APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

RANFLOCS 20 CAPSULES

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Fluoxetine hydrochloride equivalent to fluoxetine 20 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Opaque, hard gelatin, self-locked capsules of size ‘2’ with green cap and off-white body imprinted with ‘R/FXT20’ in black edible ink on cap/body, containing white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RANFLOCS 20 CAPSULES are indicated for the treatment of:

- Major depressive disorders
- Bulimia nervosa
- 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.

4.2 Posology and method of administration

Posology

Major depressive disorders

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

Obsessive-compulsive disorders

Adults: 20 mg - 60 mg daily.

Bulimia nervosa

Adults: 60 mg daily.

Due to the pharmacokinetic properties of RANFLOCS 20 CAPSULES, upward dose titration is advised at intervals of several weeks. Doses above 80 mg are not recommended for any of the indications (see section 5.2).

RANFLOCS 20 CAPSULES can be administered with or without food.

Avoid use of alcohol.

Special populations

Elderly

RANFLOCS 20 CAPSULES should be used with caution in the elderly, particularly if they have systemic illness or are receiving multiple medications for concomitant diseases. 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.

Paediatric population

Safety and efficacy of RANFLOCS 20 CAPSULES in children have not been established.

Withdrawal/discontinuation

Discontinuation of RANFLOCS 20 CAPSULES may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, asthenia, agitation, anxiety and nausea (see section 4.2).

Method of administration

For oral administration to adults only.

4.3 Contraindications

- Hypersensitivity (allergy) to the active substance, fluoxetine, or to any of the ingredients listed in section 6.1.
- Concomitant use of a monoamine oxidase inhibitor (MAOI) or within 14 days of discontinuation of therapy of MAOI (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.
- Concomitant use with pimozide.

Paediatric use

Safety and efficacy in children below 18 years of age have not been established (see section 4.4. and 4.8).

4.4 Special warnings and precautions for use

Close monitoring of patients during the first two or more weeks of treatment with RANFLOCS 20 CAPSULES 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.

Suicide/suicidal thoughts or clinical worsening

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and / or emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. Isolated cases of suicidal ideation and suicidal behaviours have been reported during RANFLOCS 20 CAPSULES therapy or early after treatment discontinuation. A causal role, however, for antidepressant in inducing such behaviour has not been established.

Some pooled analyses from reported studies of patients using antidepressants in psychiatric conditions indicate an increased risk for suicidal ideation and suicidal behaviours in paediatric and young adult (< 25 years of age) patients.

In an analysis of controlled trials in adults with major depressive disorder, the following were risk factors for suicidality:

Prior to treatment:

- greater severity of depression
- presence of thoughts of death

During treatment:

- worsening of depression
- development of insomnia

Patients being treated with RANFLOCS 20 CAPSULES should, nevertheless, be observed closely for clinical worsening and suicidality, either increases or decreases.

Medical practitioners should encourage patients of all ages to report any distressing thoughts or feelings at any time.

Because of the possibility of co-morbidity between major depressive disorders 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 psychiatric or non-psychiatric disorders.

Serotonin syndrome

A serotonin syndrome, which may be confused with neuroleptic malignant syndrome, may occur with the use of RANFLOCS 20 CAPSULES.

~~The~~ This serotonin syndrome characterized by the clustering of clinical features of changes of mental state (agitation, confusion, disorientation) and neuromuscular activity (myoclonus, hyper-reflexia, tremor, rigidity, incoordination), in combination auto immune dysfunction (especially fever, sweating, diarrhoea) may occur in patients who receive RANFLOCS 20 CAPSULES either alone or in temporal association with the use of a MAOI and other selective serotonin re-uptake inhibitors (SSRI's) or serotonergic agents. Since death and serious morbidity may follow the serotonin syndrome, RANFLOCS 20 CAPSULES should be stopped.

Monoamine oxidase inhibitors

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 RANFLOCS 20 CAPSULES with a MAOI and in patients who have recently discontinued RANFLOCS 20 CAPSULES and then started on a MAOI. Serious and fatal cases of the serotonin syndrome, some presenting with features resembling neuroleptic malignant syndrome, have been reported in patients treated with RANFLOCS 20 CAPSULES and an MAOI in temporal proximity.

Since RANFLOCS 20 CAPSULES and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping RANFLOCS 20 CAPSULES before starting a MAOI.

If RANFLOCS 20 CAPSULES has been prescribed chronically and/or at a high dose, a longer interval should be considered (see sections 4.3 and 4.5).

Cardiovascular effects

Patients with acute cardiac disease – Clinical experience is limited, therefore caution is advisable. Cases of QT interval prolongation and ventricular dysrhythmia including torsades de pointes have been reported during the post-marketing period. RANFLOCS 20 CAPSULES 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 dysrhythmias (e.g., hypokalaemia, hypomagnesaemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to RANFLOCS 20 CAPSULES (e.g., hepatic impairment), or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started. If signs of cardiac dysrhythmia occur during treatment with fluoxetine, the treatment should be withdrawn, and an ECG should be performed.

Mania

Antidepressants should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase.

Rash and possibly allergic events

RANFLOCS 20 CAPSULES 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 RANFLOCS 20 CAPSULES.

Seizures

RANFLOCS 20 CAPSULES should be given with caution in patients with a history of seizures, as there is an increased risk of seizures. RANFLOCS 20 CAPSULES should be should be discontinued in any patient who develops a seizure and should be avoided in those with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored.

Electroconvulsive therapy (ECT)

Care is advised in patients receiving electroconvulsive therapy as prolonged seizures have been reported in patients on RANFLOCS 20 CAPSULES.

Tamoxifen

RANFOLCS 20 CAPSULES, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, RANFOLCS 20 CAPSULES should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Hepatic/renal function

RANFOLCS 20 CAPSULES is extensively metabolised by the liver and excreted by the kidneys. Metabolism may be delayed. Lower doses or less frequent dosing is recommended in patients with significant hepatic impairment.

Renal function impairment - Metabolites may accumulate. A lower dose, e.g. alternate day dosing, is recommended in patients with significant hepatic dysfunction or mild to moderate renal failure (GFR 30 to 80 mL/min).

Weight loss

- RANFLOCS 20 CAPSULES may cause weight loss which could be undesirable in underweight depressed patients.

Diabetes

Glycaemic control may be altered when taking RANFLOCS 20 CAPSULES. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when fluoxetine therapy is initiated or discontinued.

Haemorrhage

Patients with a history of bleeding disorders such as altered platelet function. There have been reports of abnormal bleeding in several patients taking fluoxetine, including cutaneous bleeding abnormalities (e.g. ecchymosis and purpura) and other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) (see section 4.5). Caution is advised in patients taking SSRI's, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other medicines which may increase risk of bleeding as well as in patients with a history of bleeding disorders (see section 4.5).

Akathisia/psychomotor restlessness

Development of severe psychomotor activation (e.g. agitation, akathisia, panic) was reported also a risk factor during treatment with fluoxetine as in RANFLOCS 20 CAPSULES. The presence or emergence of these conditions prior to or during therapy suggests that consideration should be given to increased clinical monitoring or possible modification of therapy.
RANFLOCS 20 CAPSULES may cause extrapyramidal symptoms and aggravation of Parkinson's disease. RANFLOCS 20 CAPSULES should therefore be used with care in patients with extrapyramidal disorders.

Mydriasis

Mydriasis has been reported in association with RANFLOCS 20 CAPSULES; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Withdrawal symptoms on discontinuation of treatment

Discontinuation of RANFLOCS 20 CAPSULES may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, asthenia, agitation, anxiety and nausea (see section 4.2). If the decision is made to discontinue treatment, RANFLOCS 20 CAPSULES should be tapered over a period of at least one to two weeks, according to the patient's needs (see section 4.2).

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRI), such as RANFLOCS 20 CAPSULES, 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 treatment.

General

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorders as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania.

Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing RANFLOCS 20 CAPSULES, 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, the dose of RANFLOCS 20 CAPSULES should be tapered down (See Section 4.4. and 4.2).

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.

Paediatric population

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder there were increased reports of hostility and suicide related adverse events such as suicidal ideation and self-harm (See Section 4.1 and 4.2).

In reported paediatric trials, mania and hypomania were commonly reported. Therefore, regular monitoring for the occurrence of mania/hypomania is recommended. Fluoxetine should be discontinued in any patient entering a manic phase.

4.5 Interaction with other medicines and other forms of interaction

Due to the long elimination half-life of fluoxetine as contained in RANFLOCS 20 CAPSULES and norfluoxetine, the potential for interactions exist not only with concomitantly administered medicines, but with medicines administered several weeks after discontinuation of RANFLOCS 20 CAPSULES therapy.

Medicines metabolized by cytochrome isoenzyme

RANFLOCS 20 CAPSULES is an inhibitor of cytochrome P450 2D6 (CYP2D6). There is potential for interaction with other medicines that are metabolized by this enzyme, therefore, a reduction in dosage of such medicines, with initiation of therapy at the low dose range for medicines having a relatively narrow therapeutic index, may be needed when used concurrently with RANFLOCS 20 CAPSULES or within 5 weeks of discontinuing RANFLOCS 20 CAPSULES.

Metoprolol

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).

Monoamine oxidase inhibitors

RANFLOCS 20 CAPSULES should not be used concomitantly with monoamine oxidase inhibitors (see sections 4.3 and 4.4).

CNS active medicines

Lithium – both increased and decreased concentrations of lithium have been reported when used concurrently with RANFLOCS 20 CAPSULES. Close monitoring of lithium levels is recommended.
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 RANFLOCS 20 CAPSULES. The use of conservative titration schedules of these medicines and monitoring of clinical status should be considered.

Concomitant use of other medicines with serotonergic activity (e.g. Serotonin and Norepinephrine Reuptake Inhibitors, Selective Serotonin Reuptake Inhibitors, such as triptans, tramadol, tryptophane, selegiline, or St. John's Wort) may result in serotonin syndrome. Therefore, the concomitant use of RANFLOCS 20 CAPSULES with these medicines should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4).
Tryptophan - adverse reactions, including agitation, restlessness and gastro-intestinal distress have been reported when RANFLOCS 20 CAPSULES have been used in combination with tryptophan.

There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when RANFLOCS 20 CAPSULES has been administered in combination with these medicines.

The half-life of concurrently administered diazepam may be prolonged.

Medicines affecting haemostasis

RANFLOCS 20 CAPSULES use may increase the risk of bleeding abnormalities. Concomitant use of aspirin, NSAIDS, other antiplatelet aggregation inhibitors, warfarin and other anticoagulants may add to this risk. Additional clinical evaluation and more frequent INR monitoring if receiving warfarin, should be implemented. Dose adjustments may be necessary during the initiation, ongoing treatment and/or discontinuation of RANFLOCS 20 CAPSULES.

Tamoxifen

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65 to 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 usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors, such as RANFLOCS 20 CAPSULES, 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.

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine, as in RANFLOCS 20 CAPSULES, with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial medicines (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution (see sections 4.4, 4.8 and 4.9).

Cyproheptadine

There are individual case reports of reduced antidepressant activity of fluoxetine, as in RANFLOCS 20 CAPSULES, when used in combination with cyproheptadine.

Medicines inducing hyponatremia

Hyponatremia is an undesirable effect of fluoxetine, as in RANFLOCS 20 CAPSULES. Use in combination with other medicines associated with hyponatremia (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 fluoxetine, as in RANFLOCS 20 CAPSULES. 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 RANFLOCS 20 CAPSULES 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 anticoagulant effects (laboratory values and/or clinical signs and symptoms) and increased bleeding have been reported when warfarin and RANFLOCS 20 CAPSULES are given concurrently. Careful coagulation monitoring is recommended in this case and when RANFLOCS 20 CAPSULES are discontinued.

Electroconvulsive therapy (ECT)

There have been reports of prolonged seizures in patients on RANFLOCS 20 CAPSULES receiving ECT treatment (see section 4.4).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy has not been demonstrated.

RANFLOCS 20 CAPSULES use should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. However, one meta-analysis suggests a potential risk of cardiovascular defects in infants of women exposed to RANFLOCS 20 CAPSULES during the first trimester of pregnancy compared to infants of women who were not exposed to RANFLOCS 20 CAPSULES.

Use in the third trimester

At the end of pregnancy, caution should be exercised, as transitory withdrawal symptoms (e.g. transient jitteriness, difficulty feeding, tachypnoea and irritability) have been reported rarely in the neonate after maternal use near term.

Some neonates exposed to RANFLOCS 20 CAPSULES 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).

RANFLOCS 20 CAPSULES use late in the third trimester of pregnancy may increase the risk of persistent pulmonary hypertension in the newborn.

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

Breastfeeding

Fluoxetine and its metabolite norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breastfeeding infants. If treatment with RANFLOCS 20 CAPSULES is considered necessary, discontinuation of breastfeeding should be considered; however if breastfeeding is continued, the lowest effective dose of RANFLOCS 20 CAPSULES should be prescribed.

Fertility

Reported animal data have shown that fluoxetine may affect sperm quality (see section 5.3).

Human case reports with some SSRI's 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

RANFLOCS 20 CAPSULES may impair the ability to perform activities requiring mental alertness or physical coordination (operating machinery, driving a motor vehicle). Patients should be cautioned that their ability to perform potentially hazardous tasks may be impaired. They should refrain from doing so until certain how they are affected by RANFLOCS 20 CAPSULES. RANFLOCS 20 CAPSULES should be withdrawn gradually to reduce the risk of withdrawal symptoms.

4.8 Undesirable effects

a) Summary of safety profile

The most commonly reported adverse reactions in patients treated with fluoxetine as contained in RANFLOCS 20 CAPSULES 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.

In children hostility, suicidal ideation and self-harm have been reported. Withdrawal symptoms include agitation, anxiety, dizziness, fatigue, headache, malaise, nausea, sweating and vertigo.

b) Tabulated list of adverse reactions

System Organ class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia Neutropenia, Leucopenia
Immune system disorders	Frequent	Anaphylactoid reactions, including, excessive sweating, serum sickness.

Endocrine disorders	Less frequent	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Frequent Less frequent	Decreased appetite[1] Hyponatraemia Weight loss, hyponatraemia, hypothyroidism, fever
Psychiatric disorders	Frequent Less frequent	Insomnia[2], Anxiety, Nervousness, Restlessness, Tension, Libido decreased[3], Sleep disorder, Abnormal dreams[4] Depersonalisation, Elevated mood, Euphoric mood, Thinking abnormal, Orgasm abnormal[5] Bruxism, Suicidal thoughts and behaviour[6], Hypomania, Mania,

		Hallucinations, Agitation, Panic attacks, Confusion, Dysphemia, Aggression
Nervous system disorders	Frequent	Anxiety, drowsiness, headache, insomnia, tremor, nervousness, asthenia, disturbance in attention, dysgeusia, lethargy, somnolence[7]
	Less frequent	Abnormal dreams, dizziness, fatigue, agitation, hypomania, mania, dyskinesias, seizures, psychomotor hyperactivity, ataxia, balance disorder, myoclonus, memory impairment, convulsion akathisia, buccoglossal syndrome, serotonin syndrome

Eye disorders	Less frequent Less frequent	Vision blurred Mydriasis Visual disturbances
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent Less frequent	Palpitations, Electrocardiogram QT prolonged (QTcF ≥ 450 msec)[8] Ventricular arrhythmia including torsades de pointes
Vascular disorders	Frequent Less frequent	Flushing[9] Hypotension, Vasculitis, Vasodilatation
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Yawning Dyspnoea, pulmonary inflammation and/or fibrosis, epistaxis, pharyngitis
Gastro-intestinal disorders	Frequent Less frequent	Nausea, anorexia, diarrhoea Dry mouth, dyspepsia, vomiting, dysphagia,

		gastrointestinal haemorrhage[11], oesophageal pain
Hepato-biliary disorders	Less frequent Frequency unknown	Idiosyncratic hepatitis Raised serum transaminase levels
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash[12], urticarial, pruritus, hyperhidrosis Alopecia, increased tendency to bruise, cold sweat, angioedema, ecchymosis, photosensitivity reaction, purpura erythema multiforme, stevens-Johnson syndrome, toxic epidermal, necrolysis (Lyell Syndrome)
Musculoskeletal, connective tissue	Frequent Less frequent	Arthralgia Muscle twitching, myalgia
Renal and urinary disorders	Frequent	Decreased libido, sexual dysfunction (delayed or

		inhibited orgasm), frequent urination[13]
	Less frequent	Dysuria, urinary retention, micturition disorder
Pregnancy, puerperium and perinatal conditions	Frequency not known	Postpartum haemorrhage*[17]
Reproductive system and breast disorders	Frequent	Gynaecological bleeding[14], erectile dysfunction, ejaculation disorder[15]
	Less frequent	Sexual dysfunction[16], galactorrhoea, Hyperprolactinaemia, Priapism
General disorders and administration site conditions	Frequent	Fatigue[18], feeling jittery, chills
	Less frequent	Malaise, feeling abnormal, feeling cold, feeling hot, mucosal haemorrhage
Investigations	Frequent	Weight decreased, transaminases increased, Gamma-

		glutamyltransferase increased

* This event has been reported for the therapeutic class of SSRIs/SNRIs (see Section 4.4. and 4.6.

[1] Includes anorexia

[2] Includes early morning awakening, initial insomnia, middle insomnia

[3] Includes loss of libido

[4] Includes nightmares

[5] Includes anorgasmia

[6] Includes completed suicide, depression suicidal, 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

[7] Includes hypersomnia, sedation

[8] Based on ECG measurements from clinical trials

[9] Includes hot flush

[10] Includes atelectasis, interstitial lung disease, pneumonitis

[11] Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhoea haemorrhagic, melaena, and gastric ulcer haemorrhage

[12] Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash

[13] Includes pollakiuria

[14] Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage

[15] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation

[16] Occasionally persisting after treatment discontinuation

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

[18] Includes asthenia

The following have been reported in association with RANFLOCS 20 CAPSULES:
Aplastic anaemia, cerebral vascular accident, confusion, ecchymoses, eosinophilic pneumonia, gastro-intestinal haemorrhage, hyperprolactinaemia, neuroleptic malignant syndrome-like events, pancreatitis, suicidal ideation, pancytopenia, thrombocytopenia, purpura, immune-related haemolytic anaemia, vaginal bleeding (after withdrawal of the medication) and violent behaviour.
See section 4.6 for information on side effects of persistent pulmonary hypertension in the newborn.

c. Description of selected adverse reactions

Suicide/suicidal thoughts or clinical worsening

Cases of suicidal ideation and suicidal behaviour 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 the risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine treatments

Discontinuation of fluoxetine commonly 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 commonly

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 RANFLOCS 20 CAPSULES treatment 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 the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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 and section 4.4

Symptoms

Symptoms that have been reported include tachycardia, drowsiness, tremor, nausea and vomiting as well as agitation, restlessness, hypomania and seizures.

Symptoms of overdose also included cardiovascular dysfunction ranging from asymptomatic dysrhythmias (including nodal rhythm and ventricular dysrhythmias) 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.

Management

Treatment is symptomatic and supportive. There is no specific antidote for RANFLOCS 20 CAPSULES overdose. Dialysis, haemoperfusion, forced diuresis, exchange transfusion and measures to increase urine production are considered unlikely to be of benefit. Activated charcoal may be given by mouth if the amount ingested was large and treatment is within an hour of ingestion.

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. In managing overdosage, the possibility of multiple medicine involvement should be considered.

5. PHARMACOLOGICAL CLASSIFICATION

5.1 Pharmacodynamic properties

ATC Code: N06A B03 Pharmacotherapeutic group: A 1.2. Psychoanaleptics (antidepressants).
Fluoxetine is a selective serotonin (5-HT) uptake inhibitor in the central nervous system. The antidepressant and anti-obsessive compulsive effects of fluoxetine are thought to be related to its effect on serotonergic neurotransmission.

Mechanism of action

The antidepressant and anti-obsessive-compulsive action of fluoxetine is presumed to be linked to its inhibition of central nervous system (CNS) neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed after oral administration. The bioavailability is not affected by food intake.

Distribution

Fluoxetine is extensively bound to plasma proteins (about 95 %) and is widely distributed (volume of distribution 2 to 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. Peak plasma concentration is reached in 6 to 8 hours after a single dose of 40 mg.

Fluoxetine is metabolized by demethylation in the liver to the active metabolite, norfluoxetine (desmethylfluoxetine), and other unidentified metabolites. The involvement of cytochrome P450 2D6 (CYP2D6) has been identified in fluoxetine metabolism.

Elimination

The elimination half-life of fluoxetine is 4 to 6 days, whereas that of the active metabolite, norfluoxetine, is 4 to 16 days. Changes in dose will not be fully reflected in plasma for several weeks (approximately 4 half-lives). This is to be taken into consideration during dose titration or cessation of treatment. Excretion is mainly (about 60 %) via the kidney. Fluoxetine is secreted into breast milk.

Special populations

Elderly

The disposition of single doses of fluoxetine in healthy elderly subjects (> 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and non-linear disposition of the medicine, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple medicines for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209,3 ± 85,7 ng/mL at the end of 6 weeks.

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.

5.3 Preclinical safety data

There is no reported evidence of carcinogenicity or mutagenicity from in vitro or animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch

Capsule shell

Body

Yellow iron oxide

Titanium dioxide

Methylparaben

Propylparaben

Gelatin

Cap

Brilliant Blue

Titanium dioxide

Yellow Iron oxide

Methylparaben

Propylparaben

Gelatin

Printing Ink

Activated charcoal

Shellac

Isopropyl alcohol

Alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

Store at or below 25 °C, protected from light.

KEEP OUT OF REACH OF CHILDREN.

6.4 Special precautions for storage

This medicine does not require any special storage conditions

6.5 Nature and contents of container

Cartons containing 30 capsules in blister strip of 15 capsules each.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8 REGISTRATION NUMBER

34/1.2/0129

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 25 April 2003

10 DATE OF REVISION OF THE TEXT

17 July 2023

Namibia: NS3 Reg. No.:05/1.2/0198