Renal/hepatic impairment

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment. (see section 4.2 Posology and method of administration)

Diabetes

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

Epilepsy

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

Seizures

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

ECT

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

Glaucoma

As with other SSRI's, paroxetine infrequently causes mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

Cardiac conditions

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

Hyponatraemia

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

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Other haemorrhagic manifestations e.g. gastrointestinal haemorrhage have been reported. Elderly patients may be at an increased risk.

Caution is advised in patients taking SSRI's concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, acetylsalicylic acid, NSAID's, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

Parabens

Paroxetine oral suspension contains methyl and propyl hydroxybenzoate (parabens), which are known to cause urticaria; generally delayed type reactions, such as contact dermatitis, but rarely immediate reaction with bronchospasm.

Withdrawal symptoms seen on discontinuation of paroxetine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in 30% of patients treated with paroxetine compared to 20% of patients

treated with placebo. The occurrence of withdrawal symptoms is not the same as the drug being addictive or dependence producing.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Paroxetine", Section 4.2 Posology and method of administration).

4.5 Interaction with other medicinal products and other forms of Interaction

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs (including MAOIs, L-tryptophan, triptans, tramadol, linezolid, SSRIs, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of 5 $^{-}$ HT associated effects (serotonin syndrome: see Section 4.3 Contraindications and Section 4.4 Special warnings and special precautions for use).

Caution should be advised and a closer clinical monitoring is required when these drugs are combined with paroxetine.

Drug metabolising enzyme

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 paroxetine doses at the lower end of the range.

No initial dosage adjustment is considered necessary when it 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).

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.

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. clomipramine, nortriptyline, and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine see section 4.3 Contraindications), risperidone, Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.

Alcohol

As with other psychotropic drugs patients should be advised to avoid alcohol use while taking paroxetine

Oral anticoagulants

A pharmacodynamic interaction between paroxetine and oral anticoagulants may occur. Concomitant use of paroxetine and oral anticoagulants can lead to an increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should therefore be used with caution in patients who are treated with oral anticoagulants. (see section 4.4 Special warnings and special precautions for use)

NSAIDs and acetylsalicylic acid, and other antiplatelet agents

A pharmacodynamic interaction between paroxetine and NSAIDs/acetylsalicylic acid may occur. Concomitant use of paroxetine and NSAIDs/acetylsalicylic acid can lead to an increased haemorrhagic risk. (see section 4.4 Special warnings and Special Precautions for use)

Caution is advised in patients taking SSRI's, concomitantly with oral anticoagulants, drugs known to affect platelet function or increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, acetylsalicylic acid, NSAID's, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

4.6 Pregnancy and lactation

Pregnancy

A study of pregnancy outcomes following maternal exposure to antidepressants in the first trimester has suggested a possible small increase in the risk of congenital malformations e.g. ventricular septum defects, in children of mothers treated with paroxetine. Other studies, however, do not provide a signal of an association with congenital malformations.

Paroxetine should only be used during pregnancy when strictly indicated. Women planning a pregnancy and those becoming pregnant during therapy should be asked to consult their physician. Abrupt discontinuation should be avoided during pregnancy (see "Withdrawal Symptoms Seen on Discontinuation of Paroxetine", section 4.2 Posology and method of administration).

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, particularly the third trimester.

The following symptoms may occur in the neonate after maternal paroxetine use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping . These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Section 5.3 Preclinical safety data).

Lactation

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

4.7 Effects on ability to drive and use machines

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

paroxetine and alcohol is not advised.

4.8 Undesirable effects

Some of the adverse drug reactions 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.

Blood and lymphatic system disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis).

Very rare: thrombocytopenia.

Immune system disorders

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

Endocrine disorders

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

Metabolism & nutrition disorders

Common: decreased appetite

Rare: hyponatraemia.

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

Psychiatric disorders

Common: somnolence, insomnia.

Uncommon: confusion, hallucinations

Rare: manic reactions, agitation, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4 Special Warnings and Special Precautions for use).

These symptoms may also be due to the underlying disease.

Nervous system disorders

Common: dizziness, tremor.

Uncommon: extrapyramidal disorders.

Rare: convulsions.

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.

Very rare: acute glaucoma.

Cardiac disorders

Uncommon: sinus tachycardia.

Rare: bradycardia.

Vascular disorders

Uncommon: transient increases or decreases in blood pressure.

Transient increases or decreases of blood pressure have been reported following treatment with paroxetine, usually in patients with pre-existing hypertension or anxiety.

Respiratory, thoracic and mediastinal disorders

Common: yawning.

Gastrointestinal disorders

Very common: nausea.

Common: constipation, diarrhoea, dry mouth.

Very rare: gastrointestinal bleeding.

Hepato-biliary 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 have 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, pruritus.

Very rare: photosensitivity reactions.

Renal & urinary disorders

Uncommon: urinary retention.

Reproductive system & breast disorders

Very common: sexual dysfunction

Rare: hyperprolactinaemia/galactorrhoea.

Very rare: priapism.

Musculoskeletal disorders

Very rare: arthralgia, myalgia.

General disorders and administration site conditions

Common: asthenia, body weight gain.

Very rare: peripheral oedema.

WITHDRAWAL SYMPTOMS SEEN ON DISCONTINUATION OF PAROXETINE TREATMENT

Common: Dizziness, sensory disturbances, sleep disturbances, anxiety, headache.

Uncommon: Agitation, nausea, tremor, confusion, sweating, emotional instability, visual disturbances, palpitations, diarrhoea, irritability.

Discontinuation of paroxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion,sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported.

Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (see sections 4.2 Posology and Method of Administration and, 4.4 Special warnings and precautions for use).

Adverse events from paediatric clinical trials

In short term (up to 10-12 weeks) clinical trials in children and adolescents, the following adverse events were observed in paroxetine treated patients at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo were: increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Increased hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age. Additional events that were more often seen in the paroxetine compared to placebo group were: decreased appetite, tremor, sweating, hyperkinesia, hostility, agitation, emotional lability (including crying and mood fluctuations).

In studies that used a tapering regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and that occurred at a rate of at least twice that of placebo were: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain (see section 4.4 Special warnings and special precautions for use)

4.9 Overdose

Symptoms and signs

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

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under section 4.8 'Undesirable Effects', vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, 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 paroxetine was taken in conjunction with other pyschotropic drugs, with or without alcohol.

Treatment

No specific antidote is known.

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Where appropriate, the stomach should be emptied either by the induction of emesis, lavage or both. Following evacuation, 20 to 30 g of activated charcoal may be administered every 4 to 6 h during the first 24 h after ingestion. Supportive care with frequent monitoring of vital signs and careful observation is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants – selective serotonin reuptake inhibitors, ATC code: N06A B05

Mechanism of Action

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) reuptake and its antidepressant action and efficacy in the treatment of OCD, Social Anxiety disorder/Social Phobia, General Anxiety Disorder, Post-traumatic Stress Disorder and panic disorder is thought to be related to its specific inhibition of 5-HT reuptake 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 alpha1, alpha2 and beta ¯ adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and histamine (H1) 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 noradrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

In the treatment of depressive disorders, paroxetine exhibits comparable efficacy to standard antidepressants.

There is also some evidence that paroxetine may be of therapeutic value in patients who have failed to respond to standard therapy.

Morning dosing with paroxetine does not have any detrimental effect on either the quality or duration of sleep. Moreover, patients are likely to experience improved sleep as they respond to paroxetine therapy.

Dose response

In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, there are some clinical data suggesting that up-titrating the dose might be beneficial for some patients.

Long-term efficacy

The long-term efficacy of paroxetine in depression has been demonstrated in a 52 week maintenance study with relapse prevention design: 12% of patients receiving paroxetine (20-40mg daily) relapsed, versus 28% of patients on placebo.

The long-term efficacy of paroxetine in treating obsessive compulsive disorder has been examined in three 24 week maintenance studies with relapse prevention design. One of the three studies achieved a significant difference in the proportion of relapsers between paroxetine (38%) compared to placebo (59%).

The long-term efficacy of paroxetine in treating panic disorder has been demonstrated in a 24 week maintenance study with relapse prevention design: 5% of patients receiving paroxetine (10-40mg daily) relapsed, versus 30% of patients on placebo. This was supported by a 36 week maintenance study.

The long-term efficacy of paroxetine in treating social anxiety disorder and generalised anxiety disorder and Post-traumatic Stress Disorderhas not been sufficiently demonstrated.

5.2 Pharmacokinetic properties

Absorption

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Partial saturation of the first-pass effect and reduced plasma clearance occur as the body burden increases with higher single doses or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in non ¯ linear kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses.

Steady state systemic levels are attained by 7 to 14 days after starting treatment 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 is protein bound at therapeutic concentrations.

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

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

Metabolism

The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects.

Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake.

Elimination

Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus paroxetine is eliminated almost entirely by metabolism.

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

The elimination half-life is variable but is generally about 1 day.

Special patient populations

Elderly and renal/hepatic impairment

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

5.3 Preclinical safety data

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 6 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.

Reproduction toxicity studies in rats have shown that paroxetine affects male and female fertility. In rats, increased pup mortality and delayed ossification were observed. The latter effects were likely related to maternal toxicity and are not considered a direct effect on the foetus/neonate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores: Calcium phosphate (E341), sodium starch glycollate, magnesium stearate (E572).

Tablet film-coat: Hydroxypropyl methylcellulose (E464), titanium dioxide (E171), polyethylene glycol and polysorbate 80 (E433). The coating of the 30 mg tablets also contains indigo carmine (E132).

Liquid: Polacrilin potassium, dispersible cellulose (E460), propylene glycol, glycerol, (E422), sorbitol (E420), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium citrate (E331), citric acid (E330), sodium saccharin (E954), natural orange flavour, natural lemon flavour, yellow colouring (E110), simethicone emulsion, purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Tablets: Three years

Liquid: Two years

6.4 Special precautions for storage

Tablets: No special storage precautions are required.

Liquid: Do not store above 25 ° C

6.5 Nature and contents of container

Tablets: Available in Original Packs of 30 (three PVC/aluminium or PVC/PVdC aluminium blister strips of 10 tablets).

Liquid: Bottles containing 150 ml with a child-resistant closure and cup

6.6 Instructions for use and handling

None.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc

Great West Road

Brentford

Middlesex TW8 9GS.

trading as:

SmithKline Beecham Pharmaceuticals

Welwyn Garden City

Hertfordshire AL7 1EY

And/or

GlaxoSmithKline UK,

Stockley Park West,

Uxbridge,

Middlesex UB11 1BT

8. MARKETING AUTHORISATION NUMBER(S)

Seroxat 20 mg tablets: 10592/0001

Seroxat 30 mg tablets: 10592/0002

Seroxat Liquid: 10592/0092

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Seroxat 20 mg tablets: 09.01.98

Seroxat 30 mg tablets: 09.01.98

Seroxat Liquid: 09.01.02

10. DATE OF REVISION OF THE TEXT

October 2005

11. LEGAL STATUS

POM