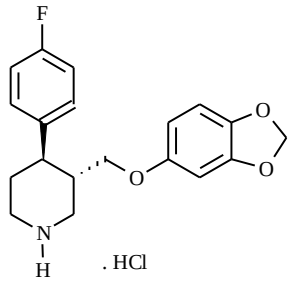
GenRx PAROXETINE TABLETS

NAME OF THE MEDICINE

Paroxetine hydrochloride.

Chemical Name: (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl]-piperidine hydrochloride.

Structural Formula:



Molecular Formula: $C_{19}H_{20}FNO_3$•HCl

Molecular Weight: 365.83

CAS Registry Number: 78246-49-8

DESCRIPTION

Paroxetine hydrochloride is an odourless, off-white powder, with a melting point range of 120°C to 138°C and solubility of 5.4 mg/mL in water. It is the hydrochloride salt of a phenylpiperidine compound.

Paroxetine is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents.

Each tablet contains 20 mg paroxetine hydrochloride, as the active ingredient.

In addition, each tablet contains the following inactive ingredients: magnesium stearate, sodium starch glycollate, anhydrous lactose, hydroxypropylcellulose, hypromellose, macrogol 8000 and titanium dioxide.

PHARMACOLOGY

Pharmacological Actions

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and efficacy in the treatment of Obsessive Compulsive Disorder, Panic Disorder, Social Anxiety Disorder/Social Phobia, Generalised Anxiety Disorder and Post-traumatic Stress Disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

In vitro studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for α_1-, α_2- and β-adrenoceptors, dopamine (D_2), 5-HT_1-like, 5-HT_2 and histamine (H_1) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate lack of CNS depressant and hypotensive properties. Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

Because the relative potencies of major metabolites of paroxetine are at most 1/50th of the parent compound, it is most unlikely that they contribute to the therapeutic effect of paroxetine.

As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan. Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature.

Paroxetine does not impair psychomotor function and does not potentiate the depressant effects of ethanol.

Animal studies indicate that paroxetine is well tolerated by the cardiovascular system and in healthy subjects, paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG.

In the treatment of depressive disorders, paroxetine exhibits comparable efficacy to standard antidepressants. There is also some evidence that paroxetine may be of therapeutic value in patients who have failed to respond to standard therapy.

In general, improvement in patients starts after one week but does not become superior to placebo until the second week of therapy. Paroxetine is effective in improving depression and suicidal ideation concurrently during the first few weeks of therapy.

Morning dosing with paroxetine does not have any detrimental effect on either the quality or duration of sleep. Moreover, patients are likely to experience improved sleep as they respond to paroxetine therapy. Where it is clinical practice to co-prescribe short-acting hypnotics with antidepressants, no additional adverse events have been recorded.

Paroxetine, in addition to its significant antidepressant effects, can improve associated symptoms of anxiety.

Pharmacokinetics

Absorption

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. As a consequence the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Partial saturation of the first-pass effect and reduced plasma clearance occur as the body burden increases, with higher single dosing or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in non-linear kinetics. These properties are a consequence of the fact that one of the enzymes that metabolises paroxetine is the readily saturable cytochrome P450 enzyme 2D6 (CYP2D6). However, because this enzyme becomes saturated early on following commencement of paroxetine treatment, the non-linearity observed during a subsequent dose increase is generally small and is confined to those subjects who achieve low plasma levels at low doses.

Distribution

Paroxetine is distributed throughout the body including the CNS. Approximately 95% of the paroxetine present in the plasma is protein bound at therapeutic concentrations.

Metabolism

Paroxetine is extensively metabolised after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than $1/50^{th}$ the potency of the parent compound at inhibiting serotonin uptake.

The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the non-linearity of paroxetine kinetics with increasing dose and increasing duration of treatment. At steady state, when CYP2D6 is essentially saturated, paroxetine clearance is governed by alternate P450 isoenzymes which, unlike CYP2D6, are not saturable at clinical doses (as evidenced by linear pharmacokinetics in CYP2D6-deficient individuals).

Because of the involvement of CYP2D6 in the metabolic clearance of paroxetine, considerable variation can occur in the plasma concentrations achieved between individuals. However, no correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy). Increased plasma concentrations of paroxetine occur in elderly subjects and in those subjects with severe renal and hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

Excretion

Approximately 64% of the dose is excreted in the urine; urinary excretion of unchanged paroxetine is generally less than 2% of dose. About 36% of the dose is excreted in the faeces, probably via the bile; faecal excretion of unchanged paroxetine represents less than 1% of the dose. Thus, paroxetine is

eliminated almost entirely by metabolism. Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of paroxetine.

The elimination half-life is variable, but is generally about 1 day. However, because of the reduction in plasma clearance which occurs on multiple dosing (non-linear kinetics – see Absorption), 7-14 days are required for the achievement of steady state. Thereafter, pharmacokinetics do not appear to change during long-term therapy. Considerable variation can occur in the plasma concentrations achieved between individuals, possibly due to variable first-pass effect and variability in clearance.

CLINICAL TRIALS

Relapse Prevention of Depression

A study of depressed outpatients who had responded to paroxetine (HAM-D total score < 8) during an initial 8-week open-treatment phase and were then randomised to continuation on paroxetine or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking paroxetine (15%) compared to those on placebo (39%).

Obsessive Compulsive Disorder

The effectiveness of paroxetine in the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 12-week placebo controlled studies (Studies 1 and 2). The results of a third placebo controlled study (study 3) support the effectiveness of paroxetine in the treatment of OCD.

Study 1 was a dose-ranging study which originally consisted of 348 patients with OCD and compared placebo, 20 mg, 40 mg or 60 mg daily. Of these 348 patients, 338 had at least one post-baseline efficacy evaluation and were included in the Intent-to-Treat (ITT) population for efficacy analyses. Paroxetine 40 mg/day and 60 mg/day were significantly superior to placebo ($p < 0.001$) in the treatment of OCD as assessed by the primary efficacy variable, mean change from baseline in the Yale-Brown Obsessive Compulsive Disorder (YBOCS) total score. Significant improvement was noted from week 6 onwards.

Studies 2 and 3 were flexible dose studies comparing paroxetine (20–60 mg daily) with clomipramine (25–250 mg daily). In Study 2, conducted in 399 patients, 391 had at least one post-baseline efficacy evaluation and were included in the Intent-to-Treat (ITT) population for efficacy analyses. Paroxetine was significantly more effective than placebo as assessed by the primary efficacy variables mean change from baseline in YBOCS total score ($p = 0.002$). In addition, the efficacy of paroxetine was comparable to that of clomipramine in this study. In study 3, conducted in 241 patients, 232 had at least one post-baseline efficacy evaluation and were included in the Intent-to-Treat (ITT) population for efficacy analyses. There was a numerically better response in paroxetine treated patients compared to placebo in the mean change from baseline in YBOCS total score, the magnitude of which was comparable to that in study 2, though this did not reach statistical significance.

Relapse Prevention of OCD

A study of OCD outpatients, who had responded to paroxetine during an initial 6-month open-treatment phase and were then randomised to continuation on paroxetine or placebo for 6 months demonstrated a significantly lower relapse rate for patients taking paroxetine (38%) compared to those on placebo (59%). The risk ratio assessment conducted in this study showed that patients randomised to placebo were 2.7 times more likely to experience a relapse compared to those patients who continued on paroxetine treatment ($p = 0.001$).

Panic Disorder

The effectiveness of paroxetine in the treatment of Panic Disorder was demonstrated in four multi-centre, placebo controlled studies of adult outpatients. Patients in all studies had Panic Disorder (DSM III-R) with or without agoraphobia. The studies were conducted over 10–12 weeks. Two of these studies also had an active comparator (clomipramine or alprazolam) arm. In all four studies, patients received either paroxetine 10–60 mg/day (n = 469), clomipramine 10–150 mg/day (n = 121), alprazolam 1–6 mg/day (n = 77) or placebo (n = 324). These studies indicated that paroxetine was superior to placebo and comparable with active comparator.

Relapse Prevention of Panic Disorder
The efficacy of paroxetine in preventing relapse of Panic Disorder was demonstrated in a 12-week double-blind relapse prevention study. Patients (n = 43) who were responders during the 10-week double-blind phase and a 3-month double-blind extension phase were re-randomised to either paroxetine (10 mg/day, 20 mg/day or 40 mg/day) or placebo. Thirty three paroxetine-treated patients and 37 placebo treated patients remained on study at week 12. Patients treated with paroxetine were significantly less likely to relapse than patients receiving placebo (5% vs. 30%; p = 0.002).

Benefit in maintenance treatment was demonstrated in a 36-week extension study which compared paroxetine 20–60 mg/day (n = 68) to clomipramine 50–150 mg/day (n = 63) or placebo (n = 45). Patients who had satisfactorily completed the 12-week double-blind phase continued on the same medication for a further 36 weeks. By week 36, 50 paroxetine patients, 43 clomipramine patients and 27 placebo patients remained on the study. Maintenance of efficacy of paroxetine was significantly superior to placebo in 2 out of 3 primary efficacy variables ($p < 0.05$) and comparable with clomipramine.

Social Anxiety Disorder / Social Phobia
The effectiveness of paroxetine in the treatment of Social Anxiety Disorder/Social Phobia was demonstrated in three 12-week, multi-centre, double-blind, randomised, parallel group, placebo controlled clinical trials (2 flexible dose, 1 dose ranging). Patients received paroxetine 20–60 mg/day (n = 522) or placebo (n = 339). These studies indicated that paroxetine was statistically superior to placebo according to either the Liebowitz Social Anxiety Scale (LSAS) or the Clinical Global Impression (CGI) scale.

In the fixed dose study, no statistically significant differences in efficacy were observed between the groups treated with 20 mg/day, 40 mg/day and 60 mg/day paroxetine.

Patients in all studies had a primary diagnosis of Social Anxiety Disorder/Social Phobia according to DSM-IV. A number of exclusion criteria excluded patients from entering the trials e.g. any other AXIS 1 disorder as a primary diagnosis in the last 6 months.

Generalised Anxiety Disorder
The effectiveness of paroxetine in the treatment of Generalised Anxiety Disorder (GAD) was demonstrated overall, in three 8-week, multi-centre, placebo controlled studies of adult outpatients with Generalised Anxiety Disorder (DSM-IV).

Study 1 was a fixed dose study and compared paroxetine 20 mg/day (n = 188) or 40 mg/day (n = 197) with placebo (n = 180). Paroxetine 20 mg and 40 mg were both demonstrated to be significantly superior to the placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items (20 mg: $p < 0.001$; 40 mg: $p < 0.001$), and the Clinical Global Impression (CGI) responder criterion (20 mg: $p = 0.002$; 40 mg: $p < 0.001$).

Two flexible-dose studies were conducted comparing paroxetine 20–50 mg daily and placebo. In study 2, paroxetine demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score ($p = 0.008$), both the HAM-A anxiety ($p = 0.001$) and tension items ($p = 0.005$), and the Clinical Global Impression (CGI) responder criterion ($p = 0.007$). Study 3 supports the use of paroxetine in the treatment of GAD. Paroxetine demonstrated statistical significance over placebo on a number of the secondary outcome measures, including the HAM-A anxiety item ($p = 0.011$) and the Clinical Global Impression (CGI) responder criterion ($p = 0.011$).

Study 4 was a long term (up to 32 weeks) relapse prevention study comparing paroxetine 20–50 mg to placebo. Following an 8-week single blind treatment phase on paroxetine, patients who responded were randomised to either paroxetine or placebo in a 24-week double-blind phase. Paroxetine was shown to be statistically superior to placebo in the proportion of patients relapsing during the double-blind phase (10.9% vs. 39.9%: $p < 0.001$).

In addition, paroxetine demonstrated statistically superiority over placebo on the mean change from double-blind baseline in the HAM-A (total, items 1 & 2: $p < 0.001$), HAD ($p < 0.001$) and SDS ($p < 0.001$) and in the proportion of responders (relative to single-blind baseline), as measured by the CGI global improvement scale (88.0% paroxetine versus 50.7% placebo; $p < 0.001$). There was a high remission rate for paroxetine patients with many becoming effectively symptom-free (73% in the retrospective analysis of HAM-A total score of ≤ 7 at week 32), whereas many patients who had switched to placebo deteriorated.

Post-Traumatic Stress Disorder
The effectiveness of paroxetine in the treatment of Post-traumatic Stress Disorder (PTSD) was studied in three 12-week, multi-centre, double-blind, randomised, parallel group, placebo controlled clinical studies (2 flexible dose, 1 dose ranging, fixed dose) of adult outpatients with a primary diagnosis of Post-traumatic Stress Disorder (DSM-IV). The efficacy of paroxetine has not been evaluated in placebo controlled trials of more than 12 weeks duration.

Study 1 was a fixed dose study and compared paroxetine 20 mg/day (n = 183) or 40 mg/day (n = 182) with placebo (n = 186). Studies 2 and 3 were flexible dose studies in which patients received paroxetine 20–50 mg/day (n = 311) or placebo (n = 318).

All three studies indicated that paroxetine was statistically superior to placebo according to the Clinician Administered PTSD Scale Part 2 (CAPS 2), and two studies showed paroxetine superior to placebo according to the Clinical Global Impression (CGI) scale. In addition, paroxetine demonstrated statistical significance over placebo on a number of the secondary outcome measures in all three studies, including the Treatment Outcome PTSD Scale (TOP 8), the Davidson Trauma Scale (DTS) and the Sheehan Disability Scale (SDS).

In a pooled analysis of the pivotal studies, paroxetine was statistically superior over placebo in patients with or without co-morbid depression. The majority of patients in these trials were women [Study 1: 68.4% (377/551), Study 2: 65.8% (202/307), Study 3: 53.7% (173/322)]. The pooled analysis showed that paroxetine is effective in the treatment of PTSD in both males and females.

INDICATIONS

Paroxetine is indicated for the treatment of:
- Major depression and for the prevention of relapse of depressive symptoms
- Obsessive Compulsive Disorder (OCD) and for the prevention of relapse of OCD
- Panic Disorder and for the prevention of relapse of Panic Disorder
- Social Anxiety Disorder / Social Phobia
- Generalised Anxiety Disorder
- Post-Traumatic Stress Disorder.

CONTRAINDICATIONS

Paroxetine is contraindicated in persons who are known to be hypersensitive to paroxetine or any of its components (see **PRESENTATION AND STORAGE CONDITIONS**).

Paroxetine should not be used in combination with pimozide (see **Interactions with Other Medicines**).

Paroxetine should not be used in combination with MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)) with MAO inhibitors or within 2 weeks of terminating treatment. Likewise, MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with paroxetine (see **PRECAUTIONS**).

Paroxetine should not be used in combination with thioridazine (see **Interactions with Other Medicines**).

PRECAUTIONS

Children and Adolescents (< 18 years)
Paroxetine is not indicated for use in children or adolescents aged <18 years. Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of paroxetine in the treatment of depression in this population. The safety and efficacy of paroxetine in children aged <7 years has not been studied.

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders. In clinical trials of paroxetine in children and adolescents, adverse events related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in patients treated with paroxetine compared to those treated with

placebo (see **ADVERSE EFFECTS**). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Clinical Worsening and Suicide Risk
The risk of suicide attempts is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Young adults, especially those with Major Depressive Disorder (MDD), may be at increased risk for suicidal behaviour during treatment with paroxetine, especially during initial treatment (generally the first 1–2 months). An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18–24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25–64 years and ≥ 65 years), no such increase was observed.

In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18–30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patients presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including the development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the medication (see **Akathisia** and **Mania and Bipolar Disorder** below; see **ADVERSE EFFECTS**). Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analysis of 24 short-term (4 to 16 weeks), placebo controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from the trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazadone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Additionally, patients with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts. All patients should be monitored for clinical worsening (including development of new symptoms) and suicidality throughout treatment, and especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases.

Family and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia
Rarely, the use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterised by an inner sense of restlessness and psychomotor agitation (such as an inability to sit or stand still usually associated with subjective distress). This is most likely to occur within the first few weeks of treatment.

Monoamine Oxidase Inhibitors (MAOIs)
Treatment with paroxetine should be initiated cautiously at least 2 weeks after terminating treatment with MAO inhibitors (see **CONTRAINDICATIONS**) and dosage increased gradually until optimal response is reached.

Patients with Renal / Hepatic Impairment
Caution is recommended in patients with severe renal impairment or in those with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control (hypoglycaemia or hyperglycaemia). Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Tricyclic Antidepressants (TCAs)
Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with paroxetine because paroxetine may inhibit TCA metabolism via the cytochrome P450 enzyme 2D6. Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced if a TCA is co-administered with paroxetine.

Serotonin Syndrome / Neuroleptic Malignant Syndrome
On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment of paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic medicines. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination with serotonin-precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome (see Serotonergic Medicines section in **Interactions with Other Medicines**).

Mania and Bipolar Disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder.

Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk of bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that paroxetine is not approved for use in treating bipolar depression. As with all antidepressants, paroxetine should be used with caution in patients with a history of mania.

Tamoxifen
Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine irreversible inhibition of CYP2D6 (see **Interactions with Other Medicines**). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative anti-depressant with little or no CYP2D6 inhibition.

Bone Fracture
Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association with fractures. The risk occurs during treatment and is greatest in the early stages of therapy. The possibility of fracture should be considered in the care of patients treated with paroxetine.

Oral Anticoagulants
(See Warfarin paragraph in INTERACTIONS section)

Tryptophan
As adverse experiences have been reported when tryptophan was administered with another selective 5-HT uptake inhibitor, paroxetine should not be used in combination with tryptophan medication (see **Interactions with Other Medicines**).

Cardiac Conditions
The usual precautions should be observed in patients with cardiac conditions. There is limited experience concerning the use of paroxetine in patients with recent myocardial infarction or unstable heart disease.

Epilepsy
As with other antidepressants, paroxetine should be used with caution in patients with epilepsy or history of convulsive disorders.

Seizures
Overall the incidence of seizures is < 0.1% in patients treated with paroxetine. Paroxetine should be discontinued in any patient who develops seizures.

ECT
The efficacy and safety of the concurrent use of paroxetine and ECT have not been studied.

Glaucoma
As with other SSRIs, paroxetine can cause mydriasis and should be used with caution in patients with narrow angle glaucoma.

Hyponatraemia
Hyponatraemia has been rarely reported, predominantly in the elderly. The hyponatraemia generally reverses on discontinuation of paroxetine.

Cognitive and Motor Performance
Clinical experience has shown that therapy with paroxetine is not associated with impairment of cognitive or psychomotor function. However, as with all psychoactive medicines, patients should be cautioned about their ability to drive a car or operate machinery.

Alcohol
Although paroxetine does not increase the mental and motor skill impairments caused by alcohol, the concomitant use of paroxetine and alcohol in patients is not advised.

Bleeding
Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). This risk may be potentiated by concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or other medicines that affect coagulation. Paroxetine should therefore be used with caution in patients concomitantly treated with medicines that increase the risk of bleeding or in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Lactose
GenRx Paroxetine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, severe lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take this medicine.

Effects on Fertility
Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality. This effect appears to be reversible following discontinuation of treatment. Changes in sperm quality may affect fertility in some men.

Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function (*i.e.* reduced pregnancy rate, increased pre- and post- implantation losses, decreased viability of pups) was found in the reproduction studies in rats at doses of 13 mg paroxetine/kg and above. Vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred in male rats at doses of 25 mg/kg/day in toxicity studies.

Use in Pregnancy (Category D)
Category D Definition: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage.

Paroxetine should not be used in pregnancy.

The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant. If a decision is taken to discontinue paroxetine treatment in a pregnant woman, the prescriber should consult **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS – Discontinuation of Treatment**.

Epidemiological studies have shown infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations.

A recent retrospective US epidemiological study of 3,581 pregnant women exposed to paroxetine or other antidepressants during the first trimester of pregnancy showed an increased risk of major congenital malformations overall for paroxetine compared to other antidepressants (odds ratio 2.20; 95% confidence interval 1.34–3.63). There was also an increased risk of cardiovascular malformations for paroxetine compared to other antidepressants (odds ratio 2.08; 95% confidence interval 1.03–4.23). These figures excluded women exposed to both antidepressants and teratogenic medicines. The majority of cardiovascular malformations were ventricular septal defects.

The prevalence of congenital malformations as a whole and cardiovascular malformation alone in the infants of women taking paroxetine and excluding women taking teratogenic medicines as well were 4% (23 cases out of 527 infants) and 2% (11 cases out of 589 infants), respectively. These rates compare with those in the general population of 3% for all congenital malformation and 1% for cardiovascular malformation [Centers for Disease Control and Prevention, USA and Metropolitan Atlanta Birth Congenital Defects Program Data (MACDP)].

A separate study based on the Swedish Medical Birth Register evaluated 4,291 infants born to mothers exposed to SSRIs in early pregnancy. Of these infants, 2.9% were reported to have a congenital malformation, which does not differ from the rate in the unexposed. The rate of congenital malformation in infants whose mothers had been exposed to paroxetine (n = 708) was 3.4%.

There have been reports of premature birth in pregnant women exposed to paroxetine or other SSRIs, although a causal relationship with these medicines has not been established.

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy. There have been reports of complications in neonates exposed to paroxetine or other SSRIs late in the third trimester of pregnancy; however, a causal association with these medicines has not been confirmed. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, somnolence and constant crying. In some neonates the complications have resulted in prolonged hospitalisation, respiratory support and tube feeding. In some instances, the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (< 24 hours) after delivery.

Epidemiological studies have shown that the use of SSRIs (including paroxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher than the rate of 1–2 per 1000 pregnancies observed in the general population.

Reproduction studies performed in rats and rabbits at oral doses of up to 43 mg/kg and 5 mg/kg, respectively, have revealed no evidence of teratogenic effects. Studies in rats have shown increased pre- and post- implantation losses and decreased postnatal survival at dose levels producing maternal toxicity. Animal reproduction studies are not always predictive of human response.

Use in Lactation
The concentrations of paroxetine detected in the breast milk of lactating women are similar to those in plasma. Neonatal mortality was increased in the offspring of rats receiving paroxetine 13 mg/kg/day and 43 mg/kg/day PO during pregnancy and lactation. The risk to the infant by paroxetine administration to lactating women is unknown. Therefore, paroxetine should not be used by lactating women unless the potential benefit outweighs the possible risk.

Discontinuation of Treatment
Discontinuation symptoms have been reported with SSRI antidepressants, including paroxetine, when they have been discontinued, particularly when treatment has been stopped abruptly (see **ADVERSE EFFECTS** and **DOSAGE AND ADMINISTRATION**). It is therefore advised that the dose should be gradually tapered when discontinuing treatment (see **DOSAGE AND ADMINISTRATION**).

Symptoms seen on discontinuation of paroxetine treatment in adults:
In clinical trials in adults, adverse events seen on treatment discontinuation occurred in 30% of patients treated with paroxetine compared to 20% of patients treated with placebo. The occurrence of discontinuation symptoms is not the same as the medicine being addictive or dependence producing as with a substance of abuse.

Dizziness, sensory disturbances (including paraesthesia, tinnitus and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea have been reported. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2–3 months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see **DOSAGE AND ADMINISTRATION, Discontinuation of Treatment**).

Symptoms seen on discontinuation of paroxetine treatment in children and adolescents:
In clinical trials in children and adolescents, adverse events seen on treatment discontinuation occurred in 32% of patients treated with paroxetine compared to 24% of patients treated with placebo. Events reported upon discontinuation of paroxetine at a frequency of at least 2% of patients and which occurred at a rate at least twice that of placebo were: emotional lability (including suicidal ideation, suicide attempt, mood changes and tearfulness), nervousness, dizziness, nausea and abdominal pain (see **ADVERSE EFFECTS**).

Use in Children and Adolescents (< 18 years)
Paroxetine is not indicated for use in children or adolescents aged < 18 years.

Controlled clinical studies in children and adolescents with major depression disorder failed to demonstrate efficacy and do not support the use of paroxetine in the treatment of depression in this population (see **PRECAUTIONS**).

The safety and efficacy of paroxetine in children aged < 7 years has not been studied.

Genotoxicity
In a two year studies conducted in mice and rats, paroxetine had no tumourigenic effect and no genotoxicity effects were observed in a battery of *in vitro* and *in vivo* tests.

INTERACTIONS WITH OTHER MEDICINES

The absorption and pharmacokinetics of paroxetine are not affected by food or antacids. Paroxetine has little or no effect on the pharmacokinetics of digoxin, propranolol and warfarin.

Pimozide

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with paroxetine. This is explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and paroxetine is contraindicated (see **CONTRAINDICATIONS**).

Medicines that Interfere with Haemostasis (NSAIDs, Aspirin, Warfarin, etc)

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic medicines that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with paroxetine.

Warfarin

A double-blind parallel group study was performed in which healthy male volunteers were given daily doses of warfarin until a stable prothrombin time (measured as an INR) was achieved. There was no clinically or statistically significant change in INR in subjects who were then dosed with paroxetine or placebo, in addition to warfarin, for 28 days.

The following tabulated results of this study show that the healthy volunteers who received paroxetine had no significant differences in coagulation factors or the prothrombin time, measured as an INR. This suggests that paroxetine has no effect on warfarin metabolism and, therefore, it would not be expected that patients receiving warfarin therapy would develop an overdosage effect when they start therapy with paroxetine. With respect to platelet function, the overall screening tests and the bleeding time were unchanged after paroxetine therapy. Pharmacokinetic analysis has shown that there appears to be no effect of paroxetine on plasma concentrations of either warfarin enantiomer and no difference in warfarin concentrations between paroxetine-dosed and placebo-dosed subjects.

INR and bleeding time results in warfarin-treated subjects given paroxetine or placebo

		Paroxetine mean		**Placebo mean**			
Parameter	**n**	**Day 1**	**Day 28**	**Day 1**	**Day 28**	**Paroxetine: Placebo***	**95% CI**
INR	21	1.58	1.30	1.50	1.36	0.92	(0.77–1.09)
Bleeding time (mins)	23	4.58	4.86	6.15	5.81	1.00	(0.82–1.23)

* point estimates and 95% confidence intervals are adjusted for baseline (day 1) by covariate analysis

Medicines Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolising enzymes. For example, cimetidine, a known drug metabolising enzyme inhibitor, can increase the bioavailability of paroxetine whereas phenytoin, a known drug metabolising enzyme inducer, can decrease it. Co-administration of a single 30 mg dose of paroxetine to subjects receiving chronic daily dosing with 300 mg phenytoin is associated with decreased paroxetine AUC and half-life of approximately 30% and an increased incidence of adverse events.

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using doses at the lower end of the range. No initial dosage adjustment is considered necessary when paroxetine is to be co-administered with known drug metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin, sodium valproate). Co-administration of paroxetine with other anticonvulsants may also be associated with an increased incidence of adverse experiences. Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

Anticonvulsants: carbamazepine, phenytoin, sodium valproate. Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

Fosamprenavir / Ritonavir
Co-administration of fosamprenavir / ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Medicines Metabolised by Cytochrome P450 2D6
As with other antidepressants, including other SSRIs, paroxetine inhibits the specific hepatic cytochrome P450 enzyme 2D6 (CYP2D6). Inhibition of CYP2D6 may lead to enhanced plasma levels of those co-administered medicines which are metabolised to a significant extent by this isoenzyme, although the clinical significance of the interaction will depend on the therapeutic window of the affected medicines.

Therefore, co-administration of paroxetine with certain tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), phenothiazine neuroleptics (e.g. perphenazine and promethazine), risperidone, atomoxetine and Type 1C antiarrhythmics (e.g. flecainide) and metoprolol should be approached with caution (dose adjustment of concomitant medicines should be considered).

Tamoxifen has an important active metabolite, endoxifen, which is produced by CYP2D6 and contributes significantly to the efficacy of tamoxifen. Irreversible inhibition of CYP2D6 by paroxetine leads to reduced plasma concentrations of endoxifen (see **PRECAUTIONS**).

Pharmacokinetic interactions with tricyclic antidepressants have been reported for all SSRIs. As for other SSRIs, dosing of paroxetine with tricyclic antidepressants is not recommended as TCA plasma levels may be elevated to levels at which there may be an increased risk of TCA-related adverse events in some patients, which can be serious. Concomitant therapy has not been evaluated for safety and efficacy.

The effects of concomitant administration of paroxetine with neuroleptics and antiarrhythmics have not been studied. Co-administration may lead to pharmacokinetic interactions and should therefore be approached with caution because of the potential increased risk of serious adverse events in some patients e.g. symptoms suggestive of Neuroleptic Malignant Syndrome.

Neuromuscular Blockers
SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium and suxamethonium.

Thioridazine
Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia, such as torsades de pointes and sudden death. As with other medicines which inhibit the hepatic enzyme CYP2D6 (including other antidepressants), paroxetine can elevate plasma levels of thioridazine. Therefore, paroxetine should not be administered with thioridazine (see **CONTRAINDICATIONS**).

Medicines Metabolised by Cytochrome P450 3A4
An *in vivo* interaction study involving the co-administration, under steady state conditions, of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no significant effect of paroxetine on terfenadine pharmacokinetics. Paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance when it is administered with terfenadine or other medicines that are CYP3A4 substrates.

Procyclidine
Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

Psychotropic Agents
A 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 medicines.

Experience in a limited number of healthy subjects has shown that paroxetine does not increase the sedation and drowsiness associated with haloperidol, amylobarbitone or oxazepam, when given in combination.

Serotonergic Medicines
As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects (serotonin syndrome) (see **PRECAUTIONS**). Caution should be advised and a closer clinical monitoring is required when serotonergic drugs [such as L-tryptophan, triptans, tramadol, SSRIs, lithium, fentanyl and St. John's Wort (*Hypericum perforatum*) preparations] are

combined with paroxetine. Concomitant use of paroxetine and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)) is contraindicated (see **CONTRAINDICATIONS**).

Symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor. The risk of using paroxetine in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if concomitant administration is required.

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

Alcohol
See **PRECAUTIONS**.

ADVERSE EFFECTS

Adverse experiences with paroxetine are generally mild in nature and do not affect the patient's life-style. Adverse experiences may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy. 13% of paroxetine treated patients (n = 2963) in worldwide short term clinical trials for depression discontinued treatment due to an adverse experience, compared to 5% receiving placebo (n = 554). In addition, 11.8% (64/542) and 9.4% (44/462) of paroxetine patients withdrew from worldwide trials in OCD (vs. placebo, 21/265, 7.9%) and Panic Disorder (vs. placebo, 32/324, 9.9%), respectively.

The most commonly observed adverse events 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, dry mouth, insomnia, sexual dysfunction, dizziness, constipation, diarrhoea, and decreased appetite.

Paroxetine is less likely than tricyclic antidepressants to be associated with dry mouth, constipation and somnolence.

The following adverse events were observed during the clinical trial programs for depression, OCD and Panic Disorder. All adverse experiences are included in the list except those reported in terms so general as to be uninformative and those experiences for which the association with the medicine was remote. It should however be noted that causality has not necessarily been established and that patients enrolled in the clinical trials may have been generally healthier than the general patient population.

Events are listed within body systems and categorised by frequency according to the following definitions:

Very common	>1/10
Common	>1/100 and <1/10
Uncommon	>1/1000 and <1/100
Rare	>1/10,000 and <1/1000
Very rare	<1/10,000

Body as a Whole

Common:	headache, asthenia, abdominal pain, fever, chest pain, trauma, back pain, malaise, pain
Uncommon:	allergic reaction, chills+§, face oedema, 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, ulcer.

Cardiovascular

Common:	palpitation, vasodilatation, postural hypotension, hypertension, syncope, tachycardia

Uncommon: bradycardia, conduction abnormalities, abnormal electrocardiogram, hypotension, migraine+, ventricular extrasystoles

Rare: angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cerebral ischaemia, cerebrovascular accident, congestive heart failure, extrasystoles, low cardiac output, myocardial infarct, myocardial ischaemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis†, thrombosis, varicose vein, vascular headache.

Gastrointestinal

Common: nausea, dry mouth, constipation, diarrhoea, appetite decrease, flatulence, vomiting, oropharynx disorder, dyspepsia, increased appetite, gastrointestinal disorder‡, tooth disorder‡, stomatitis‡

Uncommon: bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal+, mouth ulceration, rectal haemorrhage

Rare: aphthous stomatitis, bloody diarrhoea, bulimia, colitis, duodenitis, oesophagitis, faecal impaction, faecal incontinence, gastritis, gingivitis+, haematemesis, hepatitis, ileus, jaundice, melaena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue oedema, tooth caries, tooth malformation†.

Haematological / Lymphatic

Uncommon: anaemia, leukopenia, lymphadenopathy, purpura, WBC abnormality

Rare: eosinophilia, iron deficiency anaemia, leukocytosis, lymphoedema, lymphocytosis, microcytic anaemia, monocytosis, normocytic anaemia.

Endocrine

Rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Metabolic / Nutritional

Common: weight gain‡†, weight loss‡; increases in cholesterol levels

Uncommon: oedema, hyperglycaemia, peripheral oedema, thirst

Rare: alkaline phosphatase increased+, bilirubinaemia, dehydration, gout, hyperphosphataemia†, hypocalcaemia, hypoglycaemia, hypokalaemia, hyponatraemia, obesity, AST increased, ALT increased.

Musculoskeletal

Common: myopathy, myalgia, myasthenia

Uncommon: arthralgia+, arthritis, traumatic fracture

Rare: arthrosis, bursitis, cartilage disorder, myositis, osteoporosis, tetany.

Nervous System

Common: somnolence, insomnia, dizziness, tremor, headache, nervousness, anxiety, paraesthesia, libido decreased, agitation, drugged feeling, myoclonus, CNS stimulation, confusion, concentration impaired, depression, emotional lability, vertigo, abnormal dreams‡ (including nightmares), hyperthesia+

Uncommon: abnormal thinking+, akinesia, alcohol abuse, amnesia+, ataxia, convulsion, depersonalisation+, hallucinations, hyperkinesia+, hypertonia+, incoordination, lack of emotion, manic reaction, paranoid reaction

Rare: abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, circumoral paraesthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsions, hostility+, hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, reflexes increased, restless legs syndrome (RLS), stupor, withdrawal syndrome.

Respiratory

Common: respiratory disorder, yawning, pharyngitis, cough increased, rhinitis

Uncommon: asthma, bronchitis, dyspnoea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis+

Rare: emphysema†, hiccup, lung fibrosis, pulmonary oedema†, sputum increased, voice alteration.

Dermatological

Common:	sweating, rash, pruritus, sweat gland disorder‡
Uncommon:	acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, urticaria
Rare:	angioedema, contact dermatitis, erythema nodosum, herpes zoster, hirsutism†, maculopapular rash, photosensitivity, skin discolouration, skin ulcer.
Very Rare:	severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Special Senses

Common:	blurred vision, abnormal vision‡, taste perversion
Uncommon:	abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus+, keratoconjunctivitis‡
Rare:	amblyopia, specified cataract, conjunctival oedema, corneal lesion, corneal ulcer, exophthalmos, eye haemorrhage, glaucoma, hyperacusis, otitis externa, photophobia, retinal haemorrhage, taste loss, anisocoria, deafness.

Urogenital

Common:	abnormal ejaculation*, urinary frequency, female/male genital disorder*, urination impaired, impotence*
Uncommon:	abortion*, amenorrhoea*, breast pain*, cystitis, dysmenorrhoea+*, dysuria, menorrhagia*, nocturia, polyuria, urinary incontinence, urinary retention, urinary tract infection+§, urinary urgency, vaginitis+*
Rare:	breast atrophy*, female lactation*, haematuria, kidney calculus, abnormal kidney function, kidney pain, mastitis*, nephritis, oliguria, urethritis, urine abnormality, vaginal moniliasis*.

Key to Symbols

- * Incidence corrected for gender
- \+ Adverse experiences reported more frequently in OCD vs. depression clinical trials
- ‡ Adverse experience reported in OCD clinical trials
- § Adverse experiences reported more frequently in Panic disorder vs. depression clinical trials
- † Adverse experiences reported in Panic disorder clinical trials

Adverse events occurring during post-marketing surveillance

Blood & lymphatic system disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes.
Very rare: thrombocytopenia.

Immune system disorders
Very rare: severe allergic reactions (including anaphylactoid reactions, and angioedema.

Endocrine disorders
Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Metabolism & nutrition disorders
Common: increases in cholesterol levels, decreased appetite.
Rare: hyponatraemia.
Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Psychiatric disorders
Common: somnolence, insomnia, agitation, abnormal dreams (including nightmares). Uncommon: confusion, hallucinations.
Rare: manic reactions.
These symptoms may be due to the underlying disease.

Nervous system disorders
Common: dizziness, tremor, headache.
Uncommon: extrapyramidal disorders.
Rare: convulsions, akathisia, restless legs syndrome (RLS).
Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor).
Reports of extrapyramidal disorders including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication.

Eye disorders
Common: blurred vision.
Uncommon: mydriasis (see Warnings and Precautions). Very rare: acute glaucoma.

Cardiac disorders
Uncommon: sinus tachycardia.

Vascular disorders
Uncommon: postural hypotension.

Respiratory, thoracic and mediastinal disorders
Common: yawning.

Gastrointestinal disorders
Very common: nausea.
Common: constipation, diarrhoea, vomiting, dry mouth.
Very rare: gastrointestinal bleeding.

Hepatobiliary disorders
Rare: elevation of hepatic enzymes.
Very rare: hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

Elevation of hepatic enzymes has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

Skin & subcutaneous tissue disorders
Common: sweating.
Uncommon: skin rashes.
Very rare: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions

Renal & urinary disorders
Uncommon: urinary retention, urinary incontinence.

Reproductive system & breast disorders
Very common: sexual dysfunction.
Rare: hyperprolactinaemia/galactorrhoea, menstrual disorders (including menorrhagia, metrorrhagia and amenorrhoea).

General disorders & administration site conditions
Common: asthenia, body weight gain. Very rare: peripheral oedema.

Discontinuation Symptoms
Common: dizziness, sensory disturbances, sleep disturbances, anxiety, headache.
Uncommon: agitation, nausea, tremor, confusion, sweating, diarrhoea.

As with many psychoactive medicines, discontinuation of paroxetine (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including tinnitus, paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), tremor, agitation or anxiety, nausea, headache, confusion, diarrhoea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms;

it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

Adverse Events from Paediatric Clinical Trials
In paediatric clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia and agitation. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children, less than 12 years of age.

In studies that used a tapering regimen (daily dose decreased by 10 mg/day at weekly intervals to a dose of 10 mg/day for one week), symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo were: emotional lability, nervousness, dizziness, nausea and abdominal pain.

DOSAGE AND ADMINISTRATION

It is recommended that paroxetine is administered once daily in the morning with food. The tablet should be swallowed rather than chewed.

Depression
The recommended dose of paroxetine is 20 mg daily. Many patients will respond to a 20 mg daily dose. Patients not responding to a 20 mg dose may benefit from dose increases in 10 mg/day increments, up to a maximum of 50 mg/day according to the patient's response.

As with all antidepressant medicines, dosage should be reviewed and adjusted if necessary within 2 to 3 weeks of initiation of therapy and thereafter as judged clinically appropriate. Dose changes should occur at intervals of at least 1 week.

It is generally recommended that a course of antidepressant medicine treatment should continue for a sufficient period, often for several months. There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. It is generally agreed that acute episodes of depression require several months or longer of sustained medicine therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain or sustain euthymia is unknown.

Systematic evaluation of paroxetine hydrochloride has shown that efficacy was maintained for periods up to one year.

Obsessive Compulsive Disorder
The recommended dose of paroxetine is 40 mg daily. Patients should start on 20 mg and the dose can be increased weekly in 10 mg increments. Some patients will benefit from having their dose increased up to a maximum of 60 mg/day.

Maintenance Therapy
Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see **CLINICAL TRIALS**). OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms.

Panic Disorder
The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose increased weekly in 10 mg increments according to patient's response. Some patients may benefit from having their dose increased up to a maximum of 60 mg/day.

A low starting dose and slow dosage increase reduce the risk of an initial transient increase in anxiety which is generally recognised to occur early in the treatment of this disorder.

Maintenance Therapy
Long-term maintenance of efficacy was demonstrated in two studies, the first a 3-month relapse prevention trial and the second a 36-week extension study (see **CLINICAL TRIALS**). In the relapse prevention trial, patients with Panic Disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic Disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder / Social Phobia
The recommended dose is 20 mg daily. Some patients may benefit from having their dose increased up to a maximum of 50 mg/day. Patients should start on 20 mg and, according to the patient's response, the dose can be increased weekly in 10 mg increments. The lowest dose of paroxetine studied in clinical trials (20 mg) produced a statistically significant superior response to placebo.

Generalised Anxiety Disorder
The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day according to the patient's response.

Post-Traumatic Stress Disorder
The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day according to the patient's response.

Use in the Elderly
Increased plasma concentrations of paroxetine occur in elderly subjects, but the range of concentrations overlaps with that observed in younger subjects.

Dosing in elderly patients should commence at the adult starting dose and may be increased up to 40 mg daily. Dosing should not exceed 40 mg daily.

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

Use in Children and Adolescents (< 18 years)
Paroxetine is not indicated for use in children or adolescents aged < 18 years.

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of paroxetine in the treatment of depression in this population (see **PRECAUTIONS**).

The safety and efficacy of paroxetine in children aged < 7 years has not been studied.

Patients with Renal / Hepatic Impairment
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/min) or severe hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range in patients with clinically significant hepatic or renal impairment.

Discontinuation of Treatment
As with other psychoactive medications, abrupt discontinuation should generally be avoided (see **PRECAUTIONS** and **ADVERSE EFFECTS**). The taper phase regimen used in the recent clinical trials involved a decrease in the daily dose by 10 mg/day at weekly intervals.

Recent clinical trials supporting the various approved indications for paroxetine employed a taper phase regimen, rather than an abrupt discontinuation of treatment. The taper phase regimen used in GAD and PTSD clinical trials 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.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: abnormal dreams, paraesthesia, and dizziness. In the majority of patients, these events were mild and moderate and were self-limiting and did not require medical intervention.

Also during paroxetine marketing there have been spontaneous reports of adverse events upon discontinuation (particularly when abrupt), such as dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances, tremor, agitation or anxiety, nausea and sweating. Similar events have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. Paroxetine should not normally be discontinued abruptly. 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, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Prolonged Treatment
The physician who elects to use paroxetine for extended period should periodically re-evaluate the long-term usefulness of paroxetine for the individual patient.

OVERDOSAGE

Overdose with paroxetine (up to 2000 mg) alone and in combination with other medicines have been reported. Events such as coma, convulsions or ECG changes have occasionally been reported. Fatalities have been reported when paroxetine was taken in conjunction with other psychotropic medicines, with or without alcohol or, in isolated cases, when taken alone.

As with all overdose attempts, the possibility of multiple drug ingestion should be borne in mind.

Symptoms
Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under **ADVERSE EFFECTS**, sedation, involuntary muscle contractions and facial flush have been reported.

Treatment
No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated, or as recommended by the national poisons centre, where available.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

GenRx Paroxetine tablets are intended for oral administration.

Each tablet contains 20 mg paroxetine as the active ingredient.

GenRx Paroxetine 20 mg tablets
White, oval-shaped, biconvex, film-coated tablets, partial bisect and engraved “20” on one side, other side plain.
Blister packs (clear PVC, PVDC/Aluminium) of 30 tablets
AUST R 83103.

Storage
Store below 25°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

16 August 2002

DATE OF MOST RECENT AMENDMENT:

21 August 2015