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CLEAN PROPOSED PROFESSIONAL INFORMATION JULY 2026

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

XETSIA DR 30 mg (delayed release capsules)

XETSIA DR 60 mg (delayed release capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delayed-release capsule for oral administration contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg or 60 mg of duloxetine that are designed to prevent degradation of the medicine in the acidic environment of the stomach.

Contains sugar (6,72 mg sucrose in **XETSIA DR 60 mg** and 3,36 mg sucrose in **XETSIA DR 30 mg**).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

XETSIA DR 30 mg

Delayed release capsules.

Opaque blue cap/opaque white body size “3” capsules containing, white to off white coloured pellets with “WI” on cap and “D30” on body imprinted with green ink.

XETSIA DR 60 mg

Delayed release capsules.

Opaque blue cap/opaque yellowish green body size “1” capsules containing, white to off white coloured pellets with “WI” on cap and “D60” on body imprinted with white ink.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XETSIA is indicated for the treatment of depression (as defined by DSM-IV criteria). XETSIA is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).

4.2 Posology and method of administration

Posology

Depression: **XETSIA** should be initiated and maintained at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used the efficacy of the 120 mg dose was not statistically significantly different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Diabetic peripheral neuropathic pain: **XETSIA** should be administered at a dose of 60 mg once daily without regards to meals. Although doses up to 120 mg per day have been used the efficacy of the 120 mg dose was not statistically significant different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Special populations

Renal impairment: Initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function (see Sections 4.3, 4.4 and 5.2).

Hepatic impairment: Initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function (see Sections 4.3, 4.4 and 5.2).

Elderly:

No dosage adjustment is recommended for elderly patients on the basis of age.

Paediatric population

Safety and efficacy have not been established in patients under the age of 18 years.

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Discontinuation of Treatment

Abrupt discontinuation should be avoided. When stopping treatment with **XETSIA**, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see Sections 4.4 and 4.8). 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 medical practitioner may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

4.3 Contraindications

XETSIA is contraindicated in:

- Patients with known hypersensitivity to duloxetine hydrochloride, or to any of the inactive ingredients of XETSIA listed in Section 6.1.
- Pregnancy and lactation (see Section 4.6).
- Severe impairment of hepatic function (see Section 5.2).
- Advanced renal impairment (creatinine clearance < 30 ml/min) (see Section 4.4).
- Concomitant use of monoamine oxidase inhibitors (MAOIs) (see Section 4.5).
- Children under the age of 18 years (See Sections 4.4 & 4.8).

4.4 Special warnings and precautions for use

Suicide: 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 medicine in inducing such behaviour has not been established. Patients being treated with **XETSIA** 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. Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and

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non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders. The following symptoms have been reported in patients being treated with antidepressants 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 suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **XETSIA,** 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**, XETSIA** should be tapered (See Section 4.2).
Cases of suicidal ideation and suicidal behaviours have been reported during XETSIA therapy or early after treatment discontinuation.

XETSIA has not been studied in patients under the age of 18 and is not intended for use in this age group (see Section 4.3). Pooled and some individual data analyses from studies of some antidepressants in psychiatric conditions indicate a potential increased risk for suicidal ideation and suicidal behaviours in paediatric patients compared to placebo. (See also Paediatric population below.)

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

MAOIs (Monoamine Oxidase Inhibitors): XETSIA should not be used within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of **XETSIA**, at least 5 days should be allowed after stopping **XETSIA**, before starting a MAOI.
Activation of mania/hypomania: **XETSIA** should be used cautiously in patients with a history of mania.
Seizures: **XETSIA** should be used cautiously in patients with a history of a seizure disorder.

Mydriasis: Mydriasis has been reported in association with duloxetine; therefore caution should be used when prescribing **XETSIA** in patients with raised intraocular pressure or those at risk of acute-narrow angle

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glaucoma.

Renal or hepatic Impairment: Increased plasma concentrations of **XETSIA** occur in patients with renal impairment or hepatic impairment. A lower starting dose should be used in such patients. For patients with severe renal impairment see Sections 4.2, 4.3 and 5.2.

Increased blood pressure: **XETSIA** is associated with an increase in blood pressure in some patients. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate.

Elevated liver enzymes: Elevations in liver enzymes may occur in some patients treated with **XETSIA**. These are usually transient and self-limiting, or resolved upon discontinuation of **XETSIA**. Severe elevations of liver enzymes (>10x upper limit of normal) or liver injury with a cholestatic or mixed pattern have been reported, in some cases associated with excessive alcohol use. **XETSIA** should be used with caution in patients with substantial alcohol use.

Serotonin syndrome: As with other serotonergic medicines, serotonin syndrome, a potentially life-threatening condition, may occur with **XETSIA** treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs, tricyclic antidepressants or triptans), with medicines that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see Sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If concomitant treatment with **XETSIA** and other serotonergic medicines that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see Section 4.5).

St John's Wort: Adverse reactions may be more common during concomitant use of **XETSIA** and herbal

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preparations containing St John's Wort (*Hypericum perforatum*) (see Section 4.5)

Haemorrhage: There have been reports of bleeding abnormalities, such as ecchymoses, purpura, and gastrointestinal haemorrhage, with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including **XETSIA.** Caution is advised in patients taking anticoagulants and/or medicines known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (ASA), and in patients with known bleeding tendencies (see Section 4.5).

Hyponatraemia: Hyponatraemia has been reported when administering **XETSIA,** including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients, or patients treated with diuretics.

Discontinuation of treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhidrosis and vertigo. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that **XETSIA** should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) including **XETSIA**, may cause symptoms of sexual dysfunction (see Section 4.8). There have been reports

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of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Post-partum haemorrhage

There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.

Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Contains sugar (sucrose). XETSIA contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **XETSIA.**

Elderly

Data on the use of **XETSIA** 120 mg in elderly patients with major depressive disorder are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see Sections 4.2 and 5.2).

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 **'Suicide'** above and Sections 4.3 and 4.8).

Akathisia/Psychomotor restlessness

The use of **XETSIA** has been associated with the development of 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.

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4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

Due to the risk of serotonin syndrome, **XETSIA** should not be used in combination with monoamine oxidase inhibitors (MAOIs) or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping **XETSIA** before starting an MAOI (see Section 4.3).

The concomitant use of **XETSIA** with MAOIs, like moclobemide, is not recommended. The antibiotic linezolid is a MAOI and should not be given to patients treated with **XETSIA** (see Section 4.4).

Medicines metabolised by CYP1A2: In a clinical study, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of **XETSIA** with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreases the apparent plasma clearance of duloxetine by about 77 %. **XETSIA** should therefore not be administered in combination with potent inhibitors of CYP1A2 (e.g. quinolone antibiotics).

Medicines metabolised by CYP2D6:

XETSIA is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady-state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite. Therefore caution is advised if **XETSIA** is co-administered with medicines that are predominantly metabolised by CYP2D6 system and which have a narrow therapeutic index.

Inhibitors of CYP2D6:

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Because CYP2D6 is involved in **XETSIA** metabolism, concomitant use of **XETSIA** with potent inhibitors of CYP2D6 may result in higher concentrations of **XETSIA**. Paroxetine (20 mg once daily) decreases the apparent plasma clearance of duloxetine by about 37 %. Caution is advised if administering **XETSIA** with inhibitors of CYP2D6 (e.g. SSRIs).

CNS medicines: Caution is advised if **XETSIA** is taken in combination with other centrally acting medicines and substances, including alcohol.

Medicines highly bound to plasma protein:

XETSIA is highly bound to plasma proteins (>90 %), therefore administration of **XETSIA** to a patient taking another medicine that is highly protein bound may cause an increase in free concentrations of either medicine.

Serotonergic medicines: In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic medicines. Caution is advisable if **XETSIA** is used concomitantly with serotonergic medicines like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's Wort (*Hypericum perforatum*) or triptans, tramadol, pethidine, and tryptophan (see Section 4.4).

Anticoagulants and antiplatelet medicines: Caution should be exercised when **XETSIA** is combined with oral anticoagulants or antiplatelet medicines due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when **XETSIA** was co-administered to patients treated with warfarin.

Oral contraceptives and other steroidal medicines: Results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Antacids and H2 antagonists: Co-administration of duloxetine with aluminium- and magnesium-containing antacids, or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50 %

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lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of **XETSIA** in pregnant women.

Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see Section 5.3).

The potential risk for humans is unknown.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with **XETSIA**, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

As with other serotonergic medicines, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth.

The use of **XETSIA** is not recommended during pregnancy (see Section 4.3). Women should be advised to notify their medical practitioner if they become pregnant, or intend to become pregnant, during therapy.

Breastfeeding

Duloxetine is very weakly excreted into human milk, based on a study of 6 lactating patients who did not breastfeed their children. The estimated daily infant dose on a mg/kg basis is approximately 0,14 % of the maternal dose. As the safety of duloxetine in infants is not known, the use of **XETSIA** while breastfeeding is not recommended (see Section 4.3).

Fertility

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In animal studies, duloxetine had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

4.7 Effects on ability to drive and use machines

XETSIA may lead to dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that, if they develop these symptoms, they should keep away from potentially hazardous tasks, such as driving or operating machinery.

4.8 Undesirable effects

The following adverse reactions have been reported in association with duloxetine, as contained in **XETSIA:**

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations	Less frequent	Laryngitis
Immune system disorders	Less frequent	Anaphylactic reaction, hypersensitivity disorder, angioneurotic oedema
Endocrine disorders	Less frequent	Hypothyroidism
Metabolism and nutrition disorders	Frequent	Decreased appetite[1]
	Less frequent	Dehydration, hyponatraemia, SIADH, hyperglycaemia (reported especially in diabetic patients)
Psychiatric disorders	Frequent	Insomnia[2], agitation[3] , libido decreased[4], anxiety, orgasm abnormal[5], abnormal dreams
	Less frequent	Suicidal ideation[14, 16], suicidal behaviour[14, 16], sleep disorder, bruxism, disorientation , apathy, mania, hallucinations, aggression and anger[13],

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		agitation, disorientation
Nervous system disorders	Frequent	Headache[6], somnolence[7], dizziness, lethargy, tremor, paraesthesia
	Less frequent	Myoclonus, akathisia[16], nervousness, disturbance in attention, dysgeusia, dyskinesia, restless legs syndrome, poor quality sleep, serotonin syndrome[15], convulsion[10], psychomotor restlessness[15], extra-pyramidal symptoms[15], dysgeusia
Eye disorders	Frequent	Blurred vision
	Less frequent	Mydriasis , visual impairment, glaucoma
Ear and labyrinth disorders	Frequent	Tinnitus[10]
	Less frequent	Vertigo, ear pain
Cardiac disorders	Frequent	Palpitations
	Less frequent	Tachycardia , supraventricular arrhythmia, mainly atrial fibrillation
	Frequency unknown	Takotsubo cardiomyopathy
Vascular disorders	Frequent	Blood pressure increase, flushing, hot flush
	Less frequent	Syncope[11], hypertension[12, 16,], orthostatic hypotension[11], peripheral coldness, hypertensive crisis[12, 15]
Respiratory, thoracic and mediastinal disorders	Frequent	Yawning
	Less frequent	Throat tightness, epistaxis, interstitial lung disease[19], eosinophilic pneumonia[15]
Gastrointestinal disorders	Frequent	Nausea, dry mouth, constipation, diarrhoea, abdominal pain, vomiting, dyspepsia, flatulence
	Less frequent	Gastrointestinal haemorrhage[16], gastroenteritis, eructation, gastritis, dysphagia, stomatitis,

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		haematochezia, breath odour, microscopic colitis[18], stomatitis
Hepatobiliary disorders	Less frequent	Hepatitis[12], elevated liver enzymes (ALT, AST, alkaline phosphatase), acute liver injury, hepatic failure[15], jaundice[15]
Skin and subcutaneous tissue disorders	Frequent	Sweating increased, rash
	Less frequent	Night sweats, urticaria, contact dermatitis, cold sweat, photosensitivity reactions, increased tendency to bruise, Stevens-Johnson Syndrome[15], angioedema[15], cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal pain, muscle spasm
	Less frequent	Muscle tightness, muscle twitching, trismus
Renal and urinary disorders	Frequent	Dysuria, pollakiuria
	Less frequent	Urinary retention , urinary hesitation, nocturia , polyuria, urine flow decreased, abnormal urine odour
Reproductive system and breast disorders	Frequent	Erectile dysfunction, ejaculation disorder[8], ejaculation delayed
	Less frequent	Gynaecological haemorrhage, menstrual disorder, sexual dysfunction ,testicular pain, menopausal symptoms, galactorrhoea, hyperprolactinaemia, postpartum haemorrhage[15]
General disorders and administration site conditions	Frequent	Falls[17], fatigue[9]
	Less frequent	Chest pain[16] , feeling abnormal, feeling cold, thirst, chills, malaise, feeling hot, gait disturbance

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Investigations	Frequent	Weight decrease
	Less frequent	Weight increase, blood creatine phosphokinase increased, blood potassium increased, blood cholesterol increased, blood pressure increased, hepatic lab related findings

[1] Previously listed under anorexia and decreased appetite, or anorexia and appetite decreased

[2] Also includes middle insomnia (refers to middle of the night insomnia)

[3] Also includes feeling jittery, nervousness, restlessness, tension

[4] Also includes loss of libido

[5] Also includes abnormal orgasm

[6] Placebo rate was less than duloxetine rate (MDD only)

[7] Also includes hypersomnia, sedation

[8] Also includes ejaculation delayed

[9] Also includes asthenia

[10] Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.

[11] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

[12] See Section 4.4.

[13] Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

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

[15] Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials. There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy. Patients should

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be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

[16] Not statistically significantly different from placebo.

[17] Falls were more common in the elderly (≥ 65 years old).

[18] Estimated frequency based on all clinical trial data.

[19] Estimated frequency based on placebo-controlled clinical trials.

Discontinuation of Treatment

Abrupt discontinuation should be avoided. When stopping treatment with **XETSIA DR**, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see Sections 4.4 and 4.8). 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.

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 Sections 4.3 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com.

4.9 Overdose

Signs and symptoms: The predicted signs would be related to the central nervous and gastrointestinal systems (e.g. tremors, clonic convulsions, ataxia, emesis and decreased appetite).

Management of overdose: No specific antidote is known. An airway should be established. Monitoring of

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cardiac and vital signs is recommended along with appropriate symptomatic and supportive measures. Activated charcoal may be useful in limiting absorption. **XETSIA** has a large volume of distribution and forced diuresis, haemoperfusion and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A1.2. Psychoanaleptics (antidepressants).

Duloxetine is a serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (noradrenaline) reuptake inhibitor (SNRI) and is chemically unrelated to tricyclic and tetracyclic antidepressant medicines. Duloxetine weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic, or adrenergic receptors.

Duloxetine dose-dependently increases extracellular levels of serotonin and norepinephrine (noradrenaline) in various brain areas of animals.

Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and norepinephrine (noradrenaline) neurotransmission in the central nervous system (CNS).

The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the CNS.

The presumed mechanism of action of duloxetine in the treatment of depression is thought to be due to its inhibition of neuronal uptake of serotonin and norepinephrine (noradrenaline) and a resultant increase in serotonergic and noradrenergic neurotransmission in the CNS.

5.2 Pharmacokinetic properties

Absorption: Duloxetine is well absorbed after oral administration, with a C_{max} occurring 6 hours post-dose. Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). Steady state plasma concentrations are achieved after 3 days of dosing.

Distribution: Duloxetine is highly bound (90 %) to human plasma proteins primarily to albumin and alpha1-

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acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of two major metabolites (glucuronide conjugate of 4-hydroxy duloxetine, sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine). Circulating metabolites are not pharmacologically active.

Elimination: The mean elimination half-life of duloxetine is 12,1 hours. The mean plasma clearance of duloxetine is 101 L/hr.

Special populations

Gender: Pharmacokinetic differences have been identified between males and females. The mean plasma clearance was 9 % to 55 % lower in females, but the duloxetine half-life was similar between males and females.

Smoking status: Duloxetine bioavailability appears to be 34 % lower in smokers than in non-smokers.

Age: Pharmacokinetic differences have been identified between middle age and elderly females (≥ 65 years) (AUC is 24 % higher and half-life is 4,3 hours longer in the elderly).

Renal impairment: End stage renal disease (ESRD) patients receiving chronic intermittent haemodialysis had 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Therefore a lower dose should be used in patients with clinically significant renal impairment (see Section 4.3).

Hepatic impairment: Moderate liver disease (Child-Pugh Class B) affected the pharmacokinetics of duloxetine. The half-life of duloxetine was 34 hours longer in patients with cirrhosis of the liver and clearance was approximately 15 % of that for age and gender matched healthy subjects. Therefore a lower dose should be used for patients with mild to moderate liver impairment (see Sections 4.2 and 4.3).

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5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats.

Carcinogenesis, mutagenesis and impairment of fertility:

Carcinogenesis: Duloxetine was administered in the diet to rats and mice for 2 years. In rats, duloxetine did not cause any increase in incidence of expected or unusual neoplasms or decrease in the latency for any tumour type. In female mice receiving duloxetine, there was an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation. The relevance of this mouse data in humans is unknown.

Mutagenesis: Duloxetine demonstrated no mutagenic potential in a battery of *in vitro* and *in vivo* genotoxicity tests.

Impairment of fertility: Reproductive performance was not affected in male rats receiving duloxetine (45 mg/kg/day). In female rats receiving duloxetine (45 mg/kg/day), reproductive toxicity was demonstrated by a decrease in maternal food consumption and body weight, oestrous cycle disruption, depressions in live birth indices and progeny survival and progeny growth retardation. The no-observed-effect level (NOEL) for maternal toxicity, reproductive toxicity and developmental toxicity in the female fertility study was 10 mg/kg/day. The relevance of this preclinical data in humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, hypromellose phthalate, polyethylene glycol, sucrose, sodium lauryl sulphate, sugar spheres (consisting of maize starch and sucrose), triethyl citrate, talc, hard gelatine capsules consisting of FD & C Blue 2 colour, titanium dioxide, gelatine, water and sodium lauryl sulfate. In addition **XETSIA** 60 mg contains iron oxide yellow.

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

6.5 Nature and contents of container

Blister pack:

Silver coloured 25 µ aluminium foil/ 6-8 gsm HSL as the lidding material and silver coloured cold form laminate (25 µ OPA/45 µ aluminum foil/60 µ PVC) as the forming material, packed in a pre-printed unit carton containing 28 or 30 capsules.

HDPE container pack:

Round, white HDPE container with screw neck with white child-resistant polypropylene closure with pulp and heat seal liner containing 28 or 30 capsules packed in a pre-printed unit carton.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

VR

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

XETSIA DR 30 mg: 51/1.2/0933

XETSIA DR 60 mg: 51/1.2/0934

9. DATE OF FIRST AUTHORISATION

28 July 2020

10. DATE OF REVISION OF THE TEXT

08 July 2026

PM0302-01

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