SUMMARY BASIS OF APPROVAL

NDA 20-031

Applicant:
SmithKline Beecham Pharmaceuticals
Philadelphia, Pennsylvania 19101

Drug Generic Name:
Paroxetine Hydrochloride

Drug Trade Name:
Paxil

I. INDICATIONS FOR USE:

Paxil is indicated for the treatment of depression,* including severe depression and depression with associated symptoms of anxiety. It is also indicated for long-term treatment and prevention of relapse of depression. Paxil is effective in some patients who had not responded to previous tricyclic therapy. Clinicians who use Paxil should periodically re-evaluate its long-term usefulness for individual patients.

Paxil (paroxetine hydrochloride) safety and efficacy have been established in clinical trials in over 4,600 patients (ages 18 to 96 years) with depression.

In clinical trials, depression was defined as a prominent and relatively persistent depressed or dysphoric mood that usually interfered with daily functioning (nearly every day for at least two weeks). It included at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE:

Paxil is available in film-coated tablets for oral administration containing paroxetine hydrochloride equivalent to paroxetine as follows: 10 mg - yellow; 20 mg - pink (scored); 30 mg - blue; 40 mg - green; 50 mg - white.

The effectiveness of Paxil in depression (DSM-III category of major depressive disorder or Feighner's diagnostic criteria) was demonstrated in eight of thirteen six-week, placebo-controlled trials in outpatients (see Section V. Clinical Evidence of Effectiveness). Four of these studies also included an active-control, imipramine. None of these studies excluded patients with a history of resistant depression.

Additionally, a fixed-dose, parallel group, placebo-controlled study (PAR-09) was performed with patients randomized to placebo or 10 mg, 20 mg, 30 mg or 40 mg Paxil for up to 12 weeks. Treatment was initiated with the fixed-dose (i.e. no titration) and this was associated with a high dropout rate due to adverse experiences in the 30 and 40 mg groups.

This study demonstrated the lowest effective dosage of Paxil to be 20 mg/day. Moreover, results from this study suggest the occasional need for doses higher than 20 mg daily. In regards to safety, PAR 09 clearly demonstrated the need for gradual titration to higher dosage levels.

Pooled data from U.S. placebo-controlled studies (Protocols PAR-01, 02 and 03) also support the recommendation that doses greater than 20 mg are necessary in some patients. These studies used a flexible dosing schedule of 10 mg to 50 mg. In general, medication was increased during the first 3 weeks of the study in a dose titration regimen. The titration regimen reduced the dropout rate associated with'higher dosage levels, since enhanced tolerance develops at the lower doses. Analysis of the final doses indicate that the majority of patients (04%) received _> 30 mg, supporting the findings of the fixed-dose study (see Section V.B.1.e. Dose Response Study for further discussion).

It is advised that Paxil be administered as a single daily dose, usually in the morning, with or without food. Coadministration with food may decrease nausea. If a patient experiences unacceptable daytime somnolence with Paxil, consideration should be given to dosing at bedtime. The recommended initial dose is 20 mg per day and many patients appear to respond to this dose. As with all antidepressants, the full antidepressant effect may be delayed. Clinical response should be reviewed within one to three weeks of initiating therapy and thereafter as judged clinically appropriate. If indicated, the dosage may be increased in 10 mg/day increments, no more frequently than weekly. The therapeutic range is 20 to 50 mg/day. Gradual titration is recommended for patients who require higher doses of paroxetine as this allows tolerance to develop to some of the adverse experiences (e.g., nausea, headache).

As with other medications, a lower initial dosage may be considered for elderly and/or debilitated patients, and upward dose adjustments may be made if indicated. Dosage in this subpopulation should not exceed 40 mg/day.

There is no body of evidence available to answer the question of how long the patient treated with Paxil should receive therapy. It is generally agreed that acute episodes of depression usually require several months or longer of sustained pharmacologic therapy, and evidence from PAR-04 and PAR-05 suggests that long-term treatment with high-dose (i.e., the dose used in the acute phase) pharmacotherapy is effective in preventing relapse and recurrence. The physician should periodically evaluate each patient and assess the need for maintenance therapy versus the risks for recurrence.

Double-blind placebo- and imipramine-controlled evaluation of the efficacy of Paxil has shown that efficacy is maintained for periods of up to one year.

In clinical trials patients were switched immediately from tricyclic antidepressants to Paxil without untoward effects. At least 14 days should elapse between discontinuation of a MAOI or other serotonin reuptake inhibitor and initiation of Paxil therapy.

III. MANUFACTURING AND CONTROLS:

III.A. Manufacturing and Controls:

The new drug substance, paroxetine hydrochloride, is prepared by a multi-step, organic synthesis. Specifications for the new drug substance and methods to check these specifications are adequate to establish and maintain its identity, quality and purity.

Adequate specifications and test methods are also provided to identify, characterize and control the raw materials used in the synthesis of the bulk, new drug substance, and those excipients used to prepare the finished dosage form.

The manufacturing and control procedures for the tablets are adequately described and supported with data obtained to demonstrate the identity, strength, quality, and purity.

III.B. Stability Studies:

Data derived from stability studies, and the labeled storage conditions proposed are adequate to support a 36 month expiration dating for drug product packaged in high density polyethylene bottles and 24 months for the drug product packaged in single unit blister packages. An adequate stability commitment has also been made.

III.C. Methods Validation:

Analytical methods for paroxetine HCl, including a chirally specific identification, have been validated by two FDA laboratories. They have been found satisfactory for control and regulatory purposes.

III.D. Labeling:

Draft copies of immediate container labels and carton labels for capsules in bottles and blister packages are in compliance with the technical requirements pertaining to the following: proprietary name, generic name, ingredient statement, net contents, control number, expiration dating, storage conditions, prescription "Caution" statement, and applicant's name and address.

The information in the "Description", "Dosage and Administration" and "How Supplied" sections relating to chemistry and manufacturing controls is satisfactory. The trade name, PAXIL, is not in conflict with the name of any other marketed drug.

III.E. Establishment Inspection:

Manufacturing Review Branch (HFN-325), Division of Drug Quality Compliance, found operations at the facilities responsible for manufacturing, controls, packaging and labeling the finished drug product to be in compliance with the CGMP regulations.

.F. Environmental Impact Analysis Report:

An environmental impact statement has been provided in accordance with 21 CFR Part 25.21. This statement has been reviewed and found to be acceptable. Further environmental assessment is not necessary.

PHARMACOLOGY:

A. Pharmacodynamica:

Currently, the biological etiology of depression is considered to be a deficit in central noradrenergic and/or serotonergic function. The postulated mechanism of action of most clinically used antidepressants is blockade of the neuronal reuptake of norepinephrine (NE) and/or serotonin (5-HT). The earlier antidepressants were either non-selective between NE and 5-HT reuptake blockade or were selective for NE. Newer antidepressants, such as fluoxetine and sertraline, show selectivity for blockade of 5-HT reuptake.

Paroxetine is structurally dissimilar from currently marketed antidepressants. Its chemical name is (-)-trans-4tf-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy)methyl]piperidine hydrochloride hemihydrate.

In vitro, paroxetine was shown to be a potent inhibitor of the uptake of 5-HT (5~hydroxytryptamine or serotonin) into synaptosomes prepared from rat and mouse whole brain, and various regions of rat brain at low Nm concentrations. It was 8-2,500 (median 300) times more potent at inhibiting 5-HT compared to NE (norepinephrine)-uptake and it. was an even weaker inhibitor of DA (dopamine)-uptake, *in vitro.* Paroxetine was consistently more potent and selective than zimelidine, fluoxetine, sertraline, fluvoxamine and other reference antidepressants used in these in *vitro* studies.

The potency and selectivity of paroxetine for the inhibition of 5-HT uptake *in vitro* was confirmed in whole animal studies. For example, paroxetine inhibited 5-HT uptake into rat hypothalamic synaptosomes ex vivo, (ED_{50} 1.9 mg/kg p.o.) without affecting NE-uptake (ED_{50} >30mg/kg p.o.).

Paroxetine also inhibited the pharmacological and biochemical effects of agents which require uptake via the neuronal monoamine transporter complex for their activity. For example, paroxetine inhibited depletion of 5-HT in brain induced by 3-hydroxy-4-methyl-alpha-ethylphenethylamine (H75/12) in rats (ED_{50} 0.4 mg/kg p.o.) and p-chloroamphetamine (PCA) in mice, (ED_{50} 0.9 mg/kg i.p.). Furthermore, the central effects of the 5-HT precursor, 5-hydroxytryptophan, were potentiated by paroxetine in mice, {ED_{50} 0.4 mg/kg p.o.). The selectivity of paroxetine for 5-HT mechanisms was also established in these pharmacological models as paroxetine did not inhibit the action of agents that depend for their effect on the integrity of the NE-uptake carrier, i.e. inhibition of 3-hydroxy-4-methyl-alpha-methyl-phenethylamine (H77 *ill)* induced hypermotility in rats (ED_{50} >20 mg/kg s.c.). Paroxetine was consistently more potent than zimelidine, fluvoxamine and fluoxetine on 5-HT uptake

*

inhibition in all *in vivo* studies in rodents.

Radioligand binding studies demonstrated that, in contrast to tricyclic antidepressants and mianserin, paroxetine had little affinity for alpha$_1$, alpha$_2$, beta-adrenoceptors, dopamine *[Q$_2$)* , 5-HT^ 5-HT$_2$ and histamine (H$_1$) receptors, in *vitro.* Also, the compound was much less potent than mianserin in binding to central H$_1$ receptors in mice *in vivo.* Paroxetine did show some affinity for muscarinic cholinergic receptors, but much less than imipramine.

At doses that significantly inhibit 5-HT reuptake, paroxetine decreased the level of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in rat brain, whereas the level of 5-HT was unchanged. These results were compatible with the inhibition of 5-HT release from neurons due to raised intra-synaptic 5-HT as a result of 5-HT reuptake inhibition. In contrast, a similar dose of paroxetine failed to influence levels of the NE metabolite, 3-methoxy-4-hydroxyphenylethylene glycol, in rat brain. These effects on monoamine turnover confirmed the selectivity of paroxetine's effects on central 5-HT metabolism.

Paroxetine underwent extensive first-pass metabolism in the liver after oral administration and the metabolic route and pattern of metabolites of paroxetine were similar in rats, rhesus monkeys and man. The glucuronide and sulfate conjugates of the major metabolite predominate and both were considerably weaker, i.e. circa 3,000 and >10,000 times, than paroxetine as 5-HT reuptake inhibitors *in vitro.* They were also less active than paroxetine as norepinephrine reuptake inhibitors. Therefore they would be unlikely to contribute to paroxetine's therapeutic effect or to cause side-effects associated with norepinephrine uptake inhibitors.

Repeated administration of paroxetine to rat, mouse, rhesus monkey and man resulted in a profound fall in blood/platelet 5-HT levels due to inhibition of the 5-HT uptake mechanism in the platelet membrane. Inhibition of 5-HT uptake resulted in an inability to concentrate 5-HT in this tissue. The fall in platelet 5-HT, therefore, provided a measure of persistent 5-HT uptake inhibition in plasma. However the fall in platelet 5-HT did not appear to have any functional or pathological consequences. In the toxicological studies there were no indications of impairment of platelet function or of interference with hemostatic mechanisms. There have been rare reports of altered platelet function from laboratory studies in patients taking fluoxetine. There have been reports of abnormal bleeding in several patients taking fluoxetine, although it is unclear whether fluoxetine had a causative role. Increased mild bleeding events with unaltered prothrombin time were found in association with the use of paroxetine in some normal volunteers taking concomitant warfarin. The worldwide database was reviewed for adverse experiences that can be associated with a bleeding diathesis. Active controls showed a 1.5% rate, placebo 0.7% and paroxetine 1.6%. These frequencies are uncorrected for disparate duration of exposure to each treatment.

Persistently raised or lowered intrasynaptic levels of neurotransmitters result in sub- or supersensitivity of post-synaptic receptors,

respectively. Repeated administration of many antidepressants lowers the number of beta-adrenoceptors or 5-HT_2 receptors in rat brain. Paroxetine, 5 mg/kg i.p. administered for 21 days, selectively lowered the number of 5-IIT_2 receptors in this tissue. Whether this effect was related to paroxetine's antidepressant properties is not known at this time.

Cardiovascular studies in various animal species comparing the effects of paroxetine and tricyclic antidepressants such as amitriptyline, have demonstrated that paroxetine is unlikely to have the hypotensive potential or propensity to cause tachycardia or cardrtotoxicity of amitriptyline, due to the action of paroxetine through a selective 5-HT mechanism rather than actions on multiple receptors.

Drug interaction studies in animals have demonstrated that paroxetine did not potentiate the depressant effects of ethanol, nor did it potentiate the pharmacological properties of a number of centrally acting drugs including benzodiazepines, anti-convulsants and haloperidol. Interactions with monoamine oxidase inhibitors and morphine were observed. No clinically significant interactions with a number of antihypertensives, tyramine, or indomethacin were found.

ADME: Pharmacokinetics:

1. Absorption and Excretion:

Paroxetine was well absorbed from the gastrointestinal tract in all species (mouse, rat, dog, Rhesus monkey and man); however, there was evidence of incomplete and dose-dependent systemic availability of paroxetine that is probably due to substantial but dose-dependent first-pass metabolism. As a result, oral bioavailability can not be reliably calculated in any species.

There were some differences between species in routes of excretion. In rats and dogs the major route of elimination was via the biliary system to the feces. In mice, rhesus monkeys and man, however, urinary excretion was the predominant excretory pathway although biliary excretion does occur.

In all species that have been studied, less than 2% of paroxetine was excreted in the urine indicating that the compound was eliminated from the body by metabolism. Compared with animals, excretion of paroxetine and its metabolites took longer in man, a reflection of the longer plasma half-life. In man, steady-state was reached in 4 to 14 days and the terminal half-life on cessation of multiple dosing is about one day.

2. Tissue and Plasma Concentrations:

In all species there was extensive first-pass metabolism of paroxetine which leads to large amounts of metabolites entering the systemic circulation after a single oral dose of the compound. Even after an intravenous dose, metabolites accounted for a substantial portion of the compound-related material in plasma. The reduced systemic availability of paroxetine resulted from this extensive first-pass effect. However,

partial saturation of the first-pass effect occurred as doses of paroxetine were given on repeated occasions and on increasing the dose. There was also evidence of a reduced plasma clearance of paroxetine as its plasma concentration increases. As a result plasma concentrations of paroxetine during toxicology studies were much higher than expected for the dose levels employed showing markedly disproportionate increases at the higher dose levels.

This dose-dependent behavior or non-linear kinetics was observed in all species studied including man. However, in man it has been observed that patients exhibiting clear non-linearity were those in whom.plasma levels of paroxetine were initially low. By contrast, those patients with higher initial plasma levels exhibited linear pharmacokinetics. Compounds which have non-linear pharmacokinetic' properties show considerable inter-individual variability in both animals and man and this has also been observed with paroxetine.

Like all lipophilic amine compounds, paroxetine distributed extensively into tissues, particularly lung and liver. Data in rat and Rhesus monkeys revealed concentrations in these tissues 100-fold higher than those in blood. These physical data on distribution were reflected in the theoretical volumes of distribution terms calculated from plasma pharmacokinetic data: values many times bodyweight were obtained for rat, Rhesus monkey, and man. At equilibrium, less than 1% of the drug in the body was present in the plasma.

IV.B.3. Metabolism:

All species that have been studied use the same metabolic pathway. The metabolic patterns in plasma and urine are quantitatively similar. The first metabolic step in the liver is oxidation at the methylenedioxy-phenyl carbon atom. It is further metabolized, in part, by meta-methylation and conjugation (glucuronides and sulfates) to produce major metabolites in plasma, urine and bile. Para-methylation also occurs and cleavage of the ether linkage to form an alcohol which is also conjugated. Rapid conjugation means that very low levels of any free phenols exist only transiently in the plasma.

The glucuronide and sulfate conjugates of the major metabolite are considerably weaker, i.e. circa 3,000 and >10,000 times, than paroxetine as 5-HT reuptake inhibitor *in* vitro. They are also less active than paroxetine as norepinephrine reuptake inhibitors. Therefore, they are unlikely to contribute to paroxetine's therapeutic effect or to cause adverse reactions associated with norepinephrine uptake inhibitors.

Like other drugs of this class, paroxetine has recently been shown to inhibit the human cytochrome P450 IID6 isoenzyme, both *in vitro* and *in vivo.* It is possible that paroxetine and the other SSRIs may interfere with the clearance of other drugs metabolized by this particular isoenzyme (e.g., certain tricyclic antidepressants, neuroleptics, and type 1c antiarrhythmics).

IV.C. Acuta Toxicity

The oral and intravenous acute toxicity of paroxetine has been assessed in the mouse and rat. The approximate oral LD_{50} was similar for both species (mouse: 341 mg/kg and rat: 374 mg/kg). Intravenously, the approximate LD_{50} was 38 mg/kg for the mouse and 27 mg/kg for the rat. This differential between oral and intravenous toxicity is as expected. In both species, and by both routes, acute toxicity was associated with physical signs of CNS stimulation.

IV.D. Subacute/Chronic Toxicity:

IV.D.1. Studies performed (daily doses in parentheses):

Mouse (dietary administration)
1) 2 weeks (0, 12.5 and 25 mg/kg)
2) 4 weeks (0, 15, 25 and 40 mg/kg)
3) 4 weeks (0, 50, 75 and 100 mg/kg
T 4) 99 weeks, males; 105 weeks, females (0, 1, 5 and 25 mg/kg)

Rat (oral gavage administration)
1) 2 weeks (0, 5, 50 and 125 mg/kg)
2) 4 weeks (0, 4, 12 and 40 mg/kg)
3) 13 weeks {0, 4, 12 and 40 mg/kg)

Rat (dietary administration)
1) 2 weeks (0, 12.5 and 25 mg/kg)
2} 4 weeks (0, 50, 75 and 100 mg/kg)
3) 6 months (0, 1, 5 and 25) with 6 week recovery period
4) 12 months (0, 1, 5 and 25 mg/kg) with 8 week recovery period
5)105 weeks (0, 1, 5 and 20 mg/kg)

Rat (intravenous administration)
1) 2 weeks (0, 2, 5 and 12.5 mg/kg)

Rabbit (oral administration)
1) 2 weeks (0, 6, 12 and 24 mg/kg as the salt)

Dog (oral administration)
1) 5 weeks (5, 10 and 20 mg/kg)

Monkey (oral administration)
1) 4 weeks (4, 8 and 20 mg./kg)
2) 3 months (0, 0.8, 2 and ***S*** mg/kg)
3) 52 weeks (0, 1, 3.5 and 6 mg/kg) with a 6 month interim kill. With 8 weeks recovery after 52 weeks.

Monkey (intravenous administration)
1) 32 days (up to 16 mg/kg) - Maximum tolerated dose study 7 and 14 days (8 and 2mg/kg respectively).

IV.D.2. Results

Mouse: In dietary range-finding studies, deaths occurred at 50 mg/kg and above. No macroscopic abnormalities were noted in surviving mice in these studies. Reduced bodyweight gain was seen in males at 40 mg/kg. It was concluded that the high dose for a long-term dietary study in mice should not exceed 25 mg/kg.

In the carcinogenicity study there were no physical signs indicative of a reaction to treatment and none of the deaths during the study were considered to be related to paroxetine. Paroxetine was not carcinogenic in mice.

Rat: Range-finding studies indicated that doses of 40 mg/kg and above were not tolerated due to physical signs of CNS stimulation. Consequently, a high dose of 25 mg/kg by dietary administration was chosen for the 6 and 12 month studies. Hepatic effects have been demonstrated by increases in serum enzymes and/or liver weight at 25 mg/kg and above but with no evidence of hepatotoxicity on histopathological examination.

Paroxetine has an amphiphilic structure and for such compounds this leads to an accumulation of compound in lysosomes which causes impairment of phospholipid catabolism and hence accumulation of phospholipid. Phospholipidosis has been observed with paroxetine at doses of 25 mg/kg and above. The tissues affected were the lungs, mesenteric lymph nodes, epididymides and retina; effects in the retina were seen by electron microscopy only. Regression of these changes in the 12 month study was complete after an 8-week recovery period. •

It was concluded that in the 6 month and 12 month studies 5 mg/kg was the no-effect dose for target organ toxicity.

In the carcinogenicity study a reduction in bodyweight gain and food consumption was observed at the high dose of 20 mg/kg throughout the study. There was no evidence of a carcinogenic effect of paroxetine in the rat.

Rhesus Monkey: In the one month range-finding study, deaths occurred at 20 mg/kg and physical signs of CNS stimulation were seen at all dosages. Reductions in bodyweight and appetite occurred at 20 and 8 mg/kg but not at 4 mg/kg. In the 12 month study one monkey at the high dose (6 mg/kg) died unexpectedly during week 27. The cause of death could not be determined but since there was no preceding clinical deterioration it was unlikely that the death was related to treatment with paroxetine. Bodyweight gain and food consumption were reduced throughout the study at 6 mg/kg and to a lesser extent at 3.5 mg/kg during the first 6 months; there was no effect at 1 mg/kg. There were no adverse biochemical or histopathological changes at any dosage. Electron microscopy of the liver, mesenteric lymph node and retina did not show evidence of phospholipidosis.

IV.E. Mutagenicity

A battery of mutagenicity tests has been conducted *in vitro* and in *vivo* to examine for effects on specific gene loci, chromosomes and mammalian germ cells (dominant lethal assay). In addition, the ability of the compound to cause repairable DNA damage has been examined in vitro. Paroxetine did not show evidence of genotoxicity in any of these systems.

IV.F. Reproduction

IV.F.1 - Embryotoxicity/Teratogenicity

Rabbits: Dosages of 1, 3 and 6 mg/kg were administered from day 6-18 of gestation. Dams at 6 mg/kg showed some sedation and reduced weight gain. There were no adverse effects on the embryo or fetus and no teratogenic effects.

Rat: Dosages of 5, 15 and 50 mg/kg were administered from day 6-15 of gestation. Maternal toxicity was observed at 15 and 50 mg/kg at which doses there was reduced fetal weight and associated skeletal immaturity. At 50 mg/kg there was some evidence of increased post-implantation loss. There were no selective effects on the embryo or fetus or evidence of teratogenicity.

IV.F.2. Reproductive Function

In a fertility study in rats where both sexes were treated at 5, 15 and 50 mg/kg there was a reduced pregnancy rate and increased post-implantation loss at 15 and 50 mg/kg, increased pre-implantation loss at 50 mg/kg and increased post-partum loss at all dosages. At -15 and 50 mg/kg the effects were associated with marked adverse effects on the parent animals.The no-effect dose for reduced pregnancy rate was 5 mg/kg. Further studies were conducted to investigate whether the effect on pregnancy was due to the male or female or to both. These studies showed that the effect could be attributed to the male.

IV.F.3. Peri- and Post-Natal Development

Oral administration of paroxetine to pregnant rats at 1 mg/kg/day had no significant effect on peri- and post-natal development of the offspring. At 3.3 and 10 mg/kg/day treatment from day 5 postpartum had no effect on post-natal development.

V. CLINICAL EVIDENCE:

V.A. Overview of Effectiveness Data:

The clinical trials program to evaluate the effectiveness of paroxetine was carried out in adult inpatients and outpatients with diagnoses of major depressive disorder (DSM-III).

There were 8 placebo-controlled trials {PAR 01, PAR 02-01, 02-02, 02-03, 02-04, PAR 083, 1.006, 1.009), 10 placebo- and active-controlled trials (PAR 03-01, 03-02, 03-03, 03-04, 03-05, 03-06, 04, 07, 1.007, 1.012), 41 active-controlled trials (1-03, 1.04, 1.13, 1.20, 1.22, 1.25, 1.26, 1.27, 1.28, 1.28A, 1.29, 1.30, 1.32, 1.35, 1.38, 1.43, 1.46, 1.49, 4.01, 6.47, 6.64, 6.67, 6.74, 6.85, 237C/D/E/F/G/I/J/L, 238A/B/D/E/F/G, 1729M, 2216-2219, 2321-2326, 2401-2406, 6134, 6148, 6162, 7119, 7123, 7124, 7201, PAR 06, PAR 11, HQMDIII, MDB PAR/1/B/C/D/EM), 22 open trials and one placebo-controlled dose-response trial (PAR 09). Thirteen studies were designed to include only elderly patients (117A, 1.26, 1.28, 1.40, 1.42, 1.44, 1.46, 1.49, HP/84/35A, MDF/1727 M/C Comp, MDF/1728 Comp, MDF/1729, PAR 06, PAR 11), four others recruited only elderly (1.05, 117C, DFG 86/121/126, and MDF/1729M), while the remainder included adults with a wide age range (18-90 yrs.) . The duration of the studies ranged from 6 weeks to 4 years. Eighteen of the controlled trials were in hospitalized patients (1.20, 1.22, 6.47, 6.64, 6.67, 6.74, 6.85, 128A, 2216-2219, 6134, 6148, 6162, 7119, 7123, 7124, 7201, MDF 1727 M/C, PAR 07) and 8 uncontrolled trials were in hospitalized patients (1.05, 6.65, 6126, 6164, 7101, 7102, 117C, DFG 86/121/126). The remainder of the studies entered depressed outpatients.

Studies Providing Primary Evidence of Effectiveness:

1. Double-Blind Studies With a Placebo Control:

A total of 17 placebo-controlled (PAR 01, PAR 02-01, 02-02, 02-03, 02-04, PAR 09, 1.006, 1.009, PAR 083) and placebo and active-controlled trials (PAR 03-01, 03-02, 03-03, 03-04, 03-05,. 03-06, 1.012, 1.007) were conducted worldwide to assess the short-term response to paroxetine in outpatients diagnosed as having major depressive illness. Two placebo trials (PAR 04, PAR 083) also examined long-term effectiveness of paroxetine in outpatient diagnosed as having major depressive illness. Thirteen of the studies (PAR 01, PAR 02-01, 02-02, 02-03, 02-04, PAR 09, PAR 03-01, 03-02, 03-03, 03-04, 03-05, 03-06, PAR 04) were conducted in the U.S. No attempt was made to exclude patients with a history of resistant depression (by any definition).

Fifteen of these studies (PAR 01, PAR 02-01, 02-02, 02-03, 02-04, 1.006, 1.009, PAR 03-01, 03-02, 03-03, 03-04, 03-05, 03-06, 1.012, 1.007) were designed as single-center pivotal studies to demonstrate the effectiveness of paroxetine in the treatment of depression. Trials 1.012 and 1.007 did not recruit sufficiently to be considered further. Protocol PAR-09, a U.S. multicenter, fixed-dose, placebo-controlled study was designed to establish the minimum effective dose and effective dosage range of paroxetine. Six of the efficacy studies (the PAR-03 series) had a positive-control imipramine treatment arm. All of the U.S. efficacy studies had a treatment phase of 6 weeks and a flexible dosing schedule of paroxetine 10 to 50 mg given as a single morning dose. The two non-U.S. studies were the exceptions as they were of fixed dose design (30 mg in the evening), and one was a 4 week study. All the U.S. and non-U.S. efficacy studies were conducted at single study sites by single investigators and were not multicenter studies.

In order to succinctly present a very large and complex database, the

following discussion will center on the ten placebo-controlled outpatient studies of the PAR-02 protocol and PAR-03 protocol series which were conducted in the **U.S.** The PAR-09 dose response trial and the PAR 04 and PAR 083 long-term effectiveness trials will be presented later.

1.a. PAR-02 Series

Study Design:
The four stand-alone studies that followed protocol PAR-02 were six week, double blind, randomized, parallel group comparisons of paroxetine and placebo in depressed outpatients. Patients were required to meet DSM-III criteria for major depressive disorder, have a screen and baseline total score of at least 18 on the first 17 items of the 21 item Hamilton Rating Scale for Depression (HAMD), have a Raskin Depression scale score of at least 8, which was required to exceed that of the Covi Anxiety Scale score, and have a decrease of less than 20% in the HAMD total score between screen and baseline. Exclusion criteria also included significant physical illness, concurrent use of other psychotropic medication, and serious suicide risk.

Patients were randomly assigned to paroxetine or placebo. The protocol required a minimum 7-day placebo washout period for patients receiving any psychotropic medication and a minimum 14-day washout for patients receiving monoamine oxidase inhibitors. Patients who had not been receiving psychotropic medication had a placebo washout period of 4-10 days. After the washout period (to eliminate placebo responders), patients were to be titrated to an effective dosage range. The allowable dose range of paroxetine was 10 mg to 50 mg in single daily doses. All patients randomized to paroxetine began dosing at 20 mg. The protocol required six visits during the active phase of the study, a baseline visit and visits at nominal days 7, 14, 21, 28 and 42. At the day 7 visit, the investigators had the option of increasing, decreasing, or maintaining the dose depending upon the patient's response. Dose adjustment was allowed at all subsequent visits. Efficacy assessments were completed at each patient visit and included the HAMD (21-item) Total, Clinical Global Impression (CGI) Severity of Illness, Symptom Checklist-56 (SCL-56), Montgomery-Asberg Depression Rating Scale (MADRS), Patients Global Evaluation (PGE), Raskin Depression Scale and Covi Anxiety Scale. Safety assessments included physical exams, vital signs, clinical labs and adverse event reports. Concomitant psychotropic medications were prohibited.

Data are presented for the Extender (LOCF) dataset of the Intent-to-Treat population. The Intent-to-Treat population included all patients who received study drug and were subsequently evaluated for symptoms at least once during the active treatment phase of the study. Within the Intent-to-Treat population. Visit-wise (observed cases) and Extender datasets were defined. The Visit-wise dataset consisted of the assessment of each patient at each visit. The Extender dataset is based on the Visit-wise dataset with the modification that missing data are estimated by bringing forward the data from the last available assessment while the patient was receiving study medication. Thus the last efficacy scores for each patient are carried throughout the analysis even if the patient discontinued.

1.b. PAR-03 Series

Study Design:

The design of the studies in the PAR-03 series was similar to that of the PAR-02 series except there was a positive control imipramine arm in addition to placebo and paroxetine arms. The starting dose of paroxetine was 20 mg/day, given as a single morning dose; dose could be adjusted in 10 mg increments (or decrements) at weekly intervals within the dose range of 10-50 mg/day. The starting dose for imipramine was 80 mg/day, given in divided doses (30 mg in the morning and 50 mg in the evening) to reflect clinical practice. Dose could be adjusted upward in 65 mg increments (15 mg in the morning, 50 mg in the evening) to a maximum dosage of 275 mg/day. The allowable dose range for imipramine was 65-275 mg/day. The safety evaluations also included chest x-rays, ophthalmological exams, and ECGs .

I.e. Summary Results:

Table 1 provides a qualitative overview of the results of all six efficacy variables from the ten studies of the PAR-02 and PAR-03 series. Eight studies (PAR 02-01, 02-02, 02-04, 03-01, 03-02, 03-04, 03-05, 03¬06) demonstrated statistical superiority to placebo in at least two outcome variables, and five of the eight (PAR 02-01, 02-04, 03-01, 03-05, 03-06) demonstrated statistically significant superiority over placebo for both the HAMD Total and the CGI Severity of Illness item at week 4. Furthermore, for these five studies, significant improvement was also seen in the majority of the other outcome variables in addition to the HAMD Total and CGI scores. These criteria had to be met at a timepoint (usually week 4) in each study when at least 70% of the Intent-To-Treat population were still enrolled. This so-called "70% rule" is often used as a benchmark to compensate for variable drop-out rates across treatment groups. Thus, week 4 becomes the key endpoint for assessing antidepressant activity versus placebo. It is also noteworthy that the pattern of significant differences was similar at the week 6 endpoint to the results obtained at week 4. Three other trials (PAR 02-02, 03-02, 03-04) demonstrated statistical superiority in one other variable at the week 6 endpoint.

The five pivotal trials providing the most evidence for the effectiveness of paroxetine will be discussed here in greater detail. Two of these studies (PAR 02-01 and PAR 02-04) were two-armed placebo-paroxetine comparisons. The other three studies (PAR 03-01, PAR 03-05, and PA 3-06) also included an imipramine arm as the active control. Table 2 displays the mean HAMD Total and CGI Severity of Illness score improvements for these studies at the week 4 timepoint. For the changes from baseline in psychomotor rating scales presented in Table 2 and in subsequent efficacy tables, improvement is indicated by negative values.

With few exceptions, each study also showed that paroxetine was superior to placebo for the other four efficacy variables (see Table 1) . In fact, with the exception of SCL Depression factor, for which three studies failed to show statistically significant differences at the week 4 endpoint, and the HAMD Depressed Mood item, for which one study failed to demonstrate such statistical difference, statistically significant

#

changes favoring paroxetine over placebo were demonstrated for all other variables for each study. The pattern of significant differences in these psychometric scales was similar at the week: 6 endpoint, although fewer than 70% of the original population remained in the study by that assessment.

V.B.1.d. Detailed Results:

Protocol PAR 02-01
Table 3 presents demographic characteristics for study PfR 02-01.

At week four, significant differences in favor of paroxetine were noted for all efficacy variables except the HAMD Depressed Mood Item and the SCL Depression Factor (Table 4). At week six, only the SCL Depression Factor did not attain statistical significance {data not shown).

Table 5 presents HAMD Total score improvement from baseline by weekly intervals. The extender dataset (or last observation carried forward) and the visit-wise dataset each show a difference from placebo at endpoint weeks 4 and 6.

Table ***S*** compares reasons for premature termination between each of the treatment groups and demonstrated no statistically significant difference between treatment groups for any of the reasons for dropout. Table 7 presents dosing patterns for each arm of this study and shows significantly more placebo capsules than paroxetine capsules being used per day in an effort to achieve clinical response.

Protocol PAR 02-04
Table 8 presents demographic data from the PAR 02-04 study.

At week four, significant differences in favor of paroxetine were noted for all efficacy variables (Table 9). Similarly, significant differences in favor of paroxetine were noted for all efficacy variables at week six (data not shown).

Table 10 presents the HAMD Total from baseline at weekly intervals, and again shows difference from placebo by the week 2 visit. Table 11 summarizes premature termination from study by reason, again showing no statistically significant difference between treatment groups for any of the reasons **for** dropout. Table 12 presents study dosing information and shows significantly more placebo capsules than paroxetine capsules being used **per day in an** effort **to** achieve clinical response.

Protocol PAR 03-01
Table 13 presents demographic data for patients in PAR 03-01.

At both **week** 4 (Table 14) and week 6 (data not shown) evaluations, significant differences **in** favor **of** paroxetine over placebo were noted for all efficacy variables except the SCL Depression factor. In contrast, only **the** HAMD Depressed **Mood** item **and** CGI Severity of Illness variable attained statistical significance between imipramine and placebo at **week** 4. Similar results were seen at week 6. **No** statistical differences were detected between the two active treatments although the

numerical trend favored paroxetine over imipramine.

Table 15 shows the HAMD Total's mean change from baseline over time. Here again paroxetine is significantly different from placebo by week 2 and maintains that difference through the endpoints.

Tables 16 indicates statistically significant differences in the dropouts for drug-related adverse experiences between paroxetine and placebo and between imipramine and placebo. There were no statistically significant differences between paroxetine and imipramine. Table 17 presents information on dosing.

Protocol PAR 03-05
Table 18 presents demographic data for study 03-05.

At both week 4 (Table 19) and week 6 (data not shown) evaluations, significant differences in favor of paroxetine over placebo were noted for all efficacy variables except the SCL depression factor at week 4. Significant differences for imipramine versus placebo were also noted for all variables. In this study the effects of imipramine were more pronounced than those of paroxetine.

Table 20 presents the HAMD Total score mean improvement from baseline and this time shows imipramine as superior to paroxetine at weeks 4 and 6, although paroxetine was, in turn, superior to placebo.

Table 21 reveals no difference across treatment groups with regard to reason for dropout. Table 22 presents dosing information.

Protocol PAR 03-06
Table 23 summarizes the demographic distributions for study PAR 03-06.

At week 4 (Table 24), significant differences in favor of paroxetine over placebo were noted for all efficacy variables. Significant differences in favor of imipramine over placebo were noted for the HAMD Total, CGI Severity of Illness, and MADRS score, but not for the other variables. Results at week 6 (not shown) were similar to those at week 4. Paroxetine was statistically superior to placebo for all efficacy variables. Statistical significance in favor of imipramine over placebo was noted for all variables except the HAMD Retardation factor and the HAMD Depressed Mood item. No statistical differences were noted between the active treatments at week 4 or week 6. The effects of paroxetine were greater, although not significantly, than those of imipramine.
Table 25 presents the HAMD Total score's improvements over time which again shows paroxetine as significantly different from placebo at weeks 2 through 6. Tables 26 and 27 present dropout and dosing data, respectively.

.I.e. **Dose Response Study:**

PAR-09
Study Design:
This was a fixed dose, double blind, parallel-group, placebo controlled multicenter study conducted in outpatients to define the minimum

effective dose and effective dosage range in the treatment of depression. After a 4- to 14-day placebo washout, patients were randomized to placebo or to 10 mg, 20 mg, 30 mg, or 40 mg paroxetine for up to 12 weeks. Patients were started and maintained at fixed dose, with no titration.

Results:

Pair-wise comparisons of HAMD mean change scores showed significant differences between 10 mg and each of the higher doses (Table 28). The "week 1 completer" dataset includes all patients who completed at least the first 10 days of the study and is intended to compensate for the fact that patients were not titrated to the assigned dose, leading to a higher-than-normal rate of dropouts. This dataset included' 398 patients (placebo - 47; 10 mg - 91; 20mg -93; 30 mg - 83; 40 mg - 84). The mean changes in HAMD results clustered into two groups: the placebo and 10 mg treatments in one group, and the 20 mg, 30 mg, and 40 mg treatments in the second group. The interpretation is confounded by the unusually high placebo response observed in this study and the relatively small placebo sample size which is half that of the paroxetine groups. Nevertheless, statistically significant differences were noted for most efficacy variables, including HAMD mean change, when comparing the 10 mg treatment group to each of the 20 mg, 30 mg, and 40 mg treatment groups. Statistical significance was also noted for some variables in placebo comparisons with the three higher dose groups (see Table 28). In contrast, no statistically significant differences were noted between the 20 mg, 30 mg, or 40 mg treatment groups, nor was the 10 mg treatment group ever statistically different from placebo. Because 10 mg was ineffective in producing significant improvement and a significant difference was detected between the 10 mg and 20 mg treatment groups, 20 mg is established as the lowest effective dose of paroxetine.

Table 29 provides a summary of the major reasons for patients withdrawing prematurely from the PAR-09 study. The majority of adverse experiences causing patients to drop out of this fixed-dose study occurred during the first week of treatment and were dose-related. The larger initial doses of paroxetine were associated with a greater incidence of patient withdrawal due to lack of tolerability. In PAR 09, 51% of dropouts due to adverse experiences occurred in week 1. Although the 10 mg dose caused the least number of dropouts, it was less effective than placebo in this study. However, 20 mg was therapeutically active and was associated with the second least number of dropouts, thus offering additional support for 20 mg as the optimal initial dose.

Inspection of the results for 20 mg, 30 mg, and 40 mg paroxetine in Table 28 suggests little difference in efficacy between the therapies. A flat dose-response curve was seen across this range, indicating that in most patients doses above 20 mg would not be required. However, consideration of the patient dropouts in study PAR 09 due to lack of efficacy (LOE) indicated a linear decline (Table 29), suggesting that some patients may require doses of paroxetine greater than 20 mg.

Other Data Relating to Dose:

Pooled data from the US placebo-controlled studies also support the recommendation that doses greater than 20 mg are necessary in some patients. These studies used a flexible dosing schedule of 10 mg to 50

mg. In general, medication was increased during the first 3 weeks of the study in a dose titration regimen to improve tolerance although down-titration to tolerance was allowed if deemed necessary. Analysis of the final doses indicate that the majority of patients (83%) received >30 mg, supporting the findings of the fixed-dose study. Titration upwards from 20 mg improved efficacy as reflected in HAMD scores. However, this design had the effect of biasing investigators to elect to titrate upwards yielding results which may have overestimated the dose of paroxetine required to obtain a therapeutic response.

Data from two long-term U.S. studies, PAR 04 and PAR 05 (studies described under Long Term Effectiveness) offer additional support for this recommendation and used a more flexible pattern of dosing than that illustrated by fixed-dose (PAR 09) or scheduled increment studies (PAR 02 and 03 series) . PAR 04 was a long-term continuation of a short-term study (PAR 03) with a 10 mg to 50 mg dose range. Dosing data from PAR 04 show that the mean daily dose of paroxetine was 33.5 mg/day, and the mean maximum daily dose was 39.6 mg/day. At the end of the first year, 17% were receiving 50 mg/day, 3% 40 mg/day and 11% 30 mg/day. The open-label, non-comparator PAR 05 also had a 10 mg to 50 mg dose range. In this study, the mean daily dose of paroxetine was 30 mg/day, and the mean maximum daily dose was 40.4 mg/day. These two studies show that patients on a long-term regimen received paroxetine within the recommended dose range, and also indicate a trend toward doses higher than 20 mg for optimal maintenance therapy in some patients.

Dose escalation in the titration studies was associated with less risk of dropout due to adverse experiences since tolerance to many of the side effects of paroxetine develops at the lower dose. The adverse experience profile from the PAR 09 fixed dosed study (data not shown) , and the PAR 09 dropout rates (Table 29) confirm the existence of a dose-response relationship when patients are acutely confronted with higher doses without titration.

These studies indicate that 20 mg once daily is the optimal initial dose and that the therapeutic dose ranges from 20 mg to 50 mg. Many patients will respond favorably to 20 mg of paroxetine. However, dose adjustment may be required during both short- and long-term therapy in some patients.

2. **Active-Controlled Studies:**

Forty-one active control double-blind studies have been conducted worldwide in which out-patients received paroxetine or an active control (imipramine, mianserin, amitriptyline, or clomipramine). The results of nine of these trials are briefly summarized here together with the six U.S. PAR-03 studies discussed in the previous section as placebo-controlled trials. The majority of the remaining trials were analyzed only for the safety aspects of the trials. Table 30 displays the changes in the week 6 HAMD Total scores for these studies and the results show no difference in efficacy between paroxetine and standard tricyclic antidepressant therapies. Twelve studies showed no significant difference betv/een the active treatments for HAMD Total score improvement. However three studies showed significant differences

between active treatment; PAR 03-04 demonstrated paroxetine to be significantly superior to imipramine, whereas PAR 03-05 showed imipramine to be superior to paroxetine and DFG/119 favored clomipramine significantly over paroxetine.

V.C. Long-Term Effectiveness and Prevention of Relapse:

Table 31 summarizes demographic data for the three treatment groups of PAR-04. This was a long-term continuation for patients who had participated in the six 6-week PAR-03 studies. Patients who completed the PAR-03 protocol could choose either to continue receiving the same treatment in PAR-04 as they had in PAR-03 (continuation patients) or they could switch to the alternate active drug (crossover patients). All patients electing to switch from placebo were given paroxetine. Although a double-blind was maintained for one year, strict randomization was lost when patients were offered the opportunity to switch or remain on their double-blind PAR 03 treatment. Randomization was further lost as all placebo nonresponders entered into paroxetine treatment.

Tables 32 and 33 display the mean scores at the PAR-03 baseline, endpoint of PAR-03 (PAR-04 baseline), and at various time intervals across PAR-04 for the HAMD Total and CGI Severity of Illness scores using a Visit-wise dataset. Table 34 summarizes patient termination from the study by reason. Table 35 presents dosing information for the study.

The HAMD Total mean scores for patients who were maintained on the same treatment in PAR-04 as they had received in PAR-03 were, in general, similar throughout the duration of PAR-04. At the end of the year, the means for the HAMD Total among continuation patients were 9.8 for paroxetine, 6.3 for placebo, and 6.8 for imipramine. Patients who were switched to paroxetine or imipramine in PAR-04 showed a gradual reduction in the HAMD Total during the first three months of PAR-04, indicative of improvement, after which the scores were stable throughout the remainder of the study period. The overall (continuation plus cross over) HAMD Total mean scores at the end of the year were 8.4 for paroxetine, 6.3 for placebo, and 7.1 for imipramine.

Results of the CGI Severity of Illness item were similar to the HAMD Total. Continuation patients showed relatively constant mean scores throughout the duration of PAR-04. For patients who were switched to one of the active treatments, a gradual reduction was noted for the first three months, after which the scores were relatively stable. Overall, the mean scores for the CGI Severity of Illness item at the end of the year were 2.0, 1.6, and 1.7 for paroxetine, placebo, and imipramine, respectively.

Data from PAR-04 were examined retrospectively to determine duration of response and rate of relapse. Post-hoc creation of relapse categories raises the issue of data conditioned analyses in the interpretation of the results. A response was defined as a HAMD Total score of 8 or less while the patient was on medication. A relapse was defined as a HAMD Total score of 18 or greater occurring after the patient had experienced the defined response to therapy. For continuation patients in PAR-04, a response could begin at the endpoint visit of PAR-03; for crossover

patients, a response could begin at visit 07 (following one week oC active PAR-04 treatment).

Table 36 summarizes relapse data for PAR-04, including the percent of patients who relapsed, raw mean duration of response for those who relapsed, and time to relapse derived from Kaplan-Meier estimates *tor* all patients. The data show that the rate of relapse was similar between the two active treatment groups (14% and 12% for paroxetine and imipramine, respectively) . In contrast, the placebo group had a relapse rate *oZ* 23%. Paroxetine had a substantially longer duration of response and longer estimated time to relapse than did either imipramine or placebo.

These results indicate that paroxetine is as effective as standard tricyclic controls in preventing the reappearance of depressive symptoms. This finding was valid for up to one year following the index illness.

PAR-05: Protocol PAR 05 was a long term, open label, noncomparative trial in which all patients received paroxetine. Table 37 presents demographic data for the 353 patients who entered the PAR-05 study.

Table 38 presents mean HAMD Total and CGI Severity of Illness scores over the first year of the study together with mean scores for patients who entered the extension beyond one year. As expected, symptom scores improved substantially during the first 6 weeks of paroxetine therapy. Clinical improvement continued at a reduced rate throughout the remainder of the first year and was maintained during the study extension. The 76 patients who remained enrolled beyond the first year provide a cohort of patients from which there were no dropouts. This cohort demonstrated continued improvement past the first year. Table 39 presents dosing information for. the study.

Effectiveness in the Elderly:

The effectiveness of paroxetine in elderly patients was assessed in U.S. trial PAR 06/11, This was a six-week double-blind doxepin-controlled study in which 136 patients were randomized to paroxetine (91 completed) and 135 were randomized to doxepin (96 completed) . Of the 271 patients, 125 were males and 146 females. The patients in this trial were 60 years of age or older. A summary of the efficacy results (change from baseline) for the primary outcome variables at the week six endpoint are presented in Table 40 for the intent-to-treat population, extender dataset. The data indicate that paroxetine was at least equivalent to doxepin with trends to superiority. Paroxetine was also better tolerated than doxepin.

The effectiveness of paroxetine in depressed elderly patients was also assessed with an analysis conducted on patient data combined into two subgroups: 1) All worldwide double-blind, controlled studies; and 2) all worldwide double-blind, controlled studies conducted specifically in geriatric patients. MDF/2 9060/III/86/17 28M; MDUK/290 60/III/85/02 6; MDF/29060/1727/M; MDUK/29060/III/35/028; PAR 06/11; MDUK/29060/86/046 ; MDUK/29060/111/87/049

For purposes of these comparisons, an elderly patient was defined as a

patient 65 years or older (except PAR 06/11 which included patients age 60 and over) although other subsets were also examined. The results from the analysis of variance for HAMD Total and CGI scores are summarized in Table 41. The comparisons of treatment by age group showed no significant differences, indicating that symptom improvement associated with paroxetine therapy is similar among elderly and non-elderly patients. The number of elderly patients receiving placebo was relatively small (n = 21) and placebo comparisons from this pooled analysis are not presented here. Improvement seen with positive controls (also not shown) was similar.

Effectiveneas in, Severe Depression:

The effectiveness of paroxetine in patients suffering from severe depression was assessed in an analysis of worldwide patient data combined into two subgroups: 1) eleven U.S. placebo-controlled studies (protocols PAR-01 and the 02 and 03 series), and 2) all U.S. and non-U.S. double-blind inpatient (hospitalized) studies. For purposes of these comparisons, "severe" depression was defined as a total baseline HAMD score 28 or greater. The remaining patients are considered the "moderately" depressed subgroup used for comparison. The results from the analysis of variance for HAMD Totals and CGI Severity of Illness scores for the placebo-controlled studies are summarized in Table 42 together with the score results for inpatients. These data show that paroxetine is effective in the treatment of severe depression.

1) In the paroxetine-placebo comparisons, paroxetine demonstrated a statistically significant improvement over placebo in both the moderate and severe subgroups for both the HAMD Total and CGI Severity of Illness score improvement.

2) The in-patient analysis shows a significantly greater HAMD Total for severely depressed inpatients compared with the moderately depressed group, as would be expected from the higher baseline scores in the severe group. The CGI mean score improvement was not statistically significant. Pooling of data in this way was necessary because of the low enrollment rates in individual inpatient studies. Furthermore, analysis of data from hospitalized patients, especially for the Intent-to-Treat dataset, is confounded by the relatively high incidence of co-morbidity and concomitant medications, and results should be interpreted with caution.

PAR-07

This was the only double-blind, placebo-controlled study conducted in the United States in hospitalized depressed patients. This study also included an amitriptyline positive control arm. Because of the low enrollment rate and multiple protocol violations, this study was terminated before enough patients had been accrued to provide sufficient statistical power to demonstrate treatment-related differences. Nonetheless, a trend developed favoring paroxetine over placebo in this patient population (Table 43).

V.F. Effectiveness in Depression with Associated Symptoms of Anxiety:

A pooled data analysis examined whether paroxetine is effective in the treatment of major depressive disorder associated with symptoms of anxiety. Data from the U.S. PAR 01 study and studies of the PAR 02 series and the PAR 03 series were pooled to provide a total of 842 patients for paroxetine-placebo comparisons from similarly designed and executed trials. Patients were then stratified into cohorts of high anxiety (a Covi Anxiety Scale score greater than 6; n = 459) and low anxiety (a Covi score of 6 or less; n = 383). Although patients were not prospectively randomized according to high or low anxiety, 'retrospective analysis revealed that both subsets were evenly distributed among the treatment groups over the entire enrollment period. This post-hoc categorization raises the issue of data conditioned analysis in interpretation of the results. However, the cohorts were chosen by standard Covi definitions. The effects of anxiety on antidepressant response to paroxetine and placebo were evaluated for the HAMD Total and CGI Severity of Illness score changes from baseline at the week 6 endpoint. Pairwise comparison of paroxetine and placebo demonstrated significant superiority of paroxetine for both high and low anxiety groups, and antidepressant response to paroxetine was similar whether or not significant symptoms of anxiety were present. Thus paroxetine is an effective antidepressant in depressed patients with or without a substantial degree of anxiety. The summarized results are displayed in Table 44.

VI. CLINICAL EVIDENCE OF SAFETY:

VI.A. Population Exposed:

As of July 10, 1991 approximately 4126 subjects had received paroxetine in premarketing studies, phases 2 and 3.

Paroxetine	4126
Placebo	625
Active-control	1954

At the time of the NDA submission, the database in major depression included 2963 paroxetine, 554 placebo, and 1151 active control patients. Unless otherwise indicated the following discussion refers to the NDA database.

VI.B. **Demography:**

Demographically, the U.S. and Worldwide databases are similar with respect to age, gender and race. Tables 45 and 46 present tabular demographic information by treatment group and overall for both datasets.

VI.C. **Extent of Exposure:**

As of July 10, 1991, the following were the patient exposure years in the various treatment groups:

Paroxetine	1546 years
Placebo	125
Active-control	380

At the time of the NDA submission, the following were the patient exposure years in the various treatment groups:

Paroxetine	1008 years
Placebo	72
Active-control	218

Table 47 shows the number of NDA database patients who received paroxetine on the basis of duration of therapy and mean dose during treatment. As shown, 373 patients received paroxetine for one year or more. **

VI.D. Observed Adverse Events:

VI.D.1. Commonly Observed:

The most commonly observed adverse events in the worldwide database associated with the use of paroxetine (n=2963) and not seen at an equivalent incidence among placebo (n=554) treated patients were: abnormal ejaculation, asthenia, blurred vision, constipation, decreased appetite, decreased libido, dizziness, dry mouth, dyspepsia, insomnia, male genital disorders, nausea, paresthesia, somnolence, sweating, tremor, vomiting, weight gain. Many of these adverse events tolerate away over time. Clinical experience with paroxetine has shown a greatly reduced incidence of anticholinergic effects such as dry mouth, constipation and cardiovascular effects like palpitation and postural hypotension compared with the tricyclic antidepressants.

VI.D.2. Associated with Discontinuation of Treatment:

Twenty percent (321/1643) of paroxetine patients in U.S. clinical trials discontinued treatment due to an adverse event. The more common events associated with discontinuation included: nausea (4% 73/1643), somnolence (4%), asthenia (3%), insomnia (3%), dizziness (2%), and headache (2%) .

Sixteen percent (656/4126) of paroxetine patients in worldwide clinical trials discontinued treatment due to an adverse event. The more common events associated with discontinuation included: nausea (3% 139/4126), somnolence (2%), asthenia (2%), insomnia (2%), headache (2%) and ejaculatory disturbance (2%).

VI.D.3. **Incidence in Placebo-Controlled Clinical Trials:**

Table 49 lists adverse events that occurred in short-term placebo-controlled trials of similar design at a frequency of 1% or more. The Table presents the adverse experience data in three columns. The first column presents the data for those patients who started on 20 mg of paroxetine daily and did not receive a higher dose. The second column presents the data for those patients who started on 20 mg and were titrated to higher dosages. The third column presents the data for those patients in these trials who received placebo.

The data in this table is from the short-term, placebo-controlled trials

of similar design and dosage regimen. This includes the U.S. trials PAR 02, 03, and 07. In addition some data is included from the U.S. placebo-controlled fixed-dose trial PAR-09 which studied dosages of 10 mg, 20 mg, 30 mg and 40 mg daily. In keeping with the labeling recommendations, the data for those patients who were randomized to and received no more than 20 mg and the patients who received placebo is included in the table.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factoss differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied. Reported adverse events were classified using a standard COSTART-based Dictionary terminology. In placebo-controlled trials lasting longer than six weeks (up to 52 weeks), the incidence of adverse events decreased over time and no unexpected events were noted.

VI.D.4. **Other Events Observed During the Pre-marketing Evaluation of Paroxetine:**

The following is a listing of adverse events reported during clinical testing when multiple doses of paroxetine were administered to 4,126 subjects. Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events occurred in more than 1% of patients, infrequent events in 0.1 to 1.0%, and rare events in less than 0.1%.

Body as a Whole: frequent: chills, malaise, surgical procedure; ***infrequent:*** allergic reaction, carcinoma, death, face edema, infection, moniliasis, neck pain, overdose; rare: abnormal disorder, abnormal laboratory value, abscess, adrenergic syndrome, back disorder, cellulitis, cyst, hernia, intentional overdose, neck rigidity, pelvic pain, peritonitis, thorax disorder, ulcer.

Cardiovascular System: frequent: hypertension, syncope, tachycardia; ***infrequent:*** bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; rare: angina pectoris, arrhythmia, atrial fibrillation, blood pressure disorder, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: ***infrequent:*** bruxism, buccal cavity disorder, colonic disorder, dysphagia, eructation, gastritis, gastrointestinal disorder, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage, tooth disorder; rare: anal disorder, aphthous stomatitis, bloody diarrhea, bulimia,

colitis, duodenal disorder, duodenitis, enterocolonic disorder, esophagitis, esophagus disorder, fecal impactions, fecal incontinence, gastritis, gastro-duodenal (peptic) disorder, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, liver damage, melena, peptic ulcer, rectal disorder, salivary gland disorder, salivary gland enlargement, stomach disorder, stomach ulcer, stomatitis, tongue edema, tooth caries.

Endocrine System: rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroid disorder, thyroiditis.

Hemic **and** Lymphatic System: infreguent: anemia, leukopenia, lymphadenopathy, purpura; rare: abnormal erythrocytes, eosinophilia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, WBC abnormality.

Metabolic **and** Nutritional: frequent: edema, weight gain, weight loss; infreguent: hyperglycemia, peripheral edema, thirst; rare: alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, pigment disorders, SGOT increased, SGPT increased.

Musculoskeletal System: infrequent: arthralgia, arthritis, tendinous disorder, traumatic fracture; rare: arthrosis, bursitis, cartilage disorder, joint disorder, myositis, osteoporosis, tetany.

Nervous System: frequent: amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; infreguent: abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction; rare: abnormal electroencephalogram, abnormal gait, antisocial reaction, central nervous system disorder, choreoathetosis, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, nervous system disorder, neuralgia, neuropathy, nystagmus, paralysis, psychosis, psychotic depression, reflexes increased, speech disorder, stupor, withdrawal syndrome, withdrawn.

Respiratory **System:** ***frequent:*** cough increased, rhinitis; infreguent: asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis; rare: carcinoma of lung, hiccups, larynx disorder, lung disorder, lung fibrosis, sinus disorder, sputum increased, voice alteration.

Skin and Appendages: ***frequent:*** pruritus; infrequent: acne, alopecia, dermatoses, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, herpes zoster, nail disorder, urticaria; rare: angioedema, contact dermatitis, erythema nodosum, hair disorders, maculopapular rash, photosensitivity, pigmentation disorder, skin discoloration, skin melanoma, skin ulcer.

Special Senses: infrequent: abnormality of accommodation, ear disorder, ear pain, eye disorder, eye pain, pupillary disorder, mydriasis, otitis media, taste loss, tinnitus, vision disorder; rare: amblyopia, cataract, conjunctivitis, cornea disorder, corneal lesion, corneal ulcer, exophthalmos, eye appendage disorder, eye hemorrhage, glaucoma, hearing disorder, hyperacusis, middle ear disorder, otitis externa, photophobia, retinal disorders, taste disorder.

Urogenital System: *infrequent*: abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, female lactation, kidney calculus, menorrhagia, menstrual disorder, nocturia, polyuria, prostate disorder, urethritis, urinary incontinence, urinary retention, urinary tract infection, urinary urgency, vaginitis; rare: abnormal kidney function, breast atrophy, breast carcinoma, breast neoplasm, female breast disorders, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, nephritis, oliguria, penis disorder, prostatic carcinoma, urinary tract disorder, urine abnormality, uterus disorder, vaginal disorders, vaginal moniliasis.

E. Long-Term Studies:

In placebo-controlled trials lasting longer than six weeks (up to 52 weeks), the incidence of adverse events decreased over time and no unexpected events were noted. In the entire NDA database, 373 patients received paroxetine for one year or longer. No new toxicities appeared with this longer (up to 6 years) and broader exposure versus those observed in short-term trials.

F. Other Safety Findings:

F.1. Clinical Laboratory Data:

Clinical laboratory evaluations were included in planned short-term (42-day) and planned long-term (1 year or more) studies. In summary, laboratory clusters are presented for specific hematology, hepatic, and renal function measurements. The cluster data for paroxetine short-term U.S. clinical trials is included in Tables 50, 51, and 52. Small but statistically significant decreases in hemoglobin, hematocrit, and white cell count are found in paroxetine-treated patients. The clinical significance of this finding is unknown at this time. No statistically significant change in hepatic function is seen in short-term studies. No statistically or clinically significant changes are noted in renal function.

Laboratory data was also evaluated by examination of those specific cases in which laboratory values exceed predetermined safety ranges (Table 53) . The laboratory value changes seen with paroxetine are similar to those seen with other antidepressants. In all cases where the rate of abnormality for paroxetine is higher than other antidepressants {BUN, creatinine, hemoglobin, WDC elevation and platelet count), the differences between paroxetine and the other treatment groups are not statistically significant.

F.2. Vital Signs Data:

Systolic and diastolic blood pressure, pulse, temperature and weight were reported in U.S. studies, non-U.S. data were limited to blood pressure and pulse. Vital signs information was analyzed for changes associated with short- and long-term therapy, gender, age, and dose. These analyses showed that mean changes in vital signs for paroxetine-treated patients were not clinically significant and were well within range of those changes seen with other antidepressants. In U.S. short-term trials, paroxetine was not associated with the increased pulse rate seen with the tricyclic antidepressants, and was associated with weight Toss as opposed to weight gain with tricyclics, especially in obese patients. However, this trend toward weight loss was reversed in the U.S. long-term studies, in which paroxetine was associated with a small but statistically significant increase in weight. Paroxetine's effects on vital signs by dose (high/low), age and gender were consistent for all groups. In the long-term studies, the incidence of abnormal vital signs was considerably less with paroxetine than with imipramine treatment.

F.3. Physical Examinations:

In the U.S. study populations, 2181 patients (80%) had both pre-treatment and post-treatment physical examinations. A total of 155 (7%) patients had abnormal physical findings at the final evaluation that were not present at the pre-treatment exam. Of these, 126 were paroxetine-treated, 11 were placebo-treated, and 18 were treated with active control (17 imipramine-treated and 1 doxepin-treated). The greater proportion in the paroxetine group is expected due to the greater number of patients in long-term protocols in which the majority of the abnormalities were identified during the extended period of exposure. The abnormalities or changes occurring most frequently were weight gain, hypertension, and dermatological disorders. The possibility of a relationship between paroxetine and these physical changes is remote but cannot be ascertained.

F.4. **ECG** Changes:

All CRFs for premature terminations from U.S. clinical trials due to cardiac adverse experiences were reviewed by an external consultant, a board certified cardiologist. Thirty-three (of 1562 patients, 2.1%) such withdrawals occurred in paroxetine-treated patients while 19 (of 316 patients, 6.0%) occurred in imipramine-treated patients. From this comparison, paroxetine is much less likely to cause cardiac adverse experience when compared with the standard antidepressant (imipramine, doxepin, amitriptyline).

Standard 12-lead ECG recordings were made at the screening visit and at specified revisits in all U.S. clinical trials in depression. Each ECG was read in a blinded fashion by the consultant and a completed ECG report was prepared for every tracing. The analysis included heart rate, RR, PR, QRS and QT intervals as well as changes in overall ECG interpretation, rhythm, axis, conduction, morphology, myocardial infarction, ST segment, and T and U waves. The ECGs for all patients with abnormal changes from screen were reread (blinded) and clinically

evaluated. The conclusion of the analysis was that paroxetine has no clinically significant effect on the ECG.

VI.F.5. Cheat **X-Rays:**

Chest x-rays were performed in U.S. protocols PAR-03, 04, and 05, with a total of 690 patients (43%) having pre-treatment and post-treatment chest x-rays. (For purposes of this comparison, patients in both PAR-03 and its long-term extension, PAR-04, are counted as separate patients in each study.) Of these, 35 (5%) patients had abnormalities at the final evaluation that were not reported at screen; 26 (6%) paroxetine-treated patients, 3 (1%) placebo-treated patients, and 6 (4%) imipramine-treated patients. The rate of chest x-ray abnormalities was not significantly different between treatment groups. The higher percentage associated with paroxetine is most likely due to the greater number of patients in long-term protocols compared to placebo. For long-term protocols, changes in chest x-ray were noted for 6% (24/396) of the paroxetine group, 5% (5/92) of the imipramine group and 0% (0/21) of the placebo group. None of the abnormalities revealed any relationship to study drug administration or showed any trend toward any particular type of pulmonary disorder.

VI.F.6. Ophthalmic Examinations:

Four U.S. studies (PAR-01, 03, 04, 05) had an ophthalmology exam as part of the safety assessment. Of the 1637 patients in these studies, 740 (45%) had pre-treatment and post-treatment ophthalmology exams. (Again, patients in both PAR-03 and PAR-04 are counted as separate for each study. Abnormalities that were not present at the screen examination were detected in 181 (24%): 119 (25%) paroxetine-treated patients, 23 (21%) placebo-treated patients and 39 (26%) imipramine-treated patients. Although overall percentages are high, many are due to changes in pre-existing conditions, differences in ophthalmologists' opinions, or the influence of concomitant medications. Visual acuity changes are often seen although no clear relationship between visual acuity and study drug administration could be detected.

VI.G. **Safety Profile in Elderly Patients:**

Seventeen studies were performed to examine the safety and efficacy of paroxetine in the elderly (patients >60 years old). In addition, several other studies included elderly together with younger adult patients. A total of 459 paroxetine-treated elderly patients were recruited, and of these, 93 continued into treatment beyond four months.

Table 54 lists the more common adverse experiences noted after paroxetine treatment in patients under 65 and those 65 years or older, respectively. In every case, the percentage of patients under 65 who reported these adverse experiences in the paroxetine group was greater than in the placebo group. However, in all but five instances, the percentages of paroxetine-treated patients with specific adverse experiences were less than or approximately equal to those treated with a tricyclic antidepressant (clomipramine, imipramine, amitriptyline, mianserin, doxepin) (pooled comparator data shown in the table). The five

exceptions were diarrhea, nausea, nervousness, headache and abnormal ejaculation.

Among patients 65 or older, 11 of these specific adverse experiences had lower incidence rates in the paroxetine-treated patients compared with the placebo-treated patients: chest pain, diarrhea, vomiting, agitation, anxiety, insomnia, nervousness, headache, paresthesia, blurred vision, and decreased appetite. The relatively small sample size of the elderly placebo treatment group probably accounts for these differences. In all but three instances, the percentages of paroxetine-treated patients with specific adverse experiences were less than or approximately equal to those treated a tricyclic antidepressant. The three exceptions were diarrhea, nausea, and sweating.

Importantly, the percentage of paroxetine-treated patients 65 or older with these most common adverse experiences was less than or equal to those noted in the paroxetine-treated patients under 65 with only two exceptions. Postural hypotension was noted in 4% of patients 65 or older and in 2% of patients under 65 years old. The other adverse experience that occurred more frequently in the older population was weight loss (2% for patients >65 and 1% for patients <65) .

Safety has also been demonstrated in the elderly with respect to changes in standard laboratory parameters. Likewise, incidences of abnormalities in vital signs examinations were not different when comparing the elderly to the non-elderly population studied.

All safety data indicate that paroxetine, as studied, poses no increased safety risk for the elderly population. However, the elderly as a group exhibit higher plasma concentrations of paroxetine than younger subjects, although the ranges overlapped extensively with those in younger subjects. The high end of the therapeutic dose range for elderly patients (20 mg to 40 mg) is lower than that recommended for younger patients due to the higher plasma concentrations and the lack of experience with doses above 40 mg in this age group.

H. Special Safety Considerations:

H.1. Death:

As of July 10, 1991, fourteen deaths had occurred in paroxetine treated patients (Table ???) .

H.2. **Overdose** Experience:

A total of 28 paroxetine-treated patients attempted suicide by overdose with various drugs. Nine patients ingested paroxetine alone at various doses up to 850 mg, six patients took overdoses of paroxetine in combination with other substances (lorazepam, paracetamol, dihydrocodeine, alcohol, nitrazepam, hexobarbital, and placebo), and 13 patients overdosed on medication other than paroxetine or on alcohol. All of these patients fully recovered.

Symptoms of paroxetine overdose include nausea, vomiting, drowsiness,

sinus tachycardia and dilated pupils. Paroxetine overdose has not been associated with characteristic physical manifestations found with tricyclic antidepressant overdoses (such as serious cardiac arrhythmia, coma, seizures, etc.) . Management of paroxetine overdose should follow standard clinical practice in treatment of sedative drug overdose. Although clinical trial experience with overdose is limited, paroxetine was not associated with any unusual toxicity when taken in overdose.

3. Mania/Hypomania:

The worldwide incidence rates for manic reaction in unipolar patients were: paroxetine (1.1%, 30/2829), amitriptyline (1.5%), clomipramine (4.0%), imipramine (0.3%), and placebo (0.4%). The overall rate for all active controls was 1.3% (14/1065). In a subset of patients classified as bipolar, the incidence rate for manic episodes was 2.2% (3/134) for paroxetine and 11.6% (10/86) for the combined active-control groups.

The AE of manic reaction occurred in 12 (0.4%) paroxetine-treated patients, 1 (0.002%) placebo-treated patient and 11 (1.0%) active-control treated patients who dropped out due to AEs . These data suggest that the risk of precipitating manic reaction with paroxetine-treated patients is small and, in bipolar patients, may be less than that seen with classic tricyclic antidepressants.

4. Suicidal Ideation/Behavior:

To explore the possibility of a relationship between paroxetine therapy and suicidality, safety and efficacy parameters related to suicide and suicidal ideation have been reviewed in the worldwide database. The database was searched for the following investigator (i.e. verbatim) terms: suicidal ideation, suicide risk, ideas of suicide, suicidal thoughts, suicidal tendency, parasuicidal tendency, felt suicidal, became suicidal, suicidal feelings and suicidal threats. Although the pooled data provide an overall average, the results may not be homogenous among all studies due to differences in trial design. Moreover, sample sizes may vary depending on availability of data for any particular parameter being assessed. Data were available for 4668 patients who were treated with paroxetine (n=2963), placebo (n=554), and other active treatment regimens (n=1151) . A total of 10 suicides were committed by participants in paroxetine clinical trials: 5 (0.17%) patients randomized to paroxetine, 2 (0.36%) by patients randomized to placebo, and 3 (0.26%) by patients randomized to other active controls.

A total of 40 (1.4%) paroxetine-treated patients attempted suicide. In comparison, 6 (1.1%) placebo-treated and 12 (1%) active-control treated patients also attempted suicide.

The number and incidence rates of suicidal acts and attempts are summarized in Table 55. The incidence is expressed as cases per patient exposure year (PEY) where total PEYs are equal to the sum of the duration of treatment for each patient (in days), divided by 365. There were no substantive differences in the number or incidence of suicides or suicide attempts among treatment groups.

The worldwide adverse experience database was searched for suicidality as an adverse event using 10 investigator terms, and a similar incidence rate was found for the three treatment groups.

Results of psychometric instrument scale evaluations were also examined to determine the baseline level of suicidal thoughts, the mean change over time, and the emergence of suicidal thoughts at any time over 6 weeks of therapy. Suicidal ideation is assessed by item 3 of the HAMD on a 5-point scale where zero is absence and 4 is a suicide attempt. Suicidal thoughts are assessed by item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS) on a 7-point scale where zero indicates that the patient enjoys life and 6 is explicit plans for suicide.

Based on the HAMD, 22.9% of placebo-treated, 25.4% of paroxetine-treated, and 29.2% of imipramine-treated patients did not have suicidal ideation prior to treatment (i.e., a baseline score on item 3 of zero) . Responses to item 10 of the MADRS indicate that 35.3% of placebo-treated patients, 36.7% of paroxetine-treated patients, and 39.2% of imipramine-treated patients had little or no suicidal thoughts prior to treatment (i.e., baseline scores of zero or 1).

Table 56 shows the mean change from baseline for scores on item 3 of the HAMD. The scores of patients treated with paroxetine and the other active controls showed improvement compared with placebo at all post-baseline assessments, indicating a reduced level of suicidal thinking in patients with preexisting suicidal thoughts. Similarly, Table 57 presents the mean change from baseline for scores on the MADRS suicide item across treatment groups over time. These data also show improvement among paroxetine-treated patients compared with placebo, but the scores of patients on other active controls showed improvement only at weeks 1 and 2 in the comparisons with placebo.

"Emergent suicidal thoughts" were defined as those patients who had baseline scores of 0 or 1 on the HAMD suicide item and developed a score of 3 or 4 at any time during the 6-week course of therapy. No significant differences in the frequency of emergent suicidal thoughts were seen in the three treatment groups: 1.7% (29/1659) in paroxetine patients, 1.5% (5/331) in placebo patients, and 1.3% (9/683) in active-control patients.

Since the HAMD suicide item is not an interval scale, the differences between any two ratings are unlikely to be clinically equivalent. A change from zero to 1, for example, is clinically very different from a change of 1 to 2. Because of this non-linearity, a further analysis considered the emergence of suicidality over 6 weeks of therapy in patients who had no suicidal thoughts (score = zero) at baseline. No difference was seen between paroxetine (19%, 136/708) and active-control (20%, 63/317); but both treatment groups showed significantly ($p<0.001$) less emergent behavior than the placebo group (35%, 44/126).

An analysis of scores for the Anger/Hostility sub-cluster of the patient-rated Hopkins Symptom Checklist also showed significant improvement for paroxetine-treated and other active-control treated patients. Additionally, these scores were significantly more improved by paroxetine

than by other active treatments after only 1 week on therapy.

These analyses show that patients randomized to paroxetine were at no greater risk for suicidal ideation or behavior than patients randomized to placebo or other active-control therapies.

II. 5. Seizure:

In worldwide clinical trials, two seizures were reported for paroxetine-treated patients for an overall incidence rate of 0.1%. <A 33 year-old male in the U.S. experienced a single 3- to 4-minute generalized grand mal seizure approximately 20 minutes after injection of the contrast medium ISOVUE. The patient remained postical for one hour, and was administered diazepam and phenytoin. No further seizures were noted in the next six months. Although the patient was paroxetine-treated (50 mg/day for 5 months), this case most likely represents a seizure due to the iodine-based contrast agent. The second case, a 59 year-old male had a seizure on day 6 of therapy, but continued on treatment without further problems.

Other seizures occurred with imipramine (0.3%, 1/338), amitriptyline (0.3%, 1/331), clomipramine (1.0%, 2/193) and mianserin (0.6%, 1/150).

.H.6. Bleeding/Purpura:

Animal and clinical studies have shown that paroxetine and other serotonergically active antidepressants can deplete platelet serotonin levels. The fall in platelet 5-HT does not appear to have any functional or pathological consequences. Increased non-serious bleeding events were found in association with the use of paroxetine in normal volunteers administered warfarin (PAR 14-01). The worldwide database was reviewed for adverse experiences that can be associated with a bleeding diathesis. Active-controls showed a 1.5% (17/1151) rate, placebo 0.7% (4/554), and paroxetine 1.6% (46/2963).

Treatment-emergent events that may have indicated a potential bleeding diathesis were compared by treatment group for all Phase 2-3 clinical studies conducted worldwide. The analysis showed that the rate of bleeding disorders associated with paroxetine treatment was similar to the rate found with other conventional antidepressants. In particular, the 16 cases of purpura in paroxetine-treated patients were examined in detail and there appeared to be no direct relationship between purpura and duration of paroxetine treatment or concomitant medications, especially analgesics and non-steroidal anti-inflammatory drugs.

.H.7. Allergic Reactions:

The potential for paroxetine therapy to be implicated in the causality of allergic events was assessed by comparing the incidences of specific adverse events in the paroxetine, placebo, and active-control groups in the worldwide database. The adverse events selected for this assessment were asthma, arthralgia, arthritis, eosinophilia, myalgia, rash, rhinitis, and urticaria.

The range of incidence rates for allergic events was similar for the paroxetine (0.1% to 3%) and active-control (0.1% to 4%) treatment groups, and was generally similar to placebo (0.2% to 2%). The total worldwide incidence of allergic symptoms associated with paroxetine was 3%, which is less than the rate for imipramine (4%), especially when considered in light of the much longer exposure periods to paroxetine.

[1.8. Zimelidine Syndrome:

A hypersensitivity reaction resembling influenza has been associated with the antidepressant zimelidine. The zimelidine syndrome has been characterized by a complex of symptoms that include fever, pain or stiffness in muscles or joints, headache, exanthema, and hepatic effects. The onset of symptoms occurs within 3 weeks of starting zimelidine treatment, and the occurrence was seen in .at least 3% of treated patients.

The paroxetine worldwide database was searched to determine if any paroxetine-treated patients developed a cluster of two or more of the four most common manifestations of the zimelidine syndrome (fever, arthralgia/myalgia, rash, liver enzyme elevations). The reported adverse experiences also occurred with at least one day of overlap in the adverse experience report. No patient had four, or even three, concurrent signs. Arthralgia/myalgia was the most common symptom and the most nonspecific.

Therefore, no case of what may be termed zimelidine syndrome was found in the paroxetine worldwide database. While this review does not preclude the possibility of a reaction of this type, the absolute incidence can be expected to be extremely low.

.H.9. Serotonin Syndrome:

No case of serotonin syndrome was reported for any patient administered paroxetine. This is a syndrome characterized by CNS, gastrointestinal, and general symptoms which has been associated with excessive serotonergic activity. In most reports, CNS signs of hyperactivity such as myoclonus, ataxia, agitation, and nystagmus are present with nausea, vomiting, and diaphoresis and fever.

In an effort to identify any paroxetine patients who may have developed a serotonin syndrome, the data were reviewed to find all patients in the worldwide database who had symptom clusters including the CNS symptoms (fasciculation, tremor, myoclonus, ataxia, agitation, nystagmus, positive Babinski signs, CNS stimulation), gastrointestinal (nausea, vomiting, and diarrhea), and general (sweating, vasodilation, chills, and fever). For a case to be selected, at least one symptom in each of the three body systems (CNS, gastrointestinal, and general) had to have occurred in the same time period during treatment.

Based on the overall worldwide exposure to different antidepressants in the paroxetine program, the following incidence rates were seen for these symptom clusters: 1.3% for paroxetine (39/2963), 1.8% for imipramine (6/338), 2.1% for clomipramine (4/193), and 0.3% for amitriptyiine (1/331).

Symptom clusters suggesting serotonin "excess" occurred in the paroxetine-treatment group at a rate not unlike the rate seen with standard antidepressants. Whether these cases exhibit serotonin "excess" or are manifestations of the serotonin syndrome is not known.

.10. **Sexual Dysfunction:**

Sexual dysfunction is a feature of depressive illness and antidepressant treatment. Patients with major depression (DSM III) commonly experience impotence, loss of libido, premature or delayed ejaculation, lack of orgasm, or even increased libido.

Sexual dysfunction has been reported to be associated with various antidepressant drugs including imipramine, phenelzine, clomipramine, amitriptyline, mianserin, and lithium. Additionally, evidence of a serotonergic component controlling ejaculation has been reported from animal studies with evidence that fluoxetine and zimelidine may interfere with these pathways.

The spontaneously reported adverse event data from male patients in the worldwide clinical trial database with paroxetine demonstrated that delayed ejaculation was the most commonly reported of the adverse events classified under sexual dysfunction. Delayed ejaculation was reported by 9% (127/1435) of males in the worldwide database. Decreased libido (8.0%, 114/1435) was the next most commonly reported symptom. The remaining adverse events classified under sexual dysfunction had a frequency of approximately 6%.

Comparing paroxetine with other SSRIs such as fluoxetine and sertraline suggests that the incidence of sexual dysfunction may be a class phenomenon. A review of sertraline shows the incidence of male sexual dysfunction (mainly ejaculatory delay) to be 21.4% [Reimherr FW et.al., Antidepressant Efficacy of Sertraline: A Double-Blind, Placebo- and Amitriptyline-Controlled, Multicenter Comparison Study in Outpatient with Major Depression. J Clin Psychiatry, 51, 12(Suppl B) (1990)]. Another study found an 8.3% incidence of treatment-emergent sexual dysfunction for patients treated with fluoxetine [Herman JB, et al. Fluoxetine-induced sexual dysfunction. J Clin Psychiatry, 51, 1, (1990)]. Animal models suggest that these effects may arise as a direct consequence of the therapeutic action of this class of drugs, namely the inhibition of 5-HT re-uptake.

Therefore, the incidence of sexual dysfunction adverse events observed with paroxetine is similar to that seen with other antidepressants, including other specific serotonin re-uptake inhibitors.

Drug-Drug Interactions:

Digoxin (PAR 15-01): A multiple-dose, three period, open-label study in 28 male volunteers assessed the effect of chronic dosing with paroxetine (30 mg daily) on the steady-state pharmacokinetics of digoxin (0.25 mg daily), and vice versa. The pharmacokinetics of paroxetine were unaffected by co-administration of digoxin. Small reductions in plasma levels of digoxin (not statistically significant) were noted when

paroxetine was co-administered, but the plasma concentrations remained within the range associated with therapeutic efficacy. It was concluded that no clinically important pharmacokinetic interaction had occurred between the two drugs. However, since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Lithium: A multiple-dose study demonstrated that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, in the absence of sufficient clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Warfarin (PAR 14-01) : A multiple-dose, three period, open-label study in 28 male volunteers assessed the effect of chronic dosing with paroxetine (30 mg) on the steady-state pharmacokinetics of warfarin (5 mg daily), and vice versa. The results indicated that no clinically important pharmacokinetic interaction occurred between the drugs. However, mild bleeding (epistaxis, gums, petechiae) in the absence of altered prothrombin time was observed in 5 of 27 subjects after several days of treatment with paroxetine and warfarin. There is no evidence of an effect of paroxetine on prothrombin times. Coadministration of warfarin and paroxetine should be done with caution.

Monoamine Oxidase Inhibitors (MAOIs): Animal studies indicate that interactions between paroxetine and monoamine oxidase inhibitors may occur. Based on experience with the combined administration of MAOIs and tricyclic antidepressants, and the fatal interactions reported with concomitant or immediately consecutive fluoxetine and MAOI, combined use of paroxetine and MAOIs is contraindicated. At least 14 days should elapse between discontinuation of paroxetine and initiation of therapy with an MAOI.

Inhibitors of Cytochrome P450: Coadministration with drugs that inhibit the cytochrome P450 system may increase paroxetine plasma concentrations. It should be noted that there was a lack of relationship between plasma levels and toxicity or efficacy for paroxetine. Therefore, after a starting dose of 20 mg, any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

Inhibition of Cytochrome P450 IID6: ***In vitro*** studies have demonstrated that paroxetine as well as other antidepressants, including other selective serotonin reuptake inhibitors, inhibit cytochrome P450 IID6, the specific hepatic cytochrome P450 isozyme responsible for the metabolism of debrisoquine and sparteine. This may lead to increased concentrations of coadministered drugs that are metabolized by this isozyme. Such drugs include certain tricyclic antidepressants (nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (perphenazine, thioridazine), and type 1C antiarrhythmics (propafenone and flecainide). The clinical significance of this potential interaction has not been established.

Tryptophan: As with other serotonin reuptake inhibitors, animal studies indicate that an interaction between paroxetine and tryptophan may occur.

Although clinical experience with patients on concomitant tryptophan and paroxetine is limited, increased adverse experiences were observed, and have also been noted with concomitant fluoxetine and tryptophan. Paroxetine should not be coadministered with tryptophan.

Phenytoin: Coadministration of paroxetine and phenytoin, a known metabolizing enzyme inducer, is associated with decreased plasma levels of paroxetine. No initial paroxetine dosage adjustment is considered necessary with known drug enzyme inducers. Any subsequent dosage adjustments should be guided by clinical effect (tolerability and efficacy).

Sedatives: Experience in a limited number of healthy subjects has shown that paroxetine does not increase the sedation induced by amylobarbital or oxazepam, when given in combination.

Neuroleptics and Tricyclics: Experience in a limited number of healthy subjects has shown that paroxetine does not increase the sedation induced by haloperidol. Because the effects of concomitant administration of paroxetine with other neuroleptics and tricyclic antidepressants have not been studied, the concomitant use of paroxetine with these drugs should be approached with caution.

Alcohol: Paroxetine has been shown not to increase the impairment of mental and motor skills caused by alcohol, although concomitant use of paroxetine and alcohol in depressed patients is not advised.

BIOPHARMACEUTICS:

A. Bioavailability/**Dose** Proportionality/Bioequivalence:

The absolute bioavailability of paroxetine was studied in a group of volunteers who were administered the drug both orally (45 mg in solution) and by intravenous infusion (23-28 mg over about half an hour) in a cross-over study [Lund et al. Acta Pharmacol et Toxicol, 51, 351-357 (1982)]. The results indicated that paroxetine exhibited both dose level and dose route dependency in its pharmacokinetics. For instance, half-lives after oral administration (mean 17.5 h) were significantly longer than after intravenous administration (mean 12.9h). Also, areas under curves after oral dosing were much higher than predicted from intravenous clearance values. Consequently, estimates of systemic availability were inconsistent, varying widely depending on the method of calculation (values of <10% to >100% of the dose could be derived). Under these conditions of non-linear pharmacokinetics, a consequence of the partial saturability of first-pass metabolism, no single value for the absolute bioavailability of paroxetine can be meaningfully assigned.

The partial saturability of first-pass metabolism results in a non-linear dose-plasma concentration relationship in single-dose-proportionality studies (HP/84/39, PAR 12-01). At steady-state, however, the impact of this is much reduced and in many patients the dose-plasma concentration relationship is linear, or nearly so. Importantly, non-linear increases in plasma concentrations on ascending the dose-range are confined mostly to those patients exhibiting the lowest concentrations initially.

Because of: the rapidity of disintegration/dissolution of solid dosage forms relative to the protracted absorption kinetics of paroxetine (t_{max}, 4-6 hours), no bioavailability limitations due to these factors were anticipated. This was confirmed in three studies where the relative bioavailability of paroxetine from a solution and from a range of solid dosage forms (capsules, and sugar-coated and pentagonal tablets) was assessed. In a cross-over study at 30 mg in 21 subjects (PAR 12-01), no significant differences were observed in C_{max}, t_{max} or AUG after capsule and solution administration. Previously, in crossover studies at 50 mg (IIP/80/98/2) and 60 mg (HP/82/14/A/1), solution administration had yielded parameter values similar to those obtained from tablet formulations. Therefore, these solid dosage forms imposed n'o constraints on the rate or extent of bioavailability when compared to paroxetine in solution.

In regards to bioequivalence, study PAR 16-01, conducted under steady-state conditions (30 mg daily for 16 days), compared the 30 mg oval biconvex tablet formulation for U.S. marketing with the 10 mg capsule formulation used in U.S. clinical trials. These formulations were bioequivalent for all parameters associated with the extent of bioavailability of paroxetine (steady-state AUC_{τ} and C^J . The results were inconclusive with respect to the rate of bioavailability of paroxetine as described by t_{max} (due to inadequate power) although C_{max}, also partly governed by this rate, was bioequivalent. Therefore on chronic dosing, these two U.S. formulations are bioequivalent. Another study (MDUK/29060/I/87/051) demonstrated bioequivalence of the 10 mg capsule formulation used in U.S. clinical trials with the 30 mg pentagonal tablet formulation used in European clinical trials.

VII.B. Food Interaction:

Studies have demonstrated that paroxetine is well absorbed from the gastrointestinal tract and undergoes first-pass metabolism. Bioavailability is not affected by formulation (solution, capsule, or tablet), by dietary conditions (meals or milk), or by antacid (aluminum hydroxide) administration. For illustration, the studies examining the effects of food are discussed below.

Studv HP/85/3

The bioavailability of a single dose of paroxetine when administered in the fasting and non-fasting states was examined in ten volunteers. Each received single oral 30 mg doses of paroxetine, once after an overnight fast and once after a standard breakfast, in randomized sequence with an intervening seven day washout period. There was no change in the rate of availability of paroxetine. On the basis of the AUC data, no systematic changes in the extent of bioavailability of paroxetine were detected.

Studv HPG 33+35/83

The bioavailability of a single dose of paroxetine when administered under conditions of both low and high dietary fat intake was examined in eleven volunteers. Each received two single oral 30 mg doses of paroxetine during periods of dietary control (high fat or low fat), in randomized sequence with an intervening two week washout period. Broad

intersubject variability was observed for all parameters, but none differed significantly between treatments. It was concluded that the bioavailability and pharmacokinetics of paroxetine were unaffected by fat content.

C. Metabolism and Elimination:

Study HP 83/88

After a single 30 mg oral dose of radiolabeled paroxetine to each of three male volunteers, more than 99% of the administered radioactivity was recovered in urine and feces within 10 days. Of this, 64% was excreted in urine and 36% in feces. Less than 1% was excreted unchanged in feces and urine, demonstrating that paroxetine was eliminated by metabolism.

Radioactivity excretion rates in feces paralleled those in plasma and urine indicating that the fecal metabolites were derived from absorbed material, probably via the bile. Therefore, absorption of the administered dose was essentially complete. However efficient absorption from the GI tract does not give rise to high systemic availability of paroxetine because of first-pass metabolism. Thus, metabolites of paroxetine predominated in plasma soon after oral dosing and remained the major components throughout. Ultimately, however, their overall disappearance rate paralleled that of paroxetine, showing that rate of formation, rather than rate of elimination, governs metabolite kinetics.

Metabolites of paroxetine were very polar, mainly sulfate and glucuronide conjugates. Their pattern, similar in plasma and urine, indicated that paroxetine was cleared by oxidative metabolism, following the standard pathway for methylenedioxy-phenyl compounds. Thus paroxetine is initially oxidized to an unstable catechol intermediate prior to meta-methylation and conjugation which yields the major metabolite BRL 36610 (Glucuronide or sulfate, each 15% of the dose in urine) . This metabolic pathway was utilized in all species studied.

D. **Special Populations:**

D.1. **Elderly Subjects:**

A formal comparison with younger subjects was conducted in two studies in which 20 mg was administered as both single and repeated doses to subjects of both age groups (HP/86/78, HP/87/88). The age range for elderly subjects enrolled in these two studies was 64 to 79 years; younger subjects were aged 21 to 38 years. In each study plasma concentrations of paroxetine **(C_{ss}** and AUG} after the single dose were about three-fold higher in the elderly group, but the ranges overlapped extensively. This suggests that, after a single dose, systemic availability was greater in the elderly, since t^ (about 5 hours) and half-life (about 20 hours) did not differ significantly in either study from values in the younger group. Both groups of subjects reached steady-state within the 2-week period of daily dosing.

.D.2. **Renal Impairment:**

The effect of renal impairment on the pharmacokinetics of paroxetine has been investigated by administering single 30 mg doses to groups of six subjects with mild, moderate, or severe renal impairment and a control group (HP/85/70). Inter-subject variability was marked, with pharmacokinetic parameters in the four groups overlapping extensively. Plasma concentrations of paroxetine increased as renal function declined, but half-life was prolonged (by 50%) only in the most severely impaired group. Despite these trends, only the difference in AUC between the most severely impaired group and the mildly impaired and control groups was statistically significant. It was concluded that a reduction in clearance may be partly responsible for the trend towards higher plasma concentrations of paroxetine in subjects with renal impairment. There has been no clinical trial experience of paroxetine in depressed patients with renal impairment. Thus, dose should be restricted to the lower end of the dose range for patients with severe renal impairment (creatinine clearance <30 Ml/min).

.D.3. **Hepatic Dysfunction:**

The pharmacokinetics of paroxetine have been investigated after both single (HPG 2-242/84/A) and chronic 20 mg dosing regimens (HP/87/38) in patients with biopsy-proven cirrhosis. In the single dose study, plasma concentrations of paroxetine were normal, as were half-life (about 20 hours) and urinary recovery of unchanged paroxetine (<1% of dose) indicating that the clearance of a single 20 mg dose was unchanged. This finding was not seen in the multiple-dose study, in which subjects defined as having mild to moderate hepatic impairment were administered 20 mg daily and compared to a control group administered 30 mg daily. Despite the difference in dose, plasma concentrations in the hepatically impaired group were higher. Half-lives also tended to be longer, and urinary recoveries of paroxetine, although still very low, were greater in the impaired group than in the healthy subjects. Therefore, although inter-subject variability was very large (differences were not statistically significant), there is the potential for reduced clearance in hepatically impaired patients, resulting in elevated plasma concentrations of paroxetine. There has been no clinical trial experience of paroxetine in depressed patients with hepatic impairment. Thus, dose should be restricted to the lower end of the dose range for patients with severe hepatic impairment.

.E. ***In Vitro*** **Protein Binding:**

In an ***in vitro*** study, paroxetine was shown to be about 95% protein-bound at therapeutically relevant concentrations (100-400 ng/Ml).

.F. ***In Vitro*** **Dissolution:**

All proposed marketing tablet strengths and the lots used in clinical trials show acceptable ***in vitro*** dissolution when tested using USP Apparatus II (paddle) at 60 rpm in 900 Ml of simulated gastric fluid without pepsin, 37°C. They would meet a dissolution specification of 75% in 45 minutes. * FDA recommends the following in ***vitro*** dissolution

specification: not less than 75% dissolved in 45 minutes when tested using the USP Apparatus II (paddle) at 60 rpm in 900 Ml of simulated gastric fluid without pepsin.

VIII. PERTINENT ADVISORY COMMITTEE MINUTES:

IX. POST APPROVAL:

TABLE 45

Total U.S. Intent-to-Treat Population

	Paroxetine (n=1563)	Placebo (n=497)	Active-Control (n=464)	Overall (n-2523)
Mean Age (yrs)	43.42	41.63	48.41	43.99
Minimum Age (yrs)	18	19	18	18
Maximum Age (yrs)	85	73	82	85
Mean Weight (lbs)	167.55	165.81	159.01	164.95
Age Groups				
<40 years	723 (46%)	246 (50%)	167 (36%)	1136 (45%)
40-64 years	685 (44%)	233 (47%)	135 (40%)	1103 (44%)
>65 years	154 (10%}	13 (4%)	112 (24%)	284 (11%)
Sex				
Female	869 (56%)	249 (50%)	244 (53%)	1362 (54%)
Male	693 (44%)	248 (50%)	220 (47%)	1151 (46%)
Race				
White	1462 (94%)	457 (92%)	437 (94%)	2356 (93%)
Black	' 70 (5%)	28 (6%)	21 (5%)	119 (5%)
Other	30 (2%)	12 (2%)	6 (1%)	48 (2%)

Notes: In this table, a patient is counted once if the Protocol 04 treatment was a continuation of the Protocol 03 treatment and counted twice if the patient crossed over to a new medication in Protocol 04. Protocol 04 was a long-term continuation of the 6-week Protocol 03 study.

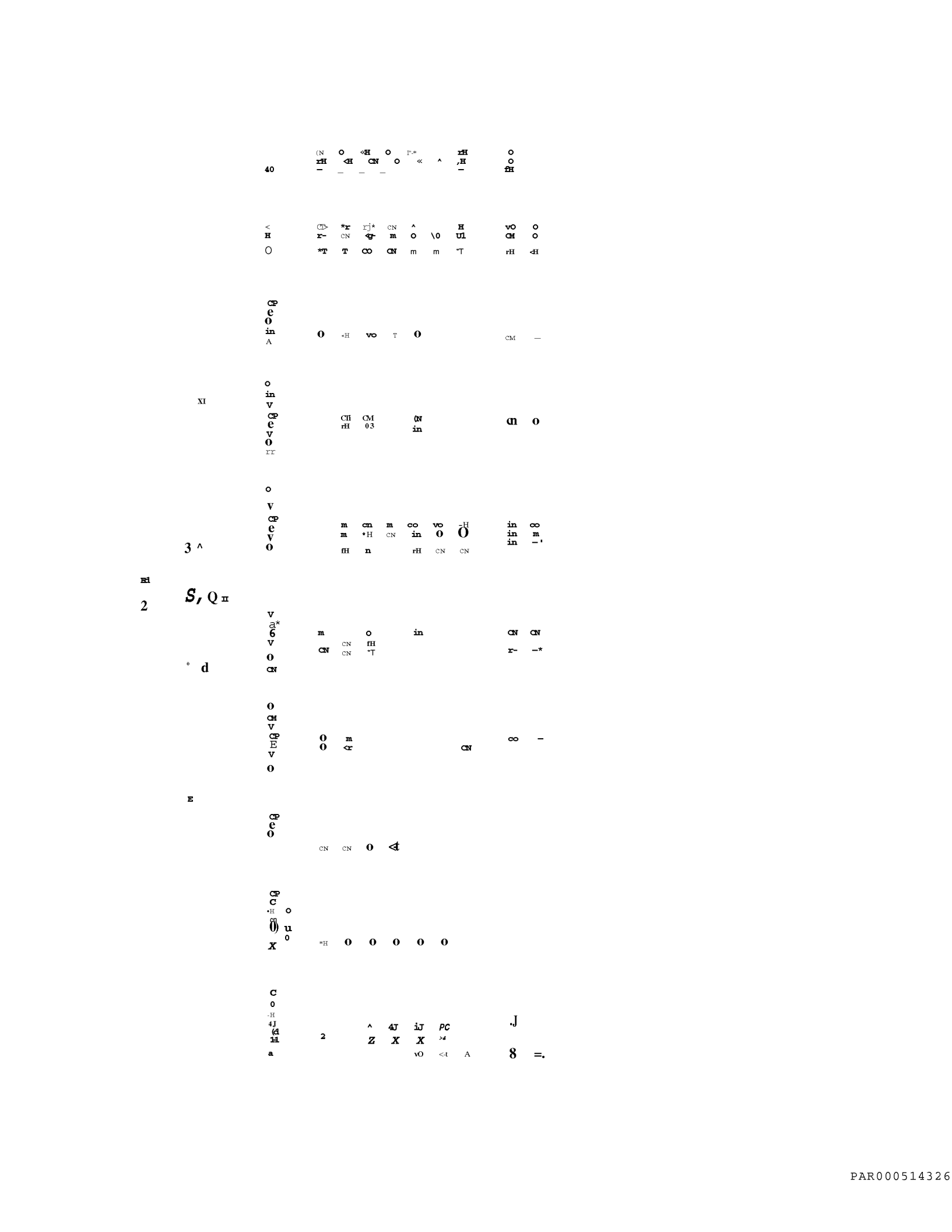
Active-control drugs in U.S. studies were imipramine, doxepin, and amitriptyline. Doxepin was used in an elderly population (n=135; mean age 62.2 yrs) accounting for the higher mean age in the active-control group.

TABLE 46

Demographic Profile Presented by Treatment Group:
Total Worldwide Intent-to-Treat Population

	Paroxetine (n=4126)		Placebo (n=625)		Active-Control <n=1954)		Overall (n=6705)	
Mean Age (yrs)	47.8		42.7		49.8		??	
Minimum Age (yrs)	15		19		17		15	
Maximum Age (yrs)	94		73		96		96	
Mean Weight (lbs)	154.5		163.3		149.9		??	
Age Groups								
<40 years	1414	(34%)	283	(45%)	598	(31%)	2295	(34%)
40-64 years	2010	(49%)	319	(51%)	946	(48%)	3275	(49%)
>65 years	693	(17%)	23	(4%)	408	(21%)	1124	(17%)
Unknown	9	- -			2	- -	11	- -
Sex								
Female	2690	(65%)	340	(54%)	1305	(67%)	4335	(65%)
Male	1435	(35%)	285	(46%)	649	(33%)	2369	(35%)
Unknown	1	- -					1	- -
Race								
White	3604	(95%)	584	(93%)	1590	(95%)	5778	(95%)
Black	91	(2%)	29	(5%)	32	(2%)	152	(2%)
Other	103	(3%)	12	(2%)	53	(3%)	173	(3%)
Unknown	328	- -			274		602	- -

Notes: In this table, a patient is counted once if the Protocol 04 treatment was a continuation of the Protocol 03 treatment and counted twice if the patient crossed over to a new medication (e.g. imipramine crossed over to paroxetine). Protocol 04 was a long-term continuation of the 6-week Protocol 03 study.



PAR000514326

TABLE 49

Treatment-Emergent Adverse Events in Placebo-Controlled Trials

Body System Preferred Term	Paroxetine <20 mg (n=169)		Paroxetine >20 mg (n=356)	
Body as a Whole				
Headache	26	15.4%	63	17.7%
Asthenia	24	14.2%	50	14.0%
Abdominal Pain	7	4.1%	10	2".8%
Fever	4	2.4%	6	1.7%
Back Pain	4	2.4%	5	1.4%
Chest Pain	5	3.0%	4	1.1%
Flu Syndrome	4	2.4%	4	1.1%
Trauma	3	1.8%	4	1.1%
Cardiovascular				
Palpitation	5	3.0%	9	2.5%
Vasodilation	2	1.2%	9	2.5%
Postural Hypotension	3	1.8%	5	1.4%
Dermatological				
Sweating	13	7.7%	41	11.5%
Rash	2	1.2%	7	2.0%
Gastrointestinal				
Nausea	46	27.2%	90	25.3%
Dry Mouth	28	16.6%	67	18,8%
Constipation	14	8.3%	52	14.6%
Diarrhea	25	14.8%	44	12.4%
Decreased Appetite	13	7,7%	20	5.6%
Flatulence	6	3.6%	15	4.2%
Dyspepsia	4	2.4%	7	2.0%
Vomiting	4	2.4%	7	2.0%
Increased Appetite	1	0.6%	6	1.7%
Oropharynx Disorder	6	3.6%	6	1.7%
Musculoskeletal				
Myopathy	2	1.2%	9	2.5%
Myalgia	2	1.2%	6	1.7%
Myasthenia	3	1.8%	6	1.7%
Nervous System				
Somnolence	32	18.9%	85	23.9%
Insomnia	15	8.9%	49	13.8%
Dizziness	18	10.7%	45	12.6%
Tremor	15	3.9%	28	7.9%
Nervousness	10	5.9%	18	5.1%
Anxiety	10	5.9%	17	4.8%
Libido Decreased	3	1.3%	13	3.7%
Paresthesia	5	3.0%	12	3.4%
Agitation	4	2.4%	3	2.2%
Drugged Feeling	3	1.8%	6	1.7%
Confusion	2	1.2%	5	1.4%
Myoclonus	4	2.4%	5	1.4%
Abnormal Dreams	2	1.2%	4	1.1%

Body System Preferred **Term**	Paroxetine <20 **mg** (n=169)		Paroxetine >20 **mg** (n=356)		Placebo (n=472)	
Respiration						
Respiratory Disorder	10	5.9%	24	6.7%	32	6.8%
Yawn	8	4.7%	13	3.7%	0	0.0%
Pharyngitis	4	2.4%	7	2.0%	16	3.4%
Special Senses						
Blurred Vision	8	4.7%	10	2.8%	7	1.5%
Taste Perversion	3	1.8%	9	2.5%	1	0.2%
Vision Disorders	4	2.4%	3	0.8%	1	0.2%
Urogenital System						
Ejaculatory Disturbance**	4	5..4%	25	14,.5%	0	0,.0%
Male Genital Disorders*	5	6..8%	15	8,.7%	0	0..0%
Impotence*	2	2..7%	5	2..9%	1	0..4%
Urinary Frequency	6	3,.6%	9	2,.5%	3	0..6%
Urination Impaired	6	3-, 6%	8	2,.2%	1	0,.2%
Female Genital Disorders*	1	1..1%	3	1..6%	0	0,.0%

* Percentage corrected for gender
\+ Primarily ejaculatory delay

TABLE 54
Percentage of Patients by Age (<65 or >65)
Experiencing Specific Adverse Experiences
Worldwide Dataset

	Paroxetine		Placebo		Active-Control	
TERM	(n=2504) <65	(n=459) >65	(n=532) <65	(n=22) >65	(n=920) <65	(n=223 >65
					%	
Nausea	26	18	12	14	14	9
Somnolence	22	13	9	5	28	30
Headache	22	12	17	13	17	12
Dry Mouth	19	15	11	14	53	53
Asthenia	16	10	6	0	15	11
Insomnia	15	8	7	14	13	7
Sweating	14	8	3	0	13	6
Constipation	13	12	8	0	21	26
Diarrhea	11	8	8	9	4	3
Dizziness	11	9	6	5	17	13
Tremor	11	9	2	0	18	11
Abnormal Ejaculation	9	0	0	0	2	0
Anxiety	5	3	2	5	4	4
Blurred vision	5	3	2	5	8	4
Paresthesia	5	3	2	5	7	5
Agitation	4	3	2	5	3	2
Decreased Appetite	4	3	2	5	3	2
Nervousness	4	2	2	5	2	2
Palpitations	4	4	2	0	8	4
Vomiting	4	2	1	5	3	2
Weight Gain	4	2	0	0	4	1
Chest Pain	3	2	2	5	2	2
Increased Appetite	2	0	1	0	3	1
Postural Hypotension	2	4	1	0	6	7
Tachycardia	2	2	1	0	5	2
Weight Loss	1	2	0	0	2	1

TABLE 55

Incidence of Suicides and Suicidal Acts
Pooled Worldwide Dataset

	Paroxetine (n=2963) 1008 PEY	Placebo (n=554) 72 PEY	Active-Control (n=1151) 218 PEY
Suicides			
No. (%)	5 (0.17)	2 (0.36)	3 (0.26)
No./PEY	0.005	0.028	0.013
Total Attempted Suicides (Overdose and Other Methods)			
No. (%)	40 (1.3)	6 (1.1)	12 (1.0)
No./PEY	0.040	0.083	0.055
Attempted Suicides (by Overdose)			
No. (%)	28 (0.9)	3 (0.5)	8 (0.7)
No./PEY	0.028	0.042	0.037

PEY - Patient Exposure Years

TABLE 56

HAMD Suicide Item: Difference from Baseline
Pooled Worldwide Dataset

	Baseline	Week 1	Week 2	Week 4	Week 6
Paroxetine	1.3	-0.5*	-0.8*	-1.0*	-1.1*
	n=2852	n=2552	n=2504	n=2200	n=1959
Placebo	1.3	-0.3	-0.5	-0.6	-0.8
	n=554	n=530	n=495	n=3*8	n=275
Active-Control	1.3	-0.5**	-0.7**	-0.9**	-1.0**
	n=1101	n=1029	n=963	n=829	n=710

* Par vs. Pla: p<0.05
** Act vs. Pla: p<0.05

TABLE 57

MADRS[1] Suicide Item: Difference from Baseline
Pooled U.S. Dataset

	Baseline[2]	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	1.83	-0.53	-0.83	-1.00	-1.17	-1.28
	n=1510	n=1457	n»1320	n=1218	n=1162	n=1050
Placebo	1.82	-0.28	-0.55	-0.66	-0.84	-0.92
	n=459	n=446	n=425	n=377	n=362	n=248
Active-Control	1.78	-0.41	-0.73	-0.78	-0.96	-1.14
	n=454	n«444	n=392	n-355	n=313	n=264
Pairwise Comparisons[3]						
Parox. vs. Placebo	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Parox. vs. Other Active	0.0075	0.1258	0.0011	0.0071	0.0713	
Placebo vs. Other Active	0.0375	0.0129	0.0832	0.0832	0.0663	

[1] Only studies performed in the U.S. used MADRS scale

[2] Kruskal-Wallis p « 0.56 for baseline treatment comparison

[3] p-values based on Wilcoxon rank-sum test

Deaths in Paroxetine-Treated Patients

Cause	Age	Sex	Treatment	Comments
Myocardial Infarction	54	M	1 month post-treatment	4 year history of genderalized arteriosclerosis, diabetes me11itus
Suicide	58	F	During 5th month	Hanging
Suicide	50	M	During 3rd month	Hanging
Suicide	56	F	During 7th week	Drowning
Suicide	18	F	6 days post-treatment	Overdose
Suicide	42	F	During 10th day	Doxepin overdose
Lung embolism	71	F	During 11th month	Also in treatment for arteriosclerotic heart disease
Murdered	55	F	During 12th month	
Cancer	79	F	During 4th month	Pre-existing bowel cancer
Myocardial Infarction	60	M	During 2nd month	
Pulmonary Embolism	74	F	During 13th day	Pre-existing diabetes mellitus and clerotic myocardiopathy
Coronary Atherosclerosis	84	M	Four days post-treatment	Pre-existing ischemia heart disease
Suicide	58	F	Day 8	Hanging
Pulmonary Embolism	73	F	2 weeks post-treatment	Secondary to deep leg vein thrombosis