

PACKAGE INSERT – ONELAR

1. NAME OF THE MEDICINAL PRODUCT

ONELAR 30 mg hard gastro-resistant capsules

ONELAR 60 mg hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 mg or 60 mg of duloxetine (as hydrochloride).

Excipient(s) with known effect:

Each 30 mg capsules contains 76.5 mg sucrose and 0.0009 mg carmoisine.

Each 60 mg capsules contains 153 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

ONELAR 30 mg: Hard gelatine capsules, size “3”, with white body and blue cap containing off white pellets

ONELAR 60 mg: Hard gelatine capsules, size “0”, with light grey body and pink cap containing off white pellets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of major depressive disorder.

Treatment of neuropathic pain associated with diabetic peripheral neuropathy in adults.

Treatment of generalised anxiety disorder.

4.2. Posology and method of administration

Posology

Major depressive disorder

The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations.

Therapeutic response is usually seen after 2-4 weeks of treatment.

After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.

Generalised anxiety disorder

The recommended starting dose in patients with generalised anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients.

In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above).

Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60 mg, escalation up to 90 mg or 120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.

After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

Diabetic peripheral neuropathic pain

The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see section 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher

dose.

Response to treatment should be evaluated after 2 months. In patients with inadequate initial response, additional response after this time is unlikely.

The therapeutic benefit should be reassessed regularly (at least every three months) (see section 5.1).

Special populations

Elderly

No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with 120 mg duloxetine per day for major depressive disorder or generalised anxiety disorder, for which data are limited (see sections 4.4 and 5.2).

Hepatic impairment

ONELAR must not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

Renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ONELAR must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Paediatric population

Duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns (see sections 4.4, 4.8 and 5.1).

The safety and efficacy of duloxetine for the treatment of generalised anxiety disorder in paediatric patients aged 7-17 years have not been established. Current available data are described in sections 4.8, 5.1 and 5.2.

The safety and efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain has not been studied. No data are available.

Discontinuation of treatment

Abrupt discontinuation should be avoided. When stopping treatment with ONELAR 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.

Method of administration

For oral use.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of ONELAR with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.5).

Liver disease resulting in hepatic impairment (see section 5.2).

ONELAR should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ONELAR is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4. Special warnings and precautions for use

Mania and seizures

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

Blood pressure and heart rate

Duloxetine 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 duloxetine, 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. Duloxetine 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 duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment

Increased plasma concentrations of duloxetine 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.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs tricyclic antidepressants or triptans), with agents 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 duloxetine and other serotonergic agents 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 ONELAR and herbal preparations containing St John's wort (*Hypericum perforatum*).

Suicide

Major Depressive Disorder and Generalised Anxiety Disorder: 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.

Other psychiatric conditions for which ONELAR is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8).

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

Diabetic Peripheral Neuropathic Pain: As with other medicinal products 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. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age

ONELAR should not be used in the treatment of children and adolescents under the age of 18 years.. 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).

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. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia

Hyponatraemia has been reported when administering duloxetine, 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 (see section 4.8). The risk of withdrawal symptoms seen with SSRI's and SNRI's 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 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 duloxetine 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

Data on the use of ONELAR 120 mg 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 duloxetine 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.

Medicinal products 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 products concomitantly should be avoided.

Hepatitis/increased liver enzymes

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Sucrose

ONELAR contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose

malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Carmoisine

ONELAR 30 mg contains carmoisine that may cause allergic reactions.

Suicidality in Children and Adolescents

Antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.

Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behaviour.

Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

The indication(s) approved in paediatric for the particular drug should be clearly stated/included.

4.5. Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine 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 ONELAR before starting an MAOI (see section 4.3).

The concomitant use of ONELAR 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 ONELAR (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine 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 duloxetine by about 77% and increased AUC_{0-t} 6-fold. Therefore ONELAR should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

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

Serotonergic agents: In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic agents. Caution is advisable if ONELAR is used concomitantly with serotonergic agents 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).

Effect of duloxetine on other medicinal products

Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

Medicinal products metabolised by CYP2D6: Duloxetine 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 ONELAR is co-administered with medicinal products 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).

Oral contraceptives and other steroidal agents: 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.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral

anticoagulants or antiplatelet agents 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.

Effects of other medicinal products on duloxetine

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

4.6. Fertility, pregnancy and lactation

Fertility

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

Pregnancy

There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure.

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

Observation data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

As with other serotonergic medicinal products, 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.

ONELAR 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.

Breast-feeding

Duloxetine is very weakly excreted into human milk. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ONELAR while breast-feeding is not recommended.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ONELAR 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 commonly reported adverse reactions in patients treated with ONELAR 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.

Table 1: Adverse reactions

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Very Rare</i>
<i>Infections and infestations</i>				
		Laryngitis		

Very common	Common	Uncommon	Rare	Very Rare
<i>Immune system disorders</i>				
			Anaphylactic reaction Hyper-sensitivity disorder	
<i>Endocrine disorders</i>				
			Hypo-thyroidism	
<i>Metabolism and nutrition disorders</i>				
	Decreased Appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration Hyponatraemia SIADH ⁶	
<i>Psychiatric disorders</i>				
	Insomnia Agitation Libido decreased Anxiety Orgasm abnormal Abnormal dreams	Suicidal ideation ^{5,7} Sleep disorder Bruxism Disorientation Apathy	Suicidal behaviour ^{5,7} Mania Hallucinations Aggression and anger ⁴	
<i>Nervous system disorders</i>				
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	
<i>Eye disorders</i>				
	Blurred vision	Mydriasis Visual impairment	Glaucoma	
<i>Ear and labyrinth disorders</i>				
	Tinnitus ¹	Vertigo Ear pain		
<i>Cardiac disorders</i>				
	Palpitations	Tachycardia Supra-ventricular arrhythmia, mainly atrial fibrillation		
<i>Vascular disorders</i>				
	Blood pressure increase ³ Flushing	Syncope ² Hypertension ^{3,7} Orthostatic hypotension ² Peripheral coldness	Hypertensive crisis ^{3,6}	
<i>Respiratory, thoracic and mediastinal disorders</i>				
	Yawning	Throat tightness Epistaxis	Interstitial lung disease Eosinophilic pneumonia ⁶	
<i>Gastrointestinal disorders</i>				
Nausea Dry mouth	Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage ⁷ Gastroenteritis Eructation Gastritis Dysphagia	Stomatitis Haematochezia Breath odour Microscopic colitis	
<i>Hepato-biliary disorders</i>				

<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Very Rare</i>
		Hepatitis ³ Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure ⁶ Jaundice ⁶	
<i>Skin and subcutaneous tissue disorders</i>				
	Sweating increased Rash	Night sweats Urticaria Dermatitis contact Cold sweat Photo-sensitivity reactions Increased tendency to bruise	Stevens-Johnson Syndrome ⁶ Angio-neurotic oedema ⁶	Cutaneous vasculitis
<i>Musculoskeletal and connective tissue disorders</i>				
	Musculo-skeletal pain Muscle spasm	Muscle tightness Muscle twitching	Trismus	
<i>Renal and urinary disorders</i>				
	Dysuria Pollakiuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased	Urine odour abnormal	
<i>Reproductive system and breast disorders</i>				
	Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction Testicular pain	Menopausal symptoms Galactorrhoea Hyperprolactinaemia Postpartum haemorrhage ⁶	
<i>General disorders and administration site conditions</i>				
Fatigue	Falls ⁸ Fatigue	Chest pain ⁷ Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance		
<i>Investigations</i>				
	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 duloxetine 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)

Description of selected adverse reactions

Discontinuation of duloxetine (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 duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

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.

Paediatric population

In general, the adverse reaction profile of duloxetine in children and adolescents was similar to that seen for adults.

4.9. Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 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 duloxetine 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

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) 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 in various brain areas of animals.

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.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin

and alpha-l 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.

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/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

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).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

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 7 $\mu\text{g/day}$ 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. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ONELAR 30 mg

Pellet Core: Sugar spheres (sucrose, maize starch)

Pellet Coating: Hypromellose 2910/5mPa·s, Crospovidone type A, Sucrose, Hypromellose Acetate Succinate, Triethyl Citrate (E1505), Talc, Macrogol 8000, Titanium Dioxide (E171)

Capsule shell: Titanium dioxide (E171), Gelatin (bovine), Patent blue V (E131), Sodium laurilsulfate, Carmoisine (E122).

This product contains substance from animal.

ONELAR 60 mg

Pellet Core: Sugar spheres (sucrose, maize starch)

Pellet Coating: Hypromellose 2910/5mPa·s, Crospovidone type A, Sucrose, Hypromellose Acetate Succinate, Triethyl Citrate (E1505), Talc, Macrogol 8000, Titanium Dioxide

Capsule shell: Titanium dioxide (E171), Gelatin (bovine), Sodium laurilsulfate, Erythrosine (E127), Iron oxide red (E172), Iron oxide black (E172)

This product contains substance from animal.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

ONELAR 30 mg hard gastro-resistant capsules : 36 months

ONELAR 60 mg hard gastro-resistant capsules : 24 months

6.4. Special precautions for storage

Do not store above 30°C

6.5. Nature and contents of container

ONELAR 30 mg hard gastro-resistant capsules: PA/Alu/PVC/Alu blisters containing 7 or 10 hard gastro-resistant capsules.

ONELAR 60 mg hard gastro-resistant capsules: transparent PVC/PE/PVDC-Alu Blisters containing 7 or 10 hard gastro-resistant capsules.

Pack sizes: blisters x 28 and 100, not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MANUFACTURER

MEDOCHEMIE LTD (FACTORY AZ), 2 Michael Erakleous Street, Agios Athanassios Industrial Area, Agios Athanassios, Limassol, 4104, Cyprus

MEDOCHEMIE LTD (CENTRAL FACTORY), 1-10 Constantinoupoloes street, 3011 Limassol, Cyprus

8. PRODUCT REGISTRATION HOLDER

KOMEDIC SDN BHD, 4 Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya

9. DATE OF REVISION OF THE TEXT

06/2022