Professional Information for DULEVE 30 & 60

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DULEVE 30 hard gastro-resistant capsules

DULEVE 60 hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipients with known effect:

Contains sugar (sucrose).

DULEVE 30: Each capsule contains 79 mg sucrose.

DULEVE 60: Each capsule contains 158 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsules.

DULEVE 30: Pink coloured, free flowing pellets filled in size 3 hard gelatine capsule with opaque blue cap and opaque white body.

DULEVE 60: Pink coloured, free flowing pellets filled in size 1 hard gelatine capsule with opaque blue cap and opaque green body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DULEVE 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:

DULEVE 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:

DULEVE should be administered 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.

Discontinuation of treatment:

Abrupt discontinuation of DULEVE should be avoided. When stopping treatment with DULEVE the dose should be gradually reduced over a period of at least 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). DULEVE 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).

DULEVE 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 DULEVE 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 sections 4.3 and 4.4.

Method of administration:

For oral use.

4.3 Contraindications

- Hypersensitivity to duloxetine or to any of the components of DULEVE (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 DULEVE with monoamine oxidase inhibitors (MAOIs) (see section 4.4).
- Children under 18 years as the safety in children has not been established.

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 DULEVE therapy or early after treatment discontinuation (see section 4.8).

Close supervision of patients, and in particular those at high risk, should accompany medicine therapy, especially in early treatment and following dose changes.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression. This risk may persist until significant remission occurs. A casual role, however, for antidepressant medicine in inducing such behaviour has not been established.

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.

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 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 DULEVE, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

As with other medicines with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above.

Doctors should encourage patients to report any distressing thoughts or feelings at any time when taking DULEVE.

Use in children and adolescents under 18 years of age:
DULEVE should not be used in the treatment of children and adolescents under the age of 18 years as safety and efficacy have not been establisthed (see section 4.3). Suicide-related behaviours (suicide attempts and suicidal thoughts), self-harm and hostility (predominantly aggression,

oppositional behaviour, and anger) were more frequently observed in clinical trials among children and 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 4.8). In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking.

Mania and seizures:

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

Blood pressure and heart rate:

DULEVE 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 DULEVE, 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. DULEVE 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 DULEVE 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 DULEVE, either dose reduction or gradual discontinuation should be considered (see section 4.8).

In patients with uncontrolled hypertension DULEVE should not be initiated.

Renal impairment:

Increased plasma concentrations of DULEVE occur in patients with severe renal impairment on haemodialysis (creatinine clearance < 30 mL/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Hepatic impairment:

Increased plasma concentrations of duloxetine occur in patients with hepatic impairment. A lower starting dose should be used in such patients (see section 4.2).

Serotonin syndrome:

Serotonin syndrome, a potentially life-threatening condition, may occur with DULEVE 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 DULEVE 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.

St John's wort:

Adverse reactions may be more common during concomitant use of DULEVE and herbal preparations

containing St John's wort (*Hypericum perforatum*).

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

Hyponatraemia:

Hyponatraemia has been reported when administering DULEVE, 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 section 4.8). In clinical trials, adverse events seen on abrupt treatment discontinuation occurred in approximately 45 % of patients treated with duloxetine as contained in DULEVE and 23 % of patients 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 DULEVE 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 DULEVE 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).

Akathisia/psychomotor restlessness:

The use of DULEVE 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. The use of more than one of these products 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 DULEVE (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. DULEVE should be used with caution in patients treated with other medicines associated with hepatic injury. DULEVE should also be used with caution in patients with substantial alcohol use.

Sexual dysfunction:

DULEVE may cause symptoms of sexual dysfunction (see section 4.8). These may continue despite discontinuation of DULEVE.

Sucrose:

DULEVE capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take DULEVE.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

Due to the risk of serotonin syndrome, DULEVE 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 DULEVE before starting an MAOI (see section 4.3).

The antibiotic linezolid is a MAOI and should not be given to patients treated with DULEVE (see sections 4.3 and 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in DULEVE metabolism, concomitant use of DULEVE 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 DULEVE by about 77 % and increased AUC_{0-t} 6-fold. Therefore, DULEVE should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

Central nervous system (CNS) medicines: The risk of using DULEVE 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 DULEVE is taken in combination with other centrally-

acting medicines or substances, including alcohol and sedative medicines (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital (phenobarbitone), sedative antihistamines).

Serotonergic medicines: Serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic medicines. Caution is advisable if DULEVE 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 with MAOIs, including moclobemide or linezolid, is contraindicated (see section 4.3).

Effect of DULEVE 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 DULEVE (60 mg twice daily). These results suggest that DULEVE is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Medicines metabolised by CYP2D6: DULEVE 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 DULEVE 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 DULEVE metabolism, concomitant use of DULEVE with inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine

(20 mg once daily) decreased the apparent plasma clearance of duloxetine by about 37 %. Caution is advised if DULEVE 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 DULEVE) 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 DULEVE 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 DULEVE 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 DULEVE:

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 DULEVE 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 DULEVE within the month prior to birth.

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 duloxetine, 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 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.

Breastfeeding:

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

Fertility:

In animal studies, DULEVE 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

DULEVE 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 DULEVE 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.

Hostility, suicidal ideation and self-harm have been reported in children treated with SSRIs or SNRIs like DULEVE.

Tabulated summary of adverse reactions:

Frequent	Less frequent
Infections and infestations	
	Laryngitis
Immune system disorders	
	Anaphylactic reaction Hypersensitivity disorder
Endocrine disorders	
	Hypothyroidism
Metabolism and nutrition disorders	
Decreased appetite	Hyperglycaemia (reported especially in diabetic patients) Dehydration Hyponatraemia SIADH[6]
Psychiatric disorders	
Insomnia	Suicidal ideation[5,7]

Agitation Libido decreased Anxiety Orgasm abnormal Abnormal dreams	Sleep disorder Bruxism Disorientation Apathy Suicidal behaviour[5,7] Mania Hallucinations Aggression and anger[4]
Nervous system disorders	
Headache Somnolence Dizziness Lethargy Tremor Paraesthesia	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	
Blurred vision	Mydriasis Visual impairment Glaucoma
Ear and labyrinth disorders	
Tinnitus[1]	Vertigo

	Ear pain
Cardiac disorders	
Palpitations	Tachycardia Supraventricular arrhythmia, mainly atrial fibrillation Takotsubo cardiomyopathy
Vascular disorders	
Blood pressure increased[3] Flushing	Syncope[2] Hypertension[3,7] Orthostatic hypotension[2] Peripheral coldness Hypertensive crisis[3,6]
Respiratory, thoracic and mediastinal disorders	
Yawning	Throat tightness Epistaxis Interstitial lung disease[10] Eosinophilic pneumonia[6]
Gastrointestinal disorders	
Nausea Dry mouth Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage[7] Gastroenteritis Eructation Gastritis Dysphagia Stomatitis Haematochezia Breath odour Microscopic colitis[9]
Hepato-biliary disorders	

	Hepatitis[3] Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury Hepatic failure[6] Jaundice[6] Bilirubin increased
Skin and subcutaneous tissue disorders	
Sweating increased Rash	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	
Musculoskeletal pain Muscle spasm	Muscle tightness Muscle twitching Trismus
Renal and urinary disorders	
Dysuria Pollakiuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased Urine odour abnormal

Reproductive system and breast disorders	
Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction Testicular pain Menopausal symptoms Galactorrhoea Hyperprolactinaemia Postpartum haemorrhage[6]
General disorders and administration site conditions	
Falls[8] Fatigue	Chest pain[7] Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance
Investigations	
Weight decrease	Weight increase Blood creatine phosphokinase increased 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 DULEVE 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 DULEVE (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 DULEVE 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 DULEVE is important. It allows continued monitoring of the benefit/risk balance of DULEVE. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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 medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for DULEVE, 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.

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-hydroxytryptamine, 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).

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 and a resultant increase in serotonergic and noradrenergic neurotransmission in the CNS.

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/h). 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Sugar spheres (consisting of sucrose and maize starch)

Hypromellose

Hypromellose acetate succinate

Micronised talc

Sucrose

Triethyl citrate

Titanium dioxide

Red iron oxide (E172).

Capsule shell:

Indigo carmine (E132)

Titanium dioxide (E171)

Gelatine

Sodium laurilsulfate

Yellow iron oxide (E172) (only in DULEVE 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 blister strips in outer carton until required for use.

6.5 Nature and contents of container

OPA/aluminium/PVC and aluminium blister strips containing 10 capsules each.

Pack size: 30 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare S.A. (Pty) Ltd

Southdowns Office Park, Building B, Ground Floor

22 Karee Street

Centurion

0157

8. REGISTRATION NUMBERS

DULEVE 30: 49/1.2/1198

DULEVE 60: 49/1.2/1199

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