Professional Information

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DUZELA 30 mg hard gastro-resistant capsules

DUZELA 60 mg hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DUZELA 30: Each capsule contains 30 mg duloxetine (as hydrochloride).

DUZELA 60: Each capsule contains 60 mg duloxetine (as hydrochloride).

Excipients with known effect:

Contains sugar (sucrose and mannitol).

DUZELA 30: Each capsule contains 64,2 mg sucrose and 6,7 mg mannitol.

DUZELA 60: Each capsule contains 128,4 mg sucrose and 13,4 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsules.

DUZELA 30: Size 3 hard gelatine capsule, consisting of a blue cap and white body with “382” imprinted in black ink on the cap and body,containing white to off-white pellets.

DUZELA 60: Size 1 hard gelatine capsule, consisting of a blue cap and green body with “383” imprinted in white ink on the cap and body,containing white to off-white pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DUZELA is indicated for:

- The treatment of depression (as defined by DSM-IV criteria).
- The treatment of diabetic peripheral neuropathic pain (DPNP).

4.2 Posology and method of administration

Posology:

Depression:

DUZELA 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.Beneficial effects may be observed within one week of treatment but may take up to four weeks.

Diabetic peripheral neuropathic pain:

DUZELA should be administered at a dose of 60 mg once daily with or without food. 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.

Discontinuation of treatment:

Abrupt discontinuation of DUZELA should be avoided. When stopping treatment with DUZELA 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 doctor may continue decreasing the dose, but at a more gradual rate.

Special populations:

Renal impairment:

The initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function (see sections 4.4 and 5.2). DUZELA must not be used in patients with severe renal impairment (see section 4.3).

Hepatic impairment:

The initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function (see sections 4.4 and 5.2). DUZELA must not be used in patients with severe hepatic impairment (see section 4.3).

Elderly patients:

No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating elderly patients, especially with a dose of 120 mg DUZELA per day for depressive disorder, for which data are limited (see sections 4.4 and 5.2).

Paediatric population:

Safety and efficacy have not been established in patients under the age of 18 years. Also see section 4.4.

Method of administration:

For oral use.

4.3 Contraindications

- Hypersensitivity to duloxetine or to any of the excipients of DUZELA (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Severe impairment of hepatic function.
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Concomitant use of DUZELA with monoamine oxidase inhibitors (MAOIs) (see section 4.4)
- Adolescents and children under the age 18 years of age (see section 4.4)
- Uncontrolled narrow angle glaucoma or hypertension

4.4 Special warnings and precautions for use

Suicide

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

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

Cases of suicidal thoughts and suicidal behaviours have been reported during DUZELA therapy or early after treatment discontinuation (see section 4.8). Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts, and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present. Doctors should encourage patients to report any distressing thoughts or feelings at any time.

Risk of 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 for antidepressant medicine in inducing such behaviour has however,not been established.

Patients being treated with DUZELA 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 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 such as DUZELA 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 DUZELA, 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, DUZELA should be tapered (see section 4.2)

Serotonin syndrome/ Neuroleptic malignant syndrome:

As with other serotonergic medicines, serotonin syndrome or neuroleptic malignant syndrome (NMS), a potentially life- threatening condition, may occur with DUZELA 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).Serotonin syndrome in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, elevated serum creatine kinase levels, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

If concomitant treatment with DUZELA and other serotonergic/ neuroleptic 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.

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 duloxetine as in DUZELA.DUZELA may increase the risk of postpartum haemorrhage (see section 4.6, 4.8). Caution is advised in patients taking anticoagulants and/or medicines known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (aspirin)), and in patients with known bleeding tendencies.

Mania and seizures:

DUZELA should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Mydriasis:

Mydriasis has been reported in association with duloxetine, therefore, caution should be used

when prescribing DUZELA to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Increased blood pressure and heart rate:

DUZELA has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with DUZELA, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. DUZELA should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when DUZELA is used with medicines that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while treated with DUZELA, either dose reduction or gradual discontinuation should be (considered see section 4.8). In patients with uncontrolled hypertension DUZELA should not be initiated.

Renal impairment:

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance < 30 mL/min). DUZELA is contraindicated in patients with severe renal impaiment (see section 4.3). See section 4.2 for information on patients with mild or moderate renal dysfunction. A lower starting dose should be used in such patients.

Hepatic impairment:

Increased plasma concentrations of duloxetine occur in patients with hepatic impairment. DUZELA is contraindicated in patients with severe hepatic impairment (see section 4.3). A lower starting or less frequent dose should be used in patients with mild to moderate impairment of hepatic

function (see section 4.2).

St John's wort:

Adverse reactions may be more common during concomitant use of DUZELA and herbal preparations containing St John's wort (*Hypericum perforatum*) (see section 4.5).

Hyponatraemia:

Hyponatraemia has been reported when administering DUZELA, including cases with serum sodium lower than 110 mmol/L. Hyponatraemia may be due to a syndrome of inappropriate antidiuretic hormone secretion (SIADH) (see section 4.8). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of ,or condition predisposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly patients,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 (see sections 4.8). In clinical trials, adverse events seen on abrupt treatment discontinuation occurred in approximately 45 % of patients treated with duloxetine as contained in DUZELA and 23 % of patient taking placebo.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 listed in section 4.8. 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 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 DUZELA should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Elderly patients:
Data on the use of 120 mg of DUZELA in elderly patients with major depressive disorder and generalised anxiety disorder are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.2).

Akathisia/psychomotor restlessness:
The use of DUZELA 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.

Medicines containing duloxetine:
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence).The use of more than one of these medicines concomitantly should be avoided.

Hepatitis/increased liver enzymes:
Cases of liver injury, including severe elevations of liver enzymes (> 10 times the upper limit of normal), hepatitis and jaundice have been reported with DUZELA (see section 4.8). Some cases were associated with excessive alcohol use. Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. DUZELA should be used with caution in patients treated with other medicines associated with hepatic injury. DUZELA should also be used with caution in patients with substantial alcohol use.

Sexual dysfunction:
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where symptoms have continued despite discontinuation of

SSRIs/SNRIs.

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 a 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.

Takotsubo cardiomyopathy

Literature shows an association between increased levels of catecholamines and the risk of Takotsubo cardiomyopathy, suggesting that inhibition of androgen receptors by duloxetine results in increased catecholamines levels and consequently cardiomyopathy. Takotsubo cardiomyopathy is reversible upon discontinuation of DUZELA and appropriate treatment.
The risk of Takotsubo cardiomyopathy could be a class effect for all SNRIs due to their mechanism of action.

MAOIs (Monoamine Oxidase Inhibitors):

DUZELA should not be used within at least 14 days of discontinuing treatment with Monoamine Oxidase Inhibitors (MAOIs) and at least 5 days should be allowed after stopping DUZELA, before starting a MAOI.

Sucrose:

DUZELA capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take DUZELA. Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Paediatric population

*Safety and efficacy of DUZELA have not been established in patients under the age of 18 years (see sections 4.3).*DUZELA should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, and anger) were more frequently observed in clinical trials among children, adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms (see section 5.1). In addition,long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

Due to the risk of serotonin syndrome, DUZELA should not be used in combination with non selective irreversible 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 DUZELA before starting an MAOI (see section 4.3).

The concomitant use of Cymbalta with selective, reversible MAOIs,like moclobemide, is not recommended (see section 4.4). The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with DUZELA (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in DUZELA metabolism, concomitant use of DUZELA with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of DUZELA by about 77 % and increased AUC_{o-t} 6-fold. Therefore, DUZELA should not be administered in combination with potent inhibitors of CYP1A2 like Fluvoxamine (see section 4.3).

Central nervous system (CNS) medicines: The risk of using DUZELA in combination with other CNS-active medicines has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when DUZELA is taken in combination with other centrally-acting medicines or substances, including alcohol and sedative medicines (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

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

linezolid is contraindicated (see section 4.3).

Effect of DUZELA on other medicines:

Medicines metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine as contained in DUZELA (60 mg twice daily). These results suggest that DUZELA is unlikely to have a clinical significant effect on the metabolism of CYP1A2 substrates.

Medicines metabolised by CYP2D6: DUZELA 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 and no dosage adjustment is recommended.
Caution is advised if DUZELA is co-administered with medicines that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).

Inhibitors of CYP2D6: Because CYP2D6 is involved in DUZELA metabolism, concomitant use of DUZELA with inhibitors of CYP2D6 may result in higher concentrations of duloxetine.
Paroxetine (20mg once daily) decreased the apparent plasma clearance of duloxetine by about 37 %. Caution is advised if DUZELA is administered with inhibitors of CYP2D6 (e.g. SSRIs).

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

Anticoagulants and antiplatelet medicines: Caution should be exercised when DUZELA 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 duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of duloxetine with warfarin under steady-state conditions, in healthy volunteers as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of *R*- or *S*-warfarin.

Medicines highly bound to plasma protein: Duloxetine is highly bound to plasma proteins (> 90 %). Therefore, administration of DUZELA to a patient taking another medicine that is highly protein bound, may cause an increase in free concentrations of either medicine.

Effects of other medicines on DUZELA:

Antacids and H_2 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 % lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of DUZELA in pregnant women has not been established (see section 4.3). Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to DUZELA within the month prior to birth (see sections 4.4, 4.8).

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 DUZELA, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

Discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with DUZELA 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.

DUZELA should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Breastfeeding:
Safety of DUZELA during breastfeeding has not been established (see section 4.3). DUZELA and/or its metabolites are excreted into the milk.

Fertility:

In animal studies, DUZELA 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

DUZELA may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile:

The most frequent reported adverse reactions in patients treated with DUZELA were nausea, headache, dry mouth, somnolence and dizziness. However, the majority of common adverse reactions were mild to moderate; they usually started early in therapy, and most tended to subside even as therapy was continued.

Tabulated summary of adverse reactions:

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	*Less frequent*	Laryngitis
Immune system disorders	*Less frequent*	Anaphylactic reaction, hypersensitivity disorder
Endocrine disorders	*Less frequent*	Hypothyroidism
Metabolism and nutrition disorders	*Frequent*	Decreased appetite
	Less frequent	Hyperglycaemia (reported especially in diabetic patients), dehydration, hyponatraemia,SIADH[6]
Psychiatric disorders	*Frequent*	Insomnia, agitation, libido decreased, anxiety, orgasm abnormal, abnormal dreams, feeling jittery, nervousness, restlessness, tension
	Less frequent	Suicidal ideation[5,7], sleep disorder, bruxism, disorientation, apathy, suicidal behaviour[5,7],mania, hallucinations, aggression and anger[4]
Nervous system disorders	*Frequent*	Headache, somnolence, dizziness, lethargy, tremor, paraesthesia, hypersomnia, sedation,
	Less frequent	Myoclonus, akathisia[7], nervousness, disturbance in attention, dysgeusia, dyskinesia, restless legs syndrome,

		poor quality sleep, serotonin syndrome[6], convulsions[1], psychomotor restlessness[6], extra-pyramidal symptoms[6]
Eye disorders	*Frequent*	Blurred vision
	Less frequent	Mydriasis, visual impairment, glaucoma
Ear and labyrinth disorders	*Frequent*	Tinnitus[1]
	Less frequent	Vertigo, ear pain
Cardiac disorders	*Frequent*	Palpitations
	Less frequent	Tachycardia, supraventricular arrhythmia, mainly atrial fibrillation
	Frequency unknown	Stress cardiomyopathy (Takotsubo cardiomyopathy)
Vascular disorders	*Frequent*	Blood pressure increased[3], flushing
	Less frequent	Syncope[2], hypertension[3,7], orthostatic hypotension[2], peripheral coldness, hypertensive crisis[3,6]
Respiratory, thoracic and mediastinal disorders	*Frequent*	Yawning
	Less frequent	Throat tightness, epistaxis, interstitial lung disease[10], eosinophilic pneumonia[6]
Gastrointestinal disorders	*Frequent*	Nausea, dry mouth, constipation, diarrhoea, abdominal pain, vomiting, dyspepsia (includes stomach discomfort), flatulence

	Less frequent	Gastrointestinal haemorrhage[7], gastroenteritis, eructation, gastritis, dysphagia, stomatitis, haematochezia, breath odour, microscopic colitis[9]
Hepato-biliary disorders	*Less frequent*	Hepatitis[3], elevated liver enzymes (ALT, AST, alkaline phosphatase), acute liver injury, hepatic failure[6], jaundice[6], bilirubin increased
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[6], angioneurotic oedema[6], 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, urine odour abnormal
Reproductive system and breast disorders	*Frequent*	Males: Erectile dysfunction. ejaculation

		disorder, ejaculation delayed, decreased libido, Females: Anorgasmia, abnormal orgasm
	Less frequent	Females: Gynaecological haemorrhage, menstrual disorder, postpartum haemorrhage[6], menopausal symptoms, Males: testicular pain, sexual dysfunction, galactorrhoea, hyperprolactinaemia
General disorders and administration site conditions	*Frequent*	Falls[8], fatigue, asthenia, rigors
	Less frequent	Chest pain[7], feeling abnormal, feeling cold, thirst, chills, malaise, feeling hot, gait disturbance
Investigations	*Frequent*	Weight decrease, increased blood pressure
	Less frequent	Weight increase, blood creatine phosphokinase, increase, blood potassium increased, blood cholesterol increased

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

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

[3] See section 4.4.

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

discontinuation.

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

[6] Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

[7] Not statistically significantly different from placebo.

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

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

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

Description of selected adverse reactions:

Discontinuation of DUZELA (particularly when abrupt) commonly leads to withdrawal symptoms. 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, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when DUZELA treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12-week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0,3 %

greater in the duloxetine-treated group.

There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine treated patients, while those laboratory tests showed a slight decrease in the routine care group.

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of DUZELA is important. It allows continued monitoring of the benefit/risk balance of DUZELA. Health care providers are requested 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. Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email or telephonically: Pharmacovigilance.africasme@sunpharma.com or tel: +27 (0)12 643 2000

4.9 Overdose

Signs and symptoms

Cases of overdoses, alone or in combination with other medicines, with duloxetine doses of 5 400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1 000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicines) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

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 for DUZELA, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after Ingestion or in symptomatic patients.

Activated charcoal may be useful in limiting absorption. Duloxetine 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

Category and class: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Other antidepressants.

ATC code: N06AX21.

Mechanism of action:

Duloxetine is a combined serotonin (5-hydroxytriptamine, 5-HT) and noradrenaline (NA) (norepinephrine) reuptake inhibitor. It weakly inhibits dopamine reuptake, with no significant affinity for histaminergic, dopaminergic, cholinergic, and adrenergic receptors. Duloxetine dose dependently increases extracellular levels of serotonin and noradrenaline (norepinephrine) in various brain areas of animals. Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and noradrenaline (norepinephrine) neurotransmission in the central nervous system (CNS).

Pharmacodynamic effects:

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50 – 60 %), partly due to gender, age, smoking status, and CYP2D6 metaboliser status.

Absorption:

Duloxetine is well absorbed after oral administration, with a C_{max} occurring 6 hours post-dose. The absolute oral bioavailability of duloxetine ranged from 32 % to 80 % (mean of 50 %). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). These changes do not have any clinical significance. Steady-state plasma concentrations are achieved after 3 days of dosing.

Distribution:

Duloxetine is approximately 96 % bound to human plasma proteins. Duloxetine binds to both albumin and alpha$_1$-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 cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites, glucuronide

conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination:

The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 L/h to 46 L/h (mean of 36 L/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 L/h to 261 L/h (mean 101 L/h).

Special populations:

Gender:

Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50 % lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age:

Pharmacokinetic differences have been identified between younger and elderly females (≥ 65 years) (AUC increases by about 25 % and half-life is about 25 % longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Smoking status:

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

Renal impairment:

End-stage renal disease 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 sections 4.2 and 4.3).

Hepatic impairment:

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).

Breast-feeding mothers:

The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7µg/day while on 40 mg twice-daily dosing.Lactation did not influence duloxetine pharmacokinetics.

Paediatric population:

Pharmacokinetics of duloxetine in paediatric patients aged 7 to 17 years with major depressive disorder following oral administration of 20 to 120 mg once daily dosing regimen was characterized using population modelling analyses based on data from 3 studies. The model predicted duloxetine steady-state plasma concentrations in paediatric patients were mostly within the concentration range observed in adult patients.

6. PHARMECUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Sugar spheres (consisting of sucrose and maize starch)

Hypromellose

Mannitol

Purified talc

Sucrose

Methacrylic acid copolymer dispersion

Triethyl citrate

Sodium hydroxide.

Capsule shell:

Gelatine

Sodium lauril sulfate

FD&C Blue 2 (E132)

Titanium dioxide (E171)

Yellow iron oxide (E172) (only in DUZELA 60).

Printing ink (edible):

Shellac

Dehydrated alcohol

Isopropyl alcohol

Butyl alcohol

Propylene glycol

Strong ammonia solution

Potassium hydroxide

Purified water

Black iron oxide (E172) (only in DUZELA 30)

Titanium dioxide (E171) (only in DUZELA 60).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original container in order to protect from light.

6.5 Nature and contents of container

DUZELA is packed in a white, round HDPE bottle with a child-resistant, white polypropylene cap with liner.

Pack sizes: 30, 90 or 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBERS

DUZELA 30: 48/1.2/0680

DUZELA 60: 48/1.2/0681

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 November 2020

10. DATE OF REVISION OF THE TEXT

11 March 2026