

**Public Assessment Report**  
**Mutual Recognition Procedure**

**Paroxetine 20mg and 30mg Film-coated Tablets**

**UK/H/1157/01-02/MR**

**UK licence no: PL 00289/0523-4**

**Teva UK Limited**

## LAY SUMMARY

Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden approved Teva UK Limited marketing Authorisation (Licence) for the medicinal product Paroxetine 20mg Film-coated tablets.

Austria, Belgium, Bulgaria, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, Latvia, The Netherlands, Poland, Slovenia and Slovakia approved Teva UK Limited marketing Authorisation (Licence) for the medicinal product Paroxetine 30mg Film-coated tablets. These are Prescription Only Medicines (POM).

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).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Paroxetine 20mg and 30mg Film-coated tablets outweigh the risks, hence Marketing Authorisations have been granted.

## TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 3
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflets	Page 27
Module 4: Labelling	Page 35
Module 5: Scientific Discussion	Page 39
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6     Steps taken after initial procedure	Page 46

## Module 1

<b>Product Name</b>	Paroxetine 20mg Film-coated Tablets Paroxetine 30mg Film-coated Tablets
<b>Type of Application</b>	Generic, Article 10.1
<b>Active Substance</b>	Paroxetine hydrochloride hemihydrate
<b>Form</b>	Film-Coated Tablets
<b>Strength</b>	20mg and 30mg
<b>MA Holder</b>	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, UK
<b>RMS</b>	UK
<b>CMS</b>	For 20mg Tablets: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden  For 30mg Tablets: Austria, Belgium, Bulgaria, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, Latvia, The Netherlands, Poland, Slovenia, Slovakia
<b>Procedure Number</b>	UK/H/1157/01-02/MR
<b>Timetable</b>	Day 90- 26/02/2008

## Module 2

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Paroxetine 20 mg Film-coated Tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg paroxetine (as paroxetine hydrochloride hemihydrate).

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Film-coated 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. 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 and without agoraphobia.
- social anxiety disorder/social phobia.
- generalised anxiety disorder.
- post-traumatic stress disorder.

##### 4.2 Posology and method of administration

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

The tablet should be swallowed rather than chewed.

##### *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 or 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).

***Post-traumatic stress 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**

Hypersensitivity to paroxetine or any of the excipients.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with paroxetine provided that there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure (see section 4.5). Treatment with paroxetine can be initiated:

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

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 substances 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.

Paroxetine should not be used in combination with pimozide (see section 4.5).

**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).

#### ***Use in children and adolescents under 18 years of age***

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

#### ***Suicide/suicidal thoughts or clinical worsening***

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

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old (see also section 5.1).

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

#### ***Akathisia / psychomotor restlessness***

The use of paroxetine has been associated with the development of akathisia, which is 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 agents. 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 glycaemic control. Insulin and / or oral hypoglycaemic dosage may need to be adjusted.

***Epilepsy***

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

***Seizures***

Overall, the incidence of seizures is less than 0.1% in patients treated with paroxetine. 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 can cause mydriasis and should be used with caution in patients with narrow-angle glaucoma or history of glaucoma.

***Cardiac conditions***

The usual precautions should be observed in patients with 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 medicinal products 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, agents known to affect platelet function or other substances 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 agent 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, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported. 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 Interaction with other medicinal products and other forms of interaction*****Serotonergic agents***

As with other SSRIs, co-administration with serotonergic agents may lead to an incidence of 5-HT-associated effects (serotonin syndrome: see section 4.4).

Caution should be advised and a closer clinical monitoring is required when serotonergic agents (such as L-tryptophan, triptans, tramadol, linezolid, SSRIs, lithium and St. John's Wort – *Hypericum perforatum* – preparations) are combined with paroxetine.

Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome (see section 4.3).

***Pimozide***

Increased pimozide levels of on average 2.5 times have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with 60 mg paroxetine. This may be explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and paroxetine is contraindicated (see section 4.3).

***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 paroxetine doses at the lower end of the range. No initial dosage adjustment is considered necessary when it is to be co-administered with known drug-metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin) or with fosamprenavir / ritonavir. Any paroxetine dosage adjustment (either after initiation or following discontinuation of an enzyme inducer) should be guided by clinical effect (tolerability and efficacy).

***Fosamprenavir / ritonavir***

Co-administration of fosamprenavir / ritonavir 700 / 100 mg twice daily with paroxetine 20 mg daily in healthy volunteers for 10 days significantly decreased plasma levels of paroxetine by approximately 55%. The plasma levels of fosamprenavir / ritonavir during co-administration of paroxetine were similar to reference values of other studies, indicating that paroxetine had no significant effect on the metabolism of fosamprenavir / ritonavir. There are no data available about the effects of long-term co-administration of paroxetine and fosamprenavir / ritonavir exceeding 10 days.

***Procyclidine***

Daily administration of paroxetine significantly increases the plasma levels of procyclidine. If anticholinergic 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 substances 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, atomoxetine, 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 agents, 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, agents 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*

Some epidemiological studies suggest a small increased risk of cardiovascular malformation (e.g. ventricular (majority) and atrial septum defects) associated with the use of paroxetine during the first trimester. The mechanism is unknown. The data suggests that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population. Available data do not suggest an increase of the overall rate of congenital malformation.

Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant. Abrupt discontinuation should be avoided during pregnancy (see "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. Since no effects are anticipated, breast-feeding can be considered.

#### 4.7 Effects on ability to drive and use machines

Paroxetine has no or negligible influence on the 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 agents, 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 ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from available data).

##### *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:* increases in cholesterol levels, decreased appetite

*Rare:* hyponatraemia

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

##### *Psychiatric disorders*

*Common:* somnolence, insomnia, agitation

*Uncommon:* confusion, hallucinations

*Rare:* manic reactions, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4). These symptoms may also be due to the underlying disease.

*Not known:* suicidal ideation, suicidal behaviour

Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation (see section 4.4).

#### ***Nervous system disorders***

*Common:* dizziness, tremor, headache

*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 neuroleptics.

#### ***Eye disorders***

*Common:* blurred vision

*Uncommon:* mydriasis (see section 4.4)

*Very rare:* acute glaucoma

#### ***Ear and labyrinth disorders***

*Not known:* tinnitus

#### ***Cardiac disorders***

*Uncommon:* sinus tachycardia

*Rare:* bradycardia

#### ***Vascular disorders***

*Uncommon:* transient increases or decreases in blood pressure, postural hypotension

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

#### ***Respiratory, thoracic and mediastinal disorders***

*Common:* yawning

#### ***Gastrointestinal disorders***

*Very common:* nausea

*Common:* constipation, diarrhoea, dry mouth

*Very rare:* gastrointestinal bleeding

#### ***Hepato-biliary disorders***

*Rare:* elevation of hepatic enzymes

*Very rare:* hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure)

Elevation of hepatic enzymes 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, urinary incontinence

#### ***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, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported.

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, fever and involuntary muscle contractions 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 substances, 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,

general anxiety disorder, post-traumatic stress disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

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

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties. In accordance with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for  $\alpha_1$ ,  $\alpha_2$  or beta-adrenoceptors, dopamine ( $D_2$ ), 5-HT<sub>1</sub>-like, 5-HT<sub>2</sub> and histamine ( $H_1$ ) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate lack of CNS-depressant and hypotensive properties.

#### ***Pharmacodynamic effects***

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

As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature. Animal studies indicate that paroxetine is well tolerated by the cardiovascular system. Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects.

Studies indicate that, in contrast to antidepressants which inhibit the uptake of 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.

#### ***Adult suicidality analysis***

A paroxetine-specific analysis of placebo-controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (aged 18-24 years) treated with paroxetine compared with placebo (2.19% vs. 0.92%). In the older age groups, no such increase was observed. In adults with major depressive disorder (all ages), there was an increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (0.32% vs 0.05%); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults (see also section 4.4).

#### ***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, generalised anxiety disorder and post-traumatic stress 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 kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses. Steady-state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled-release formulations and 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 paroxetine's therapeutic effects.

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

#### ***Elimination***

Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in 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 for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one year'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**

#### ***Core***

Calcium phosphate dibasic anhydrous

Povidone K30

Sodium starch glycolate (type A)

Magnesium stearate

#### ***Film-coating***

Titanium dioxide (E171)

Methylcellulose

Macrogol 400  
Polysorbate 80

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store in the original package in order to protect from light.

**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 or 100 film-coated tablets.

Not all pack sizes may be marketed

**6.6 Special precautions for 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(S)**

PL 00289/0523

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

30/11/2006

**10 DATE OF REVISION OF THE TEXT**

14/10/2008

**1 NAME OF THE MEDICINAL PRODUCT**

Paroxetine 30 mg Film-coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 30 mg paroxetine (as paroxetine hydrochloride hemihydrate).  
For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated 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 score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

Treatment of

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

**4.2 Posology and method of administration**

It is recommended that paroxetine is administered once daily in the morning with food.  
The tablet should be swallowed rather than chewed.

***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 or 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 10mg steps up to a maximum of 50 mg/day. Long-term use should be regularly evaluated (see section 5.1).

**Post-traumatic stress 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**

Hypersensitivity to paroxetine or any of the excipients.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with paroxetine provided that there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure (see section 4.5). Treatment with paroxetine can be initiated:

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

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 substances 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.

Paroxetine should not be used in combination with pimozide (see section 4.5).

**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).

**Use in children and adolescents under 18 years of age**

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among

children and adolescents treated with antidepressants compared to those treated with placebo. If based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

#### ***Suicide/suicidal thoughts or clinical worsening***

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

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old (see also section 5.1).

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

#### ***Akathisia / psychomotor restlessness***

The use of paroxetine has been associated with the development of akathisia, which is 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 agents. 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 glycaemic control. Insulin and / or oral hypoglycaemic dosage may need to be adjusted.

#### ***Epilepsy***

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

#### ***Seizures***

Overall, the incidence of seizures is less than 0.1% in patients treated with paroxetine. 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 can cause mydriasis and should be used with caution in patients with narrow-angle glaucoma or history of glaucoma.

**Cardiac conditions**

The usual precautions should be observed in patients with 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 medicinal products 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, agents known to affect platelet function or other substances 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 agent 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, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported. 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 Interaction with other medicinal products and other forms of interaction****Serotonergic agents**

As with other SSRIs, co-administration with serotonergic agents may lead to an incidence of 5-HT-associated effects (serotonin syndrome: see section 4.4).

Caution should be advised and a closer clinical monitoring is required when serotonergic agents (such as L-tryptophan, triptans, tramadol, linezolid, SSRIs, lithium and St. John's Wort – *Hypericum perforatum* – preparations) are combined with paroxetine.

Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome (see section 4.3).

**Pimozide**

Increased pimozide levels of on average 2.5 times have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with 60 mg paroxetine. This may be explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and paroxetine is contraindicated (see section 4.3).

***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 paroxetine doses at the lower end of the range. No initial dosage adjustment is considered necessary when it is to be co-administered with known drug-metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin) or with fosamprenavir / ritonavir. Any paroxetine dosage adjustment (either after initiation or following discontinuation of an enzyme inducer) should be guided by clinical effect (tolerability and efficacy).

***Fosamprenavir / ritonavir***

Co-administration of fosamprenavir / ritonavir 700 / 100 mg twice daily with paroxetine 20 mg daily in healthy volunteers for 10 days significantly decreased plasma levels of paroxetine by approximately 55%. The plasma levels of fosamprenavir / ritonavir during co-administration of paroxetine were similar to reference values of other studies, indicating that paroxetine had no significant effect on the metabolism of fosamprenavir / ritonavir. There are no data available about the effects of long-term co-administration of paroxetine and fosamprenavir / ritonavir exceeding 10 days.

***Procyclidine***

Daily administration of paroxetine significantly increases the plasma levels of procyclidine. If anticholinergic 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 substances 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, atomoxetine, 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 agents, 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, agents 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***

Some epidemiological studies suggest a small increased risk of cardiovascular malformation (e.g. ventricular (majority) and atrial septum defects) associated with the use of paroxetine during the first trimester. The mechanism is unknown. The data suggests that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population. Available data do not suggest an increase of the overall rate of congenital malformation.

Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician

will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant. Abrupt discontinuation should be avoided during pregnancy (see "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. Since no effects are anticipated, breast-feeding can be considered.

#### **4.7 Effects on ability to drive and use machines**

Paroxetine has no or negligible influence on the 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 agents, 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 ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from available data).

##### ***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:* increases in cholesterol levels, decreased appetite

*Rare:* hyponatraemia

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

##### ***Psychiatric disorders***

*Common:* somnolence, insomnia, agitation

*Uncommon:* confusion, hallucinations

*Rare:* manic reactions, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4). These symptoms may also be due to the underlying disease.

*Not known:* suicidal ideation, suicidal behaviour

Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation (see section 4.4).

##### ***Nervous system disorders***

*Common:* dizziness, tremor, headache

*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 neuroleptics.

**Eye disorders**

*Common:* blurred vision  
*Uncommon:* mydriasis (see section 4.4)  
*Very rare:* acute glaucoma

**Ear and labyrinth disorders**

*Not known:* tinnitus

**Cardiac disorders**

*Uncommon:* sinus tachycardia  
*Rare:* bradycardia

**Vascular disorders**

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

**Respiratory, thoracic and mediastinal disorders**

*Common:* yawning

**Gastrointestinal disorders**

*Very common:* nausea  
*Common:* constipation, diarrhoea, dry mouth  
*Very rare:* gastrointestinal bleeding

**Hepato-biliary disorders**

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

Elevation of hepatic enzymes 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, urinary incontinence

**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, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported.

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, fever and involuntary muscle contractions 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 substances, 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, general anxiety disorder, post-traumatic stress disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

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

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties. In accordance with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for  $\alpha_1$ ,  $\alpha_2$  or beta-adrenoceptors, dopamine ( $D_2$ ), 5-HT<sub>1</sub>-like, 5-HT<sub>2</sub> and histamine ( $H_1$ ) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate lack of CNS-depressant and hypotensive properties.

#### ***Pharmacodynamic effects***

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

As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature. Animal studies indicate that paroxetine is well tolerated by the cardiovascular system. Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects.

Studies indicate that, in contrast to antidepressants which inhibit the uptake of 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.

#### ***Adult suicidality analysis***

A paroxetine-specific analysis of placebo-controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (aged 18-24 years) treated with paroxetine compared with placebo (2.19% vs. 0.92%). In the older age groups, no such increase was observed. In adults with major depressive disorder (all ages), there was an increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (0.32% vs 0.05%); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults (see also section 4.4).

#### ***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, generalised anxiety disorder and post-traumatic stress 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 kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses. Steady-state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled-release formulations and 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 paroxetine's therapeutic effects.

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

#### ***Elimination***

Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in 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 for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one year'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**

#### ***Core***

Calcium phosphate dibasic anhydrous

Povidone K30

Sodium starch glycolate (type A)

Magnesium stearate

#### ***Film-coating***

Titanium dioxide (E171)

Methylcellulose

Macrogol 400

Polysorbate 80

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store in the original package in order to protect from light.

**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, 50, 56, 60 or 84 film-coated tablets.

Not all pack sizes may be marketed

**6.6 Special precautions for 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(S)**

PL 00289/0524

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

30/11/2006

**10 DATE OF REVISION OF THE TEXT**

14/10/2008

## Module 3

# Patient 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. How to take Paroxetine
4. Possible side effects
5. How to store Paroxetine
6. Further information

#### 1 WHAT PAROXETINE IS AND WHAT IT IS USED FOR

Paroxetine is a treatment for adults with depression and/or anxiety disorders. The anxiety disorders that Paroxetine is used to treat are:

- obsessive compulsive disorder (repetitive, obsessive thoughts with uncontrollable behaviour)
- panic disorder (panic attacks, including those caused by agoraphobia, which is a fear of open spaces)
- social anxiety disorder (fear or avoidance of social situations)
- post-traumatic stress disorder (anxiety caused by a traumatic event)
- generalised anxiety disorder (generally feeling very anxious or nervous).

Paroxetine is one of a group of medicines called SSRIs (selective serotonin re-uptake inhibitors). Everyone has a substance called serotonin in their brain. It is not fully understood how Paroxetine and other SSRIs work but they may help by increasing the level of serotonin in the brain. Treating depression or anxiety disorders properly is important to help you get better.

#### 2 BEFORE YOU TAKE PAROXETINE

Do **NOT** take Paroxetine

- **If you are taking medicines called monoamine oxidase inhibitors (MAOIs, including moclobemide), or have taken them at any time within the last two weeks.** Your doctor will advise you how you should begin taking Paroxetine once you have stopped taking the MAOI.
- **If you are taking an anti-psychotic called thioridazine or an anti-psychotic called pimozide.**
- **If you are allergic (hypersensitive) to paroxetine or any of the other ingredients of this medicine (listed below).**

**If any of these apply to you, tell your doctor without taking Paroxetine.**

**Take special care with Paroxetine****Check with your doctor...**

- Are you taking any other medicines (see 'Taking other medicines', inside this leaflet)?
- Do you have kidney, liver or heart trouble?
- Do you have epilepsy or have a history of fits or seizures?
- Have you ever had episodes of mania (overactive behaviour or thoughts)?
- Are you having electro-convulsive therapy (ECT)?
- Do you have a history of bleeding disorders, or are you taking other medicines that may increase the risk of bleeding (these include medicines used to thin the blood, such as warfarin, anti-psychotics such as perphenazine or clozapine, tricyclic antidepressants, medicines used for pain and inflammation called non-steroidal anti-inflammatory drugs or NSAIDs, such as acetylsalicylic acid, ibuprofen, celecoxib, etodolac, diclofenac, meloxicam)?
- Do you have diabetes?
- Are you on a low sodium diet?
- Do you have glaucoma (pressure in the eye)?
- Are you pregnant or planning to get pregnant (see 'Pregnancy and breast-feeding', inside this leaflet)?
- Are you under 18 years old (see 'Use in children and adolescents under 18 years of age', inside this leaflet)?

If you answer YES to any of these questions, and you have not already discussed them with your doctor, go back to your doctor and ask what to do about taking Paroxetine.

**Use in children and adolescents under 18 years of age**

Paroxetine should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Paroxetine for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Paroxetine for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Paroxetine. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Paroxetine in this age group have not yet been demonstrated.

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 sugar pills (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 (see section 3, 'How to take Paroxetine', inside this leaflet). In addition, patients under 18 also commonly (affecting 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).

**Thoughts of harming yourself and worsening of your condition**

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 have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.

If you get thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

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

#### Important side effects seen with Paroxetine

Some patients who take Paroxetine develop something called akathisia, where they **feel restless and feel like they can't sit or stand still**. Other patients develop something called **serotonin syndrome**, where they have some or all of the following symptoms: feeling confused, feeling restless, sweating, shaking, shivering, hallucinations (strange visions or sounds), sudden jerks of the muscles or a fast heartbeat. If you notice any of these symptoms, **contact your doctor**. For more information on these or other side effects of Paroxetine, see section 4, 'Possible side effects', inside this leaflet.

#### Taking other medicines

Some medicines can affect the way that Paroxetine works, or make it more likely that you'll have side effects.

Paroxetine can also affect the way some other medicines work. These include:

- Medicines called **monoamine oxidase inhibitors** (MAOIs, including moclobemide) – see 'Do NOT take Paroxetine', inside this leaflet
- Thioridazine or pimozide, which are **anti-psychotics** – see 'Do NOT take Paroxetine', inside this leaflet
- Acetylsalicylic acid, ibuprofen or other medicines called NSAIDs (non-steroidal anti-inflammatory drugs) like celecoxib, etodolac, diclofenac and meloxicam that are used for **pain and inflammation**
- Tramadol, a **painkiller**
- Medicines called triptans, such as sumatriptan, used to treat **migraine**
- Other **antidepressants** including other SSRIs and tricyclic antidepressants like clomipramine, nortriptyline and desipramine
- A **dietary supplement** called tryptophan
- Medicines such as lithium, risperidone, perphenazine, clozapine (called anti-psychotics) used to treat some **psychiatric conditions**
- A combination of fosamprenavir and ritonavir, which is used to treat **Human Immunodeficiency Virus (HIV) infection**
- St John's Wort, a herbal remedy for **depression**
- Phenobarbital, phenytoin, sodium valproate or carbamazepine used to treat **fits or epilepsy**
- Atomoxetine which is used to treat **attention deficit hyperactivity disorder (ADHD)**
- Procyclidine, used to relieve tremor, especially in **Parkinson's disease**
- Warfarin or other medicines (called anticoagulants) used to **thin the blood**
- Propafenone, flecainide and medicines used to treat an **irregular heartbeat**
- Metoprolol, a beta-blocker used to treat **high blood pressure and heart problems**
- Rifampicin, used to treat **tuberculosis (TB) and leprosy**
- Linezolid, an **antibiotic**.

If you are taking or have recently taken any of the medicines in this list, and you have not already discussed these with your doctor, **go back to your doctor and ask what to do**. The dose may need to be changed or you may need to be given another medicine.

**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

Do not drink alcohol while you are taking Paroxetine. Alcohol may make your symptoms or side effects worse. Taking Paroxetine in the morning with food will reduce the likelihood of you feeling sick (nausea).

**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. When all types of birth defects are taken into account, there is no difference in the number of babies born with birth defects after their mothers took paroxetine while they were pregnant compared to the overall number of birth defects that occur in the general population. You and your doctor may decide that it is better for you to change to another treatment or 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 first 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. You and your doctor may decide that you can breast-feed while you're taking Paroxetine.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Possible side effects of Paroxetine include dizziness, confusion, feeling sleepy or blurred vision. If you do get these side effects, do not drive or use machinery.

### **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.

Sometimes you may need to take more than one tablet or half a tablet. This table will show you how many tablets to take.

Dose	Number of tablets to take
10 mg	Half a 20 mg tablet
20 mg	One 20 mg tablet
30 mg	One 30 mg tablet or one and a half 20 mg tablets
40 mg	Two 20 mg tablets
50 mg	One 20 mg tablet + one 30 mg tablet or two and a half 20 mg tablets
60 mg	Three 20 mg tablets or two 30 mg tablets

The usual doses for different conditions are set out in the table below:

	Starting dose	Recommended daily dose	Maximum daily dose
Depression	20 mg	20 mg	50 mg
Obsessive compulsive disorder	20 mg	40 mg	60 mg
Panic disorder	10 mg	40 mg	60 mg
Social anxiety disorder	20 mg	20 mg	50 mg
Post-traumatic stress disorder	20 mg	20 mg	50 mg
Generalised anxiety disorder	20 mg	20 mg	50 mg

**Your doctor will advise you what dose to take when you first start taking Paroxetine.** Most people start to feel better after a couple of weeks. If you don't start to feel better after this time, talk to your doctor, who will advise you. He or she may decide to increase the dose gradually, 10 mg a time, up to a maximum daily dose.

Oral use.

Take your tablets in the morning with food.  
Swallow them with a drink of water.  
Do not chew.

Your doctor will talk to you about how long you will need to keep taking your tablets. This may be for many months or even longer.

#### **Older people**

The maximum dose for people over 65 is 40 mg per day.

#### **Patients with liver or kidney disease**

If you have trouble with your liver or severe kidney disease, your doctor may decide that you should have a lower dose of Paroxetine than usual.

#### **If you take more Paroxetine than you should**

**Never take more tablets than your doctor recommends.** If you take too many Paroxetine tablets (or someone else does), tell your doctor or a hospital straight away. Show them the pack of tablets.

Someone who has taken an overdose of Paroxetine may have any one of the symptoms listed in section 4 'Possible side effects', or the following symptoms: being sick, fever, headache, uncontrollable tightening of the muscles.

#### **If you forget to take Paroxetine**

Take your medicine at the same time every day. **If you do 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.

#### **What to do if you're feeling no better**

**Paroxetine will not relieve your symptoms straight away** – all antidepressants take time to work. Some people will start to feel better within a couple of weeks, but for others it may take a little longer. Some people taking antidepressants feel worse before feeling better. If you don't start to feel better after a couple of weeks, go back to your doctor who will advise you. Your doctor should ask to see you again a couple of weeks after you first start treatment. Tell your doctor if you haven't started to feel better.

**If you stop taking Paroxetine**

**Do not stop taking Paroxetine until your doctor tells you to.** When stopping Paroxetine, your doctor will help you to reduce your dose slowly over a number of weeks or months – this should help reduce the chance of withdrawal effects. One way of doing this is to gradually reduce the dose of Paroxetine you take by 10 mg a week. Most people find that any symptoms on stopping Paroxetine are mild and go away on their own within two weeks. For some people, these symptoms may be most severe, or go on for longer.

**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. He or she 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**

Studies show that 3 in 10 patients notice one or more symptoms on stopping paroxetine. Some withdrawal effects on stopping occur more frequently than others.

**Common side effects, likely to affect up to 1 in 10 people:**

- Feeling dizzy, unsteady or off-balance
- Feelings like pins and needles, burning sensations and (less commonly) electric shock sensations, including in the head, and buzzing, hissing, whistling, ringing or other persistent noise in the ears (tinnitus)
- Sleep disturbances (vivid dreams, nightmares, inability to sleep)
- Feeling anxious
- Headaches.

**Uncommon side effects, likely to affect up to 1 in every 100 people:**

- Feeling sick (nausea)
- Sweating (including night sweats)
- Feeling restless or agitated
- Tremor (shakiness)
- Feeling confused or disorientated
- Diarrhoea (loose stools)
- Feeling emotional or irritable
- Visual disturbances
- Fluttering or pounding heartbeat (palpitations).

**Please see your doctor if you are worried about withdrawal effects when stopping Paroxetine.**

If you have any 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. Side effects are more likely to happen in the first few weeks of taking Paroxetine.

**See the doctor if you get any of the following side effects during treatment.**

You may need to contact your doctor or go to a hospital straight away.

**Uncommon side effects, likely to affect up to 1 in every 100 people:**

- **If you have unusual bruising or bleeding**, including vomiting blood or passing blood in your stools, contact your doctor or go to a hospital straight away.
- **If you find that you are not able to pass water**, contact your doctor or go to a hospital straight away.

**Rare side effects, likely to affect up to 1 in every 1,000 people:**

- **If you experience seizures (fits)**, contact your doctor or go to a hospital straight away.
- **If you feel restless and feel like you can't sit or stand still**, you may have something called akathisia. Increasing your dose of Paroxetine may make these feelings worse. If you feel like this, **contact your doctor.**
- **If you feel tired, weak or confused and have achy, stiff or unco-ordinated muscles**, this may be because your

blood is low in sodium. If you have these symptoms, **contact your doctor.**

**Very rare side effects, likely to affect up to 1 in every 10,000 people:**

- **Allergic reactions to paroxetine.**  
If you develop a red and lumpy skin rash, swelling of the eyelids, face, lips, mouth or tongue, start to itch or have difficulty breathing or swallowing, **contact your doctor or go to a hospital straight away.**
- **If you have some or all of the following symptoms** you may have something called **serotonin syndrome.** The symptoms include feeling confused, feeling restless, sweating, shaking, shivering, hallucinations (strange visions or sounds), sudden jerks of the muscles or a fast heartbeat. If you feel like this **contact your doctor.**
- **Acute glaucoma.**  
If your eyes become painful and you develop blurred vision, **contact your doctor.**

**Other possible side effects during treatment**

**Very common side effects, likely to affect more than 1 in 10 people:**

- Feeling sick (nausea). Taking your medicine in the morning with food will reduce the chance of this happening.
- Change in sex drive or sexual function, for example, lack of orgasm and, in men, abnormal erection and ejaculation.

**Common side effects, likely to affect up to 1 in 10 people:**

- Increases in the level of cholesterol in the blood
- Lack of appetite
- Not sleeping well (insomnia) or feeling sleepy
- Feeling dizzy or shaky (tremors)
- Headache
- Feeling agitated
- Feeling unusually weak
- Blurred vision
- Yawning, dry mouth
- Diarrhoea or constipation
- Weight gain
- Sweating.

**Uncommon side effects, likely to affect up to 1 in every 100 people:**

- A brief increase in blood pressure, or a brief decrease that may make you feel dizzy or faint when you stand up suddenly
- A faster than normal heartbeat
- Lack of movement, stiffness, shaking or abnormal movements in the mouth and tongue
- Dilated pupils
- Skin rash
- Feeling confused
- Having hallucinations (strange visions or sounds)
- An inability to urinate (urinary retention) or an uncontrollable, involuntary passing of urine (urinary incontinence).

**Rare side effects, likely to affect up to 1 in every 1,000 people:**

- Abnormal production of breast milk in men and women
- A slow heartbeat
- Effects on the liver showing up in blood tests of your liver function
- Panic attacks
- Overactive behaviour or thoughts (mania)
- Feeling detached from yourself (depersonalisation)
- Feeling anxious
- Pain in the joints or muscles.

**Very rare side effects, likely to affect up to 1 in every 10,000 people:**

- Liver problems that make the skin or whites of the eyes go yellow
- Fluid or water retention which may cause swelling of the arms or legs
- Sensitivity to sunlight
- Painful erection of the penis that won't go away
- Low blood platelet count.

Some patients may develop buzzing, hissing, whistling, ringing or other persistent noise in the ears (tinnitus) when they take Paroxetine.

If you have any concerns while you are taking Paroxetine, talk to your doctor who will be able to advise you. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5 HOW TO STORE PAROXETINE

**Keep Paroxetine out of the reach and sight of children.**

Do not use Paroxetine after the expiry date which is stated on the outer packaging after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

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 substance is paroxetine. Each film-coated tablet contains 20 or 30 mg paroxetine (as hydrochloride hemihydrate).
- The other ingredients are calcium phosphate dibasic anhydrous, povidone K30, sodium starch glycolate (type A), magnesium stearate, titanium dioxide (E171), methylcellulose, macrogol 400 and polysorbate 80.

**What Paroxetine looks like and contents of the pack**

- Film-coated tablet.
- Paroxetine 20 mg Film-coated Tablets are white to off-white, round biconvex film-coated tablets, embossed with "20" and scored on one side and with "PX" on the other side. The tablet can be divided into equal halves.
- Paroxetine 30 mg Film-coated Tablets are white to off-white, round biconvex film-coated tablets, embossed with "30" and scored on one side and with "PX" on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- The 20 mg tablets are available in pack sizes of 14, 20, 28, 30, 50, 56, 60, 84 and 100 tablets.
- The 30 mg tablets are available in pack sizes of 28, 30, 50, 56, 60 and 84 tablets.
- Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

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

**Trading address:**

Leeds, LS27 OJG, England.

**Manufacturer**

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

**Pharmachemie B.V.,**

Swensweg 5, Postbus 552, 2003 RN Haarlem The Netherlands.

**Teva Santé,**

Rue Bellocier, 89107 Sens France.

**Teva Pharmaceutical Works Private Limited Company,**

Pallagi út 13, 4042 Debrecen Hungary.

This leaflet was last approved in 09-2008.



12345-U

# Module 4

## Labelling



<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>20 mg Tablets MA UK Ltd. T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>
<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>20 mg Tablets MA UK Ltd. T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>
<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>20 mg Tablets MA UK Ltd. T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>
<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>20 mg Tablets MA UK Ltd. T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 20 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>



<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>30 mg Tablets /A UK Ltd. T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>
<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>30 mg Tablets /A UK Ltd. T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>
<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>30 mg Tablets /A UK Ltd. T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>
<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>
<p>30 mg Tablets /A UK Ltd. T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxetine 30 mg Film-Coated Tablets MA Holder: TEVA UK Ltd. 12345-T</p>	<p>Paroxeti Film-Coat MA Holder: 123</p>

## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Paroxetine 20mg and 30mg Tablets in the treatment of major depressive episode, obsessive-compulsive disorder, panic disorder with or without agoraphobia, social anxiety disorder/social phobia and generalised anxiety disorder, could be approved. A national marketing authorisation was granted on 30<sup>th</sup> November 2006.

These are Mutual Recognition Procedure applications for immediate release tablets containing 20mg and 30mg paroxetine (as hydrochloride hemihydrate) as the active ingredient. The applications are submitted under Article 10.1 of Directive 2001/83/EC, as amended, cross-referencing to Glaxo SmithKline Beechams, Seroxat Tablets 20mg and 30mg (PL 10592/0001 & 2, granted 11.12.90).

Paroxetine 20 and 30mg film-coated tablets contain the active ingredient paroxetine (as hydrochloride hemihydrate) and are indicated in the treatment of major depressive episode, obsessive-compulsive disorder, panic disorder with or without agoraphobia, social anxiety disorder/social phobia and generalised anxiety disorder.

The aim of the development programme was to formulate a robust, stable and acceptable formulation of Paroxetine 20 mg and 30mg film-coated tablets comparable in performance to the reference products Seroxat 20mg and 30mg Tablets.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

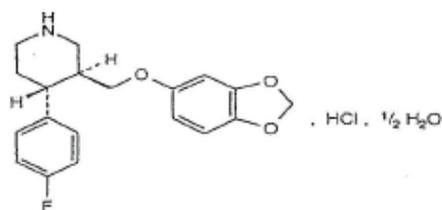
**SCIENTIFIC OVERVIEW AND DISCUSSION****QUALITY ASPECTS****General Information****Nomenclature**

INN/USAN: Paroxetine

Compendia name: Paroxetine hydrochloride hemihydrate

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

Structural Formula

Molecular Formula:  $C_{19}H_{21}FNO_3 \cdot Cl \cdot \frac{1}{2} H_2O$ 

Molecular Weight: 374.84

**General properties**

Description: White to off-white crystalline powder. Paroxetine HCl shows pseudo-polymorphism. Active substance from this source is the hemihydrate. The paroxetine HCl hemihydrate molecule is chiral with a specific optical rotation of  $-83.9 \pm 1^\circ$ . It is freely soluble in methanol and slightly soluble in water.

Paroxetine hydrochloride hemihydrate is a subject of the Ph.Eur monograph and information on the drug substance has provided by use of the DMF procedure.

A letter of access is provided.

Appropriate specifications have been provided.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

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

All potential known impurities have been identified and characterised.

Active paroxetine hydrochloride hemihydrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated, supporting the re-test period for the active substance.

## **Drug Product**

### **Description and Composition of the Drug product**

Other ingredients consists of pharmaceutical excipients, namely calcium phosphate dibasic anhydrous, povidone, sodium starch glycolate, magnesium stearate, macrogol 400, titanium dioxide (E171), polysorbate 80, methocel E5 premium, methocel E3 premium, and purified water.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory specifications and Certificates of Analysis are provided for typical batches of excipients.

### **Manufacture**

The manufacturing process is adequately summarised and a flow diagram is provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results of chemical and physical testing of the validation batches are satisfactory and show consistency and control in the manufacturing process.

### **Finished Product Specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data for tablets manufactured at the proposed manufacturing site demonstrate that the batches comply with the release specification. Satisfactory certificates of analysis are provided for the reference standards.

### **Container Closure System**

The tablets are packed in aluminium/PVC/PVdC blisters. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging comply with EU legislation regarding contact with food.

## **Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 year has been set, with a storage condition 'Store in the original package'. These are satisfactory.

## **CONCLUSIONS**

It is recommended that Marketing Authorisation is granted for these applications.

## **PRE-CLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are necessary. A non-clinical overview summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

## CLINICAL ASSESSMENT

### 1. INTRODUCTION

These are Mutual Recognition Procedure applications for Paroxetine 20mg and 30mg Film-coated Tablets submitted by TEVA UK Limited.

### 2. BACKGROUND

National Market Authorisations for these products were granted in the UK on 30<sup>th</sup> November 2006 (PL 00289/0523-4). The Market authorisations were granted under Article 10.1 of EC Directive 2001/83/EC, as amended, claiming essential similarity to Seroxat tablets 20 mg (PL 10592/001, granted 11.12.90) and Seroxat Tablets 30mg (PL 10592/0002, granted 11.12.90).

### 3. INDICATIONS

Paroxetine is a selective serotonin reuptake inhibitor, and 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. This is consistent with the reference product and is therefore satisfactory.

### 4. DOSE & DOSE SCHEDULE

Satisfactory. Consistent with cross-reference product

### 5. TOXICOLOGY

No new data

### 6. CLINICAL PHARMACOLOGY

The applicant has submitted data from a comparative bioavailability study against the cross-reference product. This was a single dose randomised two-way cross-over comparing single dose 2 x 20 mg test and reference product. 24 healthy subjects were enrolled.

#### Pharmacokinetic Variables for Deroxat (GlaxoSmithKline) and Paroxetine (Teva) Tablets

Variable	Deroxat	Paroxetine	90% CI
C <sub>max</sub> ratio	98.18	101%	0.93-1.10
AUC <sub>inf</sub> ratio	96.77	111%	0.99-1.248
T <sub>max</sub>	6.15 hours	6.0 hours	

The conclusion of the bioequivalence study conducted with the 20mg tablets can be extrapolated for the other strength (30mg).

### 7. EFFICACY

No new data

## **8. SAFETY**

No adverse events were observed in the bioavailability study

## **9. EXPERT REPORTS**

An appropriate clinical review is included in Module 2

## **10. PATIENT INFORMATION LEAFLET (PIL)**

Satisfactory

## **11. LABELLING**

Medically satisfactory

## **12. APPLICATION FORM (MAA)**

Medically satisfactory

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

The SPCs are satisfactory

## **14. DISCUSSION**

The applicant has satisfactorily demonstrated comparative bioavailability and hence bioequivalence.

## **15. MEDICAL CONCLUSION**

Marketing authorisation is recommended.

## Module 5

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
25/06/2008	Type 1A	To register a tightening of shelf life specifications for total impurities from 0.7% to 0.6%	Approved 29/07/2008
26/06/2008	Type 1A	To register a minor change to an approved test procedure of the finished product	Approved 08/08/2008
05/09/2008	Type 1A	To register Biokanol Pharma GmbH, Kehler Strasse 7, 76437 Rastatt, Germany as an additional secondary packaging site to the licence	Approved 22/09/2008
05/09/2008	Type 1A	To register Klocke Verpackungs-Service GmbH, Max-Becker-Straße 6, 76356, Weingarten, Germany as an additional secondary packaging site to the licence.	Approved 25/09/2008