**APPROVED**
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# INSTRUCTION
## for medical use

## SEMPRAVYL®

***Composition:***
*active substance:* paroxetine;
each film-coated tablet contains paroxetine hydrochloride hemihydrate equivalent to 20 mg paroxetine;
*excipients:* calcium hydrogen phosphate dihydrate, sodium starch glycolate, magnesium stearate, cover for Opadry 13B58802 white* coating.
* Opadry 13B58802 white: hypromellose, titanium dioxide (E 171), macrogol, polysorbate 80.

**Pharmaceutical form.** Film-coated tablet.
*Main physical and chemical properties:* white to off-white oval-shaped film-coated tablets with a breakline on one side and plain on the other side.

**Pharmacotherapeutic group.** Antidepressants. Selective serotonin reuptake inhibitors. ATC code: N06A B05.

***Pharmacological properties.***
*Pharmacodynamics.*
Mechanism of action.
Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and effectiveness in the treatment of obsessive compulsive disorder, social anxiety disorders / social phobia, generalised anxiety disorder, post-traumatic stress disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.
Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.
Paroxetine has low affinity for muscarinic cholinergic receptors and weak anticholinergic properties.
In contrast to tricyclic antidepressants, paroxetine has little affinity for alpha 1, alpha 2 and beta-adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and histamine (H1) receptors. Paroxetine is known to have no depressant and hypotensive effect on the central nervous system, and also does not impair psychomotor function and does not potentiate the depressant effect of ethanol.
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 electroencephalography (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 did not have a significant effect on the cardiovascular system and produced no clinically significant changes in blood pressure, heart rate and other electroencephalography (EEG) parameters after administration to healthy subjects.
In contrast to antidepressants that inhibit the uptake of noradrenaline, paroxetine has a much-reduced propensity to inhibit the antihypertensive effects of guanethidine.
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 for patients who have failed to respond to standard therapy.
Morning dosing with paroxetine does not have any effect on either the quality or duration of sleep. Moreover, patients are likely to experience improved sleep as they respond to paroxetine therapy.
*Pharmacokinetics.*
Absorption.
Paroxetine is well absorbed after oral dosing and undergoes liver metabolism. Due to liver 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 liver effect and reduced plasma clearance occur 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. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses.
Steady state systemic levels are attained by 7 to 14 days after starting treatment, and pharmacokinetics do not appear to change during long-term therapy.
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 is protein bound at therapeutic concentrations.
No correlation has been found between paroxetine plasma concentrations and clinical effect (efficacy and adverse reactions).
Metabolism.
The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects.
Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake.
Elimination.
Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which 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 liver metabolism and subsequently controlled by systemic elimination of paroxetine.
The elimination half-life is variable but is generally about 1 day.
Special populations.
*Elderly and renal/hepatic impairment.*
Increased plasma concentrations of paroxetine occur in elderly subjects and in those subjects with renal impairment or in those with hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

**Clinical characteristics.**
***Indications.***
Treatment of:

- major depressive episode;
- obsessive compulsive disorder;
- panic disorder with and without agoraphobia;
- social anxiety disorders / social phobia;
- generalised anxiety disorder;
- post-traumatic stress disorder.

***Contraindications.***

- Hypersensitivity to the paroxetine or to any of the excipients of the medicinal product;
- combination of paroxetine with monoamine oxidase inhibitors (MAOIs). In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with paroxetine provided that there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure (see "Interaction with other medicinal products and other forms of interactions" section);
  Treatment with paroxetine can be initiated:
  - two weeks after discontinuation of an irreversible MAOI, or
  - at least 24 hours after discontinuation of a reversible MAOI (e.g. moclobemide, linezolid, methylthioninium chloride (methylene blue).

  At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI;
- combination of paroxetine with thioridazine, because, as with other medicinal products which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see "Interaction with other medicinal products and other forms of interactions" section). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia, such as *torsades de pointes*, and sudden death.
- combination of paroxetine with pimozide (see "Interaction with other medicinal products and other forms of interactions" section).

***Interaction with other medicinal products and other forms of interactions.***

*Serotonergic medicinal products.*

As with other selective serotonin reuptake inhibitors (SSRIs), co-administration with serotonergic medicinal products may lead to an incidence of 5-HT associated effects (serotonin syndrome: see "Special precautions" section). Caution should be advised and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, linezolid, methylthioninium chloride (methylene blue), SSRIs, lithium, pethidine, buprenorphine containing medicinal products and St. John's Wort (*Hypericum perforatum*) preparations) are combined with paroxetine. Caution is also advised with fentanyl used in general anaesthesia or in the treatment of chronic pain. Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome (see "Contraindications" section).

*Pimozide.*

Increased pimozide levels of on average 2.5 times have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with 60 mg paroxetine. This may be explained by the known CYP2D6 inhibitory properties of paroxetine. 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" section).

*Drug metabolizing enzymes.*

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes.

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, paroxetine should be given in doses at the lower end of the range.
No initial paroxetine 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). Any paroxetine dosage adjustment (either after initiation or following discontinuation of an enzyme inducer) should be guided by clinical effect (tolerability and efficacy).
*Muscle relaxants.*
SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium and suxamethonium.
*Fosamprenavir/ritonavir.*
Co-administration of fosamprenavir/ritonavir 700/100 mg twice daily with paroxetine 20 mg daily in healthy volunteers for 10 days significantly decreased plasma levels of paroxetine by approximately 55%. The plasma levels of fosamprenavir/ritonavir during co-administration of paroxetine were similar to reference values of other studies, indicating that paroxetine had no significant effect on metabolism of fosamprenavir/ritonavir. There are no data available about the effects of long-term co-administration of paroxetine and fosamprenavir/ritonavir exceeding 10 days.
*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.
*Anticonvulsants (carbamazepine, phenytoin, sodium valproate).*
Concomitant administration with these agents does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.
*CYP2D6 inhibitory potency of paroxetine.*
As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered medicinal products metabolized by this enzyme. These include certain tricyclic antidepressants (e.g. clomipramine, nortriptyline and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine, see "Contraindications" section), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.
Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65–75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen, has been reported in the scientific literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including paroxetine) should whenever possible be avoided (see "Special precautions" section).
*Alcohol.*
As with other psychotropic medicinal products patients should be advised to avoid alcohol use while taking paroxetine.
*Oral anticoagulants.*
A pharmacodynamic interaction between paroxetine and oral anticoagulants may occur. Concomitant use of paroxetine and oral anticoagulants can lead to an increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants (see "Special precautions" section).
*Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid, and other antiplatelet agents.*

A pharmacodynamic interaction with an increased haemorrhagic risk may occur between paroxetine and NSAIDs/acetylsalicylic acid. Paroxetine should be used with caution with medicinal products known to affect platelet function or increase risk of bleeding (see "Special precautions" section).
Caution is advised when administrating SSRIs, concomitantly with oral anticoagulants, medicinal products known to affect platelet function or increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, NSAIDs, cyclooxygenase-2 (COX-2) inhibitors) to patients with a history of bleeding disorders or conditions which may predispose to bleeding.
*Pravastatin.*
An interaction between paroxetine and pravastatin has been observed in studies suggesting that co-administration of paroxetine and pravastatin may lead to an increase in blood glucose levels. Patients with diabetes mellitus receiving both paroxetine and pravastatin may require dosage adjustment of oral hypoglycaemic agents and/or insulin (see "Special precautions" section).

***Special precautions.***
Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached (see "Contraindications" and "Interaction with other medicinal products and other forms of interactions" sections).
*Paediatric population*
Paroxetine should not be used in the treatment of children and adolescents (under the age of 18 years). Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms.
In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.
*Suicide / suicidal thoughts or clinical worsening.*
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicide. 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.
Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old (see "Pharmacological properties" section).
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or

thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

*Akathisia / psychomotor restlessness.*

The use of paroxetine has been associated with the development of akathisia, which is characterized 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. In patients who develop these symptoms, increasing the dose may be detrimental.

*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 medicinal products. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterized 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 "Contraindications" and "Interaction with other medicinal products and other forms of interactions" sections).

*Mania.*

As with all antidepressants, paroxetine should be used with caution in patients with a history of mania. Paroxetine should be discontinued in any patient entering a manic phase.

*Renal/hepatic impairment.*

Caution is recommended in administering this medicinal product to patients with severe renal impairment or in those with hepatic impairment (see "Administration and dosage" section).

*Diabetes.*

In patients with diabetes, treatment with selective serotonin reuptake inhibitor may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted. Additionally, there have been studies suggesting that an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered (see "Interaction with other medicinal products and other forms of interactions" section).

*Epilepsy.*

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

*Seizures.*

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

*Electroconvulsive therapy (ECT).*

There is little clinical experience of the concurrent administration of paroxetine with ECT.

*Glaucoma.*

As with other selective serotonin reuptake inhibitors, paroxetine can cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

*Cardiac conditions.*

The usual precautions should be observed in patients with comorbid cardiac conditions.

*Hyponatraemia.*

Hyponatraemia has been reported rarely, predominantly in the elderly. Caution should also be exercised in those patients at risk of hyponatraemia, e.g. from concomitant medications and cirrhosis. The hyponatraemia generally reverses on discontinuation of paroxetine.

*Haemorrhage.*

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura with SSRIs. Other haemorrhagic manifestations, e.g. gastrointestinal and gynaecolgical haemorrhage have been reported. Elderly patients may be at an increased risk for non-menses related events of bleeding.
SSRIs/SNRIs increase the risk of postpartum haemorrhage (see "Use in pregnancy and lactation" and "Adverse reactions" sections).
Caution is therefore advised in patients taking SSRIs concomitantly with oral anticoagulants, medicinal products known to affect platelet function or other medicinal products that may increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as patients with a history of frequent coagulopathy or bleeding disorders (see "Adverse reactions" section).
*Interaction with tamoxifen.*
Paroxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, paroxetine should whenever possible be avoided during tamoxifen treatment (see "Interaction with other medicinal products and other forms of interactions" section).
*Bone fractures.*
Epidemiological studies on bone fracture risk following exposure to some antidepressants, including selective serotonin reuptake inhibitor, 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.
*Withdrawal symptoms seen on discontinuation of paroxetine treatment.*
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see "Adverse reactions" section). In clinical trials 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 withdrawal symptoms is not the same as the medicinal product being addictive or dependence producing when abusing it.
The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.
Dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability and visual disturbances have been reported following discontinuation of paroxetine. 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. Mostly 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 "Administration and dosage" section).
*Sexual dysfunction.*
SSRIs may cause symptoms of sexual dysfunction (see "Adverse reactions" section). In some cases these symptoms have continued despite discontinuation of SSRIs.
*Sodium.*
This medicinal product contains less than 1 mmol sodium (23 mg) per each tablet, that is to say essentially 'sodium-free'.

***Use in pregnancy and lactation.***
Pregnancy.

Some epidemiological studies suggest an increased risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septum defects) associated with the use of paroxetine during the first trimester. The mechanism is unknown. The data suggests that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population. Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant. Abrupt discontinuation should be avoided during pregnancy (see "Special precautions" and "Administration and dosage" sections).
Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage in women taking SSRI/SNRI within the month prior to birth (see "Special precautions" and "Adverse reactions" sections).
Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, particularly the third trimester.
The following symptoms may occur in the neonates after maternal paroxetine use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances, the complications begin immediately or soon (<24 hours) after delivery.
Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may have an increased risk of persistent pulmonary hypertension of the newborn. The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of persistent pulmonary hypertension of the newborn per 1000 pregnancies occur.
Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
Breast-feeding.
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) and no signs of medicinal product effects were observed in these infants. Since no effects are anticipated, breast-feeding can be considered.
Fertility.
Animal data and *in vitro* data have shown that paroxetine may affect sperm quality. However, reports with some SSRIs (including paroxetine) on sperm quality in men who have taken them have shown that an effect on sperm quality appears to be reversible. Impact on human fertility has not been observed so far.

***Effects on ability to drive and use machines.***
Clinical experience has shown that therapy with this medicinal product is not associated with impairment of cognitive or psychomotor function. However, as with all psychoactive medicinal products, patients should be cautioned about their ability to drive a car and operate machinery during treatment.
Although paroxetine does not increase the mental and motor skill impairments caused by alcohol, the concomitant use of paroxetine and alcohol is not advised.

***Administration and dosage.***
*Major depressive episodes.*
The recommended dose is 20 mg daily. In general, improvement in patients starts after one week but may only become evident from the second week of therapy.

As with all antidepressant medicinal products, paroxetine dosage should be carefully selected individually and adjusted accordingly within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate.
If the clinical effect of 20 mg is insufficient, the dose may be increased gradually up to a maximum of 50 mg a day in 10 mg steps according to the patient's response.
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.
*Obsessive compulsive disorder.*
The recommended dose is 40 mg daily. Patients should start on 20 mg/day and the dose may be increased gradually in 10 mg increments to the recommended dose. If after some weeks on the recommended dose insufficient response is seen some patients may require having their dose increased gradually up to a maximum of 60 mg/day.
Patients with obsessive compulsive 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 (see "Pharmacodynamics" section).
*Panic disorder.*
The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. If after some weeks on the recommended dose insufficient response is seen some patients may require having their dose increased gradually up to a maximum of 60 mg/day.
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 (see "Pharmacodynamics" section).
*Social anxiety disorders / social phobia.*
The recommended dose is 20 mg daily. If after some weeks on the recommended dose insufficient response is seen some patients may require having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see "Pharmacodynamics" section).
*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, up to a maximum of 50 mg/day according to the patient's response. Long-term use should be regularly evaluated (see "Pharmacodynamics" section).
*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, up to a maximum of 50 mg/day according to the patient's response. Long-term use should be regularly evaluated (see "Pharmacodynamics" section).
Withdrawal symptoms seen on discontinuation of paroxetine.
Abrupt discontinuation should be avoided (see "Special precautions" and "Adverse reactions" sections). The taper phase regimen used in clinical trials involved decreasing the daily dose by 10 mg at weekly intervals. 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 gradually.
Special populations.
*Use in elderly.*
Increased plasma concentrations of paroxetine occur in elderly subjects, but the range of concentrations overlaps with that observed in younger subjects. Dosing should commence at the adult starting dose. Increasing the dose might be useful in some patients, but the maximum dose should not exceed 40 mg daily.

*Patients with renal/hepatic impairment.*
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.
Method of administration.
It is recommended that paroxetine is administered once daily in the morning with food.
The film-coated tablet should be swallowed rather than chewed.
***Paediatric population.***
Paroxetine is not indicated for use in children (under 18 years of age) because controlled clinical trials have shown an association between the use of paroxetine and an increased risk of suicidal behavior and hostility. Moreover, these studies have failed to demonstrate efficacy. The safety and efficacy of paroxetine in children aged <7 years has not been studied.

***Overdose.***
Symptoms.
With paroxetine overdose, in addition to those symptoms mentioned under "Adverse reactions" section, fever and involuntary muscle contractions have been reported.
Most patients have generally recovered without serious sequalae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely with a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic medicinal products, with or without alcohol.
Treatment.
No specific antidote is known.
The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Administration of 20–30 g activated charcoal may be considered if possible within a few hours after overdose intake to decrease absorption of paroxetine. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated.

***Adverse reactions.***
Some of the adverse drug reactions listed below may decrease in intensity and frequency with continued treatment and do not generally require cessation of therapy. Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).
*Blood and lymphatic system disorders.*
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis and gynaecological bleeding).
Very rare: thrombocytopenia.
*Immune system disorders.*
Very rare: severe and potentially fatal allergic reactions (including anaphylactoid reactions and angioedema).
*Endocrine disorders.*
Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
*Metabolism and nutrition disorders.*
Common: increases in cholesterol levels, decreased appetite.
Uncommon: altered glycaemic control has been reported in diabetic patients (see "Special precautions" section).
Rare: hyponatraemia which 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, anxiety, depersonalization, panic attacks, akathisia (see "Special precautions" section).
Frequency not known: suicidal ideation, suicidal behaviour, aggression, bruxism.
Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation (see "Special precautions" section).
Cases of aggression were observed in post marketing period.
These symptoms may also be due to the underlying disease.
*Nervous system disorders.*
Common: dizziness, tremor, headache, concentration impaired.
Uncommon: extrapyramidal disorders.
Rare: convulsions, restless legs syndrome (RLS).
Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor).
Reports of extrapyramidal disorder including orofacial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medicinal products.
*Eye disorders.*
Common: blurred vision.
Uncommon: mydriasis (see "Special precautions" section).
Very rare: acute glaucoma.
*Ear and labyrinth disorders.*
Frequency not known: tinnitus.
*Cardiovascular disorders.*
Uncommon: sinus tachycardia, transient increases or decreases in blood pressure, postural hypotension.
Rare: bradycardia.
Transient increases or decreases of blood pressure have been reported following treatment with paroxetine, usually with pre-existing hypertension or anxiety.
*Respiratory, thoracic and mediastinal disorders.*
Common: yawning.
*Gastrointestinal disorders.*
Very common: nausea.
Common: constipation, diarrhoea, vomiting, dry mouth.
Very rare: gastrointestinal bleeding.
Not known: colitis microscopic
*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, pruritus.

Very rare: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions.
*Renal and urinary disorders.*
Uncommon: urinary retention, urinary incontinence.
*Reproductive system and breast disorders.*
Very common: sexual dysfunction.
Rare: hyperprolactinaemia/galactorrhoea, menstrual disorders (including menorrhagia, metrorrhagia, amenorrhoea, menstruation delayed and menstruation irregular).
Very rare: priapism.
Not known: postpartum haemorrhage.
Postpartum haemorrhage has been reported for the therapeutic class of SSRIs/SNRIs (see "Special precautions" and "Use in pregnancy and lactation" sections).
*Musculoskeletal and connective tissue disorders.*
Rare: arthralgia, myalgia.
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism leading to this risk is unknown.
*General disorders and administration site conditions.*
Common: asthenia, body weight gain.
Very rare: peripheral oedema.
*Withdrawal symptoms seen on discontinuation of paroxetine treatment.*
Common: dizziness, sensory disturbances, sleep disturbances, anxiety, headache.
Uncommon: agitation, nausea, tremor, confusion, sweating, emotional instability, visual disturbances, palpitations, diarrhoea, irritability.
Discontinuation of paroxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional lability, irritability, and visual disturbances have been reported.
Generally, these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see "Special precautions", "Administration and dosage" and "Use in pregnancy and lactation" sections).
*Adverse events from paediatric clinical trials with paroxetine.*
In paediatric clinical trials with paroxetine, an increase in the frequency of such side effects was observed: suicidal behaviour (including suicide attempts and suicidal thoughts), self-harm behaviours, hostility, decreased appetite, tremor, sweating, hyperkinesia, agitation, emotional lability (including crying and mood fluctuations), bleedings, predominantly of the skin and mucous membranes.
Suicidal thoughts and suicide attempts were mainly observed in treatment of children with major depressive disorder; hostility occurred particularly in children with obsessive compulsive disorder, and especially in children less than 12 years of age.
The following symptoms occurred after discontinuation/tapering of paroxetine: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain (see "Special precautions" section).
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any

suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

***Shelf-life.***
2 years.

**Storage conditions.**
Store at a temperature not more than 25°C in the original package.
Keep out of reach of children.

**Package.**
10 tablets in a blister, 3 blisters in a carton package.

**Conditions of supply.**
By prescription.

**Manufacturer.**
KUSUM HEALTHCARE PVT LTD.

**Location of manufacturer and its address of business activity.**
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

**Last revision date.**