SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

AROPAX CR 12,5 Controlled release tablet

AROPAX CR 25 Controlled release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

AROPAX CR tablets 12,5 mg contains paroxetine hydrochloride hemihydrate equivalent to 12,5 mg free base.

Contains sugar (lactose monohydrate 109,67 mg per tablet)

Contains Opadry Yellow 15B120039.

AROPAX CR tablets 25 mg contains paroxetine hydrochloride hemihydrate equivalent to 25 mg paroxetine free base.

Contains sugar (lactose monohydrate 109,64 mg per tablet)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

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'.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

Major Depressive Disorder:

AROPAX CR tablets are indicated for the treatment of major depressive disorder.

Panic Disorder:

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

Social Phobia:

AROPAX CR tablets have been shown to be effective in the treatment of Social Phobia.

Children and adolescents (less than 18 years):

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder (with the immediate release formulation), there were increased reports of hostility and suicide-related adverse events, such as suicidal ideation and self-harm (see section 4.3).

AROPAX CR is not indicated for use in children or adolescents aged less than 18 years (see sections 4.3 and 4.4).

The efficacy of AROPAX CR tablets has not been studied in children and adolescents aged less than 18 years; however, controlled clinical studies with AROPAX (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 section 4.4).

4.2. Posology and method of administration:

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 one week.

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 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 one week.

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 sections 4.3 and 4.4).

Renal/hepatic impairment:

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

Discontinuation of AROPAX CR:

Abrupt discontinuation should generally be avoided (see sections 4.4. and 4.8). 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 one 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 medical practitioner may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications:

Known hypersensitivity to paroxetine or any excipients of AROPAX CR.

Concomitant use with serotonin precursors (see sections 4.4 and 4.5).

Children under the age of 18 years (see section 4.4).

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 2 weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with AROPAX CR tablets (see section 4.5).

Paroxetine 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 section 4.5).

AROPAX CR should not be used in pregnancy (see section 4.6).

4.4. Special warnings and precautions for use:

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 CR 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 CR compared to those treated with placebo (see section 4.8). 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 18-24 years) treated with paroxetine compared with placebo (17/776 [2,19 %] versus 5/542 [0,92 %]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥ 65 years), no such increase was observed.

However, the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Patients with major depressive disorder 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 improvement 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 CR is prescribed can also 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 and should receive careful monitoring during treatment.

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 to therapy (see Akathisia and Mania and Bipolar Disorder below; section 4.8). Consideration should be given to changing the therapeutic regimen, including possibly discontinuing AROPAX CR, 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:

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

Serotonin Syndrome/Neuroleptic Malignant Syndrome: 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 medicines. 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 sections 4.3 and 4.5).

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 AROPAX CR is not approved for use in treating bipolar depression.

AROPAX CR 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 section 4.5). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, practitioners 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 such as AROPAX CR, have reported an association with fractures.

Renal/hepatic impairment:

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment (see section 4.2).

Symptoms seen on discontinuation of paroxetine treatment in adults:

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

Dizziness, sensory disturbances (including paraesthesia, 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 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that AROPAX CR 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', section 4.2).

Sexual dysfunction: Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

Symptoms seen on discontinuation of paroxetine treatment in children and adolescents:

In clinical trials in children and adolescents, adverse events seen on treatment discontinuation occurred in 32 % of patients treated with paroxetine compared to 24 % of patients treated with placebo. Events reported upon discontinuation of paroxetine at a frequency of at least 2 % of patients and which occurred at a rate at least twice that of placebo were: emotional liability (including suicidal ideation, suicide attempt, mood changes and tearfulness), nervousness, dizziness, nausea and abdominal pain (see section 4.8).

Haemorrhage: Skin and mucous membrane bleedings (including gastrointestinal and gynaecological bleeding) have been reported during treatment with paroxetine alone. AROPAX CR should therefore be used with caution in patients concomitantly treated with medicines that give an increased risk for bleeding and in patients with a known tendency for bleeding or those with predisposing conditions (see section 4.5).

SSRIs may increase the risk of postpartum haemorrhage (see section 4.6).

Risperidone:

Co-administration with risperidone may lead to increased toxicity thereof (see section 4.5).

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

QT Prolongation

Cases of QT interval prolongation have been reported during the post-marketing period. Paroxetine should be used with caution in patients with a (family) history of QT interval prolongation, concomitant use of anti-arrhythmic medications or other medications that may potentially prolong QT interval, relevant pre-existing cardiac disease such as heart failure, ischaemic heart disease, heart block or ventricular arrhythmias, bradycardia, and hypokalaemia or hypomagnesemia (see section 4.3 and 4.5).

Epilepsy: 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. AROPAX CR should be discontinued in any patient who develops seizures.

Electroconvulsive Therapy (ECT): There is little clinical experience of the concurrent administration of AROPAX CR with ECT.

Glaucoma: AROPAX CR can cause mydriasis and should be used with caution in patients with narrow angle glaucoma.

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

Alcohol: The concomitant use of AROPAX CR and alcohol is not advised.

AROPAX CR contains lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 2).

AROPAX CR 12,5 mg contains Opadry Yellow (15B120039): The paroxetine 12,5 mg controlled release tablet coating Opadry Yellow (15B120039) contains the colouring agent Sunset Yellow Lake (FD&C Yellow No.6 aluminium lake), an azo dye which may cause allergic-type reactions.

4.5. Interactions with other medicines and other forms of interaction:

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**: the concomitant use of paroxetine and alcohol is not advised.

Medicine metabolising enzymes:

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

When AROPAX CR is to be co-administered with a known medicine metabolising enzyme inhibitor (e.g., sodium valproate), consideration should be given to using doses at the lower end of the range.

No initial dosage adjustment is considered necessary when the AROPAX CR is to be co-administered with known medicine metabolising enzyme inducers (e.g., carbamazepine, rifampicin, phenobarbitone, phenytoin). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

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

Procyclidine: Daily administration of AROPAX CR increases significantly the plasma levels of **procyclidine**. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Anticonvulsants**:** carbamazepine, phenytoin, sodium valproate. Concomitant administration showed no 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:

Paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered medicines metabolised by this enzyme. These include certain tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine and desipramine), phenothiazine neuroleptics (e.g., perphenazine and thioridazine), risperidone, atomoxetine, certain Type 1c antidysrhythmics (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 section 4.4).

CYP3A4:

An *in vivo* interaction study revealed no effect of paroxetine on alprazolam pharmacokinetics and *vice-versa*. Concurrent administration of AROPAX CR with alprazolam and other medicines that are CYP3A4 substrates would not be expected to cause a hazard.

Serotonergic medicines:

Co-administration with serotonergic medicines may lead to an incidence of 5-HT associated effects (Serotonergic Syndrome; see sections 4.4 and 4.8).

Caution should be advised, and a closer clinical monitoring is required when serotonergic medicines (such as L-tryptophan, triptans, tramadol, linezolid, 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 section 4.3).

Pimozide:

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with AROPAX CR. 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 is contraindicated (see section 4.3).

Anticoagulants/Warfarin:

AROPAX CR should be administered with great caution to patients receiving oral anticoagulants.

Preliminary data suggest that there may be a pharmacodynamic interaction between paroxetine and warfarin, which may result in increased bleeding in the presence of unaltered prothrombin times/INRs.

4.6. Fertility, 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: AROPAX CR should not be used during pregnancy (see section 4.3).

Recent epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants, including AROPAX CR in pregnancy have reported an increase in risk of congenital malformations, particularly cardiovascular (e.g., ventricular and atrial septal defects, associated with the use of paroxetine as contained in AROPAX CR.

There have been reports of premature birth in pregnant women exposed to paroxetine or other SSRIs. AROPAX CR should not be used during pregnancy.

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 paroxetine or other SSRIs late in the third trimester of pregnancy. 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 AROPAX CR) 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 4 to 5 times higher than observed in the general population (rate of 1 to 2 per 1 000 pregnancies).

Lactation: Small amounts of paroxetine are excreted into breast milk. AROPAX CR should not be used during lactation.

4.7. 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, patients should be cautioned about their ability to drive a car and operate machinery

4.8 Undesirable effects:

Adverse 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 > 8 000 paroxetine-treated patients and are quoted as excess incidence over placebo.

Clinical Trials:

Blood & lymphatic system disorders:

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes

Metabolism & nutrition disorders:

Common: increases in cholesterol levels, decreased appetite

Psychiatric disorders:

Common: somnolence, insomnia, agitation, abnormal dreams (including nightmares)

Uncommon: confusion, hallucinations

Nervous system disorders:

Common: dizziness, tremor, headache

Uncommon: extrapyramidal disorders

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 section 4.4)

Vascular disorders:

Uncommon: postural hypotension

Respiratory, thoracic and mediastinal disorders:

Common: yawning

Gastrointestinal disorders:

Very common: nausea

Common: constipation, diarrhoea, vomiting, dry mouth

Skin & subcutaneous tissue disorders:

Common: sweating

Uncommon: skin rashes

Renal & urinary disorders:

Uncommon: urinary retention, urinary incontinence

Reproductive system & breast disorders:

Very common: sexual dysfunction

General disorders & administration site conditions:

Common: asthenia, body weight gain.

Post-Marketing:

The frequency of the following adverse events are unknown.

Blood & lymphatic system disorders: thrombocytopenia

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

Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutritional disorders: hyponatraemia

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

Psychiatric disorders: manic reactions

Nervous system disorders: convulsions, akathisia, restless legs syndrome (RLS), serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor)

Eye disorders: acute glaucoma

Gastrointestinal disorders: gastrointestinal bleeding

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

Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice, and/or liver failure), which may be fatal, have also been received. Discontinuation of AROPAX CR should be considered if there is prolonged elevation of liver function test results.

Skin & subcutaneous tissue disorders: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions

Reproductive system & breast disorders: hyperprolactinaemia/galactorrhoea, menstrual disorders (including menorrhagia, metrorrhagia and amenorrhoea); postpartum haemorrhage.

Postpartum haemorrhage has been reported for the therapeutic class of SSRIs (see sections 4.4 and 4.6).

General disorders & administration site conditions: peripheral oedema.

Symptoms seen on discontinuation of paroxetine treatment:

Common: dizziness, sensory disturbances, sleep disturbances, anxiety

Uncommon: agitation, nausea, sweating.

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, headache, nervousness, vertigo, nausea, 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 AROPAX CR treatment is no longer required, gradual discontinuation by dose tapering be carried out (see sections 4.2 and 4.4).

Reporting of suspected adverse events:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

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

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under section 4.8, fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.

Patients have generally recovered without serious sequelae even when doses of up to 2 000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic medicines with or without alcohol.

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.

5. PHARMACOLOGICAL PROPERTIES:

A 1.2 Psycho-analeptics (Antidepressants)

5.1. Pharmacodynamic properties:

Paroxetine is a selective inhibitor of serotonin (5-hydroxytryptamine, 5-HT) re-uptake and its antidepressant action and efficacy 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.

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.

The metabolites of paroxetine do not compromise its selective action on neuronal 5-HT uptake.

5.2 Pharmacokinetic properties:

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 4 to 5 hours. In addition to controlling the rate of paroxetine release *in vivo*, an enteric coat delays the start of paroxetine release until AROPAX CR tablets have left the stomach. Compared to immediate release formulations of paroxetine, controlled release tablets have a reduced absorption rate.

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 1 day.

Steady state systemic levels are attained by 7-14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy. No correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy).

Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract.

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.

Transfer to human breast milk and to the foetuses of laboratory animals, occurs in small amounts.

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

6. PHARMACEUTICAL PARTICULARS:

6.1. List of Excipients:

Hypromellose, povidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl dibehenate, methacrylic acid and ethyl acrylate copolymer dispersion, talc, triethyl citrate, Opadry yellow 15B120039 (12,5 mg tablets), 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).

6.2. Incompatibilities:

Not applicable.

6.3. Shelf-life:

36 months.

6.4. Special precautions for storage:

Store in a dry place at a temperature not exceeding 25°C.

Keep out of reach of children.

6.5. Nature and contents of container:

AROPAX CR 12,5 mg tablets:

Carton containing 28 tablets, packed in PVC/Aluminium child -resistant white blister packs, in strips of 14.

Carton containing 30 tablets, packed in PVC/Aluminium child -resistant white blister packs, in strips of 10.

AROPAX CR 25 mg tablets:

Carton containing 28 tablets, packed in PVC/Aluminium child -resistant white blister packs, in strips of 14.

Carton containing 30 tablets, packed in PVC/Aluminium child -resistant white blister packs, in strips of 10.

6.6. Special precautions for disposal:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

AROPAX CR 12,5 mg: A38/1.2/0612

AROPAX CR 25 mg: A38/1.2/0613

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION:

AROPAX CR 12,5 mg: 18 March 2005

AROPAX CR 25 mg: 18 March 2005

10. DATE OF REVISION OF TEXT:

19 December 2023

GDS-48

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