	180	-9. 2	0.5	188	-9. 4	0.5	197	-9. 5	0.5
Wk 4	180	-9. 8	0.6	188	-10.7	0. 5	197	-10.8	0. 6
Wk 6	180	-9. 9	0.6	188	-12.1**	0. 6	197	-11.7*	0. 6
Wk 8	180	-9. 6	0.7	188	-12.5***	0. 6	197	-12.2**	0. 6
OC									
Wk 1	178	-4. 9	0.4	187	-4. 6	0.4	195	-4. 7	0.4
Wk 2	168	-7. 9	0.5	174	-8. 0	0.5	183	-7. 6	0.5
Wk 3	160	-9. 6	0.5	163	-9. 9	0.5	170	-10.4	0. 5
Wk 4	160	-10.1	0. 6	157	-11.3	0. 6	164	-11.4	0. 6
Wk 6	147	-10.3	0. 6	149	-13.1***	0. 6	151	-13.3***	0. 6
Wk 8	140	-10.7	0. 7	141	-13.8***	0. 6	146	-13.9***	0. 6

† Results shown in this table are those provided in Table 12, on page 54 of the Integrated Summary of Safety in the submission.
*p<0.025, **p<0.01, *** p<0.001

Table 7.1.3 B Study 642: Summary of Baseline and Change from Baseline (Least Square Means) at Weekly Intervals HAM-A Total, by Treatment Group (ITT Efficacy Population) , similar to that provided by the sponsor.

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	N	Mean	SEM	N	Mean	SEM	Diff (CI)+	p- val
Baseline	163	23.6	0. 3	161	23.9	0. 3	0.3 (- 0. 5, 1.0)	0.472
LOCF								
Wk 1	160	-3. 8	0.4	159	-3. 9	0.4	-0.1 (- 1. 0, 0.9)	0.850
Wk 2	163	-6. 2	0.5	161	-6. 6	0.5	-0.4 (- 1. 5, 0.7)	0.479
Wk 3	163	-7. 1	0.5	161	-8. 2	0.5	-1.1 (- 2. 4, 0.2)	0.089
Wk 4	163	-8. 1	0.6	161	-9. 0	0.6	-0.9 (- 2. 3, 0.5)	0.190
Wk 5	163	-9. 3	0.6	161	-10.4	0. 6	-1. 1 (- 2. 6, 0.3)	0.127
Wk 6	163	-9. 6	0.6	161	-11.3	0. 7	-1. 6 (- 3. 2, -0. 1)	0. 041*
Wk 8	163	-9. 5	0.7	161	-11.8	0. 7	-2. 3 (- 4. 0, -0. 6)	0. 008*
OC								
Wk 1	160	-3. 8	0.4	159	-3. 9	0.4	-0.1 (- 1. 0, 0.9)	0.850
Wk 2	152	-6. 7	0.5	147	-7. 0	0.5	-0.3 (- 1. 5, 0.8)	0.576
Wk 3	146	-7. 8	0.6	134	-8. 8	0.6	-1.0 (- 2. 4, 0.3)	0.143
Wk 4	146	-8. 6	0.6	130	-9. 7	0.7	-1.1 (- 2. 6, 0.4)	0.155
Wk 5	141	-10.2	0. 7	135	-11.4	0. 7	-1. 2 (- 2. 7, 0.4)	0.141
Wk 6	140	-10.4	0. 7	132	-12.1	0. 7	-1. 8 (- 3. 4, -0. 2)	0. 032*
Wk 8	133	-10.7	0. 8	127	-13.3	0. 8	-2. 5 (- 4. 3, -0. 7)	0. 006*

+Differences in adjusted (Least Square) means; 95% CI used
*Significance for p< 0.05

Table 7.1.3 C Study 637: Summary of Baseline and Change from Baseline (Least Square Means) at Weekly Intervals HAM-A Total, by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	n	Mean	SE	n	Mean	SEM	Diff (CI)+	p- val
Baseline	183	25.9	0. 4	181	26.0	0. 4	0.1 (-0.7, 1.0)	0. 788
LOCF								
Wk 1	182	-4. 5	0.6	179	-4. 0	0.6	0. 5 (-0. 7, 1.7)	0. 396
Wk 2	183	-6. 3	0.7	181	-7. 5	0.7	-1.1 (-2.5, 0.3)	0. 114
Wk 3	183	-7. 0	0.7	181	-8. 1	0.7	-1.1 (-2.6, 0.4)	0. 141
Wk 4	183	-9. 3	0.8	181	-10.1	0. 8	-0. 8 (-2. 4, 0.8)	0. 329
Wk 6	183	-9. 8	0.8	181	-11.1	0. 8	-1. 3 (-2. 9, 0.3)	0. 111
Wk 8	183	-11.3	0. 8	181	-12.4	0. 8	-1. 1 (-2. 8, 0.5)	0. 171
OC								
Wk 1	182	-4. 5	0.6	179	-4. 0	0.6	0. 5 (-0. 7, 1.7)	0. 396
Wk 2	176	-6. 2	0.7	165	-8. 0	0.7	-1.9 (-3.3, -0. 5)	0.010*
Wk 3	168	-7. 6	0.8	149	-9. 5	0.8	-1.9 (-3.5, -0. 4)	0.016*
Wk 4	164	-10.0	0. 8	150	-11.6	0. 8	-1. 6 (-3. 3, 0.1)	0. 059
Wk 6	167	-10.3	0. 8	155	-13.1	0. 8	-2. 7 (-4. 3, -1. 1)	0.001*
Wk 8	163	-12.5	0. 8	149	-14.8	0. 8	-2. 3 (-3. 9, -0. 7)	0.005*

*Significant for p < 0.05
+Differences in adjusted (Least Square) means

Table 7.1.4 A Study 641: Summary of Baseline and Mean Change from Baseline (Least Square Means) on the COVI Anxiety Scale at Each Visit and by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo			Paroxetine					
				20 mg			40 mg		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Baseline	163	9.3	0. 1	173	9.4	0. 1	179	9.2	0. 1
LOCF									
Wk 4	162	-2. 4	0.2	172	-2. 7	0.2	176	-2. 7	0.2
Wk 8	163	-2. 3	0.2	173	-3. 3 *	0.2	179	-3. 2 *	0.2
OC									
Wk 4	159	-2. 5	0.2	156	-2. 9	0.2	160	-2. 8	0.2
Wk 8	140	-2. 6	0.2	141	-3. 7 *	0.2	144	-3. 5 *	0.2

*p<0.001 when compared to the placebo group

Table 7.1.4 B Study 642: Summary of Baseline and Mean Change from Baseline (Least Square Means) on the COVI Anxiety Scale at Each Visit and by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	N	Mean	SEM	N	Mean	SEM
Baseline	155	9.3	0. 1	152	9.3	0. 1
LOCF						
Week 4	146	-2. 1	0.2	132	-2. 4	0.2
Week 8	155	-2. 5	0.2	152	-3. 1	0.3
OC						
Week 4	140	-2. 2	0.2	115	-2. 6	0.3
Week 8	133	-2. 8	0.3	125	-3. 5*	0.3

*p<0.05 compared to placebo

Table 7.1.4 C Study 637: Summary of the Mean Change on the COVI Anxiety Scale Relative to Baseline at Each Visit and by Treatment Group : ITT Population, similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	n	Mean	SEM	n	Mean	SEM
Baseline	178	8.8	0. 2	175	9.1	0. 2
LOCF						
Week 4	178	-2. 0	0.2	172	-2. 5	0.2
Week 8	178	-2. 6	0.3	175	-3. 1	0.3
OC						
Week 4	163	-2. 1	0.3	147	-2. 6	0.3
Week 8	163	-2. 9	0.3	149	-3. 5*	0.3

P<0.05 compared to placebo

Table 7.1.5 A Study 641: Summary of Responders of the Hamilton Anxiety Rating Scale (HAM- A) Total </= 10 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo			Paroxetine					
				20 mg			40 mg		
	n	N	%	N	N	%	N	N	%
LOCF									
Wk 1	6	178	3.4%	9	187	4.8%	6	195	3.1%
Wk 2	26	180	14.4%	28	188	14.9%	30	197	15.2%
Wk 3	45	180	25.0%	44	188	23.4%	60	197	30.5%
Wk 4	51	180	28.3%	63	188	33.5%	81	197	41.1%
Wk 6	58	180	32.2%	86	188	45.7%*	94	197	47.7%*
Wk 8	59	180	32.8%	92	188	48.9%*	102	197	51.8%**
OC									
Wk 1	6	178	3.4%	9	187	4.8%	6	195	3.1%
Wk 2	25	168	14.9%	27	174	15.5%	30	183	16.4%
Wk 3	43	160	26.9%	40	163	24.5%	58	170	34.1%
Wk 4	49	160	30.6%	56	157	35.7%	71	164	43.3%
Wk 6	53	147	36.1%	77	149	51.7%*	81	151	53.6%*
Wk 8	56	140	40.0%	79	141	56.0%*	88	146	60.3%**

*p<0.01, **p<0.001 when compared to controls
n= number of responders, N= total number of patients assessed

Table 7.1.5 B Study 641: Proportion of Responders Based on CGI Global Improvement Score of 1 or 2 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.

	Placebo			Paroxetine					
				20 mg			40 mg		
	n	N	%	n	N	%	n	N	%
LOCF									
Wk 1	14	178	7.9%	14	187	7.5%	19	195	9.7%
Wk 2	35	180	19.4%	41	188	21.8%	47	197	23.9%
Wk 3	62	180	34.4%	77	188	41.0%	91	197	46.2%*
Wk 4	70	180	38.9%	93	188	49.5%	111	197	56.3%***
Wk 6	79	180	43.9%	111	188	59.0%**	130	197	66.0%***
Wk 8	82	180	45.6%	116	188	61.7%**	134	197	68.0%***
OC									
Wk 1	14	178	7.9%	14	187	7.5%	19	195	9.7%
Wk 2	34	168	20.2%	39	174	22.4%	44	182	24.2%
Wk 3	58	160	36.3%	71	164	43.3%	87	170	51.2%**
Wk 4	68	160	42.5%	84	157	53.5%	100	164	61.0%***
Wk 6	69	147	46.9%	97	149	65.1%**	114	151	75.5%***
Wk 8	73	140	52.1%	95	140	67.9%**	117	146	80.1%***

*p<0.025 **p<0.01, ***p<0.001 when compared to controls.
n= number of responders, N= total number of patients assessed

Table 7.2.1.A. Study 642: Summary of Responders of the Hamilton Anxiety Rating Scale (HAM-A) Total </= 10 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.†

	Placebo			Paroxetine		
	n	N	(%)	n	N	(%)
LOCF						
Wk 1	6	160	(3. 8)	2	159	(1. 3)
Wk 2	20	163	(12.3)	17	161	(10.6)
Wk 3	31	163	(19.0)	35	161	(21.7)
Wk 4	45	163	(27.6)	44	161	(27.3)
Wk 5	59	163	(36.2)	56	161	(34.8)
Wk 6	57	163	(35.0)	76	161	(47.2)*
Wk 8	61	163	(37.4)	88	161	(54.7)***
OC						
Wk 1	6	160	(3. 8)	2	159	(1. 3)
Wk 2	20	152	(13.2)	17	147	(11.6)
Wk 3	31	146	(21.2)	34	134	(25.4)
Wk 4	44	146	(30.1)	40	130	(30.8)
Wk 5	57	141	(40.4)	55	135	(40.7)
Wk 6	55	140	(39.3)	72	132	(54.5)**
Wk 8	58	133	(43.6)	81	127	(63.8)****

n= number of responders, N= total number of patients assessed

†Note that the following is different than that of previous tables: *p<0.05, **p<0.025, ***p.01, ****p<0.001 compared to controls using Student t-test. Significance for alpha=0.05, per sponsor.

Table 7.2.1.B. Study 642. Proportion of Responders Based on CGI Global Improvement Score of 1 or 2 at Each Visit by Treatment Group (ITT Efficacy Population), similar to that provided by the sponsor.†

	Placebo			Paroxetine		
	n	N	(%)	n	N	(%)
LOCF						
Wk 1	9	160	(5. 6)	10	159	(6. 3)
Wk 2	29	163	(17.8)	34	161	(21.1)
Wk 3	43	163	(26.4)	49	161	(30.4)
Wk 4	68	163	(41.7)	67	161	(41.6)
Wk 5	75	163	(46.0)	79	161	(49.1)
Wk 6	75	163	(46.0)	92	161	(57.1)*
Wk 8	77	163	(47.2)	100	161	(62.1) ***
OC						
Wk 1	9	160	(5. 6)	10	159	(6. 3)
Wk 2	29	151	(19.2)	34	147	(23.1)
Wk 3	43	146	(29.5)	45	134	(33.6)
Wk 4	66	146	(45.2)	60	130	(46.2)
Wk 5	72	140	(51.4)	76	135	(56.3)
Wk 6	73	140	(52.1)	87	132	(65.9)**
Wk 8	74	133	(55.6)	92	127	(72.4)***

n= number of responders, N= total number of patients assessed

†Note that the following is different than for tables on previous pages: *p<0.05, **p<0.025, ***p.01, ****p<0.001 compared to controls using Student t-test. Significance for alpha=0.05, per sponsor.

Table 7.3.1 A. Study 637: Summary of Responders Based on the HAM-A Total of </= 10 : ITT Population, similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	n	N	%	n	N	%
LOCF						
Wk 1	6	182	3.3	10	179	5.6
Wk 2	22	183	12.0	37	181	20.4*
Wk 3	44	183	24.0	50	181	27.6
Wk 4	56	183	30.6	65	181	35.9
Wk 6	75	183	41.0	83	181	45.9
Wk 8	85	183	46.4	90	181	49.7
OC						
Wk 1	6	182	3.3	10	179	5.6
Wk 2	21	176	11.9	37	165	22.4**
Wk 3	42	168	25.0	46	150	30.7
Wk 4	52	164	31.7	62	151	41.1
Wk 6	72	167	43.1	82	155	52.9
Wk 8	81	163	49.7	85	149	57.0

n= number of responders, N= total number of patients assessed
*p<0.05, **p<0.025, ***p.01, ****p<0.001 when compared to controls (Student t-test).
Significance for alpha=0.05 per sponsor.

Table 7.3.1.B. Study 637: Summary of Responders for CGI Items 1 or 2 at Each Visit : ITT Population, similar to that provided by the sponsor.

	Placebo Group			Paroxetine Group		
	n	N	%	n	N	%
LOCF						
Wk 1	15	182	8.2	17	179	9.5
Wk 2	29	183	15.8	53	181	29.3***
Wk 3	56	183	30.6	73	181	40.3
Wk 4	73	183	39.9	86	181	47.5
Wk 6	92	183	50.3	114	181	63.0**
Wk 8	91	183	49.7	114	181	63.0**
OC						
Wk 1	15	182	8.2	17	179	9.5
Wk 2	28	176	15.9	52	166	31.3****
Wk 3	54	168	32.1	66	150	44.0*
Wk 4	68	164	41.5	81	151	53.6*
Wk 6	90	167	53.9	112	155	72.3****
Wk 8	89	163	54.6	108	149	72.5***

n= number of responders, N= total number of patients assessed
*p<0.05, **p<0.025, ***p.01, ****p<0.001 when compared to controls, Student t-test.
Significance for alpha=0.05 per sponsor.

Table 8.1.1.A. Non- Fatal Serious Adverse Experiences - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Patient Number	Age (years)	Sex	Days on Study at Event Onset	Total Days on Dbl- Blind Study Drug	Serious Adverse Experience	Severity	Relationship	Action
Paroxetine								
637.017.03612	41	F	34	31	Anxiety	Severe	Probably Unrelated	None
637.031.03396	27	M	68	62	Chest Pain	Severe	Unrelated	None
637.052.03711	20	F	39	57	Anxiety	Severe	Unrelated	Dose Increased
637.092.03458	51	F	6	7	Abdominal Pain/ Gastritis	Severe	Unrelated	Drug Stopped
641.120.00972	63	F	61	60	Chest Pain	Severe	Unrelated	None
641.126.01253	48	M	12	18	Skin Carcinoma	Moderate	Unrelated	None
641.150.02452	54	M	69	56	Trauma (Car Accident)	Mild	Unrelated	None
642.216.03776	45	F	83	56	Pneumonia	Severe	Unrelated	None
642.225.04217	37	F	3	3	Hallucinations	Mild	Possibly Related	Drug Stopped
Placebo								
637.001.03297	58	M	43	55	Chest Pain	Moderate	Probably Unrelated	None
637.018.03607	65	M	33	62	Accidental Overdose	Mild	Unrelated	None
637.020.03575	56	M	26	56	Accidental Overdose	Moderate	Unrelated	None
637.057.03750	48	M	56	56	Depression	Severe	Possibly Related	Drug Stopped
637.057.03758	38	M	89	57	Nephritis	Severe	Unrelated	None
637.058.03662	32	F	41	58	Unintended Pregnancy	--	Unrelated	None
637.074.03433	52	F	5	3	Vascular Disorder	Moderate	Unrelated	None

Table 8.1.1.B. Serious Adverse Experiences - Study 646, as provided by the sponsor.

Patient Number	Age (years)	Sex	Treatment	Duration of Treatment at Onset of Event	Serious Adverse Experience	Relationship	Action/ Outcome
Paroxetine							
646.153.04604	32	F	Single- Blind Paroxetine	2 days	Overdose with benzodiazepines	Related	Drug Stopped
646.151.04531	39	F	Single- Blind Paroxetine	30 days	Grand mal convulsion	Related	Drug Stopped
646.154.04919	48	M	Single- Blind Paroxetine	11 days	Trauma (car accident)	Unrelated	Not Stated
646.307.05113	51	F	Single- Blind Paroxetine	29 days 37 days	Gastritis Bronchitis	Possibly Related Unrelated	Dose Reduced
646.150.06652	66	F	Blinded	60 days	Head Injury (fall)	Unrelated	None
646.200.04886	52	F	Single- Blind Paroxetine	1 day	Overdose (mistake in dosing instructions)	Unrelated	None
646.107.05083	52	F	Blinded	74 days	Pulmonary carcinoma	Unrelated	Death
646.302.05107	32	M	Blinded	61 days	Anxiety Insomnia Alcohol Abuse	Possibly Related	Drug Stopped

Table 8.1.2 Summary of Treatment Phase Emergent Adverse Experiences Leading to Withdrawal of 2 or More Patients by Body Systems and Preferred Terms - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Adverse Experiences Body Systems Preferred Terms	Placebo N =529 n (%)		Paroxetine N = 735 n (%)		Placebo N =529 n (%)		Paroxetine N = 735 n (%)	
	Data Source Summary+				Revised Summary++			
Body as a Whole								
Asthenia	1	(0.2)	11	(1.5)	1	(0.2)	13	(1.8)
Chest Pain	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Headache	3	(0.6)	4	(0.5)	3	(0.6)	5	(0.7)
Cardiovascular System								
Palpitation	1	(0.2)	2	(0.3)	1	(0.2)	2	(0.3)
Digestive System								
Bruxism	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.3)
Constipation	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.3)
Diarrhea	1	(0.2)	2	(0.3)	1	(0.2)	2	(0.3)
Dry Mouth	1	(0.2)	0	(0.0)	1	(0.2)	3	(0.4)
Gingivitis	0	(0.0)	2**	(0.3)	1	(0.2)	1	(0.2)
Nausea	1	(0.2)	13	(1.8)	1	(0.2)	15	(2.0)
Vomiting	1	(0.2)	3	(0.4)	1	(0.2)	3	(0.4)
Nervous System								
Agitation	1	(0.2)	2	(0.3)	1	(0.2)	2	(0.3)
Amnesia	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Anxiety	1	(0.2)	1	(0.1)	2	(0.4)	2	(0.3)
Concentration Impaired	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Confusion	0	(0.0)	2	(0.3)	1	(0.2)	2	(0.3)
Depression	1	(0.2)	3	(0.4)	2	(0.4)	3	(0.4)
Dizziness	1	(0.2)	7	(1.0)	1	(0.2)	7	(1.0)
Insomnia	1	(0.2)	5	(0.7)	2	(0.4)	5	(0.7)
Libido Decreased	2	(0.4)	3	(0.4)	2	(0.4)	5	(0.7)
Nervousness	2	(0.4)	3	(0.4)	2	(0.4)	3	(0.4)
Paresthesia	0	(0.0)	3	(0.4)	0	(0.0)	3	(0.4)
Somnolence	1	(0.2)	14	(1.9)	1	(0.2)	15	(2.0)
Thinking Abnormal	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Tremor	0	(0.0)	4	(0.5)	0	(0.0)	4	(0.5)
Respiratory System								
Respiratory Disorder	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.3)
Skin and Appendages								
Sweating	1	(0.2)	7	(1.0)	1	(0.2)	8	(1.1)
Special Senses								
Tinnitus	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.3)
Urogenital System								
*Abnormal Ejaculation	1	(0.5)	6	(2.1)	1	(0.5)	7	(2.5)
*Female Genital Disorders	0	(0.0)	1	(0.2)	0	(0.0)	3	(0.7)
*Impotence	1	(0.5)	2	(0.7)	1	(0.5)	2	(0.7)

* Percentage corrected for gender
\+ For one placebo patient and 7 paroxetine patients, AE leading to withdrawal not identified; for 3 placebo and 3 paroxetine patients AE leading to withdrawal was reported to occur after stopping study medication.
** One patient, gingivitis lead to temporary stoppage

++ Includes AEs from patients identified as having a data issue (see text of review for details)

Table 8.1.3. Comparison of Treatment Phase Emergent Adverse Experiences Occurring in 5% or More of the North American or European Populations in Any Treatment Regimen, as provided by the sponsor.

	Study 637 (Europe)				Studies 641 and 642 (N. A.)			
	Placebo		Paroxetine		Placebo		Paroxetine	
Body Systems	N= 185		N= 187		N= 344		N= 548	
Preferred Terms	n	(%)	n	(%)	n	(%)	n	(%)
Body as a Whole								
Asthenia	10	(5.4)	13	(7.0)	24	(7.0)	92	(16.8)
Headache	14	(7.6)	13	(7.0)	60	(17.4)	111	(20.3)
Infection	2	(1.1)	4	(2.1)	16	(4.7)	37	(6.8)
Digestive System								
Constipation	0	(0. 0)	8	(4. 3)	9	(2. 6)	69	(12. 6)
Decreased Appetite	0	(0. 0)	4	(2. 1)	6	(1. 7)	34	(6. 2)
Diarrhea	10	(5.4)	8	(4.3)	25	(7.3)	59	(10.8)
Dry Mouth	3	(1.6)	5	(2.7)	22	(6.4)	75	(13.7)
Dyspepsia	4	(2.2)	4	(2.1)	22	(6.4)	29	(5.3)
Nausea	5	(2.7)	38	(20.3)	23	(6.7)	110	(20.1)
Nervous System								
Dizziness	2	(1.1)	5	(2.7)	22	(6.4)	40	(7.3)
Insomnia	6	(3.2)	10	(5.3)	36	(10.5)	69	(12.6)
Libido Decreased	0	(0.0)	5	(2.7)	8	(2.3)	64	(11.7)
Nervousness	1	(0.5)	1	(0.5)	14	(4.1)	28	(5.1)
Somnolence	0	(0.0)	13	(7.0)	24	(7.0)	100	(18.2)
Tremor	1	(0.5)	11	(5.9)	3	(0.9)	23	(4.2)
Respiratory System								
Respiratory Disorder	6	(3.2)	5	(2.7)	21	(6.1)	45	(8.2)
Yawn	0	(0.0)	1	(0.5)	1	(0.3)	30	(5.5)
Skin and Appendages								
Sweating	0	(0.0)	5	(2.7)	8	(2.3)	41	(7.5)
Urogenital System								
*Abnormal Ejaculation	0	(0.0)	2	(4.2)	4	(3.0)	68	(28.9)
*Female Genital Disorders	0	(0.0)	0	(0.0)	2	(1.0)	20**	(6.4)

*Percentage corrected for gender

** Excludes patient 642.214.04609 (coding error)

Table 8.1.4.A. Predefined Clinical Laboratory Values of Potential Clinical Concern*

Parameter Hematology	Value	Units	Parameter Blood Chemistry	Value	Units
White Blood Cells	<=3, ≥ 16.0	10^ 9/ L	ALT/ SGPT	≥165	IU/ L
Basophils	≥10	%	Alkaline Phosphatase	≥390	IU/ L
Eosinophils	≥10	%	AST/ SGOT	≥150	IU/ L
Lymphocytes	≥75	%	Blood Urea Nitrogen	≥11	mmol/ L
Monocytes	≥15	%	Serum Creatinine	≥177	mcmol/ L
Segmented Neutrophils	<=15	%	Total Bilirubin	≥34	mcmol/ L
Neutrophils Bands	>10	%	Potassium	<=3.0, ≥ 6.0	Mmol/ L
Platelets	≥ 75, ≥700	10^ 9/ L	Sodium	<=126, ≥156	Mmol L
Red Blood Cells Male	<=8	10^ 12/ L	Free T3	<=3.5, ≥ 6.5	Pmol/ L
Female	<=10	10^ 12/ L	Free T4	<=10.3, ≥ 23. 2	Pmol/ L
Hematocrit Male	<=37	%TSH		≥10	mU/ L
Female	<=32	%			
Hemoglobin Male	<=115	g/ L			
Female	<=95	g/ L			

* as provided by the sponsor. Note: PCC criteria were not employed for Urine dipstick results.

Table 8.1.4.B. Predefined Changes in Vital Sign Values and Body Weight of Potential Clinical Concern as provided by the sponsor.

Systolic Blood Pressure	normal range = 90 - 180 mmHg increase of ≥40 mmHg, decrease of ≥30 mmHg
Diastolic Blood Pressure	normal range = 50 – 105 mmHg increase of ≥30 mmHg, decrease of ≥20 mmHg
Pulse Rate	normal range = 50 - 120 bpm increase or decrease of ≥30 bpm
Weight	no normal range defined increase or decrease of ≥7%

Table 8.1.5. Mean Clinical Lab Value at Baseline and Change from Baseline at Endpoint in Hematology Values - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

	Placebo N= 529			Paroxetine N=735		
Parameter	**n**	**mean**	**SD**	**n**	**mean**	**SD**
White Blood Cells (10^ 9/ L)						
Baseline	472	6.7	1. 69	613	6.7	1. 78
Change at endpoint	472	-0. 0	1.45	613	-0. 1	1.56
Basophils (10^ 9/ L)						
Baseline	472	0.0	0. 03	613	0.0	0. 03
Change at endpoint	472	-0. 0	0.04	613	-0. 0	0.04
Eosinophils (10^ 9/ L)						
Baseline	472	0.2	0. 14	613	0.2	0. 16
Change at endpoint	472	-0. 0	0.12	613	0.0	0. 14
Lymphocytes (10^ 9/ L)						
Baseline	472	2.0	0. 63	613	2.0	0. 60
Change at endpoint	472	-0. 0	0.46	613	0.0	0. 47
Monocytes (10^ 9/ L)						
Baseline	472	0.4	0. 15	613	0.4	0. 15
Change at endpoint	472	-0. 0	0.15	613	-0. 0	0.16
Segmented Neutrophils (10^ 9/ L)						
Baseline	472	4.1	1. 40	613	4.1	1. 45
Change at endpoint	472	0.0	1. 38	613	-0. 1	1.36
Platelets (10^ 9/ L)						
Baseline	472	239.6	50.27	616	240.2	53.71
Change at endpoint	472	0.5	30.09	616	2.4	29.48
Red Blood Cells (10^ 12/ L)						
Baseline	472	4.5	0. 51	614	4.5	0. 52
Change at endpoint	472	-0. 0	0.37	614	-0. 1	0.37
Hematocrit (%)						
Baseline	472	41.4	3. 80	615	41.8	3. 78
Change at endpoint	472	-0. 2	2.25	615	-0. 4	2.30
Hemoglobin (g/ L)						
Baseline	472	140.0	13.09	614	141.3	13.60
Change at endpoint	472	-1. 1	7.14	614	-1. 9	7.97

*Mean Baseline values and values for mean changes from Baseline to Endpoint were calculated based on Screening values.

Table 8.1.6 Mean Clinical Lab Value at Baseline and Change from Baseline at Endpoint in Blood Chemistry Values - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

	Placebo N= 529			Paroxetine N= 735		
Parameter	**n**	**mean**	**SD**	**n**	**mean**	**SD**
Alanine Aminotransferase (IU/ L)						
Baseline	477	19.8	13.53	631	20.4	13.22
Change at Endpoint	477	-0. 3	11.00	631	1.7	13.54
Alkaline Phosphatase (IU/ L)						
Baseline	477	67.3	20.62	631	68.3	19.99
Change at Endpoint	477	0.3	9. 68	631	3.5	11.03
Aspartate Aminotransferase (IU/ L)						
Baseline	477	18.3	6. 57	631	18.8	7. 54
Change at Endpoint	477	0.3	6. 40	631	1.8	10.40
Blood Urea Nitrogen (mmol/ L)						
Baseline	477	5.0	1. 59	631	5.0	1. 37
Change at Endpoint	477	0.1	1. 17	631	0.2	1. 22
Serum Creatinine (mcmol/ L)						
Baseline	477	78.6	19.45	631	77.7	22.28
Change at Endpoint	477	0.8	19.13	631	2.8	34.43
Total Bilirubin (mcmol/ L)						
Baseline	476	9.8	7. 68	631	9.7	8. 52
Change at Endpoint	476	-1. 4	7.25	631	-1. 6	8.17
Potassium (mmol/ L)						
Baseline	474	4.3	0. 51	629	4.3	0. 43
Change at Endpoint	474	-0. 0	0.53	629	-0. 0	0.54
Sodium (mmol/ L)						
Baseline	478	140.7	2. 26	631	140.9	2. 29
Change at Endpoint	478	0.1	2. 75	631	-0. 4	2.77

* Only assessed at Screening Visit

Table 8.1.7.A. Summary of Treatment Phase Mean Values for Vital Signs and Body Weight at Baseline and Mean Change from Baseline - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Parameter	Placebo N= 529			Paroxetine N = 735		
Timepoint	n	Mean	S. D.	n	Mean	S. D.
Systolic BP (sitting)						
Baseline	487	124.5	14.4	654	124.9	15.1
Change at Endpoint	487	-2. 0	11.7	654	-2. 0	12.4
Diastolic BP (sitting)						
Baseline	487	77.9	9. 0	654	78.1	9. 5
Change at Endpoint	487	-1. 7	8.4	654	-0. 4	8.4
Pulse						
Baseline	486	71.9	9. 4	653	72.6	9. 5
Change at Endpoint	486	0.4	9. 5	653	1.1	9. 6
Weight						
Baseline	314	76.7	17.8	475	77.1	18.2
Change at Endpoint	314	0.2	1. 9	475	-0. 1	2.3

Table 8.1.7.B. Incidence of Vital Sign and Body Weight Changes Meeting Potential Clinical Concern Criteria - Studies 637, 641 and 642 (ITT Population), as provided by the sponsor.

Parameter		Placebo		Paroxetine	
		n/ N*	(%)	n/ N*	(%)
Systolic BP (mmHg)					
	High	0/ 487	(0.0)	2/ 654	(0.3)
	Low	5/ 487	(1.0)	6/ 654	(0.9)
Diastolic BP (mmHg)					
	High	2/ 487	(0.4)	3/ 654	(0.5)
	Low	1/ 487	(0.2)	0/ 654	(0.0)
Pulse (bpm)					
	High	0/ 486	(0.0)	0/ 653	(0.0)
	Low	2/ 486	(0.4)	1/ 653	(0.2)
Weight (kg)					
	High	3/ 314	(1.0)	7/ 475	(1.5)
	Low	3/ 314	(1.0)	8/ 475	(1.7)

/s/

Karen Brugge
12/20/00 01:13:53 PM
MEDICAL OFFICER

Thomas Laughren
1/28/01 09:55:27 AM
MEDICAL OFFICER
I agree that this supplement is approvable. See memo to file for more detailed comments.--TPL

Printed by Russell Katz

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 26-Feb-2001 10:47am
From: Karen Brugge
BRUGGEK
Dept: HFD-120 WOC2 4027
Tel No: 301-594-2850 FAX t-

TO: Russell Katz (KATZR)

CC: Thomas Laughren (LAUGHREN)
CC: Paul Andreason (ANDREASONP)
Subject: Re: sNDA 20-031 S026, Paxil/GAD Subject with elevated Cr

Russ,

Re: page 37 of my review on sNDA 20-031 S026 regarding Subject 341.133.01610, 40 y.o. Hispanic male with Cr of 88.4 umol/l at baseline and Cr of 353 umol/l on Day 56 of the treatment phase. My comment in my review regarding the patient having an "abnormal baseline Cr level" appears to be incorrect. I went back and double checked the results provided in the submission and information that the sponsor sent (dated June 16,2000) in response to my request for additional info. The normal range for Cr in the units of umol/l is approximately 44-124, such that the value of 88 at baseline for the above subject is within normal limits. In a fax from the sponsor dated 8/31/2000 (in response to my inquiry about the above subject) they indicated that the baseline level was indeed within normal limits and that a follow-up level on Day 70 revealed that the Cr level "returned to within the normal range and the investigator indicated that no further laboratory evaluations were required". The sponsor also indicated that this subject also had a mildly elevated ALT of 49 IU/l on Day 56 (normal is 0-48). The sponsor did not provide any other additional information in their 8/31/200 fax in response to my request for info regarding the diagnostic work-up, diagnosis and follow-up on this patient.

Please let me know if you need anything else.

Karen