SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DUCILTIA 30 mg hard gastro-resistant capsules
Duloxetine 30 mg hard gastro-resistant capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Duloxetine 30 mg
Each hard gastro-resistant capsule contains 30 mg of duloxetine (as hydrochloride).

Excipient(s) with known effect
Each hard gastro-resistant capsule contains 1.95 mg lactose (as monohydrate).
Each hard gastro-resistant capsule contains 0.167 mg Allura Red (E129).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Duloxetine 30 mg
Opaque white body, size 2 capsule, imprinted with “30”and an opaque dark blue cap, containing 4 white to off white, round, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

Duloxetine is indicated in adults.

For further information see section 5.1.

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. Doses 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. Doses 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 dose 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 Duloxetine 120 mg per day for major depressive disorder or generalised anxiety disorder, for which data are limited (see sections 4.4 and 5.2).

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

Renal impairment
No dose 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
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 have not been studied. No data are available.

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 or to any of the excipients listed in section 6.1.

Concomitant use of Duloxetine with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.5).

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

Duloxetine 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 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.

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing Duloxetine 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 / Neuroleptic malignant syndrome

As with other serotonergic agents, serotonin syndrome, or neuroleptic malignant syndrome (NMS), a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs tricyclic antidepressants, buprenorphine 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). Serotonin syndrome in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, elevated serum creatine kinase levels, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

If concomitant treatment with duloxetine and other serotonergic/ neuroleptic 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 Duloxetine 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 Duloxetine 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. 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).

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.

Paediatric population
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 (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. 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.

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). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with duloxetine 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 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).

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/SNRIs.

Elderly
Data on the use of duloxetine 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 dose (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.

Excipients
Duloxetine 30 mg contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Duloxetine 30 mg contain Allura Red (E129), which may cause allergic reactions.
Duloxetine 30 mg contain less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

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 Duloxetine before starting an MAOI (see section 4.3).

The concomitant use of Duloxetine 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 duloxetine (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
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 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, buprenorphine, 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 dose 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* interaction studies with other medicinal products 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 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
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.

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

4.7 Effects on ability to drive and use machines

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 reactions in patients treated with duloxetine 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.

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), not known (cannot be estimated from the available data).

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

Very common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Infections and infestations					
		Laryngitis			
Immune system disorders					
			Anaphylactic reaction Hyper-sensitivity disorder		
Endocrine disorders					
			Hypo-thyroidism		
Metabolism and nutrition disorders					
	Decreased appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration Hyponatraemia SIADH[6]		

Psychiatric disorders					
	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]		
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] Convulsion[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 Supra-ventricular arrhythmia, mainly atrial fibrillation			Stress cardiomyopathy (Takotsubo cardiomyopathy)
Vascular disorders					
	Blood pressure increase[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]		
Skin and subcutaneous tissue disorders					
	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	
Musculoskeletal and connective tissue disorders					
	Musculo-skeletal 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 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).

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. HbA1c 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 HbA1c 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.

d. Paediatric population

A total of 509 paediatric patients aged 7 to 17 years with major depressive disorder and 241 paediatric patients aged 7 to 17 years with generalised anxiety disorder were treated with duloxetine in clinical trials. In general, the adverse reaction profile of duloxetine in children and adolescents was similar to that seen for adults.

A total of 467 paediatric patients initially randomized to duloxetine in clinical trials experienced a 0.1 kg mean decrease in weight at 10 weeks compared with a 0.9 kg mean increase in 353 placebo-treated patients. Subsequently, over the four- to six-month extension period, patients on average trended toward recovery to their expected baseline weight percentile based on population data from age- and gender-matched peers.

In studies of up to 9 months an overall mean decrease of 1% in height percentile (decrease of 2% in children (7-11 years) and increase of 0.3% in adolescents (12-17 years)) was observed in duloxetine-treated paediatric patients (see section 4.4).

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

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 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 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: Psychoanaleptics; 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.

Clinical efficacy and safety

Major Depressive Disorder
Duloxetine was studied in a clinical programme involving 3,158 patients (1,285 patient-years of exposure) meeting DSM-IV criteria for major depression. The efficacy of duloxetine at the recommended dose of 60 mg once a day was demonstrated in three out of three randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder. Overall, duloxetine's efficacy has been demonstrated at daily doses between 60 and 120 mg in a total of five out of seven randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder.

Duloxetine demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D) total score (including both the emotional and somatic symptoms of depression). Response and remission rates were also statistically significantly higher with duloxetine compared with placebo. Only a small proportion of patients included in pivotal clinical trials had severe depression (baseline HAM-D>25).

In a relapse prevention study, patients responding to 12 weeks of acute treatment with open-label duloxetine 60 mg once daily were randomised to either duloxetine 60 mg once daily or placebo for a further 6-months. Duloxetine 60 mg once daily demonstrated a statistically

significant superiority compared to placebo (p=0.004) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 17% and 29% for duloxetine and placebo, respectively.

During 52 weeks of placebo-controlled double-blind treatment, duloxetine-treated patients with recurrent MDD had a significantly longer symptom free period (p<0.001) compared with patients randomised to placebo. All patients had previously responded to duloxetine during open-label duloxetine treatment (28 to 34 weeks) at a dose of 60 to 120 mg/day. During the 52-week placebo-controlled, double-blind treatment phase 14.4% of the duloxetine-treated patients and 33.1% of the placebo-treated patients experienced a return of their depressive symptoms (p<0.001).

The effect of duloxetine 60 mg once a day in elderly depressed patients (≥65 years) was specifically examined in a study that showed a statistically significant difference in the reduction of the HAMD-17 score for duloxetine-treated patients compared to placebo. Tolerability of duloxetine 60 mg once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120 mg per day) are limited and thus, caution is recommended when treating this population.

Generalised Anxiety Disorder
Duloxetine demonstrated statistically significant superiority over placebo in five out of five studies including four randomised, double-blind, placebo-controlled acute studies and a relapse prevention study in adult patients with generalised anxiety disorder.

Duloxetine demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. Response and remission rates were also higher with duloxetine compared to placebo. Duloxetine showed comparable efficacy results to venlafaxine in terms of improvements on the HAM-A total score.

In a relapse prevention study, patients responding to 6 months of acute treatment with open-label duloxetine were randomised to either duloxetine or placebo for a further 6-months. Duloxetine 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo (p<0.001) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 14% for duloxetine and 42% for placebo.

The efficacy of duloxetine 30-120 mg (flexible dosing) once a day in elderly patients (>65 years) with generalised anxiety disorder was evaluated in a study that demonstrated statistically significant improvement in the HAM-A total score for duloxetine-treated patients compared to placebo-treated patients. The efficacy and safety of duloxetine 30-120 mg once daily in elderly patients with generalised anxiety disorder was similar to that seen in studies of younger adult patients. However, data on elderly patients exposed to the maximum dose (120 mg per day) are limited and, thus, caution is recommended when using this dose with the elderly population.

Diabetic Peripheral Neuropathic Pain
The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine-treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26%, respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% of patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

In an open-label long-term, uncontrolled study, the pain reduction in patients responding to 8weeks of acute treatment of duloxetine 60 mg once daily was maintained for a further 6months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item.

Paediatric population
Duloxetine has not been studied in patients under the age of 7.

Two randomized, double-blind, parallel clinical trials were performed in 800 paediatric patients aged 7 to 17 years with major depressive disorder (see section 4.2). These two studies included a 10-week placebo and active- (fluoxetine) controlled acute phase followed by six-months period of active-controlled extension treatment. Neither duloxetine (30-120 mg) nor the active control arm (fluoxetine 20-40 mg) statistically separated from placebo on change from baseline to endpoint in the Children´s Depression Rating Scale-Revised (CDRS-R) total score. Discontinuation due to adverse events was higher in patients taking duloxetine compared with those treated with fluoxetine, mostly due to nausea. During the 10-week acute treatment period, suicidal behaviours were reported (duloxetine 0/333 [0%], fluoxetine 2/225 [0.9%], placebo 1/220 [0.5%]). Over the entire 36-week course of the study, 6 out of 333 patients initially randomized to duloxetine and 3 out of 225 patients initially randomized to fluoxetine experienced suicidal behaviour (exposure adjusted incidence 0.039 events per patient year for duloxetine and 0.026 for fluoxetine). In addition, one patient who transitioned from placebo to duloxetine experienced a suicidal behaviour while taking duloxetine.

A randomised, double-blind, placebo-controlled study was performed in 272 patients aged 7-17 years with generalised anxiety disorder. The study included a 10-week placebo-controlled acute phase, followed by an 18-week extension treatment period. A flexible dose regimen was used in this study to allow for slow dose escalation from 30 mg once daily to higher doses (maximum 120 mg once daily). Treatment with duloxetine showed a statistically significantly greater improvement in GAD symptoms, as measured by PARS severity score for GAD (mean difference between duloxetine and placebo of 2.7 points [95% CI 1.3-4.0]), after 10 weeks of treatment. The maintenance of the effect has not been evaluated. There was no statistically significant difference in discontinuation due to adverse events between duloxetine and placebo groups during the 10-week acute treatment phase. Two patients who transitioned from placebo to duloxetine after the acute phase experienced suicidal behaviours while taking duloxetine during the extension phase. A conclusion on the overall benefit/risk in this age group has not been established (see also sections 4.2 and 4.8).

A single study has been performed in paediatric patients with juvenile primary fibromyalgia syndrome (JPFS) in which the duloxetine-treated group did not separate from placebo group for the primary efficacy measure. Therefore, there is no evidence of efficacy in this paediatric patient population. The randomised, double-blind, placebo-controlled, parallel study of duloxetine was conducted in 184 adolescents aged 13 to 18 years (mean age 15.53 years) with JPFS. The study included a 13-week double-blind period where patients were randomised to

duloxetine 30 mg/60 mg, or placebo daily. Duloxetine did not show efficacy in reducing pain as measured by primary outcome measure of Brief Pain Inventory (BPI) average pain score endpoint: least squares (LS) mean change from baseline in BPI average pain score at 13 weeks was -0.97 in the placebo group, compared with -1.62 in the duloxetine 30/60 mg group ($p = 0.052$). The safety results from this study were consistent with the known safety profile of duloxetine.

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing duloxetine in all subsets of the paediatric population in the treatment of major depressive disorder, diabetic neuropathic pain and generalised anxiety disorder. 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 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/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.

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.

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 (45 mg/kg/day) 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 prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures 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 reaction level was determined to be 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Pregelatinised starch (maize)
Microcrystaline cellulose
Povidone K30

Talc
Magnesium stearate
Sodium stearyl fumarate
Hypromellose Acetate Succinate (viscosity 2.4-3.6 cp)
titanium dioxide (E171),
lactose monohydrate,
hypromellose (viscosity 3 cp, 50 cp, 15 cp),
macrogol 4000,

Capsule shell:
Gelatin
Titanium dioxide (E171)
Brilliant Blue FCF (E133)
Allura Red (E129)

Printing Ink:
shellac glaze
indigo carmine aluminum lake (E132)
titanium dioxide (E171)
propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
HDPE bottles: shelf life after first opening: 30 days

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

PVC/PE/PCTFE/Al blister.

PA/Al/PVC//Al blister.
Pack sizes:
Duloxetine 30 mg: 7, 28 and 98 capsules

HDPE bottles with child-resistant polypropylene (PP) screw cap.
Pack size: 30 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
6 Dervenakion str.
15351 Pallini, Attica,
Greece

8. MARKETING AUTHORISATION NUMBER(S)

PL 17277/0347

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2020

10 DATE OF REVISION OF THE TEXT

08/11/2024