# PRODUCT MONOGRAPH

## NU-PAROXETINE

**Paroxetine (as Paroxetine Hydrochloride) Tablets**

**10mg, 20 mg and 30 mg**

**Antidepressant – Antiobsessional – Antipanic – Anxiolytic Agent – Social Phobia (Social Anxiety Disorder) Therapy – Posttraumatic Stress Disorder Therapy**

**NU-PHARM INC.**
**50 Mural Street, Units 1 & 2**
**Richmond Hill, Ontario**
**L4B 1E4**

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## THERAPEUTIC CLASSIFICATION

Antidepressant – Antiobsessional – Antipanic – Anxiolytic Agent –
Social Phobia (Social Anxiety Disorder) Therapy – Posttraumatic Stress Disorder Therapy

## ACTIONS AND CLINICAL PHARMACOLOGY

Paroxetine is a potent and selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant and anxiolytic action in the treatment of depression, obsessive-compulsive disorder (OCD), panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD).

Paroxetine is a phenylpiperidine derivative which is chemically unrelated to the tricyclic or tetracyclic antidepressants. In receptor binding studies, paroxetine did not exhibit significant affinity for the adrenergic ($\alpha_1$, $\alpha_2$, $\beta$), dopaminergic, serotonergic ($5HT_1$, $5HT_2$), or histaminergic receptors of rat brain membrane. A weak affinity for the muscarinic acetylcholine receptor was evident. The predominant metabolites of paroxetine are essentially inactive as 5-HT reuptake inhibitors.

Human Pharmacokinetics:

Paroxetine is well absorbed after oral administration. In healthy volunteers, the absorption of a single 30 mg oral dose of paroxetine was not appreciably affected by the presence or absence of

food. Owing to the extensive distribution of paroxetine into the tissues, less than 1% of the total drug in the body is believed to reside in the systemic circulation.

Paroxetine is subject to a biphasic process of metabolic elimination which involves presystemic (first-pass) and systemic pathways. First-pass metabolism is extensive, but may be partially saturable, accounting for the increased bioavailability observed with multiple dosing. The metabolism of paroxetine is accomplished in part by cytochrome P450 ($IID_6$). Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS). The majority of the dose appears to be oxidized to a catechol intermediate which is converted to highly polar glucuronide and sulphate metabolites through methylation and conjugation reactions. The glucuronide and sulphate conjugates of paroxetine are about >10,000 and 3,000 times less potent, respectively, than the parent compound as inhibitors of 5-HT reuptake in rat brain synaptosomes. Approximately 64% of an administered dose of paroxetine is eliminated by the kidneys and 36% in the faeces. Less than 2% of the dose is recovered in the form of the parent compound.

A wide range of interindividual variation is observed for the pharmacokinetic parameters. Following the single or multiple dose administration of paroxetine at doses of 20 to 50 mg, the mean elimination half-life value for healthy subjects appears to be about 24 hours, although a range of 3 to 65 hours has been reported. Both the rate of absorption and the terminal elimination half-life appear to be independent of dose. Steady-state plasma concentrations of paroxetine are generally achieved in 7 to 14 days. No correlation has been established between paroxetine plasma concentrations and therapeutic efficacy or the incidence of adverse reactions.

No clear dose relationship has been demonstrated for the antidepressant effects of paroxetine at doses above 20 mg/day. The results of fixed-dose studies comparing paroxetine and placebo in the treatment of depression, panic disorder, generalized anxiety disorder and posttraumatic stress disorder revealed a dose dependency for some adverse events.

In *healthy young volunteers* receiving a 20 mg daily dose of paroxetine for 15 days, the mean maximal plasma concentration was 41 ng/mL at steady state (see Table 1). Peak plasma levels generally occurred within 3 to 7 hours.

In *elderly subjects,* increased steady-state plasma concentrations and prolongation of the elimination half life were observed relative to younger adult controls (Table 1). Elderly patients should, therefore, be initiated and maintained at the lowest daily dosage of paroxetine which is associated with clinical efficacy.

The results from a multiple dose pharmacokinetic study in subjects with severe *hepatic dysfunction* suggest that the clearance of paroxetine is markedly reduced in this patient group (see Table 1). As the elimination of paroxetine is dependent upon extensive hepatic metabolism, its use in patients with hepatic impairment should be undertaken with caution (see DOSAGE AND ADMINISTRATION).

In a single dose pharmacokinetic study in patients with mild to severe *renal impairment,* plasma levels of paroxetine tended to increase with deteriorating renal function (see Table 2).

As multiple-dose pharmacokinetic studies have not been performed in patients with renal disease, paroxetine should be used with caution in such patients.

At therapeutic concentrations, the plasma protein binding of paroxetine is approximately 95%. After the administration of a single 50 mg oral dose to lactating women, the concentrations of paroxetine detected in breast milk were similar to those in plasma.

**TABLE 1: Steady state pharmacokinetics of paroxetine after doses of 20 mg daily (mean and range)**

| | Young Healthy Subjects [n=22] | Elderly Healthy Subjects [n=22] | Hepatically* Impaired Subjects [n=10] |
|---|---|---|---|
| $C_{max\ (ss)}$ (ng/mL) | 41 (12-90) | 87 (18-154) | 87 (11-147) |
| $T_{max\ (ss)}$ (hours) | 5.0 (3-7) | 5.0 (1-10) | 6.4 (2-11) |
| $C_{min\ (ss)}$ (ng/mL) | 21 (4-51) | 58 (9-127) | 66 (7-128) |
| $AUC_{(ss)}$ (ng.h/mL) | 660 (179-1436) | 1580 (221-3286) | 1720 (194-3283) |
| $T_{1/2}$ (hour) | 19 (8-43) | 31 (13-92) | 66 (17-152) |

* Galactose elimination capacity 30 - 70% of normal.

**TABLE 2: Pharmacokinetics of paroxetine after a single 30 mg dose in normal subjects and those with renal impairment**

| | [a]Renally Impaired Subjects Severe [n=6] | [b]Renally Impaired Subjects Moderate [n=6] | [c]Healthy Young Subjects [n=6] |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 46.2 (35.9-56.7) | 36 (3.6-59.4) | 19.8 (1.5-54.8) |
| $T_{max}$ (hour) | 6.5 (4.0-11.0) | 4.8 (1.5-9.0) | 4.3 (1-7) |
| $AUC_{\infty}$ (ng.h/mL) | 2046 (605-3695) | 1053 (48-2087) | 574 (21-2196) |
| $t_{1/2}$ (hour) | 29.7 (10.9-54.8) | 18.3 (11.2-32.0) | 17.3 (9.6-25.1) |

[a] Creatinine clearance = 13-27 mL/min.

[b] Creatinine clearance = 32-46 mL/min.

[c] Creatinine clearance > 100 mL/min.

Abbreviations:

$C_{max}$ = maximum plasma concentration; $T_{max}$ = time to reach $C_{max}$

$AUC_{ss}$ = area under the plasma concentration time curve between dosing intervals (i.e. 24 hrs) at steady-state.

$AUC_{\infty}$ = area under the plasma concentration time curve at infinity.

$t_{1/2}$ = terminal elimination half-life; ss = steady state.

## Clinical Trials

### Depression

The efficacy of paroxetine as a treatment for depression has been established in six placebo-controlled clinical trials of 6 weeks in duration performed in patients with depression (ages 18 to 73). In these studies, paroxetine was shown to be significantly more effective than placebo in treating depression according to the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI) - severity of illness.

### Obsessive-Compulsive Disorder

Three double-blind, placebo-controlled clinical trials of 12 weeks in duration have been performed to investigate the efficacy of paroxetine in obsessive-compulsive disorder: two flexible dose studies (20-60 mg/day) and one fixed dose study (20, 40 & 60 mg/day). Results for the fixed dose study and one of the flexible dose studies showed statistically significant differences from placebo in favour of paroxetine in terms of mean change from baseline to endpoint on the Yale-Brown Obsessive-Compulsive Scale and/or the National Institute of Mental Health Obsessive-Compulsive Scale. In the fixed dose study, the proportion of patients who were considered to be much or very much improved at endpoint according to a Clinical Global Impression of Improvement was 15% (13/88) in the placebo group, 20% (17/85) in the 20 mg/day group, 36% (30/83) in the 40 mg/day group, and 37% (31/83) in the 60 mg/day group. In the two flexible dose studies, placebo response rates according to this criterion were 28% (28/99) and 25% (19/75), while paroxetine response rates were 45% (89/198) and 35% (28/79), respectively.

Panic Disorder

One fixed dose and three flexible dose placebo-controlled clinical trials of 10 to 12 weeks in duration have been performed to investigate the efficacy of paroxetine in panic disorder. The fixed dose study and two of the three flexible dose studies were supportive of differences from placebo in favour of paroxetine for measures of panic attack frequency. At endpoint, in the fixed dose study, the proportion of patients who were free of panic attacks was 44% (29/66) for the placebo group, 56% (33/59) for the 10 mg/day paroxetine group, 57% (35/61) for the 20 mg/day paroxetine group, and 76% (47/62) for the 40 mg/day paroxetine group.

Social Phobia (Social Anxiety Disorder)

One fixed dose and two flexible dose placebo-controlled clinical trials of 12 weeks in duration have been performed to investigate the efficacy of paroxetine in social phobia (social anxiety disorder). These studies showed statistically significant differences from placebo in favour of paroxetine in terms of mean change from baseline to endpoint on the Liebowitz Social Anxiety Scale and the percentage of therapeutic responders according to the Clinical Global Impression of Improvement. In the fixed dose study, the proportion of patients who were considered to be much or very much improved at week 12 of treatment according to the Clinical Global Impression of Improvement was 28.3% (26/92) in the placebo group, 44.9% (40/89) in the 20 mg/day group, 46.6% (41/88) in the 40 mg/day group, and 42.9% (39/91) in the 60 mg/day group. In the two flexible dose (20-50 mg/day) studies, placebo response rates according to this criterion were 23.9% (22/92) and 32.4% (47/145), while paroxetine response rates were 54.9% (50/91) and 65.7% (90/137), respectively.

Generalized Anxiety Disorder

The effectiveness of paroxetine in the treatment of Generalized Anxiety Disorder (GAD) (DSM IV) was demonstrated in two 8-week, multicentre, placebo-controlled studies. One trial was a flexible dose (20-50 mg/day) study while the other was a multiple fixed dose (20 or 40 mg/day) study. In both studies paroxetine demonstrated statistically significant superiority over placebo on the primary outcome measure - the Hamilton Rating Scale for Anxiety (HAM-A) total score, and on a number of secondary outcomes including the HAM-A anxiety and tension items, the Clinical Global Impression (CGI) responder criterion and the Sheehan Disability Scale (SDS). An additional 8-week flexible dose study did not demonstrate a significant difference between paroxetine (20-50 mg/day), and placebo on the primary outcome measure. However, paroxetine (20-50 mg/day) was more effective than placebo on many secondary study outcomes.

Posttraumatic Stress Disorder

The efficacy of paroxetine in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12 week, multicenter placebo controlled studies (Study 1 and Study 2) in adult patients who met the DSM-IV criteria for PTSD. Study outcome was assessed by (i) the Clinician Administered PTSD Scale Part (CAPS-2) score and (ii) the Clinical Global Impression Global Improvement Item (CGI-I). The CAPS-2 is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of: reexperiencing/intrusion, avoidance/numbing and hyperarousal. The two primary outcomes for each trial were (i) change from baseline to endpoint on the CAPS-2 total score (17 items), and (ii) proportion of responders on the CGI-I, where responders were defined as patients having a score of 1 (very much improved) or 2 (much improved).

Study 1 was a 12 week study comparing fixed paroxetine doses of 20 mg or 40 mg/day to placebo. Paroxetine 20 mg and 40 mg were demonstrated to be significantly superior to placebo for the CAPS-2 total score, and on proportion of responders on the CGI-I.

Study 2 was a 12-week flexible-dose study comparing paroxetine (20 mg to 50 mg daily) to placebo. Paroxetine was demonstrated to be significantly superior to placebo for the CAPS-2 total scorer, and on proportion of responders on the CGI-I.

The majority (66-68%) of patients in these trials were women. Subgroup analyses did not indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years or older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

Comparative Bioavailability

Two comparative bioavailability studies were conducted in healthy human volunteers - one under fasting conditions and one under fed conditions. The rate and extent of absorption of paroxetine were measured and compared following oral administration of 30 mg paroxetine (one tablet of either NU-PAROXETINE or Paxil). The results from measured data are summarized as follows:

**Fasting Study:** Summary Table of the Comparative Bioavailability Data
Paroxetine (Dose: 1 x 30 mg) From Measured Data

| Parameter | Geometric Mean Arithmetic Mean (CV%) NU-PAROXETINE | Geometric Mean Arithmetic Mean (CV%) Paxil®† | Ratio of Geometric Means (%)** |
|---|---|---|---|
| $AUC_T$ | 181 | 178 | 101.7 |
| (ng•hr/mL) | 323 (114) | 313 (114) | |
| $AUC_I$ | 209 | 202 | 102.3 |
| (ng•hr/mL) | 391 (149) | 385 (163) | |
| $C_{max}$ | 11.5 | 11.6 | 99.1 |
| (ng/mL) | 15.6 (72) | 15.7 (69) | |
| $T_{max}$ (hr)* | 6.00 (18) | 6.61 (22) | - |
| $t_{1/2}$ (hr)* | 14.0 (67) | 13.4 (74) | - |

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Paxil® is manufactured by SmithKline Beecham Pharma, and was purchased in Canada.

**Fed Study:** Summary Table of the Comparative Bioavailability Data
Paroxetine (Dose: 1 x 30 mg) From Measured Data

| Parameter | Geometric Mean Arithmetic Mean (CV%) NU-PAROXETINE | Geometric Mean Arithmetic Mean (CV%) Paxil®† | Ratio of Geometric Means (%)** |
|---|---|---|---|
| $AUC_T$ | 139 | 144 | 96.2 |
| (ng•hr/mL) | 209 (81) | 210 (77) | |
| $AUC_I$ | 146 | 151 | 96.4 |
| (ng•hr/mL) | 224 (87) | 224 (83) | |
| $C_{max}$ | 7.70 | 7.56 | 101.8 |
| (ng/mL) | 9.91 (61) | 9.20 (54) | |
| $T_{max}$ (hr)* | 5.79 (28) | 6.74 (28) | - |
| $t_{1/2}$ (hr)* | 13.5 (37) | 13.2 (34) | - |

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Paxil® is manufactured by SmithKline Beecham Pharma, and was purchased in Canada.

## INDICATIONS AND CLINICAL USE

### Depression

NU-PAROXETINE (paroxetine) is indicated for symptomatic relief of depressive illness.

Clinical trials have provided evidence that continuation treatment with paroxetine in patients with moderate to moderately severe depressive disorder is effective for at least 6 months.

### Obsessive-Compulsive Disorder

NU-PAROXETINE (paroxetine) is indicated for the symptomatic treatment of obsessive-compulsive disorder (OCD). The obsessions or compulsions must be experienced as intrusive, markedly distressing, time-consuming, or interfering significantly with the person's social or occupational functioning.

### Panic Disorder

NU-PAROXETINE (paroxetine) is indicated for the symptomatic treatment of panic disorder, with or without agoraphobia.

### Social Phobia (Social Anxiety Disorder)

NU-PAROXETINE is indicated for the symptomatic relief of generalized social phobia (social anxiety disorder), a disorder characterized by marked and persistent fear, anxious anticipation, or avoidance of multiple social situations (eg. interacting with strangers, attending social gatherings, dealing with authority figures) and/or performance situations (eg. eating, writing, working while

being observed, or public speaking). A diagnosis of social phobia/social anxiety disorder should not be made unless the fear, anxious anticipation, or avoidance of social and/or performance situations interferes significantly with the person's normal routine, occupational functioning, or social life, or causes marked distress.

Generalized Anxiety Disorder

NU-PAROXETINE is indicated for the symptomatic relief of anxiety causing significant distress in patients with Generalized Anxiety Disorder (GAD).

Posttraumatic Stress Disorder

NU-PAROXETINE is indicated for the symptomatic treatment of posttraumatic stress disorder (PTSD).

PTSD as defined by DSM-IV requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to clues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger.

A diagnosis of PTSD requires that the symptoms are present for at least one month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Long-Term Use of Paroxetine

The effectiveness of paroxetine in long-term use (i.e. more than 8 weeks for GAD and 12 weeks for other indications) has not yet been established in controlled trials for OCD, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder. Therefore, the physician who elects to use NU-PAROXETINE for extended periods in these indications should periodically re-evaluate the long-term usefulness of the drug for individual patients.

## CONTRAINDICATIONS

Hypersensitivity: NU-PAROXETINE (paroxetine) is contraindicated in patients who are known to be hypersensitive to the drug or any of its components.

Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with a MAO inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have begun treatment on a MAO inhibitor. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, NU-PAROXETINE should not be used in combination with MAO inhibitors or within 2 weeks of terminating treatment with MAO inhibitors. Treatment with NU-PAROXETINE should then be initiated cautiously and dosage increased

gradually until optimal response is reached. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with NU-PAROXETINE.

Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

An *in vivo* study suggests that drugs which inhibit P450 2D6, including certain SSRI's such as paroxetine, fluoxetine and fluvoxamine, will elevate plasma levels of thioridazine. Therefore, paroxetine should not be used in combination with thioridazine.

## WARNINGS

### POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

#### Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

**Adults and Pediatrics: Additional data**

- **There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

**Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.**

**Discontinuation Symptoms**

**Patients currently taking NU-PAROXETINE should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.**

## PRECAUTIONS

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until remission occurs. Therefore, high risk patients should be closely supervised throughout therapy with appropriate consideration to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for NU-PAROXETINE (paroxetine) should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders. (see **WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**)

Epilepsy: As with other antidepressants, paroxetine should be used with caution in patients with epilepsy.

Seizures: During clinical trials, the overall incidence of seizures was 0.15% in patients treated with paroxetine. However, patients with a history of convulsive disorders were excluded from these studies. Caution is recommended when the drug is administered to patients with a history of seizures. The drug should be discontinued in any patient who develops seizures.

Activation of Mania/Hypomania: During clinical testing in depressed patients, approximately 1% of paroxetine-treated patients experienced manic reactions. When bipolar patients were considered as a sub-group the incidence of mania was 2%. As with other Selective Serotonin Reuptake Inhibitors (SSRIs), NU-PAROXETINE should be used with caution in patients with a history of mania.

Discontinuation of Treatment with NU-PAROXETINE: When discontinuing treatment, regardless of the indication for which NU-PAROXETINE is being prescribed, patients should be monitored for symptoms which may be associated with discontinuation (e.g. dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, nausea, vomiting and sweating or other symptoms which may be of clinical significance, see ADVERSE REACTIONS). A gradual reduction in the dose rather than abrupt cessation is

recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See ADVERSE REACTIONS and DOSAGE and ADMINISTRATION).

Occupational Hazards: Although paroxetine did not cause sedation or interfere with psychomotor performance in placebo-controlled studies in normal subjects, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that NU-PAROXETINE does not affect them adversely.

Use in Patients with Concomitant Illness

General: Clinical experience with paroxetine in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using paroxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Cardiac Conditions: NU-PAROXETINE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. The usual precautions should be observed in patients with cardiac conditions.

Electroconvulsive Therapy (ECT): The efficacy and safety of the concurrent use of NU-PAROXETINE and ECT have not been studied.

Use in Elderly: Administration of paroxetine to the elderly is associated with increased plasma levels and prolongation of the elimination half-life relative to younger adults (see Human

Pharmacokinetics). Elderly patients should be initiated and maintained at the lowest daily dose of paroxetine which is associated with clinical efficacy.

Approximately 800 elderly patients ( 65 years) have been treated with paroxetine in worldwide premarketing clinical trials. The pattern of adverse experiences in the elderly was comparable to that in younger patients.

Children: The safety and effectiveness of NU-PAROXETINE in children under 18 years of age have not been established.

Pregnancy and Lactation: Although animal studies have not shown any teratogenic or selective embryotoxic effects, the safety of paroxetine in human pregnancy has not been established. NU-PAROXETINE should not be used during pregnancy unless the potential benefit to the patient outweighs the possible risk to the fetus.

Post-marketing reports indicate that some neonates exposed to PAROXETINE, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see ADVERSE REACTIONS, Postmarketing Reports). When treating a pregnant woman with PAROXETINE

during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

The concentrations of paroxetine detected in the breast milk of lactating women are similar to those in plasma. Lactating women should not nurse their infants while receiving paroxetine unless in the opinion of the treating physician, breast feeding is necessary, in which case the infant should be closely monitored.

Renal Impairment: Since paroxetine is extensively metabolized by the liver, excretion of unchanged drug in urine is a minor route of elimination. However, single dose pharmacokinetic studies in subjects with clinically significant renal impairment suggest that plasma levels of paroxetine are elevated in such subjects. Paroxetine should therefore be used with caution and the dosage restricted to the lower end of the range in patients with clinically significant renal impairment.

Hepatic Impairment: Pharmacokinetic studies of paroxetine in subjects with clinically significant hepatic impairment suggest that prolongation of the elimination half-life and increased plasma levels can be expected in this patient group. NU-PAROXETINE should be used with caution and dosages restricted to the lower end of the range in patients with clinically significant hepatic impairment.

Hyponatremia: Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding: There have been several reports of abnormal bleeding (mostly ecchymosis) associated with paroxetine treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Skin and mucous membrane bleedings have been reported following treatment with paroxetine. Paroxetine should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding (e.g. anticoagulants, nonsteroidal anti-inflammatories and ASA) and in patients with a known tendency for bleeding or those with predisposing conditions.

Glaucoma: As with other SSRIs, paroxetine infrequently causes mydriasis and should be used with caution in patients with narrow angle glaucoma.

Neuroleptic Malignant Syndrome: As with other SSRIs, paroxetine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

Drug Interactions

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS.

Thioridazine: See CONTRAINDICATIONS.

Drugs Metabolized by Cytochrome P450 (CYP2D6): Like some other selective serotonin reuptake inhibitors, paroxetine inhibits the specific hepatic cytochrome P450 isozyme CYP2D6 which is responsible for the metabolism of debrisoquine and sparteine. Poor metabolizers of debrisoquine/sparteine represent approximately 5 - 10% of Caucasians. The median $C_{min}$ (ss) for

paroxetine (20 mg daily) at steady state in poor metabolizers (n=8) was almost triple that reported for extensive metabolizers (n=9). Although the full clinical significance of this effect has not been established, inhibition of CYP2D6 can lead to elevated plasma levels of co-administered drugs which are metabolized by this isozyme.

In two studies, daily dosing of paroxetine (20 mg qd) under steady state conditions increased the following mean pharmacokinetic parameters for a single (100 mg) dose of desipramine in extensive metabolizers: $C_{max}$ (2 fold), AUC (6 fold), and $t_{1/2}$ (3-5 fold). Concomitant steady-state paroxetine treatment did not result in any further impairment of desipramine elimination in poor metabolizers. Insufficient information is available to provide recommendations on the necessary dosage adjustments for tricyclic antidepressants or paroxetine, if these drugs are to be used in combination. Plasma tricyclic antidepressant concentrations may need to be monitored in such instances.

Concomitant use of NU-PAROXETINE with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either NU-PAROXETINE or the other drug. Drugs metabolized by cytochrome P450 CYP2D6 include certain tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), selective serotonin reuptake inhibitors (e.g. fluoxetine), phenothiazine neuroleptics (e.g. perphenazine), Type IC antiarrhythmics (e.g. propafenone and flecainide), and metoprolol. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered (see CONTRAINDICATIONS).

Drugs Metabolized by Cytochrome P450 (CYP3A4): An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for

CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam and cyclosporin. Based on the assumption that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's in vivo clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity would not be expected to be of clinical significance.

Serotonergic Drugs: As with other SSRIs, co-administration with serotonergic drugs (e.g. MAO inhibitors (see CONTRAINDICATIONS), L-tryptophan) may lead to an incidence of 5-HT associated effects (Serotonergic Syndrome; see ADVERSE REACTIONS).

CNS Drugs: Experience in a limited number of healthy subjects has shown that paroxetine does not increase the sedation and drowsiness associated with haloperidol, amylbarbitone or oxazepam, when given in combination. Since the effects of concomitant administration of paroxetine with neuroleptics have not been studied, the use of NU-PAROXETINE with these drugs should be approached with caution.

Food/Antacids: The absorption and pharmacokinetics of NU-PAROXETINE are not affected by food or antacids.

Cardiovascular Drugs: Multiple dose treatment with paroxetine 30 mg/day has little or no effect on the steady-state pharmacokinetics of digoxin (0.25 mg qd) or propanolol (80 mg bid).

Microsomal Enzyme Inhibition/Induction: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes.

Steady state levels of paroxetine (30 mg daily) were elevated by about 50% when cimetidine (300 mg tid), a known drug metabolizing enzyme inhibitor, was co-administered to steady-state. Consideration should be given to using doses of paroxetine towards the lower end of the range when co-administered with known drug metabolizing enzyme inhibitors.

Anticonvulsants: In a limited number of patients with epilepsy on long-term treatment with anticonvulsants (carbamazepine 600-900 mg/day, n=6; phenytoin 250-400 mg/day, n=6; sodium valproate 300-2500 mg/day, n=8) the co-administration of paroxetine (30 mg/day for 10 days) had no significant effect on the plasma concentrations of these anticonvulsants. In healthy volunteers, co-administration of paroxetine with phenytoin has been associated with decreased plasma levels of paroxetine and an increased incidence of adverse experiences. However, no initial dosage adjustment of paroxetine is considered necessary when the drug is to be co-administered with known drug metabolizing enzyme inducers (e.g. carbamazepine, phenytoin, sodium valproate) and any subsequent dosage adjustment should be guided by clinical effect. Co-administration of paroxetine with anticonvulsants may be associated with an increased incidence of adverse experiences.

Alcohol: The concomitant use of NU-PAROXETINE and alcohol has not been studied and is not recommended. Patients should be advised to avoid alcohol while taking NU-PAROXETINE.

Tryptophan can be metabolized to serotonin. As with other serotonin reuptake inhibitors, the use of NU-PAROXETINE together with tryptophan may result in adverse reactions consisting primarily of headache, nausea, sweating and dizziness as well as serotonin syndrome (see ADVERSE REACTIONS, Postmarketing Reports). Consequently, concomitant use of NU-PAROXETINE with tryptophan is not recommended.

Chronic daily dosing with phenobarbital (100 mg qid for 14 days) decreased the systemic availability of a single 30 mg dose of paroxetine in some subjects. The AUC and $t_{1/2}$ of paroxetine were reduced by an average of 25% and 38% respectively compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. No initial NU-PAROXETINE dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Anti-cholinergic Drugs: Paroxetine has been reported to increase the systemic bioavailability of procyclidine. Steady state plasma levels of procyclidine (5 mg daily) were elevated by about 40% when 30 mg paroxetine was co-administered to steady-state. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

Drugs Highly Bound to Plasma Protein: Paroxetine is highly bound to plasma protein, therefore administration of NU-PAROXETINE to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

In a study of depressed patients stabilized on lithium, no pharmacokinetic interaction between paroxetine and lithium was observed. However, since there is limited experience in patients, the concurrent administration of NU-PAROXETINE and lithium should be undertaken with caution.

A multiple dose study of the interaction between paroxetine and diazepam showed no alteration in the pharmacokinetics of paroxetine that would warrant changes in the dose of paroxetine for patients receiving both drugs. The effects of paroxetine on the pharmacokinetics of diazepam were not evaluated.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and the $5HT_1$ agonist, sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised. The possibility of such interactions should also be considered if other $5HT_1$ agonists are to be used in combination with SSRIs.

Theophylline: Reports of elevated theophylline levels associated with paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

St. John's Wort: In common with other SSRI's, pharmakodynamic interactions between paroxetine and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

## ADVERSE REACTIONS

### Commonly Observed

The most commonly observed adverse experiences associated with the use of paroxetine in clinical trials and not seen at an equivalent incidence among placebo-treated patients were: nausea, somnolence, sweating, tremor, asthenia, dizziness, dry mouth, insomnia, constipation, diarrhea, decreased appetite and male sexual dysfunction (see Tables 3 and 4).

### Adverse Events Leading to Discontinuation of Treatment

Twenty-one percent of over 4000 patients who received paroxetine in worldwide clinical trials in depression discontinued treatment due to an adverse experience. In obsessive-compulsive

disorder, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder studies, 11.8% (64/542), 9.4% (44/469), 16.1% (84/522), 10.7% (79/735) and 11.7% (79/676), respectively, of patients treated with paroxetine discontinued treatment because of adverse events. The most common events leading to discontinuation (reported by 1% or more of subjects) included: asthenia, headache, nausea, somnolence, insomnia, agitation, tremor, dizziness, constipation, impotence, abnormal ejaculation, sweating and diarrhea.

Adverse Effects Following Discontinuation of Treatment (or Dose Reduction)

Clinical Trials

The following adverse events have been reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: abnormal dreams (2.3% vs 0.5%), paresthesias (2.0% vs 0.4%), and dizziness (7.1% vs 1.5%). The majority of these events were mild to moderate, self-limiting and did not require medical intervention. These adverse events were noted in GAD and PTSD clinical trials employing a taper phase regimen for discontinuation of treatment. This regimen involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

Post-Marketing

There have been spontaneous reports of adverse events upon the discontinuation of paroxetine (particularly when abrupt), including but not limited to the following: dizziness, sensory disturbances (including paresthesias and electric shock sensations), agitation/restlessness, anxiety, nausea, vomiting, sweating, headache, and sleep disturbance. These events are

generally self-limiting. Symptoms associated with discontinuation have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these or any other symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see PRECAUTIONS and DOSAGE and ADMINISTRATION).

Clinical Trial Experience

Multiple doses of paroxetine were administered to 4126 subjects in clinical trials for depression, 542 subjects in clinical trials for OCD, 469 subjects in clinical trials for panic disorder, 522 subjects in clinical trials for social phobia (social anxiety disorder), 735 subjects in clinical trials for generalized anxiety disorder and 676 subjects in clinical trials for posttraumatic stress disorder. Untoward experiences associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing.

Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse experiences without first grouping similar types of untoward experiences into a limited (i.e., reduced) number of standardized experience categories.

Table 3 lists adverse experiences that occurred at an incidence of 1% or higher in short term (6-week) flexible dose (20 - 50 mg/day) placebo-controlled trials in depression. (An additional 460 patients participated in a fixed-dose placebo-controlled study.)

Table 4 enumerates adverse events that occurred at a frequency of 2% or more among patients on paroxetine who participated in placebo-controlled OCD trials of 12-weeks duration in which patients were dosed in the range of 20 - 60 mg/day and in placebo-controlled panic disorder trials of 10 - 12-weeks duration in which patients were dosed in the range of 10 - 60 mg/day, and in placebo-controlled social phobia (social anxiety disorder) trials of 12 weeks duration in which patients were dosed in a range of 20 to 50 mg/day in placebo-controlled generalized anxiety disorder trials of 8 weeks in which patients were dosed in a range from 10-50 mg/day and in placebo-controlled posttraumatic stress disorder trials of 12 weeks in which patients were dosed in a range from 20-50 mg/day.

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 factors differ from those which prevailed in the clinical trials. Similarly the cited incidences cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited frequencies do however 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 experiences were classified using a COSTART-based Dictionary terminology for the depression trials and an ADECS (a modified COSTART dictionary) for OCD and panic disorder trials.

**TABLE 3: Treatment-Emergent Adverse Events in Short Term Flexible Dose Placebo-Controlled Clinical Trials in Depression[1]**

| Body System | Preferred Term | Paroxetine (n=421) | Placebo (n=421) |
|---|---|---|---|
| Body as a Whole | Headache | 17.6% | 17.3% |
| | Asthenia | 15.0% | 5.9% |
| | Abdominal Pain | 3.1% | 4.0% |
| | Fever | 1.7% | 1.7% |
| | Chest Pain | 1.4% | 2.1% |
| | Trauma | 1.4% | 0.5% |
| | Back Pain | 1.2% | 2.4% |
| Cardiovascular | Palpitation | 2.9% | 1.4% |
| | Vasodilation | 2.6% | 0.7% |
| | Postural Hypotension | 1.2% | 0.5% |
| Dermatological | Sweating | 11.2% | 2.4% |
| | Rash | 1.7% | 0.7% |
| Gastrointestinal | Nausea | 25.7% | 9.3% |
| | Dry Mouth | 18.1% | 12.1% |
| | Constipation | 13.8% | 8.6% |
| | Diarrhea | 11.6% | 7.6% |
| | Decreased Appetite | 6.4% | 1.9% |
| | Flatulence | 4.0% | 1.7% |
| | Vomiting | 2.4% | 1.7% |
| | Oropharynx Disorder[2] | 2.1% | 0.0% |
| | Dyspepsia | 1.9% | 1.0% |
| | Increased Appetite | 1.4% | 0.5% |
| Musculoskeletal | Myopathy | 2.4% | 1.4% |
| | Myalgia | 1.7% | 0.7% |
| | Myasthenia | 1.4% | 0.2% |
| Nervous System | Somnolence | 23.3% | 9.0% |
| | Dizziness | 13.3% | 5.5% |
| | Insomnia | 13.3% | 6.2% |
| | Tremor | 8.3% | 1.9% |
| | Nervousness | 5.2% | 2.6% |
| | Anxiety | 5.0% | 2.9% |
| | Parethesia | 3.8% | 1.7% |
| | Libido Decreased | 3.3% | 0.0% |
| | Agitation | 2.1% | 1.9% |
| | Drugged Feeling | 1.7% | 0.7% |
| | Myoclonus | 1.4% | 0.7% |
| | CNS Stimulation | 1.2% | 3.6% |
| | Confusion | 1.2% | 0.2% |
| Respiration | Respiratory Disorder[3] | 5.9% | 6.4% |
| | Yawn | 3.8% | 0.0% |
| | Pharyngitis | 2.1% | 2.9% |
| Special Senses | Blurred Vision | 3.6% | 1.4% |
| | Taste Perversion | 2.4% | 0.2% |
| Urogenital System | *Abnormal Ejaculation[+] | 12.9% | 0.0% |
| | *Male Genital Disorders[4] | 8.0% | 0.0% |
| | Urinary Frequency | 3.1% | 0.7% |
| | Urination Impaired[5] | 2.9% | 0.2% |
| | *Impotence | 2.5% | 0.5% |
| | *Female Genital Disorders[6] | 1.8% | 0.0% |

1. Events reported by at least 1% of patients treated with paroxetine are included.

2. Includes mostly lump in throat and tightness in throat.

3. Includes mostly cold symptoms or URI.

4. Includes anorgasmia, erectile difficulties, delayed ejaculation/orgasm, sexual dysfunction and impotence.

[5] Includes difficulty with micturition and urinary hesitancy.

[6] Includes anorgasmia and difficulty reaching climax/orgasm.

* Percentage corrected for gender. Placebo: male, n=206; female, n=215. Paroxetine: male, n=201; female, n=220.

\+ Primarily ejaculatory delay. In a trial of fixed doses of paroxetine, the incidence of ejaculatory disturbance in males with 20 mg per day of paroxetine was 6.5% (3/46) versus 0% (0/23) in the placebo group.

**TABLE 4: Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive-Compulsive Disorder, Panic Disorder, Social Phobia (Social Anxiety Disorder), Generalized Anxiety Disorder and Posttraumatic Stress Disorder[1]**

| | | Obsessive-Compulsive Disorder | | Panic Disorder | | Social Phobia (Social Anxiety) Disorder | | Generalized Anxiety Disorder | | Posttraumatic Stress Disorder | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Body System | Preferred Term | Paroxetine (n=542) | Placebo (n=265) | Paroxetine (n=469) | Placebo (n=324) | Paroxetine (n=425) | Placebo (n=339) | Paroxetine (n=735) | Placebo (n=529) | Paroxetine (n=676) | Placebo (n=504) |
| Body as a Whole | Headache | 25.3% | 29.1% | 25.4% | 25.3% | 22.4% | 21.8% | 16.9% | 14.0% | 18.9% | 19.2% |
| | Asthenia | 21.8% | 13.6% | 13.6% | 4.6% | 22.4% | 13.6% | 14.3% | 6.4% | 11.8% | 4.2% |
| | Infection | 5.3% | 4.9% | 5.3% | 6.8% | 3.8% | 5.9% | 5.6% | 3.4% | 4.9% | 3.8% |
| | Abdominal Pain | 4.8% | 4.9% | 4.3% | 3.1% | 2.1% | 4.7% | 4.5% | 3.6% | 4.3% | 3.2% |
| | Chest Pain | 2.8% | 1.9% | 2.3% | 3.1% | 0.7% | 0.3% | 1.0% | 0.6% | 1.2% | 0.8% |
| | Back Pain | 2.4% | 4.9% | 3.2% | 2.2% | 1.6% | 4.1% | 2.3% | 3.6% | 3.4% | 3.4% |
| | Chills | 2.0% | 0.7% | 2.3% | 0.6% | 0.2% | 0.3% | 1.0% | 0.0% | 0.1% | 0.4% |
| | Trauma | 3.1% | 3.8% | 3.6% | 3.7% | 2.6% | 0.9% | 2.6% | 3.4% | 5.8% | 5.2% |
| Cardio-vascular | Vasodilation | 3.9% | 1.1% | 2.1% | 2.8% | 1.4% | 0.6% | 2.7% | 0.8% | 2.2% | 1.2% |
| | Palpitation | 2.0% | 0.4% | 2.3% | 2.5% | 1.2% | 1.8% | 1.1% | 1.1% | 1.0% | 0.8% |
| Derm-atologic | Sweating | 8.9% | 3.0% | 14.3% | 5.9% | 9.2% | 2.1% | 6.3% | 1.5% | 4.6% | 1.4% |
| | Rash | 3.1% | 1.9% | 2.3% | 1.5% | 0.7% | 0.3% | 1.5% | 0.9% | 1.5% | 2.0% |
| Gastro-intestinal | Nausea | 23.3% | 9.8% | 22.8% | 17.3% | 24.7% | 6.5% | 20.1% | 5.3% | 19.2% | 8.3% |
| | Dry Mouth | 18.1% | 8.7% | 18.1% | 10.8% | 8.9% | 2.9% | 10.9% | 4.7% | 10.1% | 4.8% |
| | Constipation | 15.7% | 6.4% | 7.9% | 5.2% | 5.4% | 1.8% | 10.5% | 1.7% | 5.5% | 3.4% |
| | Diarrhea | 10.3% | 9.8% | 11.7% | 6.5% | 8.5% | 5.9% | 9.1% | 6.6% | 10.5% | 5.4% |
| | Decreased Appetite | 9.0% | 3.4% | 7.0% | 2.8% | 7.8% | 1.5% | 5.2% | 1.1% | 5.9% | 2.6% |
| | Dyspepsia | 3.9% | 6.8% | 3.8% | 6.8% | 4.0% | 2.4% | 4.5% | 4.9% | 4.6% | 3.4% |
| | Flatulence | 3.0% | 4.2% | 1.7% | 2.8% | 4.0% | 2.4% | 1.4% | 2.1% | 1.0% | 1.0% |
| | Increased Appetite | 4.2% | 3.0% | 2.1% | 0.6% | 1.2% | 1.8% | 0.4% | 1.1% | 1.5% | 1.0% |
| | Vomiting | 2.2% | 3.4% | 1.9% | 1.5% | 2.4% | 0.6% | 2.7% | 2.5% | 3.0% | 2.0% |
| Musculo-skeletal | Myalgia | 3.1% | 3.8% | 2.3% | 3.4% | 4.0% | 2.7% | 2.9% | 2.6% | 1.8% | 1.8% |
| Nervous System | Somnolence | 24.3% | 7.2% | 18.8% | 10.8% | 21.6% | 5.3% | 15.4% | 4.5% | 16.0% | 4.6% |
| | Insomnia | 23.8% | 13.2% | 17.9% | 10.2% | 20.9% | 15.9% | 10.7% | 7.9% | 11.8% | 11.3% |
| | Dizziness | 12.4% | 6.0% | 14.1% | 9.9% | 11.3% | 7.1% | 6.1% | 4.5% | 6.1% | 4.6% |
| | Tremor | 10.5% | 1.1% | 8.5% | 1.2% | 8.7% | 1.2% | 4.6% | 0.8% | 4.3% | 1.4% |
| | Nervousness | 8.5% | 8.3% | 7.9% | 8.3% | 7.5% | 6.5% | 3.9% | 2.8% | 3.0% | 4.4% |
| | Libido Decreased | 7.2% | 3.8% | 8.5% | 1.2% | 11.5% | 0.9% | 9.4% | 1.5% | 5.2% | 1.8% |
| | Anxiety | 4.1% | 6.8% | 4.5.% | 4.0% | 4.7% | 4.1% | 1.6% | 0.9% | 3.8% | 4.0% |
| | Abnormal Dreams | 3.9% | 1.1% | 2.8% | 3.4% | 1.9% | 1.5% | 0.5% | 1.1% | 2.5% | 1.6% |
| | Myoclonus | 3.3% | 0.4% | 3.2% | 1.5% | 2.1% | 0.9% | 1.6% | 0.6% | 1.0% | 0.6% |
| | Concentration Impaired | 2.8% | 1.5% | 1.1% | 0.9% | 3.5% | 0.6% | 1.1% | 0.6% | 1.5% | 1.0% |
| | Depersonalization | 2.6% | 0.4% | 1.7% | 2.2% | 0.7% | 0.9% | 0.7% | 0.0% | 0.9% | 0.2% |
| | Amnesia | 2.2% | 1.1% | 0.6% | 0.0% | 0.5% | 0.3% | 0.4% | 0.6% | 1.3% | 1.0% |
| | Hyperkinesia | 2.2% | 1.5% | 0.9% | 0.9% | 1.2% | 0.0% | 0.8% | 0.0% | 1.3% | 0.2% |
| | Agitation | 1.7% | 2.3% | 4.7% | 3.7% | 2.6% | 0.9% | 1.8% | 1.1% | 1.9% | 3.2% |
| Respiratory System | Pharyngitis | 3.7% | 4.9% | 3.2% | 3.1% | 3.8% | 2.1% | 2.3% | 2.1% | 2.4% | 2.2% |
| | Rhinitis | 1.5% | 3.4% | 2.6% | 0.3% | 1.2% | 3.2% | 1.5% | 1.1% | 1.0% | 2.0% |
| | Sinusitis | 1.5% | 4.9% | 5.8% | 4.6% | 2.1% | 2.4% | 3.5% | 3.4% | 3.8% | 4.4% |
| | Yawn | 1.7% | 0.4% | 1.9% | 0.0% | 4.9% | 0.3% | 4.2% | 0.2% | 2.1% | 0.2% |

**TABLE 4: Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive-Compulsive Disorder, Panic Disorder, Social Phobia (Social Anxiety Disorder), Generalized Anxiety Disorder and Posttraumatic Stress Disorder[1]**

| | | Obsessive-Compulsive Disorder | | Panic Disorder | | Social Phobia (Social Anxiety) Disorder | | Generalized Anxiety Disorder | | Posttraumatic Stress Disorder | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Body System | Preferred Term | Paroxetine (n=542) | Placebo (n=265) | Paroxetine (n=469) | Placebo (n=324) | Paroxetine (n=425) | Placebo (n=339) | Paroxetine (n=735) | Placebo (n=529) | Paroxetine (n=676) | Placebo (n=504) |
| | Cough Increased | 1.1% | 1.9% | 2.3% | 1.5% | 0.7% | 0.9% | 0.8% | 0.8% | 1.2% | 0.6% |
| | Respiratory Disorder[1] | - | - | - | - | - | - | 6.8% | 5.1% | 3.3% | 1.0% |
| Special Senses | Abnormal Vision | 3.7% | 2.3% | 3.0% | 2.8% | 4.0% | 0.3% | 2.2% | 0.6% | 0.3% | 0.0% |
| | Taste Perversion | 2.0% | 0.0% | 1.1% | 0.6% | 0.7% | 0.6% | 0.7% | 0.8% | 0.7% | 0.8% |
| Urogenital System | Abnormal Ejaculation[2] | 23.3% | 1.3% | 20.5% | 0.9% | 27.6% | 1.1% | 24.7% | 2.0% | 12.6% | 1.6% |
| | Dysmenorrhea[2] | 1.4% | 1.9% | 2.0% | 2.3% | 4.6% | 4.4% | 1.3% | 1.2% | 1.6% | 1.3% |
| | Impotence[2] | 8.2% | 1.3% | 5.4% | 0.0% | 5.3% | 1.1% | 4.2% | 3.0% | 9.2% | 0.5% |
| | Female Genital Disorders[2,3] | 3.3% | 0.0% | 8.9% | 0.5% | 8.6% | 0.6% | 4.4% | 0.6% | 4.8% | 0.6% |
| | Urinary Frequency | 3.3% | 1.1% | 2.1% | 0.3% | 1.6% | 1.8% | 1.0% | 0.6% | 1.0% | 0.2% |
| | Urination Impaired[5] | 3.3% | 0.4% | 0.4% | 0.3% | 1.9% | 0.0% | 1.0% | 0.0% | 0.6% | 0.0% |
| | Urinary Tract Infection | 1.5% | 1.1% | 2.1% | 1.2% | 0.2% | 1.2% | 1.2% | 1.1% | 0.6% | 0.8% |

1. Events reported by at least 2% of either OCD, Panic Disorder, Social Phobia (Social Anxiety Disorder), Generalized Anxiety Disorder or Posttraumatic Stress Disorder paroxetine treated patients are included, except the following events which had an incidence on placebo ≥ paroxetine: [OCD]: depression, paresthesia, and respiratory disorder. [Panic Disorder]: flu syndrome, depression, paresthesia, respiratory disorder. [Social Phobia (Social Anxiety Disorder)]:depression, respiratory disorder. [Generalized Anxiety Disorder]: not applicable, [Posttraumatic Stress Disorder]: depression, respiratory disorder.

2. Incidence is gender-corrected.

| | |
|---|---|
| OCD: | Placebo: male, n=158; female, n=107<br>Paroxetine: male, n=330; female, n=212 |
| PANIC: | Placebo: male, n=111; female, n=213<br>Paroxetine: male, n=166; female, n=303 |
| SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER): | Placebo: male, n=180; female, n=159<br>Paroxetine: male, n=228; female, n=197 |
| GENERALIZED ANXIETY DISORDER: | Placebo: male, n=197; female, n=332<br>Paroxetine: male, n=283; female, n=452 |
| POSTTRAUMATIC STRESS DISORDER: | Placebo: male, n=190; female, n=314<br>Paroxetine: male, n=238; female, n=438 |

3. Includes anorgasmia and difficulty reaching climax/orgasm.

## Male and Female Sexual Dysfunction with SSRI's

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward

sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD and PTSD are displayed in Table 5 below.

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| Table 5: Incidence of Sexual Adverse Events in Controlled Clinical Trials | | |
|---|---|---|
| | **Paroxetine** | **Placebo** |
| **N (males)** | **1446** | **1042** |
| Decreased libido | 6-15% | 0-5% |
| Ejaculatory disturbance | 13-28% | 0-2% |
| Impotence | 2-9% | 0-3% |
| **N (females)** | **1822** | **1340** |
| Decreased libido | 0-9% | 0-2% |
| Orgasmic disturbance | 2-9% | 0-1% |

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

In the tabulations which follow, a COSTART or modified COSTART-based Dictionary terminology has been used to classify reported adverse experiences. The frequencies presented therefore represent the portion of the 4126, 542, 469, 522, 735 and 676 paroxetine-exposed individuals in depression, OCD, panic, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder trials, respectively, who experienced an event of the type cited on at least one occasion while receiving paroxetine. Experiences are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent experiences are defined as those occurring on one or more occasion in at least 1/100 patients; infrequent adverse experiences are those occurring in less than 1/100 but at least 1/1000 patients; rare experiences are those occurring in less than 1/1000 patients.

All adverse experiences are included except those already listed in Table 3 and Table 4, those reported in terms so general as to be uninformative and those experiences for which the drug cause was remote. It is important to emphasize that although the experiences reported did occur during treatment with paroxetine, they were not necessarily caused by it.

Body as a Whole

Frequent: Malaise, pain. Infrequent: Allergic reaction, chills, face edema, infection, moniliasis, neck pain, overdose. Rare: Abnormal laboratory value, abscess, adrenergic syndrome, cellulitis, chills and fever, cyst, hernia, intentional overdose, neck rigidity, pelvic pain, peritonitis, substernal chest pain, sepsis, ulcer.

Cardiovascular System

Frequent: Hypertension, syncope, tachycardia. Infrequent: Bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, ventricular extrasystoles. Rare: Angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cardiac disorder, cerebral ischemia, cerebrovascular accident, cerebrovascular disorder, congestive heart failure, extrasystoles, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular disorder, vascular headache.

Dermatological

Frequent: Pruritus. Infrequent: Acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, urticaria. Rare: Angioedema, contact dermatitis, erythema nodosum, exfoliative

dermatitis, herpes zoster, maculopapular rash, photosensitivity, skin discolouration, skin ulcer, skin hypertrophy, sweating decreased.

Endocrine

Rare: Diabetes mellitus, fertility decreased female, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Gastrointestinal

Frequent: Nausea and vomiting. Infrequent: Bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, vomiting and diarrhea, rectal hemorrhage. Rare: Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, colitis, duodenitis, esophagitis, fecal impaction, fecal incontinence, gastritis, gingivitis, hematemesis, hepatitis, ileitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue edema, tooth caries.

Hematologic and Lymphatic

Infrequent: Anemia, leukopenia, lymphadenopathy, purpura, WBC abnormality. Rare: Abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis), bleeding increased, eosinophilia, iron deficiency anemia, leukocytosis, lymphedema, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocytopenia.

Metabolic and Nutritional

Frequent: Weight gain, weight loss. Infrequent: Edema, hyperglycemia, peripheral edema, thirst. Rare: Alkaline phosphatase increased, bilirubinemia, cachexia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia (predominantly in the elderly) which is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH), non-protein nitrogen (NPN) increased, obesity, SGOT increased, SGPT increased.

Musculoskeletal

Infrequent: Arthralgia, arthritis, traumatic fracture. Rare: Arthrosis, bone disorder, bursitis, cartilage disorder, myositis, osteoporosis, tetany.

Nervous System

Frequent: CNS stimulation, concentration impaired, depression, emotional lability, vertigo.

Infrequent: Akinesia, alcohol abuse, amnesia, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction, thinking abnormal, hypesthesia. Rare: Abnormal electroencephalogram, abnormal gait, antisocial reaction, brain edema, choreoathetosis, circumoral paresthesia, confusion, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, reflexes increased, stupor, torticollis, withdrawal syndrome.

Respiratory System

Frequent: Cough increased, rhinitis. Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis. Rare: Hiccup, lung fibrosis, sputum increased, stridor, trachea disorder, voice alteration.

Special Senses

Infrequent: Abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus. Rare: Amblyopia, cataract specified, conjunctival edema, corneal lesion, corneal ulcer, exophthalmos, eye hemorrhage, acute glaucoma, hyperacusis, otitis externa, photophobia, retinal hemorrhage, taste loss, anisocoria, deafness, keratoconjunctivitis.

Urogenital System

Infrequent: Abortion*, amenorrhea*, breast pain*, cystitis, dysmenorrhea*, dysuria, menorrhagia*, nocturia, polyuria, urinary incontinence, urinary retention, urinary tract infection, urinary urgency, vaginitis*. Rare: Breast atrophy*, cervix disorder*, endometrial disorder*, female lactation*, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis*, nephritis, oliguria, salpingitis*, spermatogenesis arrest*, urethritis, urinary casts, urine abnormality, uterine neoplasm*, vaginal moniliasis*.

* Incidence corrected for gender.

Postmarketing Reports

Adverse events not listed above which have been reported since market introduction in patients taking paroxetine include acute pancreatitis, hepatic events such as elevation of hepatic enzymes, and hepatitis, sometimes associated with jaundice, and/or liver failure (in very rare circumstances, with fatal outcomes), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, thrombocytopenia, aggravated hypertension, syndrome of inappropriate ADH secretion, symptoms suggestive of hyperprolactinemia and galactorrhea, blurred vision, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment. The causal relationship between paroxetine and the emergence of these events has not been established.

There have been spontaneous reports of adverse events upon the discontinuation of paroxetine (particularly when abrupt), including but not limited to the following: dizziness, sensory disturbances (including paresthesias and electric shock sensations), agitation/restlessness, anxiety, nausea, vomiting, sweating, headache, and sleep disturbance. These events are generally self-limiting. Symptoms associated with discontinuation have also been reported for other selective serotonin reuptake inhibitors (See PRECAUTIONS).

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Patients have generally recovered without serious sequelae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic drugs, with or without alcohol.

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under 'ADVERSE REACTIONS', vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, anxiety and tachycardia have been reported.

No specific antidote is known.

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Where appropriate, the stomach should be emptied either by the induction of emesis, lavage or both. Following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of paroxetine, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken paroxetine who might ingest by accident or intent excessive quantities of a tricyclic antidepressant. In such a case,

accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

## DOSAGE AND ADMINISTRATION

**NU-PAROXETINE (paroxetine) is not indicated for use in children under 18 years of age (see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**

### GENERAL

NU-PAROXETINE (paroxetine) should be administered once daily in the morning and may be taken with or without food. The tablet should be swallowed rather than chewed.

Dose Adjustments: Based on pharmacokinetic parameters, steady-state paroxetine plasma levels are achieved over a 7 - 14 day interval. Hence, dosage adjustments in 10 mg increments should be made at 1 - 2 week intervals or according to clinician judgement.

Maintenance: During long term therapy for any indication, the dosage should be maintained at the lowest effective level.

Discontinuation of Treatment: Symptoms associated with the discontinuation of paroxetine have been reported in clinical trials and post marketing. Patients should be monitored for these and

other symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. (See PRECAUTIONS and ADVERSE REACTIONS).

A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See ADVERSE REACTIONS).

DEPRESSION

Usual Adult Dose: The administration of NU-PAROXETINE (paroxetine) should be initiated at 20 mg daily. For most patients, 20 mg daily will also be the optimum dose. The therapeutic response may be delayed until the third or fourth week of treatment.

Dose Range: For those patients who do not respond adequately to the 20 mg daily dose, a gradual increase in dosage up to 40 mg daily may be considered. The maximum recommended daily dose is 50 mg.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Usual Adult Dose: The administration of NU-PAROXETINE (paroxetine) should be initiated at 20 mg/day. The recommended dose of NU-PAROXETINE in the treatment of OCD is 40 mg daily.

Dose Range: For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.

PANIC DISORDER

Usual Adult Dose: The recommended starting dose of NU-PAROXETINE (paroxetine) in the treatment of panic disorder is 10 mg/day. The recommended dose of NU-PAROXETINE in the treatment of panic disorder is 40 mg daily.

Dose Range: For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.

SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER)

Usual Adult Dose: The recommended initial dosage is 20 mg/day. No clear dose-relationship has been demonstrated over a 20 to 60 mg/day dose range.

Dose Range: Some patients not responding adequately to a 20 mg dosage may benefit from gradual dosage increases, in 10 mg/day increments, up to a maximum of 50 mg/day.

GENERALIZED ANXIETY DISORDER

Usual Adult Dose: The recommended initial dosage is 20 mg/day.

Dose Range: Some patients not responding adequately to a 20 mg dosage may benefit from gradual dosage increases, in 10 mg/day increments, up to a maximum of 50 mg/day.

POSTTRAUMATIC STRESS DISORDER

Usual Adult Dose: The recommended starting dosage is 20 mg/day.

Dose Range: Some patients not responding adequately to a 20 mg/day dosage may benefit from gradual dosage increases, in 10 mg/day increments, up to a maximum of 50 mg/day.

SPECIAL PATIENT POPULATIONS

For any indication

Treatment of Pregnant Women During The Third Trimester: Post-marketing reports indicate that some neonates exposed to PAROXETINE, SSRIs, or other newer anti-depressants late in the third semester have developed complications requiring prolonged hospitalization, respiratory support, and tube-feeding (see PRECAUTIONS). When treating pregnant women with PAROXETINE during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering PAROXETINE in the third trimester.

Elderly: The recommended initial dose is 10 mg/day for elderly and/or debilitated patients. The dose may be increased if indicated up to a maximum of 40 mg daily.

Children: The use of NU-PAROXETINE in children under 18 years of age is not recommended as safety and efficacy have not been established in this population. (see **WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**

Renal/Hepatic Impairment: NU-PAROXETINE should be used with caution in patients with renal or hepatic impairment. The recommended initial dose is 10 mg/day in patients with clinically significant renal or hepatic impairment (see PRECAUTIONS). A maximum dose of 40 mg should not be exceeded.

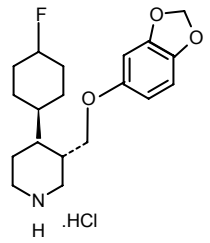
## PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Paroxetine hydrochloride anhydrous

Chemical Name(s): (-)-(3S,4R)-4-(*p*-Fluorophenyl)-3-[[(3,4-methylenedioxy) phenoxy] methyl] piperidine hydrochloride

Structural Formula:




Molecular Formula: $C_{19}H_{20}NO_3F$**.** HCl

Molecular Weight: 365.8

Melting Point: 116 - 120°C

Description: Paroxetine hydrochloride anhydrous is a white to off-white crystalline powder.

pKa and pH Values: It is not possible to measure directly the pKa of paroxetine in water owing to the aliphatic nature of the piperidine ring system and the low solubility of paroxetine base.

Measurements in 50% aqueous dimethyl sulphoxide indicate an aqueous pKa of 9.90 compared to a calculated value of 9.84.

The pH of a 0.5% (w/w) aqueous solution of paroxetine hydrochloride anhydrous is 6.0 ± 0.5.

Oil-Water Coefficient of Partition: The apparent partition coefficient of paroxetine in the octanol-water system (Poct/water) is 0.36.

Paroxetine hydrochloride anhydrous is slightly soluble in water (11.8 mg/mL at 30° C) and freely soluble in ethanol and methanol.

Composition

In addition to paroxetine, each film-coated tablet contains the non-medicinal ingredients anhydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, sodium starch glycolate, titanium dioxide, and the following colouring agents all extended on an aluminum substrate: D&C yellow #10 and FD&C yellow #6 (10 mg tablets only), D&C red #30 (20 mg tablets only), and FD&C blue #2 (30 mg tablets only).

Stability and Storage Recommendations

Store at room temperature 15 - 30° C. Protect from moisture.

## AVAILABILITY OF DOSAGE FORMS

NU-PAROXETINE 10 mg: Each bright yellow, oval, biconvex, film-coated tablet engraved "APO" on one side, and "10" on the other, contains paroxetine hydrochloride equivalent to 10 mg of paroxetine. Available in HDPE bottles of 30,100 and 250, and Apotex Long-Term Care unit dose blister packages (Apo-LTC Paks) of 620 and 700 tablets.

NU-PAROXETINE 20 mg: Each pink, oval, biconvex, film-coated tablet engraved "APO" on one side, and scored and engraved "20" on the other, contains paroxetine hydrochloride equivalent to 20 mg of paroxetine. Available in HDPE bottles of 100 and 500, unit dose blisters of 30 and 60, and Apotex Long-Term Care unit dose blister packages (Apo-LTC Paks) of 620 and 700 tablets.

NU-PAROXETINE 30 mg: Each blue, oval, biconvex, film-coated tablet engraved "APO" on one side, and "30" on the other, contains paroxetine hydrochloride equivalent to 30 mg of paroxetine. Available in HDPE bottles of 100, unit dose blisters of 30, and Apotex Long-Term Care unit dose blister packages (Apo-LTC Paks) of 620 and 700 tablets.

## INFORMATION FOR THE PATIENT

Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets as you may need to read it again. **FOR FURTHER INFORMATION OR ADVICE, PLEASE SEE YOUR DOCTOR OR PHARMACIST.**

### What you should know about NU-PAROXETINE

- NU-PAROXETINE (paroxetine hydrochloride) belongs to the family of medicines called selective serotonin reuptake inhibitors.

- NU-PAROXETINE has been prescribed to you by your doctor to relieve your symptoms of depression, obsessions and compulsions, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder or posttraumatic stress disorder. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

**What you should tell your doctor before taking NU-PAROXETINE**

- all your medical conditions, including a history of seizures, liver or kidney disease, heart problems or history of any abnormal bleeding;

- any medications (prescription or non prescription) which you are taking, especially monoamine oxidase inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide) or any other antidepressants, thioridazine, drugs used to prevent fits (anticonvulsants), drugs for Parkinson's disease, or drugs containing tryptophan;

- any natural or herbal products you are taking (e.g. St. John’s Wort);

- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding;

- your habits of alcohol consumption.

**How to take NU-PAROXETINE**

- It is very important that you take NU-PAROXETINE exactly as your doctor has instructed. Generally most people take between 20 mg to 40 mg of NU-PAROXETINE per day for depression, obsessive-compulsive disorder, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder; although your doctor may start you at 10 mg per day for panic disorder. Your doctor may increase the dose.

- Never increase the amount of NU-PAROXETINE you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to.

- You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work.

- Take your tablets in the morning, preferably with food. You should swallow the tablets whole with water. Do not chew them.

- You should avoid taking St. John's Wort if you are taking NU-PAROXETINE.

- Keep taking your tablets until the doctor tells you to stop. The doctor may tell you to continue to take your medicine for several months. Continue to follow the doctor's instructions.

- If you forget to take your tablet in the morning, take it as soon as you remember. Take your next dose at the normal time the next morning, then carry on as before.

- **Remember: This medicine has been prescribed only for you. Do not give it to anybody else.**

**When not to use NU-PAROXETINE**

Do not use NU-PAROXETINE if you are allergic to it or any of the components of its formulation (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.

**Precautions when taking NU-PAROXETINE**

- You may experience some side effects such as nausea, dry mouth, drowsiness, weakness, dizziness, sweating, nervousness, sleep disturbances and sexual problems.

Other effects may include loss of appetite, constipation, and diarrhea. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted

- **Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.**

- NU-PAROXETINE does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

- Avoid alcoholic drinks while taking NU-PAROXETINE.

- Contact your physician before stopping or reducing your dosage of NU-PAROXETINE. Symptoms such as dizziness, lightheadedness, nausea, vomiting, agitation/restlessness, anxiety, sweating, headache, sleep disturbance, electric shock sensations and other symptoms have been reported after stopping or reducing the dosage of paroxetine. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of NU-PAROXETINE to alleviate the symptoms.

- Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressants, such as PAROXETINE, during pregnancy have developed complications at birth requiring

prolonged hospitalization, breathing support and tube feeding. Reported symptoms included: feeding and / or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer anti-depressants, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

**What to do in case of overdose**

- If you have taken a large number of tablets all at once, contact your doctor or the nearest hospital emergency department immediately, even though you may not feel sick. Show the doctor your pack of tablets.

**How to store NU-PAROXETINE**

- Store at room temperature (15-30°C). Protect from moisture.
- Keep container tightly closed.
- Keep out of reach of children.

**What does NU-PAROXETINE contain**

NU-PAROXETINE (paroxetine hydrochloride) is available as 10 mg (yellow tablets), 20 mg (pink tablets), and 30 mg (blue tablets). Paroxetine is the active ingredient. Non-medicinal ingredients include: anhydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, sodium starch glycolate, titanium dioxide, D&C yellow #10 aluminum lake, FD&C yellow #6 aluminum lake (10 mg tablets only), D&C red #30 aluminum lake (20 mg tablets only), and FD&C blue #2 aluminum lake (30 mg tablets only). They do not contain sucrose, tartrazine or any other azo dyes.

**Who manufactures NU-PAROXETINE**

NU-PAROXETINE tablets are manufactured by APOTEX INC.

## PHARMACOLOGY

Animal Pharmacology

Paroxetine showed a high potency for the inhibition of 5-HT reuptake in rat hypothalamic synaptosomes ($K_i$=1.1 nM), but exerted relatively weak effects upon noradrenaline reuptake ($K_i$=350 nM). The predominant metabolites of paroxetine, a sulphate and a glucuronide conjugate, were essentially inactive as 5-HT reuptake inhibitors. Paroxetine has a low affinity for muscarinic cholinergic receptors ($K_i$ of 89 nM for displacement of [$^3$H]quinuclidinyl benzilate). Animal studies have indicated only weak anticholinergic properties.

Radioligand binding techniques in rat brain, in vitro, have indicated that paroxetine has little affinity for $\alpha_1$, $\alpha_2$ and $\beta$ -adrenoceptors, dopamine ($D_2$), 5-$HT_1$-like, 5-$HT_2$ and histamine ($H_1$) receptors at concentrations below 1 $\mu$M. This lack of interaction with post-synaptic receptors in vitro is substantiated by in vivo studies which demonstrate a lack of CNS depressant and hypotensive properties.

In mice, paroxetine ($ED_{50}$=0.4 mg/kg p.o.) was associated with potent and prolonged potentiation of the hypermotility induced by the 5-HT precursor, 5-hydroxytryptophan. Similarly, the anticonvulsant effects of 5-hydroxytryptophan in a mouse electroshock model were potentiated by paroxetine ($ED_{50}$=0.4 mg/kg p.o.). In rats paroxetine ($ED_{50}$=0.8 mg/kg p.o.) inhibited the hypermotility induced by p-chloroamphetamine, an agent which depletes neuronal 5-HT stores.

Paroxetine, 1 mg/kg i.p., in conscious rats with chronically implanted cortical electrodes, produced essentially no changes in the power spectrum and frequency analysis of the EEG.

Electrophysiological measures have demonstrated that paroxetine has a vigilance-increasing activity in animals. Oral doses of paroxetine 0.32 to 18 mg/kg to rats lengthened the waking period and shortened the slow-wave and paradoxical sleep periods in a dose-dependent fashion. As with other selective 5-HT uptake inhibitors, paroxetine, at a dose of 5 mg/kg i.p., causes symptoms of excessive 5-HT receptor stimulation when administered to rats previously given monoamine oxidase (MAO) inhibitors such as tranylcypromine or phenelzine, or the 5-HT precursor L-tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses above those generally required to inhibit 5-HT reuptake. The activating properties are not "amphetamine-like" in nature. In rats trained to discriminate d-amphetamine, 1 mg/kg i.p., from saline, no

generalization to amphetamine was observed after administration of paroxetine (0.3, 1, 3 or 10 mg/kg i.p.). Paroxetine caused seizures in mice at a lethal dose of 300 mg/kg p.o. At a dose of 50 mg/kg p.o., paroxetine lowered the threshold for electroshock-induced seizures in mice.

Animal studies indicate that paroxetine is well tolerated by the cardiovascular system. When the cardiovascular effects of paroxetine and amitriptyline were compared in the conscious rabbit and anaesthetised cat, intravenous doses of paroxetine approximately 2 to 4 times higher (on a mg/kg basis) than those of amitriptyline were required to produce significant changes in blood pressure, heart rate and electrocardiographic parameters. Similarly, in the pentobarbital anaesthetised dog, i.v. imipramine, amitriptyline and clomipramine (in doses of 10 mg/kg) caused severe atrioventricular block and ventricular arrhythmias, while equivalent doses of paroxetine resulted in only slight prolongation of the PQ interval. In addition, low doses (0.3 to 1 mg/kg) of the tricyclic antidepressants caused marked tachycardia, whereas paroxetine in doses up to 10 mg/kg had no effect on heart rate.

Studies in the spontaneous hypertensive rat indicate that, in contrast to antidepressants which inhibit the uptake of noradrenaline, paroxetine at 5 mg/kg i.v. has a much reduced propensity to inhibit the antihypertensive effect of guanethidine.

5-HT is transported into blood platelets and central neurons by a similar active uptake transporter mechanism in the cell membrane. Thus, in common with other selective 5-HT reuptake inhibitors, administration of paroxetine results in depletion of 5-HT from platelets. This has been reported after repeated daily administration of paroxetine at doses of 0.1, 1 and 10 mg/kg i.p. in mice and rats, 1 - 7.5 mg/kg p.o. in monkeys and 10 - 50 mg orally to healthy human volunteers. Similarly, whole blood 5-HT levels were shown to be depleted in depressed patients after paroxetine administration.

Human Pharmacology

Paroxetine 30 mg administered in single doses to healthy non-depressed volunteers did not impair psychomotor function which was measured by psychomotor tasks such as Morse tapping and motor manipulation, assessment of subjective perception and general assessment of arousal.

Paroxetine at doses of up to 40 mg daily produces no clinically significant changes in blood pressure, heart rate or ECG after administration to healthy subjects.

## TOXICOLOGY

In relation to the clinical dose, the acute $LD_{50}$ of paroxetine is very high in both mice and rats (approximately 350 mg/kg).

General toxicity studies have been conducted in rhesus monkeys and rats, in both of which the metabolic pathway for paroxetine is the same as in man.

The no-toxic effect levels in the rhesus monkeys and rats were 4 - 10 times and 6 - 15 times the recommended range of clinical doses respectively. At higher doses (40 mg/kg for 3 months and 25 mg/kg for 12 months), lipidosis was observed in several tissues of rats (lungs, mesenteric lymph nodes, epididymides, retinal tissues - the latter by electron microscopy only). As paroxetine is a lipophilic amine with both hydrophobic and hydrophilic moieties, it may accumulate in lysosomes leading to an impairment of lipid catabolism and, hence, the accumulation of lipids within the lysosomes. It should be noted that the slight degree of lipidosis seen in the rat was restricted to doses and plasma levels much higher than those observed in

man. In a clinical study investigating lamellated inclusion bodies in peripheral white blood cells during long term therapy, no difference between placebo and paroxetine could be detected.

No carcinogenic potential was detected in rat (dose levels of 1, 5 and 20 mg/kg/day) and mouse (dose levels of 1, 5 and 25 mg/kg/day) life-span studies. A non dose-related increase in malignant liver cell tumours occurred in male mice at 1 and 5 mg/kg/day which was statistically significant at 5 mg/kg/day. There was no increase at 25 mg/kg/day in female mice and the incidence was within the historical control range.

5-Hydroxytryptamine and compounds modulating this amine are known to affect reproductive function in animals and at high dose levels cause marked overt toxicity. Paroxetine at 15 and 50 mg/kg (hydrochloride salt) has been shown to impair reproductive function in rats.

In male rats, chronic administration of a 50 mg/kg dose has been associated with granulomatous reactions in the epididymides accompanied by atrophy and degeneration of the seminiferous tubules. There were no biologically significant effects on fertility of female rats but corpora lutea count was slightly reduced and preimplantation loss slightly increased at 50 mg/kg in association with marked maternal toxicity.

Reproduction studies were performed in rats and rabbits at doses up to 42 and 5 times the maximum recommended daily human dose (60 mg) on a mg/kg basis. These are 8.3 (rat) and 1.7 (rabbit) times the maximum recommended human dose on a $mg/m^2$ basis. These studies have revealed no evidence of teratogenic effects or of selective toxicity to the embryo.

Specific studies have demonstrated that paroxetine is unlikely to possess the potential for immunotoxicity.

Serum samples were obtained from depressed patients who had received 30 mg of paroxetine daily for between six and twelve months, from groups of rats on a repeat dose toxicity study in which daily doses of 1, 5 and 25 mg/kg of paroxetine were administered for 52 weeks, from guinea pigs epicutaneously exposed (topically under an occlusive patch) to paroxetine and from New Zealand White (NZW) rabbits parenterally (i.m. and s.c.) injected with paroxetine in Freund's adjuvant. In addition as a positive control, sera were obtained from NZW rabbits which had been immunized by i.m. and s.c. injections of Freund's adjuvant emulsions containing paroxetine chemically conjugated to bovine gamma globulin (BGG).

Serum antibody levels were assessed by enzyme- or radio-immunoassays (ELISA or RIA). No anti-paroxetine antibody activity was detected in serum samples from patients, from rats in the toxicity study, from guinea pigs epicutaneously exposed to paroxetine, or from rabbits parenterally injected with paroxetine. Serum anti-paroxetine antibody was detected in rabbits immunized with Freund's adjuvant emulsions containing paroxetine coupled with BGG, verifying that the RIA system employed was capable of detecting antibodies directed against paroxetine.

Paroxetine also did not induce contact sensitivity reactions in guinea pigs following epicutaneous exposure.

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