SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

MODIPRAN 20 TABLETS, dispersible tablets

MODIPRAN 40 TABLETS, dispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MODIPRAN 20 TABLETS: Each dispersible tablet contains 20 mg fluoxetine as the hydrochloride.

MODIPRAN 40 TABLETS: Each dispersible tablet contains 40 mg fluoxetine as the hydrochloride.

Excipient with known effect:

Contains sugar: lactose monohydrate.

MODIPRAN 20 TABLETS: Each dispersible tablet contains 71,2 mg lactose monohydrate.

MODIPRAN 40 TABLETS: Each dispersible tablet contains 142,4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablets.

MODIPRAN 20 TABLETS: White, round and biconvex tablets with a one-sided score notch. Slight smell of fruit and peppermint.

MODIPRAN 40 TABLETS: White, round and biconvex tablets with a cross “snap-tab” score notch (divisible into quarters). Slight smell of fruit and peppermint.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MODIPRAN TABLETS is indicated for the treatment of:

- Major depressive disorders.
- Obsessive-compulsive disorder. The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming or interfering significantly with the person's social or occupational functioning.
- Bulimia nervosa.

4.2 Posology and method of administration

Posology

Major depressive disorders:

Adults and elderly patients: 20 mg daily, preferably in the morning.

Bulimia nervosa:

Adults: 60 mg daily.

Obsessive-compulsive disorder:

Adults: 20 mg to 60 mg daily.

The recommended dose may be increased or decreased. MODIPRAN 20 TABLETS cannot be used for downward dose titration. Doses above 80 mg daily are not recommended for any of the indications. Due to the pharmacokinetic properties of MODIPRAN TABLETS, upward dose titration is advised at intervals of several weeks (see section 5.2).

MODIPRAN TABLETS can be administered with or without food. Avoid use of alcohol (see section 4.5).

MODIPRAN TABLETS may be taken dissolved in a small quantity of water, or may be swallowed whole, with water.

Special populations

Elderly patients

MODIPRAN TABLETS should be used with caution in the elderly - dosages above 20 mg daily are not recommended (see section 5.2).

Hepatic impairment and/or concurrent disease

For patients who have concurrent illnesses or hepatic impairment, a lower dose or less frequent dosing should be considered.

Withdrawal/discontinuation

Discontinuation of MODIPRAN TABLETS may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, asthenia, agitation, anxiety and nausea (see section 4.4).

Paediatric population

Safety and efficacy of MODIPRAN TABLETS in children younger than 18 years have not been established.

Method of administration

For oral administration to adults only.

4.3 Contraindications

- Hypersensitivity to fluoxetine or to any of the excipients listed in section 6.1.
- Concomitant use of a monoamine oxidase inhibitor (MAOI).

At least 14 days should elapse between discontinuing an MAOI and initiating therapy with MODIPRAN TABLETS. In view of the long half-life of MODIPRAN TABLETS, at least 5 weeks should elapse after stopping

therapy with MODIPRAN TABLETS before starting an MAOI. If MODIPRAN TABLETS has been prescribed chronically and/or at a high dose, a longer interval should be considered. There have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, the serotonin syndrome, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation, progressing to delirium and coma in patients receiving MODIPRAN TABLETS with an MAOI and in patients who have recently discontinued MODIPRAN TABLETS and are then started on an MAOI. Serious and fatal cases of the serotonin syndrome, some with features resembling neuroleptic malignant syndrome, have been reported in patients treated with MODIPRAN TABLETS and an MAOI in temporal proximity (see section 4.4).

- Severe renal function impairment (GFR < 30 mL/min), as accumulation may occur during chronic treatment.
- Concomitant use with linezolid.
- Concomitant use with metoprolol when used in cardiac failure (see section 4.5).
- Concomitant use with pimozide.
- Children under the age of 18 years (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Serotonin syndrome

A serotonin syndrome, which may be confused with neuroleptic malignant syndrome, may occur in patients who receive MODIPRAN TABLETS either alone or in temporal association with the use of an MAOI and other selective serotonin re-uptake inhibitors (SSRIs), serotonergic medicines and/or neuroleptic medicines. Concomitant administration of MODIPRAN TABLETS and buprenorphine/opioids may also result in serotonin syndrome (see section 4.5). This syndrome is characterised by the clustering of clinical features of changes of mental state (irritability, extreme agitation progressing to delirium and coma, confusion, disorientation) and neuromuscular activity (myoclonus, hyper-reflexia, tremor, rigidity, dyscoordination), in combination with autonomic dysfunction (especially fever, sweating, gastrointestinal symptoms) with possible rapid fluctuations of vital signs. Since death and serious morbidity may follow the serotonin syndrome, MODIPRAN TABLETS should be stopped.

Rash and allergic reactions

MODIPRAN TABLETS should be discontinued in patients who develop a rash or other allergic reactions. Rash, anaphylactoid reactions and serious systemic events involving the skin, kidney, liver or lung have been reported in patients receiving MODIPRAN TABLETS.

Suicide/suicidal thoughts or clinical worsening

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking

antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established.

Patients with a history of suicide-related events, 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 antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients younger than 25 years old.

Patients being treated with MODIPRAN TABLETS should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.

Other psychiatric conditions for which MODIPRAN TABLETS are prescribed can also be associated with an increased risk of suicide-related events. Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressant medicines for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania and mania). Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing MODIPRAN TABLETS, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, MODIPRAN TABLETS should be tapered (see section 4.2). Close monitoring of patients during the first two or more weeks of treatment with MODIPRAN TABLETS is recommended, as improvement may not occur during this period. Close supervision of high risk patients, e.g. patients with suicidal tendencies due to major depressive episodes, is recommended

The same precautions observed when treating patients with depression should be applied when treating patients with obsessive-compulsive disorders, as co-morbidity between these conditions is well established

Children and adolescents under 18 years of age

Safety and efficacy in children under 18 years of age have not been established (see section 4.3). Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressant medicines, such as MODIPRAN TABLETS, compared to those treated with placebo (see section 4.3).

Cardiovascular effects

Clinical experience in acute cardiac disease is limited, therefore caution is advisable. Cases of QT interval prolongation and ventricular arrhythmia, including torsades de pointes, have been reported during the post-marketing period (see sections 4.5, 4.8 and 4.9). MODIPRAN TABLETS should be used with caution in patients with conditions such as congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to arrhythmias (e.g., hypokalaemia, hypomagnesaemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to MODIPRAN TABLETS (e.g., hepatic impairment) or concomitant use with medicines known to induce QT prolongation and/or torsade de pointes (see section 4.5). If patients with stable cardiac disease are treated, an electrocardiogram (ECG) review should be considered before treatment is started. If signs of cardiac arrhythmia occur during treatment with MODIPRAN TABLETS, the treatment should be withdrawn and an ECG should be performed.

Withdrawal symptoms seen on discontinuation of MODIPRAN TABLETS

Withdrawal symptoms when treatment is discontinued occur frequently, particularly if discontinuation is abrupt (see section 4.8). 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), headache, sleep disturbances (including insomnia and intense dreams), asthenia, tremor, confusion, agitation, anxiety and nausea and/or vomiting are the most reported reactions. 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. 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 MODIPRAN TABLETS should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see "*Withdrawal/discontinuation*", section 4.2).

Other precautions

Seizures

Seizures are a potential risk with antidepressant medicines, such as MODIPRAN TABLETS, and therefore it should be introduced cautiously in patients with a history of seizures. Treatment should be discontinued in any patient who develops a seizure or where there is an increase in seizure frequency. MODIPRAN TABLETS should be avoided in those with unstable seizure disorders/epilepsy. Patients with controlled epilepsy should be carefully monitored.

Electroconvulsive therapy (ECT)

Care is advised in patients receiving ECT, as prolonged seizures have been reported in patients on MODIPRAN TABLETS.

Hepatic/renal function

MODIPRAN TABLETS is extensively metabolised by the liver and excreted by the kidneys. Metabolism may be delayed in patients with hepatic function impairment. Lower doses or less frequent dosing is recommended in patients with significant hepatic impairment. Metabolites may accumulate in patients with renal function impairment. Dose adjustment may be necessary in mild to moderate renal failure (GFR 30 to 80 mL/min).

Weight loss

MODIPRAN TABLETS may cause weight loss, which could be undesirable in underweight depressed patients. The weight loss is usually proportional to baseline body weight.

Diabetes

In patients with diabetes mellitus, treatment with an SSRI, such as MODIPRAN TABLETS, may alter glycaemic control. Hypoglycaemia has occurred during therapy with MODIPRAN TABLETS and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic medication dosage may need to be adjusted when treatment with MODIPRAN TABLETS is initiated or discontinued.

Haemorrhage

There have been reports of altered platelet function and/or abnormal cutaneous bleeding, such as ecchymosis and purpura with SSRIs as in MODIPRAN TABLETS. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine as in MODIPRAN TABLETS. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported. SSRIs/serotonin and norepinephrine reuptake inhibitors (SNRIs) may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g. atypical antipsychotic medicines, such as clozapine, phenothiazines, most tricyclic antidepressants (TCAs), aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)) or other medicines that may increase risk of bleeding, as well as in patients with a history of bleeding disorders (see section 4.5).

Akathisia/psychomotor restlessness

The use of MODIPRAN TABLETS has been associated with the development of severe psychomotor activation (e.g. panic, agitation and extrapyramidal symptoms, such as akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still). 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. MODIPRAN TABLETS should therefore be used with caution in patients with extrapyramidal disorders

Mydriasis

Mydriasis has been reported in association with fluoxetine, as in MODIPRAN TABLETS. Therefore, caution should be used when prescribing MODIPRAN TABLETS in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Sexual dysfunction

SSRIs, such as MODIPRAN TABLETS, or SNRIs may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Mania

Antidepressant medicines, such as MODIPRAN TABLETS, should be used with caution in patients with a history of mania/hypomania. MODIPRAN TABLETS should be discontinued in any patient entering a manic phase.

Tamoxifen

Fluoxetine, a potent inhibitor of cytochrome P450 2D6 (CYP2D6), may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, MODIPRAN TABLETS should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Excipient warnings

MODIPRAN TABLETS contains lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MODIPRAN TABLETS.

MODIPRAN TABLETS contains less than 1 mmol sodium (23 mg) per dispersible tablet, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Due to the long elimination half-life of MODIPRAN TABLETS and norfluoxetine, the potential for interactions exists not only with concomitantly administered medicines but also with medicines administered several weeks after discontinuation of MODIPRAN TABLETS therapy.

Contraindicated combinations

Monoamine oxidase inhibitors (see section 4.3)

Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with an irreversible, non-selective MAOI. These cases presented with features resembling serotonin syndrome (which may be confounded with, or diagnosed as, neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of a medicine interaction with an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Therefore, MODIPRAN TABLETS is contraindicated in combination with an irreversible, non-selective MAOI (see section 4.3). Because of the two weeks-lasting effect of the latter, treatment with MODIPRAN TABLETS should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing treatment with MODIPRAN TABLETS before starting an irreversible, non-selective MAOI.

Metoprolol used in cardiac failure

Risk of metoprolol adverse events including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine (see section 4.3).

Not recommended combinations

Tamoxifen

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65 – 75 % reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant use of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including MODIPRAN TABLETS) should whenever possible be avoided (see section 4.4).

Alcohol

In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable (see section 4.2).

Mequitazine

Risk of mequitazine adverse events (such as QT prolongation) may be increased because of an inhibition of its metabolism by MODIPRAN TABLETS.

Combinations requiring caution

MODIPRAN TABLETS should be used cautiously when co-administered with:

Phenytoin

Changes in blood levels have been observed when combined with fluoxetine, as in MODIPRAN TABLETS. In some cases, manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant medicine and to monitoring clinical status.

Serotonergic medicines (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St John's wort (Hypericum perforatum))

There have been reports of mild serotonin syndrome when SSRIs were given with medicines also having a serotoninergic effect. Therefore, the concomitant use of MODIPRAN TABLETS with these medicines should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4).

Lithium

Both increased and decreased concentrations of lithium have been reported when used concurrently with MODIPRAN TABLETS. Close monitoring of lithium levels is recommended.

Tryptophan

Adverse reactions, including agitation, restlessness and gastrointestinal distress have been reported when MODIPRAN TABLETS has been used in combination with tryptophan.

Central nervous system (CNS) active medicines

Phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, imipramine and desipramine: Changes in blood levels, sometimes with clinical manifestations of toxicity, have been reported when these medicines are used concomitantly with MODIPRAN TABLETS. The use of conservative titration schedules of these medicines and monitoring of clinical status should be considered. The half-life of concurrently administered diazepam may be prolonged.

There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when MODIPRAN TABLETS has been administered in combination with these medicines.

Buprenorphine/opioids

MODIPRAN TABLETS should be used cautiously when co-administered with buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicines that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicines cannot be excluded. Therefore, co-administration of MODIPRAN TABLETS with medicines that prolong the QT interval, such as class IA and III antiarrhythmic medicines, antipsychotic medicines (e.g. phenothiazine derivatives, haloperidol), TCAs, certain antimicrobial medicines (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), antimalaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution (see sections 4.4, 4.8 and 4.9).

Medicines affecting haemostasis

Treatment with MODIPRAN TABLETS may increase the risk of bleeding abnormalities. Concomitant use of oral anticoagulants, whatever their mechanism, platelets antiaggregants, including aspirin and NSAIDs, may add to this risk. Clinical monitoring, and more frequent monitoring of international normalised ratio (INR) with oral anticoagulants, should be made. A dose adjustment during treatment with MODIPRAN TABLETS and after its discontinuation may be suitable (see sections 4.4 and 4.8).

Cyproheptadine

There are individual case reports of reduced antidepressant activity of MODIPRAN TABLETS when used in combination with cyproheptadine.

Medicines inducing hyponatraemia

Hyponatraemia is an undesirable effect of MODIPRAN TABLETS. Use in combination with other medicines associated with hyponatraemia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk (see section 4.8).

Medicines lowering the epileptogenic threshold

Seizures are an undesirable effect of MODIPRAN TABLETS. Use in combination with other medicines which may lower the seizure threshold (for example, TCAs, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk.

Plasma protein binding

As MODIPRAN TABLETS is bound to plasma protein, its plasma concentration or that of other protein bound medicines, such as warfarin and digoxin, could be altered when used concomitantly. Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms) and increased bleeding has been reported when warfarin and fluoxetine are given concurrently. Careful coagulation monitoring is recommended in this case and when MODIPRAN TABLETS is discontinued.

Other medicines metabolised by CYP2D6:

MODIPRAN TABLETS is a strong inhibitor of CYP2D6 enzyme; therefore, concomitant therapy with medicines also metabolised by this enzyme system may lead to medicine interactions, notably those having a narrow therapeutic index (such as flecainide, propafenone and nebivolol) and those that are titrated, but also with atomoxetine, carbamazepine, TCAs and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if MODIPRAN TABLETS has been taken in the previous 5 weeks. If MODIPRAN TABLETS is added to the treatment regimen of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy have not been established.

Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall, the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Transitory withdrawal symptoms (e.g. transient jitteriness, difficulty feeding, tachypnoea and irritability) have been reported less frequently in the neonate after maternal use near term. Some neonates exposed to MODIPRAN TABLETS late in the third trimester developed complications resulting in prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and

constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs, or possibly, withdrawal syndrome. In some cases, the clinical picture is consistent with serotonin syndrome (see section 4.4)

Epidemiological data have suggested that the use of SSRIs (as in MODIPRAN TABLETS) in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1 000 pregnancies. In the general population 1 to 2 cases of PPHN per 1 000 pregnancies occur.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure, as in MODIPRAN TABLETS, within the month prior to birth (see sections 4.4 and 4.8).

Breastfeeding

Safety and efficacy during breastfeeding have not been established.

Fluoxetine and its metabolite, norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breastfeeding infants.

Fertility

Fluoxetine may affect sperm quality.

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

MODIPRAN TABLETS may impair the ability to perform activities requiring mental alertness or physical coordination (e.g. operating machinery, driving a motor vehicle). Patients should be cautioned that their ability to perform potentially hazardous tasks maybe impaired.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in patients treated with MODIPRAN TABLETS were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

List of adverse reactions

Blood and lymphatic system disorders

Less frequent: Thrombocytopenia, neutropenia, leucopenia.

Immune system disorders

Less frequent: Anaphylactoid reactions, serum sickness.

Endocrine disorders

Less frequent: Inappropriate antidiuretic hormone secretion.

Frequency unknown: Hypothyroidism.

Metabolism and nutrition disorders

Frequent: Decreased appetite (including anorexia).

Less frequent: Hyponatraemia.

Psychiatric disorders

Frequent: Insomnia (including early morning awakening, initial insomnia, middle insomnia), anxiety, nervousness, restlessness, tension, decreased libido (including loss of libido), sleep disorder, abnormal dreams (including nightmares).

Less frequent: Depersonalisation, elevated mood, euphoric mood, abnormal thinking, abnormal orgasm abnormal (including anorgasmia), bruxism, suicidal thoughts and behaviour*, hypomania, mania, hallucinations, agitation, panic attacks, confusion, dysphemia, aggression.

Nervous system disorders

Frequent: Headache, disturbance in attention, dizziness, dysgeusia, lethargy, somnolence (including hypersomnia, sedation), tremor.

Less frequent: Psychomotor hyperactivity, dyskinesia, ataxia, balance disorder, myoclonus, memory impairment, seizures, akathisia, buccoglossal syndrome, serotonin syndrome.

Frequency unknown: Drowsiness.

Eye disorders

Frequent: Vision blurred.

Less frequent: Mydriasis.

Frequency unknown: Visual disturbances.

Ear and labyrinth disorders

Less frequent: Tinnitus.

Cardiac disorders

Frequent: Palpitations, ECG QT prolonged (QTcF ≥ 450 msec) (based on ECG measurements from clinical trials).

Less frequent: Ventricular arrhythmia including torsades de pointes.

Vascular disorders

Frequent: Flushing (includes hot flush).

Less frequent: Hypotension, vasculitis, vasodilatation.

Respiratory, thoracic and mediastinal disorders

Frequent: Yawning.

Less frequent: Dyspnoea, epistaxis, pharyngitis, pulmonary events, (inflammatory processes of varying histopathology and/or fibrosis, including atelectasis, interstitial lung disease, pneumonitis).

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, vomiting, dyspepsia, dry mouth.

Less frequent: Dysphagia, gastrointestinal haemorrhage (includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, haemorrhagic diarrhoea, melaena and gastric ulcer haemorrhage), oesophageal pain.

Hepatobiliary disorders

Less frequent: Idiosyncratic hepatitis.

Skin and subcutaneous tissue disorders

Frequent: Rash (includes erythema, exfoliative rash, heat rash, erythematous rash, follicular rash, generalised rash, macular rash, macular-papular rash, morbilliform rash, papular rash, pruritic rash, vesicular rash, umbilical erythema rash), urticaria, pruritis, excessive sweating.

Less frequent: Alopecia, increased tendency to bruise, cold sweat, angioedema ecchymosis, photosensitivity reaction, purpura, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome).

Musculoskeletal and connective tissue disorders

Frequent: Arthralgia.

Less frequent: Muscle twitching, myalgia.

Renal and urinary disorders

Frequent: Frequent urination (includes pollakiuria).

Less frequent: Dysuria, urinary retention, micturition disorder.

Reproductive system and breast disorders

Frequent: Gynaecological bleeding (includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia,

polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage), erectile dysfunction, ejaculation disorder (includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation).

Less frequent: Sexual dysfunction (delayed or inhibited orgasm, occasionally persisting after treatment discontinuation), galactorrhoea, hyperprolactinaemia, priapism.

Frequency unknown: Postpartum haemorrhage[#].

General disorders and administration site conditions

Frequent: Fatigue (includes asthenia), feeling jittery, chills.

Less frequent: Malaise, feeling abnormal, feeling cold, fever, mucosal haemorrhage.

Investigations

Frequent: Weight decreased.

Less frequent: Transaminases increased, gamma-glutamyltransferase increased.

*Includes completed suicide, suicidal depression, intentional self-injury, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt, morbid thoughts, self-injurious behaviour. These symptoms may be due to underlying disease.

[#] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

The following side effects have been reported with MODIPRAN TABLETS, but no causal relationship has been established: aplastic anaemia, cerebral vascular accident, confusion, seizures, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome, which resolved following medicine discontinuation), eosinophilic pneumonia, gastrointestinal haemorrhage, hyperprolactinaemia, erythema multiforme, angioedema, movement disorders developing in patients with risk factors (including medicines associated with such events) and worsening of pre-existing movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, suicidal ideation, pancytopenia, immune-related haemolytic anaemia, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after withdrawal of the medication and violent behaviour.

Description of selective adverse reactions

Suicide/suicidal thoughts or clinical worsening:

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

Bone fractures:

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine treatments:

Discontinuation of fluoxetine frequently leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most frequently reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged (see section 4.4). It is therefore advised that when treatment with MODIPRAN TABLETS is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

See section 4.8.

Symptoms

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose that have been reported include tachycardia, drowsiness, tremor, nausea and vomiting as well as agitation, restlessness, hypomania, seizures, cardiovascular dysfunction ranging from asymptomatic arrythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of torsades de pointes), pulmonary dysfunction and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Treatment

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. There is no specific antidote for overdose with MODIPRAN TABLETS. Dialysis, haemoperfusion, exchange transfusion and measures to increase urine production are considered unlikely to be of benefit. Activated charcoal, which may be given with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple medicine involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a TCA if they are also taking, or have recently taken, MODIPRAN TABLETS.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors.

ATC code: N06A B03.

Mechanism of action

Fluoxetine is a selective serotonin (5-HT) reuptake inhibitor in the CNS. The antidepressant and anti-obsessive-compulsive effects of fluoxetine are thought to be related to its effect on serotonergic neurotransmission. Fluoxetine has practically no affinity to other receptors such as α1-, α2-, and β-adrenergic; serotonergic; dopaminergic; histaminergic1; muscarinic; and gamma-aminobutyric acid (GABA) receptors.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed from the gastrointestinal tract after oral administration. The bioavailability is not affected by food intake.

Distribution

Fluoxetine is extensively bound to plasma proteins (about 95 %) and it is widely distributed (volume of distribution: 20 – 40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Biotransformation

Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is primarily metabolised by demethylation in the liver to the active metabolite, norfluoxetine, and other unidentified metabolites. The involvement of CYP2D6 has been identified in fluoxetine metabolism.

Elimination

The elimination half-life of fluoxetine is 4 to 6 days, whereas that of active metabolite, norfluoxetine, is 4 to 16 days. These long half-lives are responsible for persistence of the medicine for 5 to 6 weeks after discontinuation. Excretion is about 80 % renal and approximately 15 % in the faeces.

Special populations

Elderly patients: Kinetic parameters are not altered in healthy elderly patients when compared to younger subjects.

Hepatic insufficiency: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.

Renal insufficiency: After single-dose administration of fluoxetine in patients with mild, moderate, or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline, Croscarmellose sodium, Crospovidone, Lactose monohydrate, Magnesium stearate, Maize starch, pregelatinised, Peppermint flavour 290147, Plum flavour 213175, Saccharin sodium, Silica, colloidal anhydrous, Sodium cyclamate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C in the original container. Protect from light. Keep the blister strips in the carton until required for use.

6.5 Nature and contents of container

MODIPRAN 20 TABLETS is packed in aluminium/aluminium blister strips. 10 tablets per blister strip. 3 blister strips per carton (30 tablets).

MODIPRAN 40 TABLETS is packed in aluminium/aluminium blister strips. 10 tablets per blister strip. 3 blister strips per carton (30 tablets).

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

MODIPRAN 20 TABLETS: 32/1.2/0103

MODIPRAN 40 TABLETS: 32/1.2/0104

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 August 2002

10 DATE OF REVISION OF THE TEXT

23 March 2023

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