PRESCRIBING INFORMATION

PAROTIN 20, PAROTIN 30

1. NAME OF THE MEDICINAL PRODUCT
Parotin 20 tablets
Parotin 30 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Parotin 20: each tablet contains 20mg of Paroxetine (as Hydrochloride)
Parotin 30: each tablet contains 30mg of Paroxetine (as Hydrochloride)
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Parotin 20: White to off-white round, bisected, biconvex film coated tablets.
Parotin 30: White to off-white round, biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Adults:
Depressive disorders
Obsessive compulsive disorder
Panic disorder with or without agoraphobia
Social phobia
Generalised Anxiety Disorder
Posttraumatic stress disorder
Children and adolescents (<18 years)
Paroxetine is not indicated for use in children or adolescents aged <18 years (see 4.4 Special warnings and precautions for use).
Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of paroxetine in the treatment of depression in this population. (See 4.4 Special warnings and precautions for use)
The safety and efficacy of paroxetine in children aged <7 years has not been studied.

4.2 Posology and method of administration
It is recommended that Parotin is administered once daily in the morning with food. The tablet should be swallowed whole or crushed and swallowed immediately.

Depressive disorder:
Adults
The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from dose increases in 10mg/day increments, up to a maximum dosage of 50mg/day according to the patient's response. As with all antidepressant drugs, dosage should be reviewed and adjusted if necessary within 2 to 3 weeks of initiation of therapy and thereafter as judged clinically appropriate.
Patients with depression should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months.

Obsessive compulsive disorder:
Adults
The recommended dose is 40 mg daily. Patients should start on 20 mg and can be increased weekly in 10 mg increments. Some patients will benefit from having their dose increased 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.
Panic disorder:
Adults
The recommended dose is 40 mg daily. Patients should be started on 10mg/day and the dose increased weekly in 10mg increments according to patient's response. Some patients may benefit from having their dose increased up to a maximum of 60mg/day.
A low initial starting dose is recommended to minimize the risk of a potential worsening of panic symptomatology, which is generally recognized to occur early in the treatment of this disorder.
Patients with Panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer.

Social Phobia
Adults
The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day according to the patient's response.
Generalised Anxiety Disorder
Adults
The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day to the patient's response.
Post-traumatic stress disorder
Adults
The recommended dose is 20mg daily. Some patients not responding to a 20mg dose may benefit from having dose increases in 10mg increments as required, up to a maximum of 50 mg/day according to the patient's response.

General Information
DISCONTINUATION OF PAROXETINE
As with other psychoactive medications, abrupt discontinuation should generally be avoided (see sections 4.4 Special warnings and precautions for use & 4.8 Undesirable effects). The taper phase regimen used in recent clinical trials involved a decrease in the daily dose by 10 mg/day at weekly intervals.
When a daily dose of 20 mg/day was reached, patients were continued on this dose for one week before treatment was stopped. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

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 and may be increased up to 40 mg daily.
• ***Children and adolescents (<18 years)***
Paroxetine is not indicated for use in children or adolescents aged <18 years (see 4.1 Therapeutic Indications and 4.4 Special warnings and precautions for use).
• ***Renal/hepatic impairment***
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.

4.3 Contraindications
-Known hypersensitivity to paroxetine and excipients.
-Paroxetine should not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) or within 2 weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with paroxetine (see 4.5 Interaction with other medicinal products and other forms of interaction).
-Paroxetine should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see 4.5 *Interaction with other medicinal products and other forms of interaction*). 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 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use
Children and Adolescents (<18 years)
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders. In clinical trials of paroxetine in children and adolescents, adverse events related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in patients treated with paroxetine compared to those treated with placebo (see 4.8 Undesirable effects). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.
Clinical worsening and suicide risk in adults
Young adults, especially those with Major Depressive Disorder (MDD), may be at increased risk for suicidal behaviour during treatment with paroxetine. An analysis of placebo controlled trials of adults with psychiatric

disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts).
However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.
Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk persists until significant remission occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.
Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour and these conditions may be co-morbid with MDD.
Additionally, patients with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts. All patients should be monitored for clinical worsening (including development of new symptoms) and suicidality throughout treatment, and especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.
Patients, (families and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the drug therapy (see Akathisia and Mania and Bipolar Disorder below; 4.5 Undesirable Effects).
Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Akathisia

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

Serotonin Syndrome/Neuroleptic Malignant Syndrome

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment of paroxetine, particularly when given in combination with other serotonergic drugs (including triptans) , with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotic or other dopamine antagonists. Symptoms of serotonin syndrome may include mental status changes (eg, agitation, hallucinations, and coma), autonomic instability (eg, tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (eg, hyperreflexia and incoordination), and/or gastrointestinal tract symptoms (eg, nausea, vomiting, and diarrhea). Severe cases can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.
A concomitant treatment of depression with MAOIs and Paroxetine is contraindicated.
Parotin-treated patients receiving triptans should be observed closely, particularly during initiation of therapy, dose increases, or the addition of another serotonergic drug.
Concomitant use of Parotin with serotonin precursors (eg, tryptophan) is not recommended. Treatment with Parotin and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately in patients in whom symptoms of serotonin syndrome develop.

Mania and Bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar
disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that paroxetine is not approved for use in treating bipolar depression. As with all antidepressants, paroxetine should be used with caution in patients with a history of mania.

Monoamine Oxidase Inhibitors

Treatment with paroxetine should be initiated cautiously at least 2 weeks after terminating treatment with MAO inhibitors and dosage of paroxetine should be increased gradually until optimal response is reached (see Serotonin syndrome/ Neuroleptic Malignant Syndrome, 4.3 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction).

Renal/hepatic impairment

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

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

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

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

Glaucoma: As with other SSRI's, paroxetine can cause mydriasis and should be used with caution in patients with narrow angle glaucoma.

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

Hemorrhage: Skin and mucous membrane bleedings (including gastrointestinal bleeding) have been reported following treatment with paroxetine. Paroxetine should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding, and in patients with a known tendency for bleeding or those with predisposing conditions.

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

Symptoms seen on discontinuation of paroxetine treatment in adults:

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

Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea have been reported. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are selflimiting 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 "Discontinuation of Paroxetine", 4.2 Posology and method of administration).

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects (Serotonin Syndrome/ Neuroleptic Malignant Syndrome; see 4.4 Special Warnings and Precautions for use).

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

Concomitant use of paroxetine and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) is contraindicated (see 4.3 Contraindications).

Pimozide

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

Drug metabolising enzymes

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

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using doses at the lower end of the range.

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

Procyclidine
Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anticholinergic effects are seen, the dose of procyclidine should be reduced.
Anticonvulsants
Carbamazepine, phenytoin, sodium valproate. Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.
CYP2D6 inhibitory potency of paroxetine
As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered drugs metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. amitriptyline, nortriptyline,imipramine and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine, see 4.3 Contraindications), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide)
and metoprolol.
Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite and hence reduced efficacy of tamoxifen.
CYP3A4
An in vivo interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics.
A similar in vivo interaction study revealed no effect of paroxetine on alprazolam pharmacokinetics and vice-versa.
Concurrent administration of paroxetine with terfenadine, alprazolam and other drugs that are CYP3A4 substrates would not be expected to cause a hazard.
Clinical studies have shown the absorption and pharmacokinetics of paroxetine to be unaffected or only marginally affected (i.e. at a level which warrants no change in dosing regimen) by:
• food
• antacids
• digoxin
• propranolol
• alcohol: paroxetine does not increase the impairment of mental and motor skills caused by alcohol, however, the concomitant use of paroxetine and alcohol is not advised.

4.6 Pregnancy and lactation
Pregnancy
Animal studies have not shown any teratogenic or selective embryotoxic effects.
Recent epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septal defects), associated with the use of paroxetine.
The data suggest that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population.
The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe paroxetine if the potential benefit outweighs the potential risk. If a decision is taken to discontinue paroxetine treatment in a pregnant woman, the prescriber should consult 4.2 Posology and method of administration - Discontinuation of Paroxetine and 4.4 Special Warnings and Precautions for use
– Symptoms seen on discontinuation of paroxetine treatment in adults.
There have been reports of premature birth in pregnant women exposed to paroxetine or others SSRIs, although a causal relationship with drug therapy has not been established.
Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, becausethere have been reports of complications in neonates exposed to paroxetine or other SSRIs late in the third trimesterof pregnancy. However, a causal association with drug therapy has not been confirmed. Reported clinical findings have included: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In some instances the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (<24 hours) after
delivery.
In one epidemiological study, the use of SSRIs (including paroxetine) after the first 20 weeks of pregnancy, wasassociated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1000 women, compared to 1 to 2 per 1000 women in the general population.

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

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

4.8 Undesirable effects
Some of the adverse experiences listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports. The frequencies of the common and uncommon events were generally determined from pooled safety data from a clinical trial population of >8000 paroxetine-treated patients and are quoted as excess incidence over placebo. Rare and very rare events were generally determined from postmarketing data and refer to reporting rate rather than true frequency.

Blood & lymphatic system disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis).
Very rare: thrombocytopenia.
Immune system disorders
Very rare: allergic reactions (including urticaria and angioedema).
Endocrine disorders
Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
Metabolism & nutrition disorders
Common: 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.
These symptoms may be due to the underlying disease.
Nervous system disorders
Common: dizziness, tremor, headache .
Uncommon: extrapyramidal disorders.
Rare: convulsions , akathisia.
Very rare: Reports of extrapyramidal disorders including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication.
Eye disorders
Common: blurred vision.
Uncommon: mydriasis (see 4.4 Special Warnings and Precautions for use).
Very rare: acute glaucoma.
Cardiac disorders
Uncommon: sinus tachycardia
Vascular disorders
Uncommon: postural hypotension.
Respiratory, thoracic and mediastinal disorders
Common: yawning.
Gastrointestinal disorders
Very common: nausea.
Common: constipation, diarrhoea, 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 & subcutaneous tissue disorders

Common: sweating.
Uncommon: skin rashes.
Very rare: photosensitivity reactions.

Renal & urinary disorders

Uncommon: urinary retention.

Reproductive system & breast disorders

Very common: sexual dysfunction.
Rare: hyperprolactinaemia / galactorrhoea.

General disorders & administration site conditions

Common: asthenia, body weight gain.
Very rare: peripheral oedema.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)- like reactions:

Very rare: mental status changes (eg, agitation, hallucinations, and coma), autonomic instability (eg, tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (eg, hyperreflexia and incoordination), and/or gastrointestinal tract symptoms (eg, nausea, vomiting, and diarrhea).
Severe cases can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. (see 4.4 Special Warnings and Precautions for Use).

Symptoms seen on discontinuation of paroxetine treatment:

Common: Dizziness, sensory disturbances, sleep disturbances, anxiety, headache.
Uncommon: Agitation, nausea, tremor, confusion, sweating, diarrhea.
As with many psychoactive medicines, discontinuation of paroxetine (particularly when abrupt) may lead tosymptoms such as dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, headache, tremor, confusion, diarrhoea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient
group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (see 4.2 Posology and Method of Administration &4.4 Special Warnings and Precautions for Use).

Adverse Events from Paediatric Clinical Trials

In paediatric clinical trials the following adverse events, were reported at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide crying and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia and agitation. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major
Depressive Disorder. Hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age).
In studies that used a tapering regimen (daily dose decreased by 10 mg/day at weekly intervals to a dose of 10 mg/day for one week), symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo were: emotional lability, nervousness, dizziness, nausea and abdominal pain. (see 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Symptoms and Signs

A wide margin of safety is evident from available overdose information on paroxetine.
Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under '4.8 Undesirable effects', vomiting, fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.
Patients have generally recovered without serious sequelae even when doses of up to 2000 mg of paroxetine have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic drugs, with or without alcohol.

Treatment

No specific antidote is known.
The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Where appropriate, the stomach should be emptied by lavage. 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

Mechanism of Action

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and itsantidepressant action and effectiveness in the treatment of OCD and Panic Disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

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

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

In accordance with this selective action, in vitro studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for alpha1, alpha2 and beta-adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and

histamine (H1) receptors. This lack of interaction with post-synaptic receptors in vitro is substantiated by in vivo studies which demonstrate lack of CNS depressant and hypotensive properties.

Pharmacodynamic Effects

Paroxetine does not impair psychomotor function and does not potentiate the depressant effects of ethanol. As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature.

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

Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects. Studies indicate that, in contrast to antidepressants which inhibit the uptake of nor-adrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

5.2 Pharmacokinetic properties

Absorption

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism.

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

Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy.

Distribution

Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma.

Approximately 95% of the paroxetine present in the plasma is protein bound at therapeutic concentrations.

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

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

Metabolism

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

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

Elimination

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

NOTE: The alternative wording given below may be used to replace the above statement:

About 64% of the dose is excreted in the urine; urinary excretion of unchanged paroxetine is generally less than 2% of the dose. About 36% of the dose is excreted in the faeces, probably via the bile; faecal excretion of 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 and hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.
The results of studies performed to date have revealed no evidence of any effect of paroxetine on the immune system.

5.3 Preclinical safety data

Toxicology studies have been conducted in rhesus monkeys and albino rats; in both, the metabolic pathway is similar to that described for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one year duration at doses that were 6 times higher than the recommended range of clinical doses.
Carcinogenesis: In two year studies conducted in mice and rats, paroxetine had no tumorigenic effect.
Genotoxicity: Genotoxicity was not observed in a battery of in vitro and in vivo tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Parotin 20: Calcium Hydrogen Phosphate dehydrate, Povidone, Starch, Magnesium stearate, White Opadry , Macrogol
Parotin 30: Calcium Hydrogen Phosphate dehydrate, Povidone, Starch, Magnesium stearate, White Opadry, Macrogol

6.2 Incompatibilities

Not applicable

6.2 Shelf-life

36 months

6.4 Special precautions for storage

This medicine should be stored at ≤ 25 °C/
Store in the original package.

6.5 Nature and content of container

10, 15, 20, 30, 50 or 60 tablets packed in PVC/Aluminium blisters, in cardboard boxes.
Not all the pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MANUFACTURER

CTS Chemical Industries Ltd.
3 Hakidma St., Kiryat Malachi, Israel

8. MARKETING AUTHORIZATION HOLDER

CTS Chemical Industries Ltd.
3 Hakidma St., Kiryat Malachi, Israel

9. MARKETED BY:

CTS Ltd.
4 Haharash St., Hod-Hasharon , Israel

The format of this leaflet was determined by the Ministry of Health
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