AROPAX CR 12.5
AROPAX CR 25
Paroxetine hydrochloride hemihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

12.5 mg tablets: Yellow, round, biconvex, debossed, film-coated tablets with bevelled edges. One face is engraved with 'GSK' and the other face is engraved with '12.5'.

25 mg tablets: Pink, round, biconvex, debossed, film-coated tablets with bevelled edges. One face is engraved with 'GSK' and the other face is engraved with '25'.

Each AROPAX CR (controlled release) tablet contains paroxetine hydrochloride hemihydrate equivalent to 12.5 mg or 25 mg paroxetine free base.

AROPAX CR tablets contain lactose.

CLINICAL INFORMATION

Indications

Adults

Major Depressive Disorder: AROPAX CR tablets are indicated for the treatment of major depressive disorder (MDD).

Panic Disorder: AROPAX CR tablets have been shown to be effective in the treatment of panic disorder with or without agoraphobia.

Social Anxiety Disorder/Social Phobia: AROPAX CR Tablets have been shown to be effective in the treatment of Social Anxiety Disorder/Social Phobia.

The effectiveness of AROPAX CR tablets in the long-term treatment of Social Anxiety Disorder/Social Phobia has not been evaluated. Therefore, if AROPAX CR tablets are to be administered for extended periods in the treatment of Social Anxiety Disorder/Social Phobia, the physician should periodically re-evaluate the long-term usefulness of AROPAX CR for the individual patient.

Children and adolescents (less than 18 years)

All Indications: AROPAX CR is not indicated for use in children or adolescents aged less than 18 years (*see Warnings and Precautions*).

The efficacy of AROPAX CR tablets has not been studied in children or adolescents aged less than 18 years; however, controlled clinical studies with AROPAX IR (immediate release) tablets in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of AROPAX CR in the treatment of depression in this population (*see Warnings and Precautions*).

The safety and efficacy of AROPAX CR in children aged less than 7 years has not been studied.

Dosage and Administration

Pharmaceutical form: Controlled release tablets

Adults

AROPAX CR tablets should be administered as a single daily dose, usually in the morning, with or without food. Patients should be informed that AROPAX CR tablets should not be chewed or crushed and should be swallowed whole.

Major Depressive Disorder: The recommended initial dose is 25 mg/day. Some patients not responding to a 25 mg dose may benefit from dose increases in 12.5 mg/day increments, up to a maximum of 62.5 mg/day according to patient response. Dose changes should occur at intervals of at least 1 week.

As with all antidepressant drugs, dosage should be reviewed and adjusted if necessary within 2 to 3 weeks of initiation of therapy and thereafter as judged clinically appropriate.

Patients with depression should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months.

Panic Disorder: Patients should begin treatment on 12.5 mg/day and the dose increased weekly in 12.5 mg/day increments according to patient response. Some patients may benefit from having their dose increased up to a maximum of 75 mg/day.

A low initial starting dose is recommended to minimise the potential worsening of panic symptomatology which is generally recognised to occur early in the treatment of this disorder.

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/Social Phobia: The recommended initial dose is 12.5 mg daily. Some patients not responding to a 12.5 mg dose may benefit from having dose increases in 12.5 mg/day increments as required, up to a maximum of 37.5 mg/day according to the patient's response. Dose changes should occur at intervals of at least 1 week.

General Information

Other Populations

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 12.5 mg/day and may be increased up to 50 mg/day.

Children and adolescents (less than 18 years): AROPAX CR is not indicated for use in children or adolescents aged less than 18 years (*see Indications, Warnings and Precautions*).

Renal/hepatic impairment: Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min) or in those with hepatic impairment. The dosage should be restricted to the lower end of the range.

DISCONTINUATION OF AROPAX CR

As with other psychoactive medications, abrupt discontinuation should generally be avoided (*see Warnings and Precautions, Adverse Reactions*). The taper phase regimen used in recent clinical trials involved a decrease in the daily dose by 10 mg/day (equivalent to 12.5 mg/day CR tablets) at weekly intervals.

When a daily dose of 20 mg/day (equivalent to 25 mg/day CR tablets) 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.

Contraindications

Known hypersensitivity to paroxetine and excipients.

AROPAX CR tablets should not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)) or within two weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within two weeks of cessation of therapy with AROPAX CR tablets (*see Interactions*).

AROPAX CR tablets should not be used in patients receiving medications that can prolong QT interval and are also metabolised by CYP450 2D6, such as thioridazine or pimozide (*see Interactions*).

Warnings and Precautions

Children and Adolescents (less than 18 years): Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. In clinical trials of AROPAX 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 AROPAX compared to those treated with placebo (*see Adverse Reactions*). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Clinical worsening and suicide risk in adults: Young adults, especially those with MDD, may be at increased risk for suicidal behaviour during treatment with AROPAX

CR. 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 ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18 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. This risk persists 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. Other psychiatric conditions for which AROPAX is prescribed can be associated with an increased risk of suicidal behaviour, and these conditions may also be co-morbid with MDD. 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 development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the drug therapy (*see Akathisia and Mania and Bipolar Disorder below; Adverse Reactions*).

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.

Akathisia: Rarely, the use of AROPAX or other selective serotonin reuptake inhibitors (SSRIs) have 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.

Serotonin Syndrome/Neuroleptic Malignant Syndrome: On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with AROPAX CR treatment, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with AROPAX CR 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. AROPAX CR should not be used in combination with serotonin-precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome *(see Contraindications, Interactions).*

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/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.

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

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

Monoamine Oxidase Inhibitors: Treatment with AROPAX CR should be initiated cautiously at least two weeks after terminating treatment with MAO inhibitors and dosage of AROPAX CR should be increased gradually until optimal response is reached (*see Contraindications, Interactions*).

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

Epilepsy: As with other antidepressants, AROPAX CR 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 drug 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 SSRIs, paroxetine can cause mydriasis and should be used with caution in patients with narrow angle glaucoma.

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

Haemorrhage: Skin and mucous membrane bleedings (including gastrointestinal and gynaecological bleeding) have been reported following treatment with paroxetine. Paroxetine should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding, and in patients with a known tendency for bleeding or those with predisposing conditions (*see Adverse Reactions*). SSRIs may increase the risk of postpartum haemorrhage (see Pregnancy and Lactation)

Cardiac Conditions: The usual precautions should be observed in patients with cardiac conditions.

QT Prolongation: Cases of QT interval prolongation have been reported, although causality with paroxetine has not been established.

Paroxetine should be used with caution in patients with a history of QT interval prolongation, patients taking anti-arrhythmic or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease.

For further information, *see Contraindications and Interactions*.

Symptoms seen on discontinuation of AROPAX CR treatment in adults: In clinical trials in adults, adverse events seen on treatment discontinuation occurred in 30% of patients treated with AROPAX CR 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, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea have been reported. Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within two weeks, though in some individuals they may be prolonged (two to three months or more). It is therefore advised that *AROPAX* should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (*see "Discontinuation of AROPAX CR", Dosage and Administration*).

Sexual dysfunction

SSRIs may cause symptoms of sexual dysfunction (see Adverse Reactions). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

Symptoms seen on discontinuation of AROPAX CR 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 AROPAX CR compared to 24% of patients treated with placebo. Events reported upon discontinuation of AROPAX CR 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 Reactions*).

AROPAX CR 12.5 and AROPAX 25 contain lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose

malabsorption should not take this medicine

AROPAX CR 12.5 tablets only: AROPAX CR 12,5 mg controlled release tablet coating (Opadry Yellow: YS-1-2007) contains the colouring agent Sunset Yellow Lake (FD&C Yellow No. 6 aluminium lake), an azo dye which may cause allergic-type reactions.

Interactions

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

Concomitant use of AROPAX CR and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)) is 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. This is explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and AROPAX CR tablets is contraindicated (*see Contraindications*).

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

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). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

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

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 does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

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

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 drugs metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. amitriptyline, nortriptyline, imipramine and desipramine), phenothiazine neuroleptics (e.g.

perphenazine and thioridazine, *see Contraindications*), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol.

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

CYP3A4: An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no 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.

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**
- **alcohol:** paroxetine does not increase the impairment of mental and motor skills caused by alcohol, however, the concomitant use of AROPAX CR and alcohol is not advised.

Pregnancy and Lactation

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

Pregnancy: Animal studies have not shown any teratogenic or selective embryotoxic effects.

Epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septal defects), associated with the use of paroxetine. The data suggest that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population.

The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant and should only prescribe

AROPAX CR if the potential benefit outweighs the potential risk. If a decision is taken to discontinue AROPAX CR treatment in a pregnant woman, the prescriber should consult *Dosage and Administration - Discontinuation of AROPAX CR* and *Warnings and Precautions – Symptoms seen on discontinuation of AROPAX CR treatment in adults*.

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

Observational data have provided evidence of an increased risk (less than two-fold) of postpartum haemorrhage following exposure to SSRIs within one month prior to birth.

Neonates should be observed if maternal use of AROPAX CR continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to AROPAX CR 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 some instances, the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances, the complications were reported to have arisen either immediately or soon (<24 hours) after delivery.

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

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

Effects on Ability to Drive and Use Machines

Clinical experience has shown that therapy with AROPAX CR 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 AROPAX CR and alcohol is not advised.

Adverse Reactions

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 (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports. Common and uncommon events were generally determined from pooled safety data from a clinical trial population of >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 & lymphatic system disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes.
Very rare: thrombocytopenia.

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

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

Metabolism & nutrition disorders
Common: increases in cholesterol levels, decreased appetite.
Rare: hyponatraemia.

Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Psychiatric disorders
Common: somnolence, insomnia, agitation, abnormal dreams (including nightmares).
Uncommon: confusion, hallucinations.
Rare: manic reactions.

These symptoms may be due to the underlying disease.

Nervous system disorders
Common: dizziness, tremor, headache.
Uncommon: extrapyramidal disorders.
Rare: convulsions, akathisia, restless legs syndrome (RLS).
Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor).

Reports of extrapyramidal disorders including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication.

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

Cardiac disorders
Uncommon: sinus tachycardia.

Vascular disorders
Uncommon: postural hypotension.

Respiratory, thoracic and mediastinal disorders
Common: yawning.

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

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

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

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

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

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

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

Symptoms seen on discontinuation of paroxetine treatment:
Common: dizziness, sensory disturbances, sleep disturbances, anxiety, headache.
Uncommon: agitation, nausea, tremor, confusion, sweating, diarrhoea.

As with many psychoactive medicines, discontinuation of AROPAX CR *(*particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, headache, tremor, confusion, diarrhoea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (*see Dosage and Administration, 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 obsessive compulsive disorder, and especially in younger children less than 12 years of age).

In studies that used a tapering regimen (daily dose decreased by 10 mg/day at weekly intervals to a dose of 10 mg/day for one week), symptoms reported during the taper phase or upon discontinuation of AROPAX CR 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*).

Overdose

Symptoms and Signs

A wide margin of safety is evident from available overdose information on AROPAX CR.

Experience of AROPAX CR in overdose has indicated that, in addition to those symptoms mentioned under Adverse Reactions, 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 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when AROPAX CR was taken in conjunction with other psychotropic drugs 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. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated, or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Anatomical Therapeutic Chemical (ATC) code: N06A B05.

Pharmacotherapeutic group: Antidepressants – selective serotonin reuptake inhibitors

Mechanism of Action

Paroxetine is a potent and selective inhibitor of serotonin (5-hydroxytryptamine, 5-HT) re-uptake and its antidepressant action and efficacy in the treatment of OCD and panic disorder is thought to be related to its specific inhibition of serotonin re-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 animal studies have indicated only weak anticholinergic properties.

In accordance with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for $alpha_1$, $alpha_2$ and beta-adrenoceptors, dopamine (D2), 5-HT_1 like, 5-HT_2 and histamine (H_1) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate lack of CNS depressant and hypotensive properties.

Pharmacodynamic Effects

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

Animal studies indicate that paroxetine is well tolerated by the cardiovascular system.

Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects.

Studies indicate that, in contrast to antidepressants which inhibit the uptake of nor-adrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

Pharmacokinetics

Absorption: Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. AROPAX CR tablets control the dissolution rate of paroxetine over a period of four to five hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until AROPAX CR tablets have left the stomach. Compared to immediate release formulations of paroxetine, controlled release tablets have a reduced absorption rate.

Due to first-pass metabolism, the amount of paroxetine available to the systemic

circulation is less than that absorbed from the gastrointestinal tract.

Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations 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 in the plasma is protein bound at therapeutic concentrations.

No correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy).

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 the therapeutic effects of paroxetine.

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 metabolism and subsequently controlled by systemic elimination of paroxetine.

The elimination half-life is variable but is generally about one day.

Special Patient Populations

Elderly and Renal/Hepatic Impairment: Increased plasma concentrations of paroxetine occur in elderly subjects, in subjects with severe renal and in those with hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

Non-Clinical Information

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 one-year duration at doses that were six times higher than the recommended range of clinical doses.

Carcinogenesis: In two-year studies conducted in mice and rats, paroxetine had no tumorigenic effect.

Genotoxicity: Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet cores: Hypromellose; Povidone; Lactose Monohydrate; Magnesium Stearate; Colloidal silicon dioxide; Glyceryl behenate and the following colourants: Yellow Ferric Oxide (12.5 mg tablets) and Red Ferric Oxide (25 mg tablets).

Tablet coating: Methacrylic Acid Copolymer Dispersion; Talc; Triethyl citrate, Opadry Yellow, YS-1-2007 (12.5 mg tablets, includes the colouring agent Sunset Yellow Lake (FD&C Yellow No. 6 aluminium lake)), Opadry Pink, Y-1-1262 (25 mg tablets).

For important information about some of these excipients *see Warnings & Precautions*.

Shelf-Life

The expiry date is indicated on the packaging.

The storage conditions are detailed on the packaging.

Nature and Contents of Container

AROPAX CR 12.5 mg tablets:
Carton containing 28 tablets, packed in white blister packs, in strips of 14.
or
Carton containing 30 tablets, packed in white blister packs, in strips of 10.

AROPAX CR 25 mg tablets:
Carton containing 28 tablets, packed in white blister packs, in strips of 14.
or
Carton containing 30 tablets, packed in white blister packs, in strips of 10.

Not all presentations are available in every country.

Incompatibilities

There are no known incompatibilities with AROPAX CR tablets.

Use and Handling

No special instructions.

Name and address of the holder of the certificate of registration

GlaxoSmithKline South Africa (Pty) Ltd

57 Sloane Street

Bryanston, 2021
South Africa

Manufacturer:
GlaxoSmithKline Inc
7333 Mississauga Road North
Mississauga,
Ontario
Canada, L5N 6L4

Registration numbers:
Botswana:
Aropax CR 12,5: Reg No BOT0801414 S2
Aropax CR 25: Reg No BOT0801413 S2

Namibia:
Aropax CR 12,5: Reg No 11/1.2/0022 NS3
Aropax CR 25: Reg No 11/1.2/0023 NS3

Version number: GDS48/IPI26

Date of issue: 08 December

2021

PATIENT LEAFLET

AROPAX CR 12.5
AROPAX CR 25
Paroxetine hydrochloride hemihydrate

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again. If you have any questions, ask your doctor or pharmacist.

This medicine has been prescribed for you personally. Don't pass it on to other people - it may harm them even if their symptoms seem to be the same as yours.

In this leaflet

What AROPAX CR is and what it is used for

The active ingredient in AROPAX CR is paroxetine, which belongs to a group of medicines called SSRIs (*selective serotonin reuptake inhibitors*). In adults aged 18 years and over AROPAX CR is used to treat:

- major depressive disorder
- panic attacks, including those caused by a fear of open spaces (*agoraphobia*)
- anxiety caused by situations such as socialising or performance.

These conditions can occur when the amount of a substance called serotonin in the brain is reduced. Paroxetine works by increasing serotonin levels in the brain.

Before you take AROPAX CR

Don't take AROPAX CR

- if you are **allergic** (*hypersensitive*) to paroxetine or any other ingredients of AROPAX CR (listed in Section 6)
- if you are taking or have recently taken (within the last two weeks) **medicines for depression** called **monoamine oxidase inhibitors (MAOIs)**
- if you are taking or have recently taken (within the last two weeks) an **antibiotic** medicine called **linezolid**
- if you are taking or have recently taken (within the last two weeks) a medicine called methylthioninium chloride (**methylene blue**)
- if you are taking **medicines called thioridazine or pimozide** (usually used to treat **schizophrenia**).

  ➔ If you think any of these apply to you, **don't take AROPAX CR** until you have checked with your doctor.

Take special care with AROPAX CR

AROPAX CR is not recommended for people aged under 18. The effectiveness of AROPAX CR has not been demonstrated in this age group. Medicines used to treat depression and other mental health problems may increase the risk of suicidal thoughts and behaviour in children and adolescents aged under 18 years. There is no information on the long term safety of AROPAX CR in this age group.

Before you take AROPAX CR your doctor needs to know:

- if you have taken **medicines for depression called MAOIs** and the date you stopped taking them
- if you have taken an antibiotic called **linezolid** and the date you stopped it
- if you are taking **tamoxifen** (used to treat or prevent breast cancer)
- if you have ever had **episodes of hyperactivity, elation and irritability** *(mania)*
- if you have ever had **periods of mania alternating with periods of depression** (*bipolar mood disorder*)
- if you have **kidney or liver disease**
- if you have **heart disease**
- if your **heart tracing (electrocardiogram/ECG) has an abnormality known as prolonged QT interval** or you are taking medicines that may affect the QT interval in the ECG
- if you have **epilepsy**
- if you suffer from **glaucoma** (a condition caused by raised pressure in the eye)
- if you have a history of **bleeding problems**, or are taking medicines that increase your risk of bleeding.

➔ **Check with your doctor** if you think any of these may apply to you. Your doctor will decide whether AROPAX CR is suitable for you, or if you need extra check-ups.

Thoughts of suicide or worsening of your condition

If you are depressed, you may sometimes have suicidal thoughts or thoughts of harming yourself. Since medicines like AROPAX CR take time to work (usually about 2 weeks, but sometimes longer), suicidal thoughts or thoughts of harming yourself may continue

or increase, particularly when you start taking AROPAX CR.

You may be more likely to think like this if you:

- are a young adult
- have previously had thoughts of this nature
- have recently had a change in dose.

If you have distressing thoughts or experiences, or if you notice that you feel worse or develop new symptoms while you're taking AROPAX CR:

➔ **Contact your doctor or go to a hospital straight away.**

You may find it helpful to tell a relative or close friend that you are depressed and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Conditions you need to look out for

Medicines like AROPAX CR used to treat mental health problems can on rare occasions cause serious conditions called Serotonin Syndrome and Neuroleptic Malignant Syndrome. You must look out for certain symptoms while you are taking AROPAX CR, to reduce the risk of any problems. See '*Conditions you need to look out for' in* ***Section 4***.

Akathisia

Medicines used to treat some mental health problems can cause a feeling of inner restlessness and the urge to move (*akathisia)*. This is a rare side effect of AROPAX CR and is most likely to occur in the first few weeks of treatment.

➔ **Tell your doctor as soon as possible** if you get these symptoms.

Sexual Dysfunction

Medicines like AROPAX (so called SSRIs) may cause symptoms of sexual dysfunction (see Possible side effects). In some cases, these symptoms have continued after stopping treatment.

Bone fracture

There is an increased risk of bone fracture (breaking a bone) in people taking medicines like AROPAX CR. This risk is greatest during the early stages of treatment.

Alcoholic drink and AROPAX CR

It is recommended that you don't drink alcohol while you're taking AROPAX CR.

Other medicines and AROPAX CR

Tell your doctor or pharmacist if you're taking any other medicines, if you've taken any recently, or if you start taking new ones. This includes herbal medicines and other medicines you bought without a prescription.

Some medicines must not be taken with AROPAX CR, see '**Don't take AROPAX CR**' at the beginning of **Section 2**.

Taking AROPAX CR with medicines which may raise serotonin levels in the brain, can increase your risk of side effects (See '*Conditions to look out for' in* ***Section 4***). These include:

- triptans (used to treat **migraine**)
- tramadol (used to treat **pain**)
- tryptophan or SSRIs (used to treat **depression**)
- St. John's Wort (a herbal remedy used to treat **depression**)
- lithium (used to treat **some mental health problems**)
- fentanyl (used in **anaesthesia** or to treat **chronic pain**).

➔ **Tell a doctor or pharmacist** if you are taking any of these. You should be closely monitored while you are taking them with AROPAX CR.

Some medicines can affect how AROPAX CR works. AROPAX CR can also affect how some other medicines work. These include:

- carbamazepine, phenobarbital and phenytoin which are usually used to treat **fits** (seizures or epilepsy)
- mivacurium and suxamethonium (used in **anaesthesia**)
- rifampicin (used to treat **tuberculosis)**
- fosamprenavir and ritonavir (used to treat **HIV**)
- procyclidine (used to treat **Parkinson's disease**)
- amitriptyline, nortriptyline, imipramine and desipramine (used to treat **depression**)
- perphenazine and risperidone (used to treat **some mental health problems**)
- atomoxetine (used to treat **attention deficit hyperactivity disorder, ADHD**)
- propafenone and flecainide (used to treat **an irregular heart beat**)
- metoprolol (used to treat **high blood pressure**)
- tamoxifen (used to treat or prevent **breast cancer or fertility problems**).

➔ **Tell a doctor or pharmacist** if you are taking any of these. Your doctor may decide to adjust your dose.

Pregnancy and breast-feeding

AROPAX CR is not usually recommended for use during pregnancy. If you are **pregnant** or **think you could be,** or if you are **planning to become pregnant, speak to your doctor immediately**. **Your doctor** will consider the benefit to you and the risk to your baby of taking AROPAX CR while you're pregnant.

- Some studies have reported an increase in the risk of birth defects, particularly heart defects, in babies whose mothers were taking AROPAX CR in the first few months of pregnancy. These studies found that about 1 in 50 babies (2%) whose

mothers received AROPAX CR in early pregnancy had a heart defect, compared with the normal rate of 1 in 100 babies (1%) seen in the general population.

- A birth complication called persistent pulmonary hypertension of the newborn (PPHN) has been seen in babies whose mothers were taking antidepressants including AROPAX CR during pregnancy. In PPHN, the blood pressure in the blood vessels between the baby's heart and the lungs is too high. The risk of PPHN occurring in babies whose mothers used antidepressants like AROPAX CR late in pregnancy was reported to be 4 to 5 times higher than the risk of PPHN seen in the general population which is about 1 to 2 cases per 1000 pregnancies.
- If you take AROPAX CR near the end of your pregnancy there may be an increased risk of excessive vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders.Your doctor or midwife should be aware that you are taking AROPAX CR so they can advise you.
- There have been reports of premature births for mothers taking AROPAX CR during pregnancy. It is not known if these are due to the use of AROPAX CR.

If AROPAX CR is used until delivery, the following symptoms have been reported in babies immediately or within the first 24 hours after birth. Again, it is not known if these symptoms are due to the use of AROPAX CR. The symptoms are:

- trouble with breathing
- a blue-ish skin or being too hot or cold
- vomiting or not feeding properly
- being very tired, not able to sleep or constant crying
- stiff or floppy muscles
- tremors, jitters or fits.

➔ If your baby has any of these symptoms when it is born, or you are concerned about your baby's health, **contact your doctor or midwife for advice.**

The ingredients in AROPAX CR can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you take AROPAX CR.

Medicines like AROPAX CR may affect your sperm. Fertility may be reduced in some men during treatment with AROPAX CR.

Driving and using machines

Tradename can make you feel dizzy or confused and can affect your eyesight.

➔ **Don't drive or use machines** if you get side effects such as these.

AROPAX CR 12.5 contains Sunset Yellow

AROPAX CR 12.5 contains the colouring agent Sunset Yellow which may cause allergic-type reactions.

➔ **Check with your doctor** that AROPAX CR 12.5 is suitable for you**.**

AROPAX CR 12.5 and AROPAX 25 contain lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking AROPAX CR.

How to take AROPAX CR

Always take AROPAX CR exactly as your doctor has told you to. Check with your doctor or pharmacist if you're not sure.

How much to take

The starting dose of AROPAX CR depends on your illness. It is usually 12.5 mg or 25 mg once a day. Your doctor may gradually increase your dose to help control your symptoms.

If you are over 65, or have liver or kidney problems, the maximum dose may be reduced.

How to take

Swallow your AROPAX CR tablets whole with some water. Don't chew, crush or split the tablets — if you do, there is a danger you could overdose, because the medicine may be released into your body too quickly.

Take AROPAX CR in the morning.

You can take AROPAX CR with or without food.

How long to take it for

The duration of treatment will depend on your illness. Whilst people usually feel some improvement within two weeks or so, it can take longer for the medicine to have its full effect.

Even after you start to feel better, it is important to keep taking AROPAX CR for as long as your doctor recommends to help prevent symptoms from returning. This can be several months after recovery from depression and may even be longer for panic disorder.

If you forget to take AROPAX CR

Don't take an extra dose to make up for a missed one. Just take your next dose at the usual time.

➔ **If you are not sure what to do,** ask your doctor or pharmacist.

If you take too much AROPAX CR

If you take too much AROPAX CR you are more likely to get side effects (see **Section 4**). Taking too much AROPAX CR may also cause blood pressure changes, uncontrollable muscle contractions, anxiety, a high temperature, and a fast heart beat.

➔ If you take too much AROPAX CR, **contact your doctor or pharmacist for advice.** If possible, show them the AROPAX CR pack.

Don't stop AROPAX CR without advice

Don't stop taking AROPAX CR without talking to your doctor first. Your dose needs to be reduced gradually, otherwise you may get side effects (see *'Symptoms seen when AROPAX CR is stopped'* at the end of **Section 4**).

Possible side effects

Like all medicines, AROPAX CR can cause side effects, but not everybody gets them.

Conditions to look out for

Severe allergic reactions. These are very rare in people taking AROPAX CR. Signs include:

- raised and itchy rash (hives)
- swelling, sometimes of the face or mouth (angioedema), causing difficulty in breathing
- collapse or loss of consciousness.

➔ **Contact a doctor immediately** if you get these symptoms**.** Stop taking AROPAX CR.

Serotonin Syndrome and Neuroleptic Malignant syndrome

Medicines that may increase serotonin activity in the brain can cause a condition called Serotonin Syndrome. This is a very rare side effect of AROPAX CR. Taking AROPAX CR with other medicines which may also raise serotonin activity in the brain, can increase the risk of this serious side effect (see '*Other medicines and AROPAX CR'* in **Section 2***).* Another condition called Neuroleptic Malignant Syndrome is a rare side effect of medicines used to treat mental health problems.

The symptoms of both Serotonin Syndrome and Neuroleptic Malignant Syndrome are similar. Usually more than one of the following symptoms will occur:

- tremor
- sudden uncontrollable jerky movements
- muscle stiffness
- difficulty sitting still
- feeling very agitated or irritable
- feeling hot or sweaty
- increase in heart rate.

The severity can increase, leading to loss of consciousness.

➔ **Contact your doctor urgently** if you get these symptoms**.**

Akathisia

Medicines used to treat some mental health problems can cause a feeling of inner restlessness and the urge to move (*akathisia)*. This is a rare side effect of AROPAX CR, and is most likely to occur in the first few weeks of treatment.

➔ **Tell your doctor as soon as possible** if you get these symptoms.

Very common side effects

These may affect **more than 1 in 10** people:

- feeling sick (nausea)
- a change in sex drive or sexual function.

Common side effects

These may affect **up to 1 in 10** people:

- decreased appetite
- difficulty in sleeping (insomnia) or feeling drowsy
- feeling agitated
- feeling dizzy
- tremors
- headache
- blurred vision
- yawning
- dry mouth
- constipation
- diarrhoea
- being sick (vomiting)
- sweating
- feeling weak
- abnormal dreams (including nightmares)
- weight gain.

Common side effects that may show up in blood tests:

- increase in cholesterol.

Uncommon side effects

These may affect **up to 1 in 100** people:

- bruising or unusual bleeding mainly of the skin and moist areas such as the mouth
- feeling confused
- seeing or hearing things that are not really there (*hallucinations*)
- involuntary muscle movements of the face, twisting movements of the body, arms and legs, tremor
- dilated pupils
- a faster than normal heart beat
- low blood pressure (may cause dizziness, light-headedness or fainting when standing up from a sitting or lying position)
- skin rashes
- unable to pass urine (*urinary retention*) or loss of control of the bladder (*urinary incontinence*).

Rare side effects

These may affect **up to 1 in 1,000** people:

- a feeling of restlessness and difficulty sitting or standing still (*akathisia*)
- episodes of hyperactivity, elation and irritability (*mania*)
- fits (*seizures*)
- irresistible urge to move the legs (*Restless Legs Syndrome*)
- abnormal secretion of breast milk in men and women
- menstrual period disorders (including heavy periods, bleeding between periods and absence of periods).

Rare side effects that may show up in blood tests:

- decrease in sodium levels in the blood (especially in the elderly)
- increase in substances (*enzymes*) from the liver
- increase in a hormone called prolactin.

Very rare side effects

These may affect **up to 1 in 10,000** people:

- Serotonin Syndrome
- skin rash, which may blister, and looks like small targets (central dark spots surround by a paler area, with a dark ring around the edge) called *erythema multiforme*
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*)
- a widespread rash with blisters and skin peeling on much of the body surface (*toxic epidermal necrolysis*)
- increased amounts of a hormone (ADH) that causes water retention
- glaucoma (a condition caused by raised pressure in the eye)
- bleeding in the digestive system (passing blood in the stools or black stools)
- inflammation of the liver (*hepatitis*), sometimes causing yellowing of the skin and the whites of the eyes (*jaundice)*
- increased sensitivity of the skin to sunlight
- swelling of hands, ankles or feet.

Very rare side effects that may show up in blood tests:

- decrease in number of blood platelets (cells that help blood to clot).

If you get side effects

➔ **Tell your doctor or pharmacist** if any of the side effects listed becomes **severe or troublesome**, or if you notice any side effects not listed in this leaflet.

Symptoms seen when AROPAX CR is stopped

Stopping medicines used for treating mental health problems often causes unwanted symptoms. The symptoms are more likely to occur in the first few days of stopping treatment and usually go away within a few weeks.

If you need to stop taking AROPAX CR, your doctor may reduce your dose gradually. This should help to reduce any effects and their severity.

Common symptoms seen when AROPAX CR is stopped:

These may affect **up to 1 in 10** people;

- dizziness
- feelings like pins and needles, electric shock sensations and persistent noise in the ears (*tinnitus*)
- sleep disturbances including intense dreams
- feeling anxious
- headache.

Uncommon symptoms seen when AROPAX CR is stopped:

These may affect **up to 1 in 100** people:

- feeling restless or agitated
- feeling sick (nausea)
- tremors
- feeling confused
- sweating
- diarrhoea.

➔ **Talk to your doctor** if these symptoms become **severe or troublesome**.

How to store AROPAX CR

Keep out of the reach and sight of children.

Store in a dry place, at a temperature not exceeding 25 ºC.

Do not take AROPAX CR after the expiry date shown on the pack.

If you have any unwanted AROPAX CR tablets, don't dispose of them in your waste water or household rubbish. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

Further information

What AROPAX CR contains

The active substance is paroxetine as paroxetine hydrochloride hemihydrate.

AROPAX CR tablet*s* come in different strengths.

Each tablet contains either:

12.5 mg or 25 mg paroxetine.

The other ingredients are: Hypromellose, povidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer dispersion, talc, triethyl citrate, Opadry yellow, YS-1-2007 (12,5 mg tablets, includes the colouring agent Sunset Yellow Lake (FD&C Yellow No. 6 aluminium lake)), Opadry pink, Y-1-1262 (25 mg tablets) and the following colourants: yellow ferric oxide (12,5 mg tablets) and red ferric oxide (25 mg tablets).

AROPAX CR tablets contain lactose.

What AROPAX CR looks like and contents of the pack

12.5 mg tablets: Yellow, round, biconvex, debossed, film-coated tablets with bevelled edges. One face is engraved with 'GSK' and the other face is engraved with '12.5'.

Carton containing 28 tablets, packed in white blister packs, in strips of 14.

or

Carton containing 30 tablets, packed in white blister packs, in strips of 10.

25 mg tablets*:* Pink, round, biconvex, debossed, film-coated tablets with bevelled edges. One face is engraved with 'GSK' and the other face is engraved with '25'.

Carton containing 28 tablets, packed in white blister packs, in strips of 14.

or

Carton containing 30 tablets, packed in white blister packs, in strips of 10.

Not all presentations are available in every country.

Name and address of the holder of the certificate of registration

GlaxoSmithKline South Africa (Pty) Ltd
57 Sloane Street
Bryanston, 2021
South Africa

Registration details:

Botswana:
AROPAX CR 12,5: Reg No BOT0801414 S2
AROPAX CR 25: Reg No BOT0801413 S2

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Version number: GDS48/IPI26

Date of issue: 8 December

2021