SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Duloxetine 40 mg hard gastro-resistant capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant capsule, hard contains 40 mg of duloxetine (as hydrochloride).

Excipient with known effect:

Each 40 mg capsule contains 128.33 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsules, hard.

Duloxetine 40 mg: Opaque blue cap/opaque orange body size ‘2’ (approximately 17.80 mm lock length) hard gelatin capsule imprinted with ‘H’ on cap and ‘D3’ on body with black ink, filled with white to off white colored pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Duloxetine is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI).

Duloxetine is indicated in adults.

For further information see section 5.1.

4.2 Posology and method of administration

Posology
The recommended dose of Duloxetine is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.

However, limited data are available to support the efficacy of Duloxetine 20 mg twice daily.

The efficacy of Duloxetine has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining Duloxetine with a pelvic floor muscle training (PFMT) programme may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Hepatic impairment
Duloxetine must not be used in women 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). Duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Paediatric population

The safety and efficacy of duloxetine for the treatment of stress urinary incontinence has not been studied. No data are available.

Special populations

Elderly
Caution should be exercised when treating the elderly.

Discontinuation of treatment
Abrupt discontinuation should be avoided. When stopping treatment with Duloxetine 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(s) or to any of the excipients listed in section 6.1.

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

Duloxetine should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors - MAOIs (see section 4.5).

Duloxetine should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacin 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 Duloxetine 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

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

Serotonin syndrome

Concomitant administration of duloxetine and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

St John's wort

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

Mydriasis

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

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. Duloxetine may increase the risk of postpartum haemorrhage (see section 4.6). 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.

Discontinuation of treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with Duloxetine and 24% of patients taking placebo.

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).

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.

Depression, suicidal ideation and behaviour

Although Duloxetine is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medicinal product. 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 a 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 medicinal products 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 duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on Duloxetine therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of Duloxetine is recommended (see section 4.2).

Use in children and adolescents under 18 years of age

Duloxetine 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 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. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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.

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.

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 the symptoms have continued despite discontinuation of SSRIs/SNRI.

Sucrose

Duloxetine hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Duloxetine should be used cautiously when co-administered with serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (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 Duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

CNS medicinal products: Caution is advised when Duloxetine 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 duloxetine 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 Duloxetine 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. 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.

Effects of other medicinal products on duloxetine

Antacids and H_2 antagonists: Co-administration of duloxetine with aluminium- and magnesium-containing antacids or 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 studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Fertility, Pregnancy and lactation

Fertility

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

Pregnancy

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

Two large observational studies do not suggest an overall increased risk of major congenital malformation (one from the US including 2,500 exposed to duloxetine during the first trimester and one from the EU including 1,500 exposed to duloxetine during the first trimester). The analysis on specific malformations such as cardiac malformations shows inconclusive results.

In the EU study, maternal exposure to duloxetine during late pregnancy (at any time from 20 weeks gestational age to delivery) was associated with an increased risk for preterm birth (less than 2-fold, corresponding to approximately 6 additional premature births per 100 women treated with duloxetine late in pregnancy). The majority occurred between 35 and 36 weeks of gestation. This association was not seen in the US study.

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

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).

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.

Duloxetine 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 based on a study of 6 lactating patients, who did not breast feed their children. 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 Duloxetine 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. Duloxetine 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

a. Summary of the safety profile

The most commonly reported adverse events in patients treated with duloxetine in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouth fatigue and constipation. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

b. Tabulated summary of adverse reactions

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials.

Table 1: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

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

Very common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Infections and infestations				
		Laryngitis		
Immune system disorders				
		Hyper-sensitivity disorder	Anaphylactic reaction	
Endocrine disorders				
		Hypo-thyroidism		
Metabolism and nutrition disorders				
	Appetite decreased	Dehydration	Hyperglycaemia (reported especially in diabetic patients) Hyponatraemia SIADH[6]	
Psychiatric disorders				
	Insomnia Agitation Libido decreased Anxiety Sleep disorder	Bruxism Disorientation Apathy Orgasm abnormal Abnormal dreams	Suicidal behaviour[5,6] Suicidal ideation[5,7] Mania[6] Hallucinations Aggression and anger[4,6]	
Nervous system disorders				
	Headache Dizziness Lethargy Somnolence Tremor Paraesthesia	Nervousness Disturbance in attention Dysgeusia Poor quality sleep	Serotonin syndrome[6] Convulsions[1,6] Myoclonus Akathisia[6] Psychomotor restlessness[6] Extra-pyramidal symptoms[6] Dyskinesia Restless legs syndrome	

Eye disorders				
	Blurred vision	Mydriasis Visual impairment Dry eye	Glaucoma	
Ear and labyrinth disorders				
	Vertigo	Tinnitus[1] Ear pain		
Cardiac disorders				
		Palpitations Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation[6]	
Vascular disorders				
	Hypertension[3, 7] Flushing	Syncope[2] Blood pressure increase[3]	Hypertensive crisis[3] Orthostatic hypotension[2] Peripheral coldness	
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	Gastrointestinal haemorrhage[7] Gastroenteritis Stomatitis Eructation Gastritis Dysphagia Flatulence Breath odour	Haematochezia Microscopic colitis[9]	
Hepato-biliary disorders				
		Hepatitis[3] Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure[6] Jaundice[6]	
Skin and subcutaneous tissue disorders				
	Sweating increased	Rash Night sweats	Stevens-Johnson	Cutaneous vasculitis

		Urticaria Dermatitis contact Cold sweat Increased tendency to bruise	Syndrome[6] Angio-neurotic oedema[6] Photo-sensitivity reactions	
Musculoskeletal and connective tissue disorders				
		Musculo-skeletal pain Muscle tightness Muscle spasm Trismus	Muscle twitching	
Renal and urinary disorders				
		Urinary hesitation Dysuria Nocturia Pollakiuia Urine odour abnormal	Urinary retention[6] Polyuria Urine flow decreased	
Reproductive system and breast disorders				
		Gynaecological haemorrhage Menopausal symptoms	Menstrual disorder Galactorrhoea Hyperprolactinaemia Postpartum haemorrhage[6]	
General disorders and administration site conditions				
Fatigue	Asthenia Chills	Chest pain[7] Falls[8] Feeling abnormal Feeling cold Thirst Malaise Feeling hot	Gait disturbance	
Investigations				
		Weight decrease Weight increase Blood cholesterol increased Blood creatine phosphokinase increased	Blood potassium 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)
[9] Estimated frequency based on all clinical trial data.
[10] Estimated frequency based on placebo-controlled clinical trials.

c. 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.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Yellow Card Scheme; Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Pharmacodynamic effects

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

Clinical efficacy and safety

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to

duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: In all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54% and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of duloxetine has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of duloxetine compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, duloxetine may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, $p<0.001$). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, $p<0.001$).

Duloxetine *and Prior Continence Surgery:* There are limited data that suggest that the benefits of duloxetine are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

Duloxetine *and Pelvic Floor Muscle Training (PFMT):* During a 12-week blinded, randomised, controlled study, duloxetine demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than duloxetine alone or PFMT alone.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with duloxetine in all subsets of the paediatric population in the treatment of stress urinary incontinence. See section 4.2 for information on paediatric use.

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 sulfate 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/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 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

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

Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposure levels below maximum clinical exposure (AUC).

Studies in juvenile rats reveal transient effects on neurobehaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Sugar spheres (sucrose and maize starch)
Hypromellose (E464)
Crospovidone (E1202)
Talc (E553b)
Sucrose
Carboxy methyl ethyl cellulose
Povidone (E1201)
Titanium dioxide (E171)
Macrogol (E1521)
Polysorbate 80 (E433)

Capsule shell:

Gelatin
Titanium dioxide (E171)
Sodium laurilsulfate (E487)
Indigo carmine (E132)
Iron oxide yellow (E172)
Iron oxide red (E172)

Printing ink:

Shellac (E904)
Propylene glycol (E1520)
Black iron oxide (E172)
Potassium hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-Aluminium blister.

Duloxetine is available in blister pack of 28, 56 and 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/1229

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/03/2021

10 DATE OF REVISION OF THE TEXT

08/07/2021