The Medicines and Healthcare products Regulatory Agency (MHRA) granted Teva UK Limited Marketing Authorisations (licences) for the medicinal products Paroxetine 20 mg Film-Coated Tablets (PLs 00289/0521 and 00289/0523) and Paroxetine 30 mg Film-Coated Tablets (PLs 00289/0522 and 00289/0524). These medicines are available on prescription for the treatment of various types of depression and anxiety disorders. Paroxetine Film-Coated Tablets are also used for treating panic disorders and obsessive compulsive disorders.

Paroxetine helps keep normal levels of the chemical serotonin in the body. Serotonin is found naturally in the brain and it is thought that it may help control mood. Having low levels of serotonin is thought to be one cause of depression and other related conditions.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Paroxetine 20 mg and 30 mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
PAROXETINE 20 MG AND 30 MG FILM-COATED TABLETS

PL 00289/0521-4

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Paroxetine 20 mg and 30 mg Film-Coated Tablets to Teva UK Limited on 30 November 2006. These are prescription-only medicines (POM).

These abridged applications are submitted according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Seroxat Tablets (Smithkline Beecham PLC).

These are immediate-release tablets containing 20 mg and 30 mg of the active ingredient paroxetine hydrochloride hemihydrate, a selective serotonin reuptake inhibitor. The tablets are indicated for depressive illness, obsessive-compulsive disorder, panic disorder (with or without agoraphobia), social anxiety disorder/social phobia and generalised anxiety disorder.

The MAA forms, SPC, PIL and labelling are satisfactory. The pharmaceutical, preclinical and clinical expert reports have been written by appropriately qualified professionals.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE**

Paroxetine hydrochloride hemihydrate has a Drug Master File. The drug substance manufacturer has committed to inform the MA holder of any changes in the manufacturing process.

**General Information**

**Nomenclature**

INN/USAN: Paroxetine hydrochloride

Compendia name: Paroxetine hydrochloride hemihydrate

Chemical Name: \((-\) - (3S, 4R)-4-(p-fluorophenyl) -3-[(3,4- methylene dioxy)phenoxy-methyl]-piperidine hydrochloride hemihydrate

**Structure**

Structural Formula

![Structural Formula](image)

Molecular Formula: \(C_{19}H_{21}FNO_3.Cl*1/2\,H_2O\)

Molecular Weight: 374.84

**General properties**

Description: White to off-white powder. The applicant states that paroxetine HCl exists in two pseudopolymorphic forms. Active substance from this source is the hemihydrate. The paroxetine HCl hemihydrate molecule is chiral with a specific optical rotation of \(-83.9\pm1\). It is freely soluble in methanol and slightly soluble in water.

The drug substance manufacturing process has been described and is satisfactory. All materials used in the manufacture of the drug substance are appropriately controlled.
All tests and limits listed in the specification are appropriate to ensure the quality of the drug substance. The batch data generated have shown that the batches of drug substance produced comply with Ph.Eur requirements and the specification.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

A Certificate of Analysis is presented for the in-house reference standard that shows compliance with the proposed specification.

The drug substance is packaged in a suitable container.

Appropriate stability data have been generated, supporting a retest period of 2 years with the drug substance stored in its original packaging.

**DRUG PRODUCT**

**Description and qualitative composition of the drug product**

20mg Tablet: White to off-white, round, biconvex, film-coated tablet, embossed with ‘20’ and scored on one side and with ‘PX’ on the other side.

30mg Tablet: White to off-white, round, biconvex, film-coated tablet, embossed with ‘30’ and scored on one side and with ‘PX’ on the other side.

The qualitative and quantitative compositions of the tablets have been provided. All ingredients used comply with a suitable pharmacopoeial specification.

Tablets are contained in blisters that are packaged in an outer carton (pack sizes 14, 20, 28, 30, 30 (calendar packs), 50, 56, 60, 84 and 100 tablets).

**Components of the drug product**

The physico-chemical properties of the drug substance have been adequately summarised. The function of each added ingredient has been adequately summarised. The excipients used are conventional, with well-established pharmaceutical uses.

**Pharmaceutical development**

The aim of the development process was to develop an immediate-release coated tablet that was essentially similar to the brand leader’s product (Seroxat tablet, UK). The composition, dissolution profiles and impurity profiles of the product and brand leader were compared and found to be essentially similar.

**Manufacture**

Valid copies of Manufacturing Authorisations and a satisfactory flowchart showing all sites involved in the manufacture of the finished product are presented.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength and the results are satisfactory.
Finished product specifications
The finished product specifications include adequate tests to control the physical, chemical and microbiological aspects of the product and to ensure the product’s compliance with Ph.Eur requirements for coated tablets. Test methods have been adequately validated and acceptance limits have been justified. Batch data comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container closure system
Tablets are packaged in transparent or white opaque PVC coated with PVDC and backed with AL foil. In-house specifications, supplier’s specifications and typical Certificates of Analysis are given for the packaging materials and are satisfactory. All primary packaging complies with EC Directive 90/128, relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, with the storage conditions “Store in the original package”.

Comparative bioavailability and bioequivalence study.
Bioequivalence studies conducted in line with GLP/GCP requirements confirm that Paroxetine 20 mg and 30 mg Film-Coated Tablets are essentially similar to the reference product.

Pharmaceutical Conclusion
Marketing Authorisations may be granted.

The requirements for essential similarity between the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

1. INTRODUCTION

This national abridged application claims essential similarity to Seroxat tablets 20 mg (PL 10592/0001).

2. INDICATIONS

Satisfactory

3. DOSE AND DOSE SCHEDULE

Satisfactory. Consistent with cross-reference product

4. TOXICOLOGY

No new data

6. CLINICAL PHARMACOLOGY

The applicant has submitted data from a comparative bioavailability study carried out against the cross-reference product. This was a single dose, randomised, two-way cross-over study comparing a single dose of 2 x 20 mg test and reference product. Twenty-four healthy subjects were enrolled.

The 90% Confidence Intervals for AUC0-inf, AUCt and Cmax were 0.99-1.248, 1.01-1.26 and 0.93-1.10, respectively.

7. EFFICACY

No new data

8. SAFETY

No adverse events were observed in the bioavailability study

9. EXPERT REPORTS

An appropriate clinical review has been submitted by the applicant.
10. **PATIENT INFORMATION LEAFLET (PIL)**

Satisfactory

11. **LABELLING**

Medically satisfactory

12. **APPLICATION FORM (MAA)**

Medically satisfactory

13. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPCs for these products are satisfactory

14. **DISCUSSION**

The applicant has satisfactorily demonstrated comparative bioavailability and hence bioequivalence.

15. **MEDICAL CONCLUSION**

Granting of marketing authorisations is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Paroxetine 20 and 30 mg film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, no significant preclinical or clinical safety concerns were identified and benefit has been shown to be associated with Paroxetine 20 and 30 mg film-coated tablets. The risk benefit is therefore considered to be positive.
PAROXETINE 20 MG AND 30 MG TABLETS

PL 00289/0521-4

STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 18 December 2002</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 24 January 2003</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 10 February 2003 and the quality dossier on 2 May 2003</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 6 March 2003 and on the quality dossier on 22 December 2003</td>
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<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 10 May 2004</td>
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<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 8 February 2005</td>
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<td>7</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 15 February 2006</td>
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<td>8</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 29 June 2006</td>
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<td>9</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 16 August 2006</td>
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<td>10</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 29 September 2006</td>
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<td>11</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 4 October 2006</td>
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<td>12</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 2 November 2006</td>
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<tr>
<td>13</td>
<td>The application was determined on 30 November 2006</td>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

20 mg strengths:

1. NAME OF THE MEDICINAL PRODUCT

Paroxetine 20 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paroxetine hydrochloride hemihydrate equivalent to 20 mg paroxetine free base.
For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
White, to off-white, round biconvex film-coated tablet, embossed with "20" and scored on one side and with "PX" on the other side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of
- major depressive episode.
- obsessive compulsive disorder (OCD).
- panic disorder with or without agoraphobia.
- social anxiety disorder/social phobia.
- generalised anxiety disorder.

4.2. Posology and method of administration

It is recommended that paroxetine is administered once daily in the morning with food.

Major depressive episode
The recommended dose is 20 mg daily. In general, improvement in patients starts after one week but may only become evident from the second week of therapy.
As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. In some patients, with insufficient response to
20 mg, the dose may be increased gradually up to a maximum of 50 mg a day in 10 mg steps according to the patient’s response.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

**Obsessive compulsive disorder**
The recommended dose is 40 mg daily. Patients should start on 20 mg/day and the dose may be increased gradually in 10 mg increments to the recommended dose. If after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months of even longer (see section 5.1).

**Panic disorder**
The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. 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. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer (see section 5.1).

**Social anxiety disorder/social phobia**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day.

Long-term use should be regularly evaluated (see section 5.1).

**Generalised anxiety disorder:**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).
**General information**

*Withdrawal symptoms seen on discontinuation of paroxetine*
Abrupt discontinuation should be avoided (see section 4.4 and section 4.8). The taper phase regimen used in clinical trials involved decreasing the daily dose by 10 mg at weekly intervals. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

**Special 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 the adult starting dose. Increasing the dose might be useful in some patients, but the maximum dose should not exceed 40 mg daily.

*Children and adolescents (7-17 years)*
Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behaviour and hostility. In addition, in these trials, efficacy has not been adequately demonstrated (see section 4.4 and section 4.8).

*Children aged below 7 years*
The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.

*Renal/Hepatic Impairment:*
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.

### 4.3. Contraindications

Known hypersensitivity to paroxetine or any of the excipients.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Treatment with paroxetine can be initiated:
- two weeks after discontinuation of an irreversible MAOI, or
- at least 24 hours after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.
Paroxetine should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see section 4.5). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

4.4. Special warnings and precautions for use

Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached (see section 4.3 and section 4.5).

*Children and adolescents (7-17 years)*

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. In clinical trials, increased suicidal-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with paroxetine compared to those treated with placebo. In addition, in these trials, efficacy has not been adequately demonstrated and long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking (see section 4.8).

*Suicide/suicidal ideation*

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicidal behaviour or thoughts, or those 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.

There is a possibility of an increased risk of suicide-related behaviour in young adults aged 18-29. Young adults should therefore be monitored carefully throughout treatment.
There are insufficient data concerning the risk of suicide-related behaviour in treatment-naïve patients, but careful monitoring might be warranted.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms occur.

**Akathisia**
The use of paroxetine 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. In patients who develop these symptoms, increasing the dose may be detrimental.

**Serotonin syndrome/neuroleptic malignant syndrome**
On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment with paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination with serotonin precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome (see section 4.3 and section 4.5).

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

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

**Diabetes**
In patients with diabetes, treatment with an SSRI may alter glycaemia 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. Paroxetine 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 SSRIs, 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 SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

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). 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 of
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).

4.5. Interactions 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 and section 4.4).
Caution should be advised and a closer clinical monitoring is required when these drugs are combined with paroxetine.

**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).

**Procyclidine**
Daily administration of paroxetine significantly increases 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 the 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), risperidone, certain Type
Ic 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
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
increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine
should be used with caution in patients who are treated with oral
anticoagulants (see section 4.4).

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).
Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, 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
Data on a limited number of exposed pregnancies provide no indication of an
increased risk of congenital malformations in the newborn.

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).

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 the 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/fetal development, parturition or post-natal development (see section 5.3).

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

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

**Metabolism and nutrition disorders**
- **Common:** decreased appetite
Rare: hyponatraemia
Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to SIADH.

Psychiatric disorders
Common: somnolence, insomnia
Uncommon: confusion, hallucinations
Rare: manic reactions, agitation, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4)
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 disorder 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 of decreases in 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 has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

**Skin and subcutaneous tissue disorders**
- **Common:** sweating
- **Uncommon:** skin rashes, pruritus
- **Very rare:** photosensitivity reactions

**Renal and urinary disorders**
- **Uncommon:** urinary retention

**Reproductive system and breast disorders**
- **Very common:** sexual dysfunction
- **Rare:** hyperprolactinaemia/galactorrhoea
- **Very rare:** priapism

**Musculoskeletal disorders**
- **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 self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

**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 at least twice that of
placebo: 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, 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 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).

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 in section 4.8, 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 with a fatal outcome, but generally when paroxetine 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. 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) uptake and its antidepressant action and effectiveness in the treatment of OCD, social anxiety disorder/social phobia, generalised anxiety disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has a 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 or beta-adrenoceptors, dopamine (D_2), 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 depressants 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-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 (20-40 mg 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 (10-40 mg 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 has 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 pharmacokinetics. 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 the 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 fetuses 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 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 the 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 with 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 in 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's 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 fetus/neonate.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

Calcium phosphate dibasic anhydrous  
Povidone  
Sodium starch glycolate  
Magnesium stearate  
Titanium dioxide (E171)  
Methylcellulose  
Macrogol  
Polysorbate

6.2. **Incompatibilities**

Not applicable.

6.3. **Shelf life**

3 years.

6.4. **Special precautions for storage**

Store in the original package.

6.5. **Nature and contents of container**

Transparent PVC/PVdC aluminium blisters.

White opaque PVC/PVdC aluminium blisters.

Blisters in cardboard boxes containing: 14, 20, 28, 30, 50, 56, 60, 84 & 100 Film-coated tablets.

Not all pack sizes may be marketed

6.6. **Instruction for use and handling (use and disposal)**

No special requirements.
7. MARKETING AUTHORISATION HOLDER

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

Trading address:
Leeds, LS27 OJG, England

8. MARKETING AUTHORISATION NUMBER

PL 00289/0521

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2006

10. DATE OF REVISION OF THE TEXT

30/11/2006

1. NAME OF THE MEDICINAL PRODUCT

Paroxetine 20 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paroxetine hydrochloride hemihydrate equivalent to 20 mg paroxetine free base.
For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
White, to off-white, round biconvex film-coated tablet, embossed with "20" and scored on one side and with "PX" on the other side.
The tablet can be divided into equal halves.
4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of
- major depressive episode.
- obsessive compulsive disorder (OCD).
- panic disorder with or without agoraphobia.
- social anxiety disorder/social phobia.
- generalised anxiety disorder.

4.2. Posology and method of administration

It is recommended that paroxetine is administered once daily in the morning with food.

**Major depressive episode**
The recommended dose is 20 mg daily. In general, improvement in patients starts after one week but may only become evident from the second week of therapy. As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. In some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 50 mg a day in 10 mg steps according to the patient’s response.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

**Obsessive compulsive disorder**
The recommended dose is 40 mg daily. Patients should start on 20 mg/day and the dose may be increased gradually in 10 mg increments to the recommended dose. If after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months of even longer (see section 5.1).

**Panic disorder**
The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. 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. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.
Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer (see section 5.1).

**Social anxiety disorder/social phobia**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day.
Long-term use should be regularly evaluated (see section 5.1).

**Generalised anxiety disorder:**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).

**General information**

*Withdrawal symptoms seen on discontinuation of paroxetine*
Abrupt discontinuation should be avoided (see section 4.4 and section 4.8). The taper phase regimen used in clinical trials involved decreasing the daily dose by 10 mg at weekly intervals. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

**Special 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 the adult starting dose. Increasing the dose might be useful in some patients, but the maximum dose should not exceed 40 mg daily.

**Children and adolescents (7-17 years)**
Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behaviour and hostility. In addition, in these trials, efficacy has not been adequately demonstrated (see section 4.4 and section 4.8).

**Children aged below 7 years**
The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.
Renal/Hepatic Impairment:
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.

4.3. Contraindications

Known hypersensitivity to paroxetine or any of the excipients.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Treatment with paroxetine can be initiated:
- two weeks after discontinuation of an irreversible MAOI, or
- at least 24 hours after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.

Paroxetine should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see section 4.5). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

4.4. Special warnings and precautions for use

Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAOI inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached (see section 4.3 and section 4.5).

Children and adolescents (7-17 years)
Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. In clinical trials, increased suicidal-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with paroxetine compared to those treated with placebo. In addition, in these trials, efficacy has not been adequately demonstrated and long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking (see section 4.8).

Suicide/suicidal ideation
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. As
improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicidal behaviour or thoughts, or those 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.

There is a possibility of an increased risk of suicide-related behaviour in young adults aged 18-29. Young adults should therefore be monitored carefully throughout treatment.

There are insufficient data concerning the risk of suicide-related behaviour in treatment-naïve patients, but careful monitoring might be warranted.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms occur.

**Akathisia**

The use of paroxetine 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. In patients who develop these symptoms, increasing the dose may be detrimental.

**Serotonin syndrome/neuroleptic malignant syndrome**

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment with paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination
with serotonin precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome (see section 4.3 and section 4.5).

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

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

**Diabetes**
In patients with diabetes, treatment with an SSRI may alter glycaemia 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. Paroxetine 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 SSRIs, 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 SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

**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). 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 of 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).

**4.5. Interactions 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 and section 4.4).
Caution should be advised and a closer clinical monitoring is required when these drugs are combined with paroxetine.

**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).

**Procyclidine**

Daily administration of paroxetine significantly increases 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 the 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), risperidone, certain Type Ic 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 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 increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants (see section 4.4).

**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).

Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, 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**

Data on a limited number of exposed pregnancies provide no indication of an increased risk of congenital malformations in the newborn.

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).

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 the 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/fetal development, parturition or post-natal development (see section 5.3).

**Lactation**

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

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

**Metabolism and nutrition disorders**
*Common:* decreased appetite
*Rare:* hyponatraemia
Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to SIADH.

**Psychiatric disorders**
*Common:* somnolence, insomnia
*Uncommon:* confusion, hallucinations
*Rare:* manic reactions, agitation, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4)
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 disorder 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 of decreases in 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 has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

Skin and subcutaneous tissue disorders
Common: sweating
Uncommon: skin rashes, pruritus
Very rare: photosensitivity reactions

Renal and urinary disorders
Uncommon: urinary retention

Reproductive system and breast disorders
Very common: sexual dysfunction
Rare: hyperprolactinaemia/galactorrhoea
Very rare: priapism

Musculoskeletal disorders
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 self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

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 at least twice that of placebo: 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, 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 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).

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 in section 4.8, 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 with a fatal outcome, but generally when
paroxetine 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. 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) uptake and its antidepressant action and effectiveness in the treatment of OCD, social anxiety disorder/social phobia, generalised anxiety disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has a 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 or 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 depressants 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-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 (20-40 mg 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 (10-40 mg 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 has 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 pharmacokinetics. 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 the 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 fetuses 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 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 the 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 with 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 in 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's 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 fetus/neonate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium phosphate dibasic anhydrous
Povidone
Sodium starch glycolate
Magnesium stearate
Titanium dioxide (E171)
Methylcellulose
Macrogol
Polysorbate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.
6.4. **Special precautions for storage**

Store in the original package.

6.5. **Nature and contents of container**

Transparent PVC/PVdC aluminium blisters.

White opaque PVC/PVdC aluminium blisters.

Blisters in cardboard boxes containing: 14, 20, 28, 30, 50, 56, 60, 84 & 100 Film-coated tablets.

Not all pack sizes may be marketed

6.6. **Instruction for use and handling (use and disposal)**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

*Trading address:*
Leeds, LS27 OJG, England

8. **MARKETING AUTHORISATION NUMBER**

PL 00289/0523

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30/11/2006

10. **DATE OF REVISION OF THE TEXT**

30/11/2006
30 mg strengths:

1. **NAME OF THE MEDICINAL PRODUCT**

Paroxetine 30 mg Film-coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains paroxetine hydrochloride hemihydrate equivalent to 30 mg paroxetine free base.

For excipients see 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablets

White, to off-white, round biconvex film-coated tablet, embossed with "30" and scored on one side and with "PX" on the other side.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

Treatment of
- major depressive episode.
- obsessive compulsive disorder (OCD).
- panic disorder with or without agoraphobia.
- social anxiety disorder/social phobia.
- generalised anxiety disorder.

4.2. **Posology and method of administration**

It is recommended that paroxetine is administered once daily in the morning with food.

**Major depressive episode**

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

As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. In some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 50 mg a day in 10 mg steps according to the patient’s response.
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

**Obsessive compulsive disorder**
The recommended dose is 40 mg daily. Patients should start on 20 mg/day and the dose may be increased gradually in 10 mg increments to the recommended dose. If after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months of even longer (see section 5.1).

**Panic disorder**
The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. 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. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer (see section 5.1).

**Social anxiety disorder/social phobia**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).

**Generalised anxiety disorder:**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).

**General information**

*Withdrawal symptoms seen on discontinuation of paroxetine*
Abrupt discontinuation should be avoided (see section 4.4 and section 4.8). The taper phase regimen used in clinical trials involved decreasing the daily dose by 10 mg at weekly intervals. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the
previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

*Special 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 the adult starting dose. Increasing the dose might be useful in some patients, but the maximum dose should not exceed 40 mg daily.

**Children and adolescents (7-17 years)**
Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behaviour and hostility. In addition, in these trials, efficacy has not been adequately demonstrated (see section 4.4 and section 4.8).

**Children aged below 7 years**
The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.

**Renal/hepatic impairment**
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.

4.3. **Contraindications**

Known hypersensitivity to paroxetine or any of the excipients.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Treatment with paroxetine can be initiated:
- two weeks after discontinuation of an irreversible MAOI, or
- at least 24 hours after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.

Paroxetine should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see section 4.5). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.
4.4. Special warnings and precautions for use

Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached (see section 4.3 and section 4.5).

Children and adolescents (7-17 years)

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. In clinical trials, increased suicidal-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with paroxetine compared to those treated with placebo. In addition, in these trials, efficacy has not been adequately demonstrated and long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking (see section 4.8).

Suicide/suicidal ideation

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicidal behaviour or thoughts, or those 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.

There is a possibility of an increased risk of suicide-related behaviour in young adults aged 18-29. Young adults should therefore be monitored carefully throughout treatment.

There are insufficient data concerning the risk of suicide-related behaviour in treatment-naïve patients, but careful monitoring might be warranted.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal ideation/behaviour or thoughts of
harming themselves and to seek medical advice immediately if these symptoms occur.

**Akathisia**
The use of paroxetine 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. In patients who develop these symptoms, increasing the dose may be detrimental.

**Serotonin syndrome/neuroleptic malignant syndrome**
On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment with paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination with serotonin precursors (such as L-tryptophan, oxtiriptan) due to the risk of serotonergic syndrome (see section 4.3 and section 4.5).

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

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

**Diabetes**
In patients with diabetes, treatment with an SSRI may alter glycaemia 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. Paroxetine 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 SSRIs, 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 SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

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). 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 of 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).

4.5. Interactions 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 and section 4.4).
Caution should be advised and a closer clinical monitoring is required when these drugs are combined with paroxetine.

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).

Procyclidine
Daily administration of paroxetine significantly increases 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 the 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), risperidone, certain Type Ic 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 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 increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants (see section 4.4).

**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). Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, 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**
Data on a limited number of exposed pregnancies provide no indication of an increased risk of congenital malformations in the newborn.

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).

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 the later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertension, 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/fetal development, parturition or post-natal development (see section 5.3).

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

Endocrine disorders

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

Metabolism and nutrition disorders

Common: decreased appetite
Rare: hyponatraemia
Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to SIADH.

Psychiatric disorders
Common: somnolence, insomnia
Uncommon: confusion, hallucinations
Rare: manic reactions, agitation, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4)
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 disorder 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 of decreases in 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 has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

**Skin and subcutaneous tissue disorders**
- **Common:** sweating
- **Uncommon:** skin rashes, pruritus
- **Very rare:** photosensitivity reactions

**Renal and urinary disorders**
- **Uncommon:** urinary retention

**Reproductive system and breast disorders**
- **Very common:** sexual dysfunction
- **Rare:** hyperprolactinaemia/galactorrhoea
- **Very rare:** priapism

**Musculoskeletal disorders**
- **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 self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

**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 at least twice that of
placebo: 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, 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 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).

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 in section 4.8, 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 with a fatal outcome, but generally when paroxetine 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. 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) uptake and its antidepressant action and effectiveness in the treatment of OCD, social anxiety disorder/social phobia, generalised anxiety disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has a 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 or 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 depressants 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-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 (20-40 mg 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 (10-40 mg 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 has 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 pharmacokinetics. 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 the 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 fetuses 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 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 the 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 with 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 in 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's 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 fetus/neonate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium phosphate dibasic anhydrous
Povidone
Sodium starch glycolate
Magnesium stearate
Titanium dioxide (E171)
Methylcellulose
Macrogol
Polysorbate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in the original package.

6.5. Nature and contents of container

Transparent PVC/PVdC aluminium blisters.

White opaque PVC/PVdC aluminium blisters.

Blisters in cardboard boxes containing: 28, 30, 56, & 84 Film-coated tablets.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (use and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORISATION NUMBER

PL 00289/0522

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2006

10. DATE OF REVISION OF THE TEXT

30/11/2006

1. NAME OF THE MEDICINAL PRODUCT

Paroxetine 30 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paroxetine hydrochloride hemihydrate equivalent to 30 mg paroxetine free base.
For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
White, to off-white, round biconvex film-coated tablet, embossed with "30" and scored on one side and with "PX" on the other side.

4. CLINICAL PARTICULARS
4.1. **Therapeutic indications**

Treatment of  
- major depressive episode.  
- obsessive compulsive disorder (OCD).  
- panic disorder with or without agoraphobia.  
- social anxiety disorder/social phobia.  
- generalised anxiety disorder.

4.2. **Posology and method of administration**

It is recommended that paroxetine is administered once daily in the morning with food.

**Major depressive episode**
The recommended dose is 20 mg daily. In general, improvement in patients starts after one week but may only become evident from the second week of therapy.  
As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. In some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 50 mg a day in 10 mg steps according to the patient’s response.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

**Obsessive compulsive disorder**
The recommended dose is 40 mg daily. Patients should start on 20 mg/day and the dose may be increased gradually in 10 mg increments to the recommended dose. If after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months of even longer (see section 5.1).

**Panic disorder**
The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. 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. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.
Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer (see section 5.1).

**Social anxiety disorder/social phobia**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).

**Generalised anxiety disorder:**
The recommended dose is 20 mg daily. If, after some weeks on the recommended dose, insufficient response is seen, some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).

**General information**

*Withdrawal symptoms seen on discontinuation of paroxetine*
Abrupt discontinuation should be avoided (see section 4.4 and section 4.8). The taper phase regimen used in clinical trials involved decreasing the daily dose by 10 mg at weekly intervals. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

**Special 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 the adult starting dose. Increasing the dose might be useful in some patients, but the maximum dose should not exceed 40 mg daily.

**Children and adolescents (7-17 years)**
Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behaviour and hostility. In addition, in these trials, efficacy has not been adequately demonstrated (see section 4.4 and section 4.8).

**Children aged below 7 years**
The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.

**Renal/hepatic impairment**
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with
hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.

4.3. **Contraindications**

Known hypersensitivity to paroxetine or any of the excipients.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Treatment with paroxetine can be initiated:

- two weeks after discontinuation of an irreversible MAOI, or
- at least 24 hours after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.

Paroxetine should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see section 4.5). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

4.4. **Special warnings and precautions for use**

Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached (see section 4.3 and section 4.5).

**Children and adolescents (7-17 years)**

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. In clinical trials, increased suicidal-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with paroxetine compared to those treated with placebo. In addition, in these trials, efficacy has not been adequately demonstrated and long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking (see section 4.8).

**Suicide/suicidal ideation**

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.
Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicidal behaviour or thoughts, or those 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.

There is a possibility of an increased risk of suicide-related behaviour in young adults aged 18-29. Young adults should therefore be monitored carefully throughout treatment.

There are insufficient data concerning the risk of suicide-related behaviour in treatment-naïve patients, but careful monitoring might be warranted.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms occur.

**Akathisia**

The use of paroxetine 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. In patients who develop these symptoms, increasing the dose may be detrimental.

**Serotonin syndrome/neuroleptic malignant syndrome**

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment with paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination with serotonin precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome (see section 4.3 and section 4.5).
Mania
As with all antidepressants, paroxetine should be used with caution in patients with a history of mania. Paroxetine should be discontinued in any patient entering a manic phase.

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

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemia 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. Paroxetine 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 SSRIs, 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 SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine,
phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

**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). 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 of 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).

**4.5. Interactions 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 and section 4.4).

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

*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).

**Procyclidine**
Daily administration of paroxetine significantly increases 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 the 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), risperidone, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.

**Alcohol**
As with other psychotrophic drugs, patients should be advised to avoid alcohol 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 increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants (see section 4.4).

**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). Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or increase the risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, 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
Data on a limited number of exposed pregnancies provide no indication of an increased risk of congenital malformations in the newborn.

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).

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 the 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/fetal development, parturition or post-natal development (see section 5.3).

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

**Endocrine disorders**

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

**Metabolism and nutrition disorders**

*Common:* decreased appetite

*Rare:* hyponatraemia

Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to SIADH.

**Psychiatric disorders**

*Common:* somnolence, insomnia

*Uncommon:* confusion, hallucinations

*Rare:* manic reactions, agitation, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4)

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

**Skin and subcutaneous tissue disorders**
*Common:* sweating
*Uncommon:* skin rashes, pruritus
*Very rare:* photosensitivity reactions

**Renal and urinary disorders**
*Uncommon:* urinary retention

**Reproductive system and breast disorders**
*Very common:* sexual dysfunction
*Rare:* hyperprolactinaemia/galactorrhoea
*Very rare:* priapism

**Musculoskeletal disorders**
*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 self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

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 at least twice that of placebo: 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, 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 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).

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 in section 4.8, 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 with a fatal outcome, but generally when
paroxetine 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. 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) uptake and its antidepressant action and effectiveness in the treatment of OCD, social anxiety disorder/social phobia, generalised anxiety disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has a 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_ or beta-adrenoceptors, dopamine (D_2_), 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 depressants 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-recommended doses. However, there are some clinical data suggesting that uptitrating 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 (20-40 mg 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 (10-40 mg 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 has 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 pharmacokinetics. 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 the 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 fetuses 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 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 the 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 with 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 in 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's duration at doses that were 6 times higher than the recommended range of clinical doses.

Carcinogenesisis

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 fetus/neonate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium phosphate dibasic anhydrous
Povidone
Sodium starch glycolate
Magnesium stearate
Titanium dioxide (E171)
Methylcellulose
Macrogol
Polysorbate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.
6.4. **Special precautions for storage**

Store in the original package.

6.5. **Nature and contents of container**

Transparent PVC/PVdC aluminium blisters.

White opaque PVC/PVdC aluminium blisters.

Blisters in cardboard boxes containing: 28, 30, 56, & 84 Film-coated tablets.

Not all pack sizes may be marketed.

6.6. **Instruction for use and handling (use, and disposal)**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

*Trading address:*
Leeds, LS27 OJG, England

8. **MARKETING AUTHORISATION NUMBER**

PL 00289/0524

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30/11/2006

10. **DATE OF REVISION OF THE TEXT**

30/11/2006
PRODUCT INFORMATION LEAFLET

PAROXETINE 20 and 30 mg FILM-COATED TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

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 further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. What Paroxetine is and what it is used for
2. Before you take Paroxetine
3. Possible side effects
4. How to store Paroxetine
5. Further information

1. WHAT PAROXETINE IS AND WHAT IT IS USED FOR

• Paroxetine belongs to a group of drugs called selective serotonin re-uptake inhibitors (SSRIs). Serotonin is a chemical that, in the brain, passes messages between nerve cells and may help to control mood. Paroxetine brings the level of serotonin back to normal.
• Paroxetine is used to treat the symptoms, and prevent a recurrence of, depression and any accompanied anxiety, obsessive compulsive disorder (OCD), panic attacks (with or without agoraphobia - fear of going into public places) and generalised anxiety disorder. It is also used to treat social anxiety disorder (social phobia).

2. BEFORE YOU TAKE PAROXETINE

Do NOT take Paroxetine:

• If you are allergic (hypersensitive) to paroxetine or any of the other ingredients of this medicine
• If you are taking the medicine used in the treatment of schizophrenia
• If you are taking, or have taken in the past 2 weeks, a monoamine oxidase inhibitor (MAOI) also used to treat depression, e.g. selegiline or moclobemide.

Take special care with Paroxetine:

• If you have a history of manic (periods of unusually elevated high mood and activity)
• If you have kidney, liver or heart problems
• If you have a history of bleeding disorders or a tendency to bleed
• If you have epilepsy
• If you have diabetes
• If you have glaucoma (increased pressure in the eye)
• If you have been told that you have low levels of sodium
• If you are due to receive electroconvulsive therapy (ECT).

Thoughts of harming yourself:

People who are depressed and/or suffer from anxiety disorders can sometimes have thoughts of harming or killing themselves. These may be increased when you first start taking antidepressants, since these medicines all take time to work.

Certain groups of patients may be more likely to think like this:

• If you are a young adult, for example aged 18 to 25
• If you have previously had thoughts about harming or killing yourself.
• If you get these thoughts at any time, contact your doctor or go to a hospital straight away.

Taking other medicines

Check with your doctor if you are taking any of the following:

• Antidepressants (other than SSRIs) or other anti-depressants such as clomipramine, mirtazapine and desipramine
• The herbal remedy St John’s Wort (Hypericum perforatum), used to treat depression
• Medicines such as fluoxetine, sertraline, paroxetine, venlafaxine and clomipramine (known as anti-psychotics), used to treat some psychiatric conditions
• Phenoxybutil, phenytin or carbamazepine, used to treat fits or epilepsy
• Procyphenile (used to relieve tension, especially in Parkinson’s Disease)
• Anxiety, epilepsy, or other medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib, etodolac, meloxicam and refetachic that are used to treat pain and inflammation
• Tramadol (a painkiller)
• Medicines called tricyclics, such as sumatriptan (used to treat migraine)
• Medicines used to thin the blood (anticoagulants), such as warfarin
• Medicines used to treat an irregular heartbeat, such as propafenone and flecainide
• Metoprolol, beta-blocker used to treat high blood pressure and heart problems
• Rifampicin (used to treat tuberculosis (TB) and leprosy)
• Unasulid (an antibiotic)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Paroxetine with food and drink

You are advised not to drink alcohol whilst taking these tablets.

Pregnancy and breast-feeding

If you are already taking Paroxetine and have just found out that you are pregnant, you should talk to your doctor immediately. Also, if you are planning to get pregnant, talk to your doctor. This is because some studies have suggested an increase in the risk of heart defects in babies whose mothers received Paroxetine in the first few months of pregnancy. These studies found that less than 2 in 100 babies (2%) whose mothers received Paroxetine in early pregnancy had a heart defect, compared with the normal rate of 1 in 100 babies (1%) seen in the general population. You and your doctor may decide that it is better for you to gradually stop taking Paroxetine while you are pregnant. However, depending on your circumstances, your doctor may suggest that it is better for you to keep taking Paroxetine.

If you are taking Paroxetine in the last 3 months of pregnancy, let your midwife know as your baby might have some symptoms when it is born. These symptoms usually begin during the last 24 hours after the baby is born. They include not being able to sleep or feed properly, trouble with breathing, a blue-ish skin or being too hot or cold, being sick, crying a lot, stiff or floppy muscles, lethargy, tremors, jitters or fits. If your baby has any of these symptoms when it is born and you are concerned, contact your doctor or midwife who will be able to advise you.

Paroxetine may get into breast milk in very small amounts. If you are taking Paroxetine, go back and talk to your doctor before you start breast-feeding.

Driving and using machines

Your tablets may make you feel sleepy or dizzy. Do not drive or operate machinery if you are affected.

3. HOW TO TAKE PAROXETINE

Always take Paroxetine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Take the tablets each morning with food. The tablets should be swallowed whole with a drink of water and not chewed.

The usual dose is:

• Adults: Depression and social anxiety disorder (social phobia): One 20 mg tablet daily. Where necessary your doctor may increase this to a maximum of 60 mg daily. Obsessive compulsive disorder (OCD): 40 mg daily. Your doctor will start you on a lower dose and increase this gradually. The maximum dose is 60 mg a day. Panic disorder: 40 mg daily. Your doctor will start you on a dose of 10 mg a day and increase this gradually. The maximum dose is 80 mg a day. Generalised anxiety disorder: One 20 mg tablet daily. Your doctor may increase your dose gradually up to a maximum dose of 50 mg a day.

• Elderly: Your doctor will start you on the normal adult dose which he may increase up to a maximum of 40 mg a day.

• Patients with severe liver or kidney problems: The recommended dose is 30 mg per day.

• Children and adolescents under 18: Not recommended.

Paroxetine will not relieve your symptoms straight away. You should start to feel better after a week or two, although it may take longer.

If you take more Paroxetine than you should

If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital causality department or your doctor immediately. An overdose is likely to cause
nausea, vomiting, shaking, dilated pupils, dry mouth, irritability, sweating and insomnia. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Paroxetine
If you forget a dose, and you remember before you go to bed, take it straight away. Carry on as usual the next day.

If you only remember during the night, or the next day, leave out the missed dose. You may possibly get withdrawal effects, but these should go away after you take your next dose at the usual time.

If you stop taking Paroxetine
Do not stop taking your tablets suddenly. When your doctor decides to stop your tablets, your dose will be reduced gradually over a period of a number of weeks or months to help reduce the chance of withdrawal effects.

If you get withdrawal effects when you are coming off your tablets your doctor may decide that you should come off them more slowly. If you get severe withdrawal effects when you stop taking Paroxetine, please see your doctor, who may ask you to start taking your tablets again and come off them more slowly.

If you do get withdrawal effects, you will still be able to stop Paroxetine.

Possible withdrawal effects when stopping treatment:

Common (affecting fewer than one person in 10 but more than one person in 100):
- Feeling dizzy, unsteady or off-balance
- Faints and needles, electric shock sensations
- Sleep disturbances (e.g. dreams, nightmares, inability to sleep)
- Feeling nervous
- Headaches

Uncommon (affecting fewer than one person in 100 but more than one person in 500):
- Feeling sick, diarrhoea
- Sweating
- Feeling restless or agitated
- Tremor (shakiness)
- Feeling confused
- Feeling emotional or irritable
- Visual disturbances
- Rumbling or pounding heartbeat (palpitations)

Generally these side effects are mild and do not last for a very long time but in some people they may be more serious or last longer.

If you have further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Paroxetine can cause side effects, although not everybody gets them.

If you experience the following, stop taking Paroxetine and tell your doctor immediately or go to the casualty department at your nearest hospital:
- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat which may cause difficulty swallowing or breathing).

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

The following side effects have been reported at the approximate frequencies shown:

Very common (affecting more than one person in 10):
- Feeling sick
- Change in sex drive or sexual function, for example, lack of orgasm and, in men, abnormal erection and ejaculation.

Common (affecting fewer than one person in 10 but more than one person in 100):
- Decreased appetite
- Not sleeping well (insomnia) or feeling sleepy
- Feeling dizzy or shaky
- Lack of strength or energy, weakness
- Vomiting, dry mouth
- Sweating
- Diarrhoea or constipation
- Weight gain.

Uncommon (affecting fewer than one person in 100 but more than one person in 1000):
- Unusual bruising or bleeding
- Feeling confused or having hallucinations
- Impairment of voluntary movement, tremors, tics, abnormal movements in the mouth and tongue, changes in muscle tone, slowness of movement
- Brief increase or decrease in blood pressure, a faster than normal heartbeat
- Skin rashes, itching
- Inability or difficulty in urinating (passing water).

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):
- Low blood levels of sodium, which can cause tiredness and confusion, muscle twitching, fits or coma
- Obsessive behaviour or thoughts (mania), agitation, anxiety, a feeling of things being unreal, panic attacks, feeling restless and like you can’t sit or stand still
- Fits (convulsions)
- A slow heartbeat
- Effects on the liver that show up in blood tests of your liver function
- Production of breast milk in both men and women
- Pain in the joints or muscles.

Very rare (affecting fewer than one person in 10,000):
- Increased bleeding, reduction in blood platelets, which increases risk of bleeding or bruising
- Allergic reaction including itchiness, rash and swelling of the face, lips, mouth or throat

- A condition known as syndrome of inappropriate anti-diuretic hormone secretion (SIADH), the symptoms of which include weight gain, feeling or being sick, muscle cramps, confusion and fits

- A condition known as serotonin syndrome, the symptoms of which include agitation, confusion, sweating, hallucinations, sudden jerks of the muscles, shivering, a fast heartbeat and shakiness
- Acute glaucoma - the symptoms are painful eyes and blurred vision
- Skin reactions caused by exposure to sunlight
- Painful reaction of the penis that won’t go away
- Fluid or water retention which may cause swelling of the arms or legs
- Liver problems that make the skin or whites of the eyes go yellow

If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. CHILDREN AND ADOLESCENTS UNDER 18

Paroxetine should not be used for children and adolescents under 18 years because it has not been proven to be an effective medicine for this age group. Also, patients under 18 have an increased risk of side effects such as suicidal thoughts and harming themselves when they take Paroxetine. If your doctor has prescribed Paroxetine for you (or your child) and you want to discuss this, please go back to your doctor.

In studies of Paroxetine in under 18s, common side effects that affected less than 1 in 10 children/adolescents were: an increase in suicidal thoughts and suicide attempts, deliberately harming themselves, being hostile, aggressive or unfriendly, lack of appetite, shaking, abnormal sweating, hyperactivity (having too much energy), agitation, changing emotions (including crying and changes in mood). These studies also showed that the same symptoms affected children and adolescents taking placebo instead of Paroxetine, although these were seen less often. Some patients in these studies of under 18s had withdrawal effects when they stopped taking Paroxetine. These effects were mostly similar to those seen in adults after stopping Paroxetine. In addition, patients under 18 also commonly less than 1 in 10 experienced stomach ache, feeling nervous and changing emotions (including crying, changes in mood, trying to hurt themselves, thoughts of suicide and attempting suicide).

HOW TO STORE PAROXETINE

Keep Paroxetine out of the reach of sight and children. Store in the original packaging. Do not use Paroxetine after the expiry date shown on the outer packaging.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Paroxetine contains:
- The active ingredient is paroxetine (as hydrochloride hydrate), 20 or 30 mg
- The other ingredients are calcium phosphate, povidone, sodium starch glycolate, magnesium stearate, titanium dioxide (E171), methylcellulose, magnesium and polyparlate.

What Paroxetine looks like and contains of the pack:
- Paroxetine 20 mg film-coated Tablets are white, to-off-white, round biconvex 4-mm-coated tablets, embossed with “20” and scored on one side and with “PX” on the other side.
- Paroxetine 30 mg film-coated Tablets are white, to-off-white, round biconvex 6-mm-coated tablets, embossed with “30” and scored on one side and with “PX” on the other side.

The 30 mg tablets are available in a pack size of 30 tablets.

The 20 mg tablets are available in a pack size of 30 tablets.

Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Eastbourne, BN23 6AG.
Distributed by TEVA UK, Leeds, LS17 6JG.

This leaflet was last revised: June 2006
PACKAGING

20 mg strength

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30 mg strength

Foil:

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