8.2.2 Digestive System

8.2.2.1 Adequacy of Assessment

Within the clinical development program, digestive system AEs and liver function tests were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on the digestive system. Summarized information on liver function tests in Group 1, placebo-controlled, short-term studies is shown in Appendices 8.1.6.3.1.1 and 8.1.6.3.2.4.

8.2.2.2 Serious Digestive System Events Considered Possibly, Probably, or Definitely Related to Citalopram

The bulk of the evidence for digestive system SAEs make a causal relationship with citalopram unlikely.

8.2.2.3 Serious Digestive System Events Unlikely to be Citalopram-Related

Abdominal pain

Abdominal pain was considered an SAE in seven patients in Group 1 and 3 studies on citalopram. The narratives in these cases noted other probable causes of abdominal pain in most of these patients (irritable bowel syndrome, Crohn's disease, influenza). It was listed as a cause of dropout in three cases; one of these had a history of irritable bowel syndrome; the other two occurred one week or less after beginning citalopram and may ~~have~~ been caused by the drug:

Study 92302, #1185: A 75 y.o. female experienced abdominal pain and vomiting after one day of treatment with 20 mg of citalopram, and dropped out of the study for these reasons, though the investigator (for unspecified reasons) did not think the symptoms were drug-related.

Study 88105, #680: A 33 y.o. female experienced severe abdominal pain and diarrhea after 7 days of treatment with 40 mg and withdrew from the study.

In the fixed dose study 91206, abdominal pain did not overall appear to have a relationship to citalopram treatment (Appx. 8.1.5.3.1)

In the post-marketing DSU database, there were two cases of abdominal pain reported as associated with citalopram use.

Abdominal pain is a nonspecific classification and there does not appear to be any pattern in those very few cases occurring while on citalopram.

Vomiting

Vomiting was listed as an SAE in four patients in Group 1 and 3 studies. One case is noted above under abdominal pain (#1185); in the other cases other

illnesses were present (Crohn's disease, myocardial infarction). In the fixed dose study 91206, vomiting did not appear to be related to citalopram (Appx. 8.1.5.3.1).

One person dropped out of a Group 2 study because of nausea and vomiting.

In the post-marketing DSU database, there were 5 cases of vomiting reported as associated with citalopram use.

Other Serious Digestive System Events

Of the 95 deaths of citalopram patients in the development program (Groups 1 and 3), nine (9%) were due to GI system problems and did not appear to be related to citalopram treatment (1 appendicitis, 1 gastric ulcer, and 1 cholecystitis, 1 gastric carcinoma, 3 pancreatic cancer, 1 rectal cancer, and 1 bile duct cancer).

In addition, there were 5 dropouts secondary to SAEs in Group 1 studies from digestive system problems other than those noted above; most appeared to be unrelated to citalopram treatment (one abdominal pain with a history of irritable bowel syndrome, one exploratory laparotomy for abdominal symptoms, one hemorrhoids, one cholecystitis, and one pancreatic cancer diagnosed after an elevated bilirubin was found).

Other SAEs noted which do not appear to be drug-related and which occurred in four or fewer cases: gastric cancer, rectal cancer, bile duct cancer, appendicitis, hemorrhoids, gastric ulcer, and cholelithiasis/cholecystitis. The following SAEs occurred in single patients: constipation, [redacted] gastroenteritis, ileitis, ileus, pancreatitis, and hepatic infection.

In the post-marketing DSU database, there were 8 cases of hepatitis, one case of hepatic necrosis, two cases of "hepatocellular damage", and 3 cases of pancreatitis reported as associated with citalopram use. An additional case of biopsy proven hepatic necrosis was reported 9/25/97 in an adverse event report to the FDA. The 59 y.o. male patient was noted to have an elevated bilirubin 4 weeks after beginning treatment with 20 mg citalopram. He was also on metoprolol and pentoxiphyllin, neither of which has hepatic necrosis in its labeling. He recovered completely. This SAE then should be included in labeling underpostmarketing reports.

Another 15-day report of necrotizing hepatitis, biopsy proven, was reported in the October 31, 1996 submission: A 47 y.o. woman was hospitalized for hypertension one month after starting citalopram; an enlarged liver and increased alkaline phosphatase were found. There was no history of alcohol abuse; the problem resulted in prolonged hospitalization.She was also on: bromazepam, bendrofluazide (a thiazide diuretic), and gestodene + ethinylestradiole.In the Martindale reference, bromazepam is said to be similar to diazepam, which has been associated with rare reports of hepatic necrosis.

Adverse Event-Related Dropouts (Nonserious) Due to Laboratory Abnormalities in Group 1 Studies

Nine patients who withdrew from Group 1 studies because of laboratory abnormalities had abnormalities in liver function tests (Table 8.1.6.3.3). One patient was found to have infectious hepatitis. Most of the patients had medical conditions or were on concurrent medication that also could have contributed to the abnormalities, which usually occurred within the first 2 months of treatment and showed no relationship to dose. Followup information was available only for patients in long term studies; three out of four showed recovery into the normal range by the next visit while continuing on citalopram. One patient with alcohol abuse/dependence and one with pancreatic cancer had jaundice. None were noted to have progressed to severe liver disease.

8.2.3 Hemic and Lymphatic System

8.2.3.1 Adequacy of Assessment

Within the clinical development program, hemic and lymphatic system AEs including laboratory parameters were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on the hemic and lymphatic system. Summarized information on hematologic tests in Group 1, placebo-controlled, short-term studies is shown in Appendices 8.1.6.3.1.2 and 8.1.6.3.2.5.

8.2.3.2 Hemic and Lymphatic System Events Considered Possibly, Probably, or Definitely Related to Citalopram

None of the SAEs in this system appeared to be related to citalopram treatment.

8.2.3.3 Hemic and Lymphatic System Events Unlikely to be Citalopram-Related

Pulmonary embolism

Of the 95 deaths of citalopram patients in the development program (Groups 1 and 3), 8 (8.3%) were attributed to hemic disorders: 7 of these were due to pulmonary embolism which occurred in elderly debilitated people with medical problems including COPD and dementia, and in one case a fractured femur. There were a total of 7 cases of pulmonary emboli classified as an SAE in Group 1 (n=4) and 3 studies and none on placebo.

Other Serious Hemic and Lymphatic System Events

The other death included in this system is a case of anemia secondary to colon cancer.

The only ADO listed for this system was a patient with lymphocytic leukemia,

though no specific reason for dropout is indicated in the narrative summary; lymphocytic abnormalities were seen at baseline, and he continued with treatment for 4 months without an exacerbation of this problem.

Other SAEs include three patients with anemia (two were anemic at baseline; two had cancer and one had B_{12} deficiency), one hematoma, one DVT in a patient also on estrogen replacement, one case of leukocytosis and increased platelets, these blood findings were present at baseline in a jaundiced patient with alcohol dependence and were diagnosed as benign neutrophilic leukocytosis.

In the post-marketing DSU database, there was one case of aplastic anemia, one case of pancytopenia, one case of eosinophilia, 2 cases of granulocytopenia, one case of leucopenia, and 6 cases of thrombocytopenia reported as associated with citalopram use.

Adverse Event-Related Dropouts (Nonserious) Due to Laboratory Abnormalities in Group 1 Studies

(Appx. 8.1.6.3.4) Study 91206, #603: A 41 y.o. female with a history of thalassemia minor anemia, low H/H at baseline (10.0/32.1%) became lower after 2 weeks of treatment with citalopram (8.7/28.1%) so the patient was dropped from the study. No other reported AEs were related to the anemia.

8.2.4 Metabolic and Endocrine Systems

8.2.4.1 Adequacy of Assessment

Within the clinical development program, metabolic and endocrine systems AEs and laboratory assessments were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on the metabolic and endocrine systems. Summarized information on clinical chemistry tests in Group 1, placebo-controlled, short-term studies is shown in Appendices 8.1.6.3.1.1 and 8.1.6.3.2.4.

8.2.4.2 Metabolic and Endocrine System Events Considered Possibly, Probably, or Definitely Related to Citalopram

Hyponatremia

In Group 1 placebo-controlled, short-term studies, three (0.3%) patients on citalopram and none on placebo had hyponatremia (120, 124, and 125 mmol/l) (Appendix 8.1.6.3.2.4, section 8.1.6.3.2); none were classified as an SAE and all three normalized on continued drug treatment.

In the post-marketing DSU database, there were 16 cases of hyponatremia and 3 cases of SIADH reported to be associated with citalopram use. In four 15-day safety reports submitted to the DNDP in the past year, all hyponatremia cases were in elderly patients on other medications, with one in addition abusing alcohol. All recovered with treatment.

Hyponatremia, though rare, can have serious consequences if undiagnosed, and has been associated with the use of other SSRIs. It is recommended that it be included as a precaution in labeling based on the postmarketing reports.

8.2.4.3 Metabolic and Endocrine System Events Unlikely to be Citalopram-Related

The only death classified within this group was a patient with uremia that was clearly secondary to her breast cancer and its treatment. There were three ADOs: one patient was an insulin-dependent diabetic with hypoglycemia (study 86141, #310) whose insulin dose was in need of reduction; another patient with hyperglycemia prior to treatment (study 91206, #621), and another who discontinued medication prior to surgery for a thyroid nodule. An additional patient listed in Appx. 8.1.6.3.3, which lists withdrawals due to chemistry abnormalities, had hypokalemia and renal insufficiency due to vomiting and laxative abuse (study 8213, #1235); she is also noted under the G-U system (section 8.2.10.3). There were no other ADOs related to abnormal laboratory values for this system.Other SAEs included: one case of hypercalcemia in a 45 y.o. woman after over 14 months of treatment with 20 mg daily with no additional information, ketoacidosis in 41 y.o. insulin dependent diabetic 6 weeks after beginning citalopram, and hypoglycemia in a 61 y.o. diabetic on several other medications, 4.5 months after beginning citalopram.

Adverse Event-Related Dropouts (Nonserious) Due to Laboratory Abnormalities in Group 1 Studies

There were no other ADOs related to laboratory abnormalities for this system.

8.2.5 Musculoskeletal System

8.2.5.1 Adequacy of Assessment

Within the clinical development program, musculoskeletal system AEs and laboratory assessments were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on the musculoskeletal system.

8.2.5.2 Musculoskeletal System Events Considered Possibly, Probably, or Definitely Related to Citalopram

None of the SAEs in Group 1 and 3 studies or abnormal laboratory parameters in this system appeared to be related to citalopram treatment.

8.2.5.3 Musculoskeletal System Events Unlikely to be Citalopram-Related

In Group 1 and 3 studies, there were no deaths classified under this system. There were three ADOs: two in elderly women with a fractured ankle and a fractured femur, and one 43 y.o. woman diagnosed with polymyalgia rheumatica after 8 months of citalopram treatment in which partial recovery was documented one year later. Other SAEs include: fractured great trochanter in

an 82 y.o. woman, vertebral fracture after a fall in a 69 y.o. woman, a 45 y.o. man with a "bone disorder" on which there is no further information, one patient with arthritis temporarily discontinued citalopram in preparation for hip surgery, another patient with a history of arthritis and one with arthrosis on which there is little information.

8.2.6 Nervous System

8.2.6.1 Adequacy of Assessment

Within the clinical development program, nervous system AEs were regularly documented. In addition, psychomotor studies completed are summarized in section 8.1.9.
These evaluations are felt to be adequate to evaluate the effect of citalopram on the nervous system.

8.2.6.2 Nervous System Events Considered Possibly, Probably, or Definitely Related to Citalopram

Mania

Mania-hypomania was examined by the sponsor as an adverse event of special interest. In Group 1 studies, 41 patients had a manic reaction (this preferred term also includes hypomania) as a TEAE, 40 were on citalopram (0.96%) and one was on placebo (0.17%). Twenty-six of these were classifed as hypomania by investigators. All occurred while being treated with 40 mg of citalopram or less. Twenty-three of the reported TEAEs occurred after treatment for 8 weeks or longer.

In Group 1, placebo-controlled trials, there were 9 cases of mania/hypomania (out of 1320 patients or 0.68%) on citalopram and one case (out of 575 patients or 0.17%) on placebo.

Six cases of manic reactions classified as an SAE occurred in ~~G~~roup 1 and 3 studies in patients on citalopram; none in the placebo group were considered SAEs. For three of these patients, mania was a reason for withdrawing from the study. Manic reactions occurred from 24 days to 8 months after beginning treatment with citalopram, 20-40 mg.

In the post-marketing DSU database, there were 9 cases of mania reported as associated with citalopram use.

The sponsor's literature search identified 3 cases of mania associated with citalopram use that didn't add any new information.

As for other antidepressants, it is recommended that activation of mania/hypomania be included as a precaution in labeling.

Seizures

Twelve patients (0.06%) had seizures classifed as an SAE while on citalopram,

and none on placebo in Group 1 and 3 studies. Four of these were classified as grand mal. ADOs included one patient with petit mal seizure and one with grand mal. For Group 1 studies, the crude incidence on citalopram was 5/4168 (0.12%).

Of the patients who experienced seizures while on citalopram, four had a prior history of seizures, two others had other conditions that predispose to seizures (stroke, Alzheimer's). In two patients, the use of other medications could have contributed to seizure activity (tranquilizer abuse, theophylline). Seizures occurred from 5 days to 12 months after beginning treatment, at doses of 20 and 40 mg.

Convulsions were examined by the sponsor as an adverse event of special interest. In Group 1 studies, 18 patients were reported as having a seizure as a TEAE; 12 of these were on citalopram, 4 were on placebo, and 2 were on other anti-depressants. The incidence rate for citalopram-treated Group 1 patients was 0.009/PEY, for placebo patients it was 0.020/PEY. There was no effect of gender, dose, or treatment duration found on seizure incidence.

There were 24 cases identified via the post-marketing DSU database, five of these were classified as grand mal and one as localized.

The incidence of seizures classified as a SAE in Group 1 studies (0.12%) is similar to that reported with other antidepressants. It is recommended that seizures be included as a precaution in labeling.

Serotonin Syndrome

No cases of serotonin syndrome were reported in Group 1, 2 and 3 studies.

In the post-marketing DSU database, there were 8 cases of serotonin syndrome reported as associated with citalopram use. The sponsor's literature search yielded four cases. One describes serotonin syndrome following a single parenteral administration of 20 mg citalopram in a 71 y.o. woman with depression. She showed mental status changes, agitation, diaphoresis, abdominal pain, hyperreflexia, and tremor. She returned to normal 3 days after discontinuing citalopram. In the other three, serotonin syndrome was the suspected cause of death by overdose with citalopram in combination with the MAOI moclobemide. The patients were men, aged 29, 34, and 41. Death occurred within 3-16 hours; symptoms included severe tremors, convulsions, hyperthermia, and loss of consciousness. Blood citalopram levels were five-fold the therapeutic average in one case (1.7 mg/L), slightly higher than average in one case (0.5 mg/L), and at the normal therapeutic average in the third case (0.3 mg/L). All three subjects had also taken other drugs: alcohol in one case, benzodiazepines in another, and carbamazepine, benzodiazepine and alcohol in the third case.

As for other SSRIs, the potential for interaction with a MAOI leading to serotonin syndrome should be included under contraindications, warnings, and precautions in labeling.

Confusion

In Group 1 and 3 studies, six patients experienced confusion as an SAE while on citalopram, and none on placebo. The youngest of these was 56 y.o., ages of the others ranged At least three of the patients had a history of dementia, and in at least three of the cases patients were on other psychotropic drugs.

In the fixed dose study 91206, confusion occurred in 2% of patients at each dosage level and 1% on placebo (Appx 8.1.5.3.1). (In the Group 1 short-term, placebo-controlled trials, it occurred in 0.6% of placebo patients and 1.1% of citalopram patients, so it is not included in the sponsor's 2% table in proposed labeling).

In the post-marketing DSU database, there were 13 cases of confusion reported as associated with citalopram use.

Confusion may be related to citalopram in a small percentage of patients as seen in study 91206 and is appropriately included in labeling under "Other Events Observed During Premarketing".

Tremor

In Group 1 and 3 studies, two patients on citalopram experienced tremor classified as an SAE, and none on placebo. In one patient, tremor began 2 weeks after starting citalopram (40 mg) and the patient also had nausea. In the other, tremor began 6 weeks after starting citalopram (40 mg), on discharge from the hospital and it was associated with severe anxiety.

In the fixed dose study 91206, tremor occurred in of patients in the citalopram dosage groups and 0% on placebo (Appx. 8.1.5.3.1). (In the Group 1 short-term, placebo-controlled trials, it occurred in 6% of placebo patients and 8% of citalopram patients.)

In the post-marketing DSU database, there were 10 cases of tremor reported as associated with citalopram use.

Tremor is appropriately included in proposed labeling in the TEAE table.

Extrapyramidal Disorder

In Group 1 and 3 studies, there were three cases of parkinsonism reported as SAEs, two responsible for drop-out, and one case of aggravated parkinsonism. No cases were reported on placebo. All patients were elderly, in one case symptoms continued after citalopram was stopped. In another, the patient had a history of tremor and was also on neuroleptics. For Group 1 studies, the crude incidence was 2/4168 (0.05%).

In the fixed dose study 91206, extrapyramidal disorder, parkinsonism, and hypokinesia did not occur, though hypertonia was recorded in 2% of patients on

20, 40, and 60 mg and none on placebo (Appx. 8.1.5.3.1). (In the Group 1 short-term, placebo-controlled trials, extrapyramidal symptoms occurred in < 1% of citalopram patients).

In the post-marketing DSU database, there were 15 cases of extrapyramidal disorder and one case of aggravated parkinsonism reported as associated with citalopram treatment.

The literature review done by the sponsor yielded one reference which reported 11 cases of extrapyramidal symptoms (parkinsonism) during citalopram treatment. Two of the cases involved worsening of parkinsonism. Symptoms decreased or disappeared in 8 cases 1-2 weeks after citalopram was discontinued. Eight of the patients were taking concomitant benzodiazepines, seven were taking other concomitant medications. In only one case were there no concomitant meds. Ages of the patients ranged from 43 to 85 years.

Parkinsonism is appropriately included in labeling as a rare adverse reaction.

8.2.6.3 Nervous System Events Unlikely to be Citalopram-Related

Suicide Attempt

Crude incidence of suicide attempt in Group 1 and 3 studies was 129/19,666 (0.66%) for citalopram treated patients, 12/792 (1.5%) for patients on placebo, and 24/1576 (1.5%) for patients treated with an active comparator. These events most likely represent a lack of efficacy for depression.

Suicide accounted for 28% of the deaths in the development program for citalopram-treated patients, and 28.5% for placebo patients. The incidence rate of suicide attempts in Group 1 studies was 0.068 events/PEY for citalopram patients and 0.067 events/PEY for placebo. Restricting the Group 1 patients to those with depression, the suicide attempt rates were 0.079 events/PEY for citalopram and 0.097 events/PEY for placebo. Citalopram patients in Group 1 controlled studies also had reductions in suicidality measures on the HAM-D (item #3) and MADRS (item #10). In citalopram treated patients, 8.6% vs. 16.1% on placebo had an increase on HAM-D item #3 ≥ 1 point; 1.9% vs. 4.2% had an increase of ≥ 2 points, and 0.4% in both groups had an increase ≥ 3 points. For the MADRS item #10, 9.1% of citalopram patients vs. 17.7% of placebo patients had an increase ≥ 1 point; 2.7% vs. 7.1% had an increase ≥ 2 points; 0.5% vs. 2.2% had an increase ≥ 3 points, and 0% vs. 1.3% had an increase ≥ 4 points.

In Group 1 studies, the incidence of suicide attempts was higher in patients taking 20-60 mg/day than in those taking less than 20 mg daily (80 of 3401 patients or 2.4% vs. 11 of 662 patients or 1.7%). Duration of citalopram treatment did not have a relationship to suicide attempts.

In Group 1 studies, 14 citalopram-treated patients made suicide attempts other than by overdose; 6 died. Thirty-three patients attempted overdose, 18 of these involved drugs other than citalopram. Information on the 16 involving citalopram is reviewed in section 8.1.12 and Appx. 8.1.12.1.

In the post-marketing DSU database, there were 49 reported suicide attempts (25 died) and 60 reported overdoses (six died)(no overlap between cases). Appx. 8.1.12.2 contains information on the overdose fatalities.

One depressed patient made a suicide attempt in a Group 2 study (study 88117).

It is recommended that the standard precaution on suicide be included in labeling.

Psychosis

In Group 1 and 3 studies while on citalopram, 3 patients experienced an SAE classified as psychosis, 2 as schizophrenic reaction, 8 as depression psychotic, and 3 hallucination. None of these SAEs occurred in placebo patients. Seven of the patients with psychotic depression were ADOs, all three with hallucination were ADOs, and one classified as psychosis was ADO.

Of the three patients with the SAE "psychosis", one had a history of schizophrenia; the other two were elderly and receiving 40 mg of citalopram daily, with the psychosis occurring 6-12 weeks after beginning treatment. The two patients with "schizophrenic reaction" had a history of psychosis prior to treatment; one had a history of manic-depression. Of the 8 patients with "depression psychotic", two had a history of same prior to treatment, symptoms occurred in one elderly patient one week after discontinuing citalopram. For most of the others no psychotic symptoms were described in the narratives, but were described as having melancholia. Of the three patients under "hallucination", one was elderly (88 y.o.) and experienced visual hallucinations shortly after a dosage increase to 40 mg, another was on numerous other meds for asthma and panic disorder.

In the fixed dose study 91206 (n=650), the only indication of a psychotic reaction while on citalopram was in one patient who had hallucinations while on 60 mg. (In the Group 1 short-term, placebo-controlled trials, it occurred in < 1% of citalopram patients).

In the post-marketing DSU database, there were 4 cases of psychosis and 14 cases of hallucination reported as associated with citalopram use.

The bulk of the evidence indicates that psychosis is generally not related to citalopram use; the inclusion of psychosis in labeling under "Other Events Observed During Premarketing" is appropriate.

Anxiety

Anxiety or nervousness was considered an SAE in 15 (0.08%) patients on citalopram and one (0.13%) patient on placebo in Group 1 (n=10) and 3 studies. Two were ADOs. Two were reported as having panic attacks. Two patients had a history of anxiety prior to treatment and one had ongoing alcohol abuse/dependence. In one case the anxiety was also associated with a traumatic event. Doses ranged from 20-60 mg, and the events occurred from 3-

179 days after beginning treatment.

In the fixed dose study 91206, nervousness and anxiety rates were similar to those on placebo (Appx. 8.1.5.3.1) (In the Group 1 short-term, placebo-controlled trials, nervousness and anxiety occurred in 3% of placebo patients and 4% of citalopram patients and is therefore included in proposed labeling in the TEAE table).

In the post-marketing DSU database, there were 11 cases of anxiety and three of nervousness reported as associated with citalopram use.

Dizziness

In Group 1 and 3 studies, three patients on citalopram and none on placebo had dizziness as an SAE. Two patients with dizziness were ADOs. Patients were elderly (over 80 yrs) except one who was 57 years old. One patient had a history of dizziness and vertebro-basilar insufficiency.

In the fixed dose study 91206, dizziness occurred at ≥ twice the placebo rate at 20 and 40 mg but not at 10 and 60 mg (Appx. 8.1.5.3.1). (In the Group 1 short-term, placebo-controlled trials, it occurred in 10% of placebo patients and 11% of citalopram patients and is therefore included in the TEAE table in proposed labeling).

In the post-marketing DSU database, there were 12 cases of dizziness reported as associated with citalopram use.

Vertigo

In Group 1 and 3 studies, two patients on citalopram and none in the placebo group had vertigo as an SAE. Both were over 80 yrs. old. One had atherosclerosis and was on multiple other meds.

In the fixed dose study 91206, vertigo occurred in 1% of patients on placebo, 20 mg and 40 mg, and 0% at 10 and 60 mg (Appx. 8.1.5.3.1). (In the Group 1 short-term, placebo-controlled trials, it occurred in < 1% of citalopram patients).

In the post-marketing DSU database, there were 4 cases of vertigo reported as associated with citalopram use.

Vertigo is appropriately included in proposed labeling as an infrequent to rare adverse reaction.

Headache

In Group 1 and 3 studies, three patients on citalopram experienced headache classified as an SAE, and none on placebo. Headaches began 6-18 days after starting citalopram.

In the fixed dose study 91206, headache incidence was similar among placebo

and dosage groups (Appx. 8.1.5.3.1). (In the Group 1 short-term, placebo-controlled trials, it occurred in 27.5% of citalopram patients and 27.2% on placebo).

In the post-marketing DSU database, there were 10 cases of headache reported as associated with citalopram use.

Headache is appropriately included in proposed labeling as a "frequent" adverse reaction in the "Other Events Observed During the Premarketing Evaluation" section.

Other Nervous System Events Unlikely to be Citalopram-Related

Study 93401, #65: 74 y.o. male with sudden death 34 days after starting citalopram (20 mg), probably due to a cerebrovascular accident. The patient had a history of diabetes and atrial fibrillation and was on several other meds.

Other nervous system SAEs causing dropout from Group 1 and 3 studies: agitation (4), aggressive reaction (2), paranoid reaction (1), hemiparesis (1), MS-like syndrome (1), myasthenia gravis-like syndrome (1), quadriplegia (after car accident) (1).

The following psychiatric SAEs were also reported: drug abuse (6) drug dependence (2), aggressive reaction (2), the following were reported for one case each: insomnia, nervousness, euphoria, somnolence, appetite increased.

The following neurologic SAEs were each reported in one case: delirium, dementia, hyperkinesia, meningism, neuroleptic malignant syndrome.

There were 7 cases of neuroleptic malignant syndrome, 3 cases of neuropathy, and 15 cases of paresthesia reported in the post-marketing DSU database as associated with citalopram use.

8.2.7 Respiratory System

8.2.7.1 Adequacy of Assessment

Within the clinical development program, respiratory system AEs were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram in the respiratory system.

8.2.7.2 Respiratory System Events Considered Possibly, Probably, or Definitely Related to Citalopram

None of the respiratory system SAEs appeared to be related to citalopram treatment.

8.2.7.3 Respiratory System Events Unlikely to be Citalopram-Related

Pneumonia

There were 12 deaths under the respiratory system in Group 1 and 3 studies, 8 of these were due to pneumonia in elderly people. There were 7 other cases of pneumonia reported as SAEs. A total of 10 pneumonia cases were recorded as TEAEs in Group 1 studies; 7 were SAEs, three of these died. Most of these cases and all the deaths were from the open study 8213. There was one nonserious case of pneumonia on placebo in Group 1 studies. One ADO was due to pneumonia in an elderly patient.

One elderly depressed patient had pneumonia in a Group 2 study.

Other Respiratory System Events Unlikely to be Citalopram-Related

In Group 1 and 3 studies, one death was ascribed to bronchitis and one to "respiratory disorder" in elderly patients. The latter patient had alcoholism and severe medical problems including cirrhosis. Two other deaths were secondary to pulmonary cancer. One ADO in an elderly patient was ascribed to dyspnea 2 weeks after starting citalopram, which was due to myocardial infarction. Other SAEs included aspiration (1), asthma (2), bronchitis (2), dyspnea (2), pneumothorax (1), pulmonary edema (1), pulmonary cancer (1).

8.2.8 Dermatologic System

8.2.8.1 Adequacy of Assessment

Within the clinical development program, dermatologic system AEs were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on the dermatologic system.

8.2.8.2 Dermatological System Events Considered Possibly, Probably, or Definitely Related to Citalopram

Angioedema

Study 91403, #21: 72 y.o. male developed edema of the lower face, diagnosed as angioedema, followed by widespread exanthema about 4 months after beginning citalopram (10 mg). Citalopram was discontinued and symptoms abated after 2 days of treatment with antihistamines. Comcomitant meds were levodopa/benserazide and ibuprofen. The latter is known to cause angioedema, though it can't be ruled out that citalopram could have contributed.

Angioedema was reported to be associated with citalopram in 5 cases in the post-marketing DSU database.

It is recommended that angioedema be included as a rare adverse reaction in labeling.

8.2.8.3 Dermatological System Events Unlikely to be Citalopram-Related

There were no deaths or ADOs in the dermatologic system.

The only other dermatologic SAE occurred in a 45 y.o. female who developed dermatitis 14 months after beginning citalopram (20 mg). No concurrent meds, no further information from the narrative.

In the post-marketing DSU database there were 3 cases of erythema multiforme, one case of epidermal necrolysis, and one case of Stevens-Johnson syndrome reported as associated with citalopram use. Erythema multiforme is appropriately included in the "Other Events Observed During Non-US Postmarketing" section in proposed labeling.

8.2.9 Special Senses

8.2.9.1 Adequacy of Assessment

Within the clinical development program, AEs related to special senses were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on special senses. This is also discussed in section 8.1.9.1.

Ophthalmological effects were specifically examined by the sponsor because preclinical studies had suggested the possibility of ocular pathology. Mydriasis and light-induced ocular lesions were observed during a two-year study in light-sensitive albino rats. Retinal degeneration, lens opacities, and keratitis were observed. No pathology was seen in rats in shorter studies of 1.5 years or less using higher doses, and no pathology was seen in mice out to two years, or in a one year dog study.

The eyes of patients in study 88A were specifically examined pre- and post-drug, and evaluation of post-marketing DSU database events for ocular problems was done. Study 88A was an open study conducted in depressed patients. Doses were 10-80 mg daily, for one year. These parameters were assessed: visual acuity, slit lamp exam with biomicroscopy of the anterior eye, tonometry, and fundoscopic exam. The study was suspended at FDA request due to cardiac toxicity findings in pre-clinical studies. Sixty-eight patients had been enrolled, for a maximum of 48 weeks. Thirty-nine had complete ophthalmologic data. Twenty males (median age 40 yrs.) were treated from 2-48 weeks (median 16 weeks) and 19 females (median age 52 yrs.) were treated for 1-48 weeks (median 18 weeks).

8.2.9.2 Special Senses Events Considered Possibly, Probably, or Definitely Related to Citalopram

None of the special senses SAEs appeared to be related to citalopram treatment.

8.2.9.3 Special Senses Events Unlikely to be Citalopram-Related

In Group 1 and 3 studies, one patient complained of blurred vision and was shown to have a cataract; its presence had been documented 5 years prior to

the study. Another patient with diplopia was on multiple other meds and died of a stroke one month after this complaint. An ophthalmologist thought she had an abducens palsy.

Exam at treatment termination in study 88A revealed no abnormalities for the 30 patients with normal exams at baseline, and no new abnormalities for the others.

Events reported via the post-marketing DSU database were similar to those reported in the development program and included 4 cases of "vision abnormal", two cases of "accommodation abnormal", and one case each of conjunctivitis, corneal edema, diplopia, glaucoma, mydriasis, photophobia, and photopsia.

In the post-marketing DSU database there were 5 cases of tinnitis reported as associated with citalopram use.

8.2.10 Genitourinary System

8.2.10.1 Adequacy of Assessment

Within the clinical development program, genitourinary system AEs and laboratory assessments were regularly documented. These evaluations are felt to be adequate to evaluate the effect of citalopram on the genitourinary system. Summarized information on urinalyses in Group 1, placebo-controlled, short-term studies is shown in Appendices 8.1.6.3.1.3 and 8.1.6.3.2.6.

Male ejaculatory dysfunction and female anorgasmia were evaluated by the sponsor as AEs of special interest. The Group 1 database for male subjects was searched for terms indicating ejaculation dysfunction, including premature ejaculation, ejaculatory failure, impotence, and erectile dysfunction. The Group 1 database for female subjects was searched for anorgasmia.

8.2.10.2 Genitourinary System Events Considered Possibly, Probably, or Definitely Related to Citalopram

None of the SAEs in this system appear to be possibly related to citalopram treatment.

Ejaculatory Dysfunction as an Adverse Event of Special Interest

In the fixed dose study 91206, 'ejaculation failure' and 'ejaculation disorder' occurred in 0% of patients on placebo and in from 2-4% in each dosage group; impotence occurred in 0% on placebo and 1-7% in each dosage group (Appx. 8.1.5.3.1). In the Group 1 short-term, placebo-controlled trials, 'ejaculation failure' occurred in 4.2% of citalopram patients and 1% on placebo; 'ejaculation disorder' occurred in 2.4% of patients on citalopram and 0% on placebo; impotence occurred in 3% of citalopram patients and in 0.4% on placebo.

No dose relationship was found for these problems, which tended to occur within 4 weeks after starting citalopram. In the seven Group 1 short-term,

placebo-controlled studies in depressed patients (n_{cit}=425 males), there were 2 ADOs secondary to male reproductive system dysfunction while on citalopram, and none on placebo. One ADO was for ejaculation failure and one for prostatic disorder (prostatic hypertrophy).

In the literature search done by the sponsor, a case report in a 47 y.o. man with anorgasmia on 60 mg of citalopram daily reported successful treatment of the problem, continuing the 60 mg dose, with cyproheptidine (4 mg/day).

Ejaculatory disorder and impotence are appropriately included in the proposed labeling in the TEAE table.

Female Anorgasmia as an Adverse Event of Special Interest

In the analysis of female anorgasmia as an adverse event of special interest in all Group 1 studies, 101 patients (3.6% of Group 1 females) treated with citalopram and 2 (0.6%) treated with placebo were identified. Anorgasmia occurred primarily (58%) in the 20-39 mg/day dose range. It also tended to occur within 4 weeks after starting citalopram.

In the seven Group 1 short-term, placebo-controlled studies in depressed patients (n_{cit}=638 females), there were no ADOs secondary to anorgasmia.

In the fixed dose study 91206, female anorgasmia occurred in 0% of patients on placebo and in one patient (< 1%) while on 40 mg (Appx. 8.1.5.3.1). In the Group 1 short-term, placebo-controlled trials, it occurred in 2.5% of citalopram patients and 0% on placebo.

It is recommended that female anorgasmia be included in labeling in the TEAE table.

8.2.10.3 Genitourinary System Events Unlikely to be Citalopram-Related

In Group 1 and 3 studies, there were 2 deaths associated with this system in elderly patients diagnosed with renal cancer about 6 weeks after beginning citalopram. There were 13 ADOs from Group 1 and 3 studies: renal insufficiency (1) (in a 42 y.o. female who was abusing laxatives and vomiting and developed hypokalemia and renal insufficiency due to the laxative abuse-study 8213, #1235), micturition disorder (1) (described only as "micturition difficulties" in a 66 y.o. man after 5 days of treatment), pregnancy (6), prostatectomy/hypertrophy (2), vaginal hemorrhage (1), breast cancer (2). In the placebo groups for Group 1 and 3 studies there were no SAEs in the genitourinary system with the exception of one unintended pregnancy and one case of breast fibroadenosis.

In addition to the ADOs noted above, SAEs in the urinary system included: micturition frequency (1), cystocele (1), urinary retention (1)(with benign prostatic hypertrophy), urinary tract infection (2).

In addition to the ADOs noted above, SAEs in the male reproductive system included: prostatic adenoma (2), prostatic disorder (prostatic hypertrophy) (1), testis disorder (1) (investigator terms:strained or drawn up testicles).

In addition to the ADOs noted above, SAEs in the female reproductive system in Group 1 and 3 studies included: leukoplakia genital (1), menorrhagia (1), ectopic pregnancy (1), unintended pregnancy (1), hysterectomy (6), gynecological problems (1), ovarian cyst (1), uterine cancer (1), uterine fibroid (1), breast cancer (3), benign breast neoplasm (2). In the 5 patients with breast cancer, diagnosis of the cancer was made after 1-8.5 months after treatment with citalopram began, three cases were in woman under 60, three were 60 and over.

8.2.11 Miscellaneous

8.2.11.1 Adequacy of Assessment

Miscellaneous serious AEs from Group 1, 2, and 3 studies, that didn't fit into any of the systems above are covered here and appeared to be adequately assessed. WHO body systems used for their classification by the sponsor are Body as a Whole-General Disorders and Resistance Mechanism Disorders. In addition, there is an Other category (not WHO) and an Unspecified category (not WHO).

8.2.11.2 Miscellaneous Events Considered Possibly, Probably, or Definitely Related to Citalopram

Allergic reaction

Study 94001, #183: 34 y.o. female developed a rash with itching over the whole body, fever, and swollen lymphatic glands 11 weeks after starting citalopram (20-40 mg). Liver enzymes and eosinophils were elevated. There were no concomitant medications. No further information was available in the submission from this Group 3 study.

In the post-marketing DSU database, there were 7 cases of allergic reaction reported as associated with citalopram use. One of these was reported as serious; it led to hospitalization.

Rash and urticaria are appropriately included in labeling as 'frequent' and infrequent', respectively, in the section on Other Premarketing Events Observed.

8.2.11.3 Miscellaneous Events Unlikely to be Citalopram-Related

In Group 1 and 3 studies:

Study 93401, #755: Sudden death in a 87 y.o. female with hypertension, gastritis with GI bleeding who was cachectic, dehydrated, and had numerous infected decubiti. She was probably septic and died 3 days after stopping a 5.5 month course of citalopram.

Two other deaths, one classified as neoplasm malignant and one as condition aggravated occurred in elderly people, the first with numerous medical problems and meds who died of pneumonia or an occult cancer, the other was a dementia patient whose dementia symptoms worsened after citalopram was started and who died shortly thereafter, no specific cause of death is noted. Two other deaths not reviewed elsewhere are listed under "Body as a Whole" by the sponsor, these were in 96 and 97 y.o. females with multiple medical problems and meds with cause of death reported as old age.

Dropouts due to SAEs in the "Body as a Whole" category included: noncardiac chest pain (2), malaise (1), therapeutic response decreased (1) (actually no response to 4 weeks of treatment, dose unknown), alcohol intolerance (2) (i.e., alcohol abuse and delirium tremens), allergic reaction (1) (to codeine).

One case of a dropout due to a nonserious laboratory abnormality (Appx. 8.1.6.3.3) with little other information is included here. An elderly patient (study 8213, #428) on no other meds, was found to have an increased alkaline phosphatase that had not decreased on followup after citalopram discontinuation at an unknown time interval.

Other SAEs noted under "Body as a Whole": influenza-like symptoms (2), noncardiac chest pain (2), malaise (2), anaphylactoid reaction (1) (to codeine), asthenia (1), therapeutic response decreased (29) (lack of efficacy), alcohol intolerance (1) ("acute alcoholism"), back pain (1), condition aggravated (4)(depression worsened in one case after 3 weeks of treatment and patient brought to ECT, in two other cases anxiety increased a few days to 3 weeks after starting drug, and in one case schizophrenic symptoms became worse), hospitalization (7) (three for lack of efficacy, one for surgery for rectal tumor, one for traumatic injuries, one overdose, and one dementia patient for social reasons), nasal polyp (1), traumatic injury (1) (car accident).
The sponsor list 8 SAEs under "Resistance Mechanism Disorders". There was one death in this group, in an elderly man with diabetes and liver cancer who became septic. There were 5 ADOs: abcess in buttocks, infected hand wound, pneumococcal infection, and 2 cases of influenza. Other SAEs listed here include another case of flu and a case of otitis media.

The sponsor lists 57 other patients who had SAEs that have not been covered elsewhere in this review under "Others (Not WHO)". Twenty-six of these are listed under "Hospitalization", none of these were deaths or ADOs. Reasons for hospitalizations were primarily for surgery, one was for ECT, 5 others were for depression. Twenty patients in this category were listed under traumatic injury which included fractures, car accidents, and falls. There was one death in this group secondary to traumatic injuries suffered in an accident. There are 9 cases listed under trauma non-pathological, which also include fractures, falls, and car accidents. There were 4 ADOs in this group. The 8 additional cases noted in a category called "Unspecified" were categorized by the sponsor on request and included patients with lack of efficacy, traumatic injuries, prostate tumor, and suicide attempt.

8.3 Summary of Key Serious Adverse Findings

8.3.1 Hyponatremia

In post-marketing DSU database reports, there were 16 cases of hyponatremia and 3 cases of SIADH reported to be associated with citalopram use. In four safety reports sent to the DNDP in the past year, four patients, who were all elderly and on other medications, with one in addition abusing alcohol, had hyponatremia. All recovered with treatment.

In Group 1 placebo-controlled, short-term studies, three (0.3%) patients on citalopram and none on placebo had hyponatremia (Appendix 8.1.6.3.2.4); none were classified as an SAE and all three normalized on continued drug treatment.

8.3.2 Mania

Forty patients (1%) on citalopram in Group 1 studies became manic or hypomanic, and one became manic on placebo. Mania was considered a serious AE in 6 patients in Group 1 and 3 studies and was a reason for withdrawal in 3 patients. These reactions usually occurred with treatment with 40 mg or less, and slightly more occurred after 8 weeks of treatment than earlier in the course. Mania was also documented in reports to the postmarketing DSU and in the literature.

8.3.3 Seizures

In Group 1 and 3 studies, 12 patients (0.06%) on citalopram had seizures that were classified as SAEs. At least 8 of these has predisposing medical conditions or a history of seizures. For Group 1 studies, the crude incidence on citalopram was 5/4168 (0.12%). There was no effect of dose or treatment duration. Eighteen cases were identified in the postmarketing DSU database.

8.3.4 Serotonin Syndrome

There were 8 cases of serotonin syndrome reported in the postmarketing DSU database and 4 cases in the literature. In one case citalopram alone had been administered parenterally and the patient recovered after 3 days. The other 3 involved overdoses of citalopram and moclobemide.

9.0 Labeling Review

The clinical sections of the sponsor's proposed labeling, which were submitted with the NDA, were reviewed.

Clinical Trials

The sponsor proposes to indicate that citalopram performed significantly better than placebo on various HAM-D subfactor scores, including the melancholia subfactor. However, validation of the melancholia subfactor as a clinically meaningful cluster of symptoms is lacking and, thus, it is recommended that mention of this subfactor be deleted from labeling. otherwise, this section, deseribing the studies establishing the efficacy of citalopram for major depression, is accurate as written. A statement on the range of ages of patients in the trials could be added.

Indications and usage

The last paragraph should be revised to indicate that efficacy in maintaining an antidepressant response for up to 24 (not 32) weeks was demonstrated. otherwise, this section is accurate as written.

Contraindications

This section is adequate as written.

Warnings

This section is adequate as written.

Precautions

GENERAL

In Group 1 studies, activation of mania/hypomania was reported in 1% of patients as a TEAE (n=40 on citalopram, n=1 on placebo).In the Group I placebo-controlled trials, the incidence of mania/hypomania was 0.68% on citalopram and 0.18% on placebo. These numbers should be used in labeling rather than the 0.1% figure which is in the proposed labeling.

Hyponatremia should be added as a precaution. In Group 1 placebo--controlled, short-term studies, three (0.3%) patients on citalopram and none on placebo had hyponatremia, and there have been several post-marketing reports, usually in elderly patients on other medications.

Interference with Cognitive and Motor Function

The statement in this section should be qualified, as the two studies done to assess cognitive and motor performance were quite limited.A more standard statement should be substituted:Any psychoactive drug may impair judgment, thinking or motor skills. Although in two small uncontrolled studies citalopram did not impair psychmotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram therapy does not affect their ability to engage in such activities.

These statements should be put in the "Information for Patients" section.

Completing Course of Therapy

In the Information for patients section, the proposed labeling says "although symptoms of depression may improve noticeably as early as one week after beginning treatment. . . . " This should be changed to :"may improve noticeably in one to four weeks."

Drug Interactions

Alprazolam was shown by the sponsor to be the only benzodiazepine tested that altered serum concentrations of citalopram and its metabolite demethylcitalopram (DCT), increasing them by 20% and 48%, respectively. Other benzodiazepines tested: oxazepam, diazepam, temazepan, clonazepam, lorazepam, chlorazepam, and chlordiazepoxide. A number of neuroleptics (perphenazine, thioridazine, haloperidol, chlorpromazine) reportedly did not affect serum citalopram or its metabolites. Clomipramine increased citalopram and DCT concentrations by 94% and 250%, respectively.This information could be added to labeling.

If any information on the effect of phenytoin and theophylline on citalopram concentrations and vice versa is available it should be added. Any information on the effects of drugs that are substrates of $P_{450}IIIA_4$ should also be added.

The statement of the alcohol precaution could be qualified a bit, from "does not produce or potentiate" to "has not been shown to produce or potentiate."

Pediatric Use

Change "children" to "pediatric patients."

Geriatric Use

Pharmacokinetic studies showed no differences in PK parameters between old and young people. This could be added if biopharm thinks the studies done were adequate.

otherwise, the "Precautions" section is adequate as written, though I would like to check with the biopharm reviewer on the Drug Interactions section and the pharmacology reviewer on carcinogenesis, mutagenesis, fertility, and pregnancy effects, when their reviews are completed.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Insomnia, somnolence, dry mouth, and asthenia should be added to the list of AEs here that have an incidence of at least 1% and occur at least twice the placebo incidence, as indicated in NDA Panel 5.1.1-1. Or Table 8.1.2.2 from the review: "Number (%) of Dropouts Secondary to Adverse Events from Short-Term, Placebo--Controlled Group 1 Studies" could be used instead. This table was constructed based on the data in NDA Panel 5.1.1-1.

Commonly Observed Adverse Events

The sponsor's statement here refers to events from the short-term, placebo-controlled studies, which are tabulated in Vol.1.298, Table 8.1.5.3.1.1 of the NDA submission.For the review, we chose to use the fixed dose study 91206 to ascertain AE incidence. In this review, Table 8.1.5.4: "Common and Drug-Related Treatment Emergent Adverse Events:Study 91206" shows the incidence of events that occurred in at least 5% of any dosage group of citalopram patients and occurred at least twice the placebo rate.Several more events meet the criteria using study 91206.

Incidence in Controlled Clinical Trials

The table the sponsor uses here includes all placebo-controlled clinical trials. For the review, we used the fixed dose study 91206.The 2% ADR table used is in Appx.8.1.5.3.1 of the review; it is quite extensive. There are 2 events which may be clinically important, that came out in the 91206 study with an incidence of at least 2% and twice the placebo rate, which did not come out in the TEAE table the sponsor included for labeling. These are bradycardia and palpitations. The incidences are quite low: for bradycardia, 2% in 3 of the 4 dosage groups and 0% on placebo and at the highest dose (60 mg), and for palpitations, 4% in the 20 mg group, and 2% on placebo and in the other dosage groups.They would probably be adequately represented in the following "Other Events" section as infrequent events.

In Table 1 of the proposed labeling, anorgasmia is not included though it occurred in 2.5% of citalopram-treated females, which is statistically significantly different from the 0% on placebo ($p < 0.05$, Fishers Exact). In addition, though not statistically significant, dysmenorrhea occurred in 2.4% of citalopram patients and 1.6% of placebo patients. As Table 1 cites events reported by at least 2% of citalopram patients, it should also be included in the table, rather than in the footnote at the bottom, where it is included as having a $\leq$ incidence on placebo.

The term "Micturition Disorder" in the table is nonspecific. In looking in the AE dictionary, it does not refer to urinary frequency, but to a number of terms that are just as vague: delayed micturition, impaired or difficult micturition/urination, micturition/urinary disturbances/problems, poor stream, and water works problems. The term could be footnoted as including mostly "difficulties with micturition" and "urinary hesitancy."

Dose Dependency of Adverse Events: The sponsor has not included anything in this section in the proposed labeling. The data from the large fixed dose study (91206) was used to address the doserelatedness of adverse events. In the NDA submission, a trend test (Jonckheere's) was applied to the citalopram dose groups to determine statistical significance for a trend. The events meeting these criteria included: insomnia ($p<0.004$), fatigue ($p<0.000$), somnolence ($p<0.004$), increased sweating ($p<0.001$), yawning ($p<0.004$), and impotence ($p<0.006$). This statement could be added or the information could be shown in a table.

Adaptation to Certain Adverse Events: Information on this was not provided in the submission; omission of this section is not objectionable.

The information on laboratory tests, weight, vital signs, and ECGs is adequate as written.

Other Events Observed During the Premarketing Evaluation of (citalopram hydrobromide)

This section is adequate if Table 1 in the proposed labeling is used, except for the following: in the submission TEAE table that Table I in the proposed labeling comes from, the term "headache," rather than "migraine" is used, and should be used here; as noted above, hyponatremia occurred in 0.3% of patients in short-term, placebo-controlled studies and should be added under "Metabolic and Nutritional Disorders" as an infrequent or rare event rather than under the postmarketing information.

There are a number of terms that are too vague to be meaningful: abnormal ECG, heart disorder, speech disorder, thyroid disorder, endocrine disorder,tooth disorder, pain, bone disorder, tendon disorder, sleep disorder, abnormal thinking, menstrual disorder, uterine disorder, prostatic disorder, testis disorder, penis disorder, respiratory disorder, skin disorder, abnormal urine, urethral disorder.

In looking in the adverse events dictionary, some of the investigator terms used under the above WHO terms are just as vague and I did not see any that were of serious concern. For some, such as prostate disorder, prostatic hypertrophy covers most of the investigator terms listed, but I guess it is not a WHO term; prostatic disorder may be the standard WHO term used for this. We could request that the sponsor attempt to classify these events more specifically if possible.

Postmarketing Reports

The term "hepatic function abnormal" is vague and a more specific one should be used if its meaning is not covered by other terms already in labeling.

Necrotizing hepatitis or hepatic necrosis should be added based on the following:

A case of biopsy proven necrotizing hepatitis was reported in a 15-day report submitted by the sponsor 11/6/97. The 69 y.o. man, after 4 weeks of treatment with 20 mg of citalopram, had dark urine, abnormal stools, pruritis. Concurrent meds were metoprolol & pentoxifylline, neither of which have hepatic necrosis listed in their labeling. He recovered.

Another 15-day report of necrotizing hepatitis, biopsy proven, was reported in the October 31, 1996 submission: A 47 y.o. woman was hospitalized for hypertension one month after starting citalopram; an enlarged liver and increased alkaline phosphatase (758 U/L) were found. There was no history of alcohol abuse; the problem resulted in prolonged hospitalization. She continues to be monitored. She was also on: bromazepam, bendrofluazide (a thiazide diuretic), and gestodene + ethinylestradiole.In the Martindale reference, bromazepam is said to be similar to diazepam, which has been associated with rare reports of hepatic necrosis.

Drug Abuse and Dependence

This section is adequate as written.

Overdosage

Add: ECG monitoring should be done. The potential usefulness of charcoal should be addressed by biopharmaceutics. Also, in postmarketing reports ventricular arrhythmia has been rarely reported.

Dosage and Administration

The section on initial treatment should be revised based on dose--response data from study 91206 (efficacious at 40 and 60 mg/day, not at 10 and 20 mg/day) and the dosing range used in study 85A (20-80 mg/day). As concluded in section 7.4, it does seem clear that the target dose range should include 40 to 60 mg/day, although it is less clear whether doses as low as 20 mg/day are effective and whether patients who are treated with 60 mg/day and who have a suboptimal response would benefit from a dose increase up to 80 mg/day.

Therefore, it is recommended that patients be initially treated with 20 mg/day, with an increase to 40 mg/day after one week. Patients not responding to 40 mg/day may benefit from a dose increase to 60 mg/day. Given limited experience with doses over 60 mg/day (i.e., a total of only 90 Group 1 patients received a mean daily dose >60 mg/day), higher doses cannot be recommended despite the possibility of enhanced efficacy with a further dose increase.

Otherwise, this section is acceptable.

Foreign Labeling

The labeling from 27 foreign countries was reviewed. Other countries where citalopram is approved use the sponsor's or one of the submitted countries' labeling. No additional safety issues were identified.

10.0 Conclusions

There is sufficient evidence to support the claim of efficacy of citalopram for major depression in doses of 40-60 mg/day.

Additionally, citalopram in the dose range of 20 to 60 mg/day has demonstrated efficacy in the prevention of depressive relapse for up to 24 weeks.

There is adequate evidence of reasonable safety under the conditions of use in the proposed labeling.

11.0 Recommendations

From a clinical standpoint, it is recommended that citalopram be approved for the treatment of major depression.

The labeling issues raised in section 9.0 should be addressed by the sponsor prior to finalization of labeling.

Additionally, it is recommended that the sponsor be requested to conduct an adequate, well-controlled study of citalopram in treating depression in children and adolescents.

/S/

Susan Molchan, M.D.
March 11, 1998

/S/

Gregory M. Dubitsky, M.D.
March 11, 1998

3-12-98

I agree that this NDA is approvable. See memo to file for more detailed comments.

/S/ MD

TL, DDP

cc: NDA 20-822
HFD-120
HFD-120/TLaughren
/GDubitsky
/SMolchan
/PDavid