

## Arrow – Paroxetine

Paroxetine (as hydrochloride) 20 mg tablets

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### Presentation

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Arrow - Paroxetine is a white, film-coated, oval, biconvex tablets with 'PX | 20' on one side and '>' on the other side. Each tablet contains 22.22 mg of paroxetine hydrochloride equivalent to 20 mg of paroxetine.

Arrow - Paroxetine tablets also contain the following excipients: magnesium stearate, sodium starch glycolate, mannitol, microcrystalline cellulose, Eudragit E100 and Opadry White AMB OY-B-28920. The tablets are gluten free.

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### Uses

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#### **Actions**

Paroxetine is a potent selective serotonin reuptake inhibitor (SSRI). Its antidepressant action and effectiveness in the treatment of obsessive compulsive disorder (OCD) and panic disorder is thought to be related to its specific inhibition of serotonin [5-hydroxytryptamine (5HT)] uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants. It has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties. In accordance with these selective actions, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for alpha<sub>1</sub>, alpha<sub>2</sub> and beta-adrenoceptors, dopamine (D<sub>2</sub>), 5HT<sub>1</sub> like, 5HT<sub>2</sub> and histamine (H<sub>1</sub>) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies, which demonstrate lack of central nervous system (CNS) depressant and hypotensive properties.

As with other selective 5HT uptake inhibitors, paroxetine causes symptoms of excessive 5HT receptor stimulation when administered to animals previously given monoamine oxidase inhibitors or tryptophan. Behavioural and electroencephalographic (EEG) studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5HT 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. In healthy subjects, paroxetine produces no clinically significant changes in blood pressure, heart rate and electrocardiograph (ECG). Studies indicate that, in contrast to antidepressants that inhibit the uptake of

noradrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

### **Pharmacodynamics**

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 a clinical practice to co-prescribe short-acting hypnotics with antidepressants, no additional adverse events have been recorded.

In addition to its significant antidepressant effects, paroxetine can improve associated symptoms of anxiety.

### **Clinical trials**

#### **Relapse prevention of depression**

A study of depressed outpatients who had responded to paroxetine (Hamilton depression score total < 8) during an initial 8-week open treatment phase and were then randomised to continuation on 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 (OCD)**

The effectiveness of paroxetine in the treatment of 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 that originally consisted of 348 patients with OCD and compared placebo with paroxetine 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 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 to 60 mg daily) with clomipramine (25 to 250 mg daily). In Study 2 conducted in 399

patients, 391 had at least one post-baseline efficacy evaluation and were included in the ITT population for efficacy analyses. Paroxetine was significantly more effective than placebo as assessed by the primary efficacy variable 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 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, although this did not reach statistical significance.

### **Relapse prevention of obsessive compulsive disorder**

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 multicentre, placebo controlled studies of adult outpatients. Patients in all studies had panic disorder (Diagnostic and Statistical Manual, 3rd Edition, DSM III-R) with or without agoraphobia. The studies were conducted over 10 to 12 weeks. Two of these studies also had an active comparator (clomipramine or alprazolam) arm. In all four studies, patients received either paroxetine 10 to 60 mg/day ( $n = 469$ ), clomipramine 10 to 150 mg/day ( $n = 121$ ), alprazolam 1 to 6 mg/day ( $n = 77$ ) or placebo ( $n = 324$ ). These studies indicated that paroxetine was superior to placebo and comparable with active comparator.

The combination of paroxetine and cognitive-behavioural therapy has been shown to be significantly more effective than cognitive-behavioural therapy alone in the treatment of panic disorder.

### **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, 20 or 40 mg/day) or placebo. Thirty-three patients treated with paroxetine and 37 patients treated with placebo remained on study at week 12. Patients treated with paroxetine were significantly less likely to relapse than patients receiving placebo (5% versus 30%;  $p = 0.002$ ).

Benefit in maintenance treatment was demonstrated in a 36-week extension study, which compared paroxetine 20 to 60 mg/day ( $n = 68$ ) to clomipramine

50 to 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, the number of patients remained on the study were 50 for paroxetine, 43 for clomipramine and 27 for placebo. Maintenance of efficacy of paroxetine was significantly superior to placebo in two out of three primary efficacy variables ( $p < 0.05$ ), and comparable with clomipramine.

### **Social anxiety disorder or social phobia**

The effectiveness of paroxetine in the treatment of social anxiety disorder or social phobia was demonstrated in three 12-week, multicentre, double blind, randomised parallel group, placebo controlled clinical trials (two flexible dose, one dose ranging). Patients received paroxetine 20 to 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 paroxetine 20, 40 and 60 mg per day.

Patients in all studies had a primary diagnosis of social anxiety disorder or 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 (GAD)**

The effectiveness of paroxetine in the treatment of GAD was demonstrated overall, in three eight week, multicentre, placebo controlled studies of adult outpatients with GAD (DSM-IV).

Study 1 was a fixed dose study and compared paroxetine 20 mg (n = 188) or 40 mg/day (n = 197) with placebo (n = 180). Paroxetine 20 and 40 mg were both demonstrated to be significantly superior to 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 on the CGI responder criterion (20 mg:  $p = 0.002$ ; 40 mg:  $p < 0.001$ ).

Two flexible dose studies were conducted comparing paroxetine 20 to 50 mg daily and placebo. In Study 2, paroxetine demonstrated statistically significant superiority over placebo on the HAM-A total score ( $p = 0.008$ ), both the HAM-A anxiety ( $p = 0.001$ ) and tension items ( $p = 0.005$ ), and on the 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 CGI responder criterion ( $p = 0.011$ ).

Study 4 was a long-term (up to 32 weeks) relapse prevention study that compared paroxetine 20 to 50 mg with 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 versus 39.9%:  $p < 0.001$ ).

In addition, paroxetine demonstrated statistical superiority over placebo on the mean change from double blind baseline in the HAM-A (total, items 1 and 2:  $p < 0.001$ ), total Hospital Anxiety and Depression (HAD) scale ( $p < 0.001$ ) and Sheehan Disability Scale (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 (PTSD)**

The effectiveness of paroxetine in the treatment of PTSD was studied in three 12-week, multicentre, double blind, randomised, parallel group, placebo controlled clinical studies (two flexible dose, one dose ranging, fixed dose) of adult outpatients with a primary diagnosis of PTSD (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 to 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 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 SDS.

In a pooled analysis of the pivotal studies, paroxetine was statistically superior over placebo in patients with or without comorbid 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.

### **Pharmacokinetics**

#### **Absorption**

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism.

Due to first-pass metabolism, 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 doses 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 is generally small and is confined to those subjects who achieve low plasma levels at low doses.

### **Distribution**

Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma. Approximately 95% of the paroxetine present in the plasma is protein bound at therapeutic concentrations. However, there is no correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy).

Paroxetine is excreted into human breast milk, and transferred in small amounts to the foetuses of laboratory animals.

### **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 indicates that the metabolites have no more than one-fiftieth the potency of the parent compound at inhibiting serotonin uptake and, thus, it is most unlikely that they contribute to the therapeutic effect of paroxetine. Metabolism does not compromise paroxetine's selective actions on neuronal 5HT 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).

### **Elimination**

About 64% of the dose is excreted in the urine. Urinary excretion of unchanged paroxetine is generally less than 2% of the 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 to 14 days are required for the achievement of steady-state. Thereafter, its pharmacokinetics does 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.

### **Special patient groups**

In elderly patients and those subjects with severe renal and/or hepatic impairment, the plasma concentrations of paroxetine are increased, but the range of plasma concentrations in these patients overlaps that of healthy adult subjects.

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## **Indications**

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### ***Arrow - Paroxetine is indicated for adults in the following conditions:***

- depression of all types, including reactive and severe depression and depression accompanied by anxiety, and the prevention of relapse and recurrence of further depressive episodes
- 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 or social phobia
- generalised anxiety disorder
- post-traumatic stress disorder.

### **Children and adolescents**

Arrow - Paroxetine is not indicated for use in children or adolescents aged less than 18 years old (see **Warnings and Precautions**). The safety and efficacy of paroxetine in children aged less than 7 years old has not been studied.

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## **Dosage and Administration**

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Arrow - Paroxetine is administered once daily in the morning\* with food. The tablet can be halved, but should be swallowed rather than chewed.

\* Based on observed beneficial effects on sleep, it is recommended that the dose be taken in the morning. If, however, a patient experiences unacceptable daytime somnolence with paroxetine, consideration should be given to dosing at bedtime.

## **Depression**

The recommended dose of Arrow - 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 drugs, dosage should be reviewed and adjusted if necessary within 2 or 3 weeks of initiation of therapy and thereafter as judged clinically appropriate. Dose changes should occur at intervals of at least 1 week.

Patients with depression should be treated for a sufficient period to ensure that they are free from symptoms. This period may be 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 drug therapy. It is not known whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain or sustain euthymia.

## **Obsessive compulsive disorder (OCD)**

The recommended dose 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*

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. This period may be several months or even longer.

## **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 the 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, in which is generally recognised to occur early in the treatment of this disorder.

### *Maintenance therapy*

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.

Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer.

### **Social anxiety disorder or 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.

### **Generalised anxiety disorder (GAD)**

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 (PTSD)**

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.

The use of paroxetine beyond 12 weeks has not been investigated in clinical trials for PTSD.

### **Special patient groups**

#### Elderly patients

Dosing 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 that is associated with clinical efficacy.

#### Impaired renal and/or hepatic functions

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/minute) 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.

#### Children and adolescents (< 18 years)

Arrow - Paroxetine is not indicated for use in children or adolescents aged less than 18 years old. The safety and efficacy of paroxetine in children aged less than 7 years old has not been studied.

### **Discontinuation of treatment**

As with other psychoactive medications, abrupt discontinuation should generally be avoided (see **Warnings and Precautions** and **Adverse Effects**). The taper phase regimen used in the recent clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg was reached, patients were continued on this dose for 1 week before treatment was stopped.

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.

Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. It should not normally be discontinued abruptly. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

### **Prolonged treatment**

Doctors who elect to use paroxetine for an extended period should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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## **Contraindications**

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Arrow - Paroxetine is contraindicated in:

- patients with known hypersensitivity to paroxetine or to any component of the product (see **Further Information**)
- combination with monoamine oxidase inhibitors (MAOIs) or within 2 weeks of terminating treatment with MAOIs; likewise, MAOIs should not be introduced within 2 weeks of cessation of therapy with paroxetine (see **Warnings and Precautions**)
- combination with linezolid, an antibiotic that is a reversible non-selective MAO inhibitor
- combination with pimozide (see **Interactions**)
- combination with thioridazine (see **Interactions**).

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## **Warnings and Precautions**

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### **Children and adolescents (< 18 years)**

Paroxetine is not indicated for use in children or adolescents aged less than 18 years old. Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and did not support the use of paroxetine in the treatment of depression in this population. The safety and efficacy of paroxetine in children aged less than 7 years old 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 to 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 to 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 to 64 years and greater than or equal to 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 [11/3,455 (0.32%) versus 1/1,978 (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 to 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.

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 comorbid 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.

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 or 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 drug therapy (see **Akathisia** and **Mania and bipolar disorder** in this section, and **Adverse Effects**). Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

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.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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

#### *Pooled analysis*

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 (OCD 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 (bupropion, mirtazapine, nefazadone, venlafaxine).

### **Monoamine oxidase inhibitors (MAOIs)**

Treatment with paroxetine should be initiated cautiously at least 2 weeks after terminating treatment with MAOIs and dosage increased gradually until optimal response is reached (see **Contraindications** and **Interactions**).

### **Tricyclic antidepressants (TCA)**

Caution is indicated in the co-administration of 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.

### **Use with 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's irreversible inhibition of CYP2D6 (*see Interactions section*). This risk may increase with longer duration of co-administration. When tamoxifen is used for the prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

### **Serotonin syndrome or 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 drugs. 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 tryptophan, oxitriptan) due to the risk of serotonergic syndrome (see **Interactions - Serotonergic drugs**).

### **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.

### **Mania and bipolar disorder**

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed or 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 for 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.

### **Abnormal 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 gastro-protection should be considered for high risk patients.

### **Hyponatraemia**

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

### **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 a history of convulsive disorders.

### **Seizures**

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

### **Electroconvulsive therapy (ECT)**

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

### **Glaucoma**

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

### **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**). 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 drug being addictive or dependence producing as with a substance of abuse.

Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache and 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. They are also self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 to 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**).

### **Renal and/or hepatic impairment**

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment (see **Dosage and Administration**).

### **Carcinogenesis and mutagenesis**

In 2-year studies conducted in mice and rats, paroxetine had no tumorigenic effect, and no genotoxicity effects were observed in a battery of *in vitro* and *in vivo* tests.

Toxicology studies have been conducted in rhesus monkeys and albino rats. In both, the metabolic pathway is similar to that described for humans. As

expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to 1-year duration at doses that were six times higher than the recommended range of clinical doses.

### **Impairment of fertility**

Serotonergic drugs 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 reproduction studies in rats at paroxetine doses of 13 mg/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.

Reproduction studies performed in rats and rabbits at oral doses of up to 43 and 5 mg/kg, respectively, have revealed no evidence of teratogenic effects. Animal reproduction studies are not always predictive of human response.

### **Use in pregnancy (Category D)**

Paroxetine should not be used in pregnancy, unless the potential benefit outweighs the possible risk. 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 - Discontinuation of treatment** and **Warnings and Precautions - Symptoms seen on discontinuation of paroxetine treatment in adults**.

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 5,956 infants born to 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 1.8; 95% confidence interval 1.2 - 2.8). There was also an increased risk of cardiovascular malformations for paroxetine compared to other antidepressants (odds ratio 1.5; 95% confidence interval 0.8 - 2.9). These figures excluded women exposed to both antidepressants and teratogenic drugs. The majority of cardiovascular malformations were ventricular septal defects.

The prevalence of congenital malformations as a whole and cardiovascular malformation alone in these infants was 4% and 1.5% for paroxetine versus 2% and 1% for other antidepressants, 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 study based on the Swedish Medical Birth Register evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs, including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations compared to the entire registry population (odds ratio 1.8; 95% confidence interval 1.1 - 2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was approximately 2% versus 1% in the entire registry population. No increase in the overall risk for congenital malformations was observed in these infants exposed to paroxetine.

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, because 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 drug therapy has not been confirmed. Reported clinical findings have included: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In a majority of instances, the complications were reported to have arisen either immediately or soon (< 24 hours) after delivery. These features are consistent with either a direct toxic effect of SSRIs [and serotonin noradrenaline reuptake inhibitors (SNRIs)] or, possibly, a neonatal drug discontinuation or withdrawal syndrome.

In one epidemiological study, the use of SSRIs (including paroxetine) after the first 20 weeks of pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1000 women, compared to 1 to 2 per 1000 women in the general population.

Animal studies have not shown any teratogenic or selective embryotoxic effects, and data on a limited number of exposed pregnancies in humans provide no indication of an increased risk of congenital malformations in the newborn. There have been reports of premature birth in pregnant women exposed to paroxetine or other SSRIs, although a causal relationship with drug therapy has not been established. Paroxetine should not be used during pregnancy unless the potential benefit outweighs the possible risk.

### **Use in lactation**

Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (< 2 ng/ml) or very low (< 4 ng/ml). No signs of drug effects were observed in these infants. Nevertheless, paroxetine should not be used during lactation unless the expected benefits to the mother justify the potential risks for the infant.

In animal studies, neonatal mortality was increased in the offspring of rats receiving oral paroxetine 13 and 43 mg/kg/day during lactation.

## **Effects on ability to drive or operate machinery**

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

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

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## **Adverse Effects**

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Adverse experiences with paroxetine are generally mild in nature and do not affect the patient's lifestyle. Some of the adverse experiences listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy. Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $<1/10$ ), uncommon ( $\geq 1/1,000$ ,  $<1/100$ ), rare ( $\geq 1/10,000$ ,  $<1/1,000$ ), very rare ( $<1/10,000$ ), including isolated reports. The frequencies of common and uncommon events were generally determined from pooled safety data from a clinical trial population of more than 8000 paroxetine treated patients and are quoted as excess incidence over placebo. Rare and very rare events were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

### **Blood and lymphatic system disorders**

*Uncommon:* abnormal bleeding, predominantly of the skin and mucous membranes (including ecchymosis, purpura, haematomas, and very rarely epistaxis, vaginal bleeding and gastrointestinal bleeding)  
*Very rare:* thrombocytopenia

### **Immune system disorders**

*Very rare:* allergic reactions (including urticaria and angioedema)

### **Endocrine disorders**

*Very rare:* syndrome of inappropriate anti-diuretic hormone secretion (SIADH)

### **Metabolism and nutrition disorders**

*Common:* decreased appetite

*Rare:* hyponatraemia (hyponatraemia has been reported predominantly in elderly patients and is sometimes due to SIADH)

### **Psychiatric disorders**

*Common:* somnolence, insomnia, agitation

*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

*Very rare:* serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor)

Reports of extrapyramidal disorders including orofacial 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 - Glaucoma**)

*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, 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 also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

### **Skin and subcutaneous tissue disorders**

*Common:* sweating

*Uncommon:* skin rashes

*Very rare:* photosensitivity reactions

### **Renal and urinary disorders**

*Uncommon:* urinary retention, urinary incontinence

### **Reproductive system and breast disorders**

*Very common:* sexual dysfunction

*Rare:* hyperprolactinaemia or galactorrhoea

### **General disorders**

*Common:* asthenia

*Very rare:* peripheral oedema

### **Symptoms seen on discontinuation of paroxetine treatment**

*Common:* dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), anxiety, headache

*Uncommon:* agitation, nausea, tremor, confusion, sweating, diarrhoea

In a 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, Warnings 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 OCD and especially in younger children (less than 12 years old).

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 (see **Warnings and Precautions**).

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## **Interactions**

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Clinical studies have shown the absorption and pharmacokinetics of paroxetine to be unaffected or only marginally affected (i.e. at a level which warrants no change in dosing regimen) by food, antacids, digoxin, propranolol

and alcohol (see below, **Alcohol**). Paroxetine has little or no effect on the pharmacokinetics of digoxin, propranolol and warfarin (see below, **Warfarin**).

### **Serotonergic drugs**

As with other SSRIs, co-administration with serotonergic drugs [e.g. MAOIs (see **Contraindications**), tryptophan that is metabolised to serotonin, buspirone and sumatriptan] may lead to an incidence of 5HT associated effects (serotonin syndrome). 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 and close clinical monitoring is advised if concomitant administration is required.

As with other antidepressants, paroxetine should be used with caution in combination with preparations of St John's wort (*Hypericum perforatum*) as increased serotonergic effects may occur.

Concomitant use of paroxetine and linezolid, an antibiotic that is a reversible non-selective MAO inhibitor, is also contraindicated (see **Contraindications**).

### **Pimozide**

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with paroxetine. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and paroxetine is contraindicated (see **Contraindications**).

### **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 drugs which inhibit the hepatic enzyme CYP450 2D6 (including other antidepressants), paroxetine can elevate plasma levels of thioridazine. Therefore, paroxetine should not be administered with thioridazine (See **Contraindications**).

### **Drugs 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 phenytoin 300 mg is associated with decreased paroxetine area under the curve (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 the drug 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).

### **Drugs metabolised by cytochrome P450 2D6**

As with other antidepressants, including other selective serotonin reuptake inhibitors (SSRIs), paroxetine inhibits the specific hepatic cytochrome P450 2D6 enzyme (CYP2D6). This may lead to enhanced plasma levels of those co-administered drugs 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 drug.

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

Inhibition of CYP2D6 may decrease plasma concentrations of the active tamoxifen metabolite endoxifen, resulting in reduced therapeutic effect of tamoxifen (*see Warnings and Precautions*)

Pharmacokinetic interactions with TCAs 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 therefore should 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.

### **Drugs 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. A similar *in vivo* interaction study revealed no effect of paroxetine on alprazolam pharmacokinetics and vice versa. Concurrent administration of paroxetine with terfenadine, alprazolam and other drugs that are CYP3A4 substrates would not be expected to cause a hazard.

### **Fosamprenavir or ritonavir**

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

### **Procyclidine**

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

### Medicines that interfere with haemostasis

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of NSAIDs, 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 overdose 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

| Parameter            | n  | Paroxetine mean |        | Placebo mean |        | Paroxetine: Placebo* | 95% CI      |
|----------------------|----|-----------------|--------|--------------|--------|----------------------|-------------|
|                      |    | Day 1           | Day 28 | Day 1        | Day 28 |                      |             |
| 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

### 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.

### 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.

### **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 drugs. 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.

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## **Overdosage**

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### **Symptoms and Signs**

A wide margin of safety is evident from available overdose information on paroxetine. Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under **Adverse Effects**, vomiting, fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.

Patients have generally recovered without serious sequelae even when doses of up to 2,000 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.

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

### **Treatment**

No specific antidote is known. The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Where appropriate, the stomach should be emptied by lavage. Following evacuation, 20 to 30 g of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. Supportive care with frequent monitoring of vital signs and careful observation is indicated.

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## **Pharmaceutical Precautions**

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Store below 25°C.

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## **Medicines Classification**

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Prescription Only Medicine

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## **Package Quantities**

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Blister packs and bottles of 30 tablets

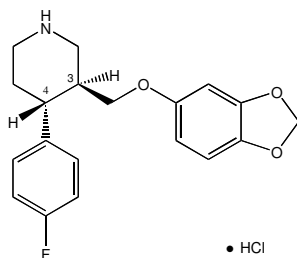
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## Further Information

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Arrow - Paroxetine contains paroxetine hydrochloride, which is a white to off-white crystalline powder that is slightly soluble in water and sparingly soluble in ethanol and dichloromethane.

The chemical name for paroxetine hydrochloride is (3S,4R)-3- [(1,3-benzodioxol-5-yloxy) methyl]-4- (4-fluorophenyl) piperidine hydrochloride. The structural formula of paroxetine is:



$C_{19}H_{20}NO_3F.HCl$  , Molecular weight: 365.83, CAS: 78246-49-8

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## Name and Address of Sponsor

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## Date of preparation:

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