**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

DULOXETINE BOEHRINGER INGELHEIM 30 mg hard gastro-resistant capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 mg of duloxetine (as hydrochloride)

Excipients: sucrose 8.6 mg.
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Opaque white body, imprinted with '30 mg' and an opaque blue cap, imprinted with '9543'.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of diabetic peripheral neuropathic pain in adults.

### 4.2 Posology and method of administration

For oral use.

*Adults*
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 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).

*Elderly*
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating the elderly (see section 5.2).

*Children and adolescents*
There is no experience in children and adolescents (see section 4.4).

*Hepatic impairment*
DULOXETINE BOEHRINGER INGELHEIM should not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

*Renal insufficiency*
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). DULOXETINE BOEHRINGER INGELHEIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3)..

*Discontinuation of treatment*
Abrupt discontinuation should be avoided. When stopping treatment with DULOXETINE BOEHRINGER INGELHEIM 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.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of DULOXETINE BOEHRINGER INGELHEIM with nonselective, irreversible Monoamine Oxidase Inhibitors (MAOIs) is contraindicated (see section 4.5).

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

DULOXETINE BOEHRINGER INGELHEIM should not be used in combination with fluvoxamine, ciprofloxacin or enoxacine (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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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. ee section 4.2 for information on patients with mild or moderate renal dysfunction.

*Use with antidepressants*
Caution should be exercised when using DULOXETINE BOEHRINGER INGELHEIM in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.

*St John's wort*
Undesirable effects may be more common during concomitant use of DULOXETINE BOEHRINGER INGELHEIM and herbal preparations containing St John's wort (Hypericum perforatum).

*Depression, suicidal ideation and behaviour*
Although DULOXETINE BOEHRINGER INGELHEIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. 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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM is recommended (see section 4.2).

*Use in children and adolescents under 18 years of age*
No clinical trials have been conducted with duloxetine in paediatric populations. DULOXETINE BOEHRINGER INGELHEIM 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.

*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). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

*Hyponatremia*
Hyponatremia has been reported rarely, predominantly in the elderly, when administering DULOXETINE BOEHRINGER INGELHEIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

*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 BOEHRINGER INGELHEIM and 23% 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).

*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 episodes as well as 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*
DULOXETINE BOEHRINGER INGELHEIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.



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

*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 BOEHRINGER INGELHEIM is taken in combination with other centrally acting medicinal products and substances including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

*Monoamine Oxidase Inhibitors (MAOIs):* due to the risk of serotonin syndrome, DULOXETINE BOEHRINGER INGELHEIM should not be used in combination with nonselective 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 BOEHRINGER INGELHEIM before starting an MAOI (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of DULOXETINE BOEHRINGER INGELHEIM with selective, reversible MAOIs is not recommended (see section 4.4).

*Serotonin syndrome:* in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if DULOXETINE BOEHRINGER INGELHEIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (Hypericum perforatum), venlafaxine or triptans, tramadol, pethidine and tryptophan.

*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 BOEHRINGER INGELHEIM 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 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.

*Inhibitors of CYP 1A2:* 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 $AUC_{o-t}$ 6-fold. Therefore DULOXETINE BOEHRINGER INGELHEIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

*Inducers of CYP1A2:* Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

## 4.6 Pregnancy and lactation

*Pregnancy*
There are no 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 (see section 5.3).
The potential risk for humans is unknown. As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. DULOXETINE BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 6828 patients, 4199 on duloxetine and 2629 on placebo).
The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with DULOXETINE BOEHRINGER INGELHEIM were: nausea; headache, dry mouth and somnolence and dizziness.

*Table 1: Adverse reactions*
Frequency estimate: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥ 1/10,000 and <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 | Frequency not known |
|---|---|---|---|---|---|
| *Investigations* | | | | | |
| | Weight decrease | Weight increase<br>Creatine phosphokinase increased | Blood cholesterol increased | | |
| *Cardiac Disorders* | | | | | |
| | Palpitations | Tachycardia<br>Supra-ventricular arrhythmia, mainly atrial fibrillation | | | |
| *Nervous System Disorders* | | | | | |
| Headache (14.3%)<br>Somnolence | Tremor<br>Paraesthesia | Myoclonus<br>Nervousness<br>Disturbance in | Convulsion[1] | | Serotonin syndrome<br>Extra-pyramidal |

| Very common | Common | Uncommon | Rare | Very Rare | Frequency not known |
|---|---|---|---|---|---|
| (10.7%)<br>Dizziness (10.2%) | | attention<br>Lethargy<br>Dysgeusia<br>Dyskinesia<br>Restless legs syndrome<br>Poor quality sleep | | | symptoms<br>Akathisia<br>Psychomotor restlessness |
| *Eye Disorders* | | | | | |
| | Blurred vision | Mydriasis<br>Visual disturbance | Glaucoma | | |
| *Ear and Labyrinth Disorders* | | | | | |
| | Tinnitus[1] | Vertigo<br>Ear pain | | | |
| *Respiratory, thoracic and mediastinal disorders* | | | | | |
| | Yawning | Throat tightness<br>Epistaxis | | | |
| *Gastrointestinal Disorders* | | | | | |
| Nausea (24.3%)<br>Dry mouth (12.8%) | Constipation<br>Diarrhoea<br>Vomiting<br>Dyspepsia<br>Flatulence | Gastroenteritis<br>Eructation<br>Gastritis | Stomatitis<br>Breath odour<br>Haematochezia | | Gastrointestinal haemorrhage |
| *Renal and Urinary Disorders* | | | | | |
| | | Urinary Retention<br>Dysuria<br>Urinary hesitation<br>Nocturia<br>Polyuria<br>Urine flow decreased | Urine odour abnormal | | |
| *Skin and Subcutaneous Tissue Disorders* | | | | | |
| | Sweating increased<br>Rash | Night sweats<br>Urticaria<br>Dermatitis contact<br>Cold sweat<br>Photo-sensitivity reactions<br>Increased tendency to bruise | | | Angio-neurotic oedema<br>Stevens-Johnson Syndrome |
| *Musculoskeletal and connective tissue disorders* | | | | | |
| | Musculo-skeletal pain<br>Muscle | Muscle twitching | Trismus | | |

| Very common | Common | Uncommon | Rare | Very Rare | Frequency not known |
|---|---|---|---|---|---|
| | tightness<br>Muscle spasm | | | | |
| *Endocrine disorders* | | | | | |
| | | | Hypo-thyroidism | | |
| *Metabolism and Nutrition Disorders* | | | | | |
| | Decreased Appetite | Hyperglycemia (reported especially in diabetic patients) | Dehydration<br>Hyponatremia | | SIADH |
| *Infections and infestations* | | | | | |
| | | Laryngitis | | | |
| *Vascular Disorders* | | | | | |
| | Flushing | Blood pressure increase<br>Peripheral coldness<br>Orthostatic hypotension[2]<br>Syncope[2] | | | Hypertension<br>Hypertensive crisis |
| *General Disorders and Administration Site Conditions* | | | | | |
| | Fatigue<br>Abdominal pain | Feeling abnormal<br>Feeling cold<br>Thirst<br>Chills<br>Malaise<br>Feeling hot<br>Gait disturbance | | | Chest pain |
| *Immune system disorders* | | | | | |
| | | | Hyper-sensitivity disorder<br>Anaphylactic reaction | | |
| *Hepato-biliary disorders* | | | | | |
| | | Elevated liver enzymes (ALT, AST, alkaline phosphatase)<br>Hepatitis[3]<br>Acute liver injury | | | Jaundice<br>Hepatic failure |
| *Reproductive System and Breast Disorders* | | | | | |
| | Erectile dysfunction | Ejaculation disorder<br>Ejaculation delayed<br>Sexual | Menopausal symptoms | | |

| Very common | Common | Uncommon | Rare | Very Rare | Frequency not known |
|---|---|---|---|---|---|
| | | dysfunction<br>Gynaecological haemorrhage | | | |
| *Psychiatric Disorders* | | | | | |
| | Insomnia<br>Agitation<br>Libido decreased<br>Anxiety<br>Orgasm abnormal<br>Abnormal dreams | Sleep disorder<br>Bruxism<br>Disorientation<br>Apathy | Mania<br>Hallucinations<br>Aggression and anger[4] | | Suicidal ideation [5]<br>Suicidal[5] behaviour |

[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 of 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)

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor ,headache, 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.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. 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.

### 4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400mg 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.

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.

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.

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% 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 8-weeks of acute treatment of DULOXETINE BOEHRINGER INGELHEIM 60 mg once daily was maintained for a further 6-months as measured by change on the Brief Pain Inventory(BPI) 24-hour average pain item.

### 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.
Duloxetine is well absorbed after oral administration with a Cmax 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. 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.

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 5hydroxy,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.

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 approximatively 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 Cmax 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.

*Nursing 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 (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).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Capsule content:**
Hypromellose.
Hypromellose Acetate Succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate.

**Capsule shell:**
30 mg:
Gelatin
Sodium Lauryl Sulfate
Titanium Dioxide (E171)
Indigo Carmine (E132)
Edible Green Ink

Edible Green Ink contains:
Black Iron Oxide-Synthetic (E172)
Yellow Iron Oxide- Synthetic (E172)
Propylene glycol
Shellac.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30 C.

### 6.5 Nature and contents of container

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

DULOXETINE BOEHRINGER INGELHEIM 30 mg is available in packs of 7, 28 and 98 capsules.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany.

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/471/003-005

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8th October 2008

## 10. DATE OF REVISION OF THE TEXT

## 1. NAME OF THE MEDICINAL PRODUCT

DULOXETINE BOEHRINGER INGELHEIM 60 mg hard gastro-resistant capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: sucrose 17.2 mg.
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Opaque green body, imprinted with '60 mg' and an opaque blue cap, imprinted with '9542'.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of diabetic peripheral neuropathic pain in adults.

### 4.2 Posology and method of administration

For oral use.

*Adults*
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 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).

*Elderly*
*Diabetic Peripheral Neuropathic Pain*: No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating the elderly (see section 5.2).

*Children and adolescents*
There is no experience in children and adolescents (see section 4.4).

*Hepatic impairment*
DULOXETINE BOEHRINGER INGELHEIM should not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

*Renal insufficiency*
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). DULOXETINE BOEHRINGER INGELHEIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

*Discontinuation of treatment*
Abrupt discontinuation should be avoided. When stopping treatment with DULOXETINE BOEHRINGER INGELHEIM 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.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of DULOXETINE BOEHRINGER INGELHEIM with nonselective, irreversible Monoamine Oxidase Inhibitors (MAOIs) is contraindicated (see section 4.5).

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

DULOXETINE BOEHRINGER INGELHEIM should not be used in combination with fluvoxamine, ciprofloxacin or enoxacine (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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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.

*Use with antidepressants*
Caution should be exercised when using DULOXETINE BOEHRINGER INGELHEIM in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.

*St John's wort*
Undesirable effects may be more common during concomitant use of DULOXETINE BOEHRINGER INGELHEIM and herbal preparations containing St John's wort (Hypericum perforatum).

*Depression, suicidal ideation and behaviour*
Although DULOXETINE BOEHRINGER INGELHEIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. 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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM is recommended (see Section 4.2).

*Use in children and adolescents under 18 years of age*
No clinical trials have been conducted with duloxetine in paediatric populations. DULOXETINE BOEHRINGER INGELHEIM 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.

*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). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

*Hyponatremia*
Hyponatremia has been reported rarely, predominantly in the elderly, when administering DULOXETINE BOEHRINGER INGELHEIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

*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 BOEHRINGER INGELHEIM and 23% 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).

*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 episodes as well as 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*
DULOXETINE BOEHRINGER INGELHEIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.



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

*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 BOEHRINGER INGELHEIM is taken in combination with other centrally acting medicinal products and substances including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

*Monoamine Oxidase Inhibitors (MAOIs):* due to the risk of serotonin syndrome, DULOXETINE BOEHRINGER INGELHEIM should not be used in combination with nonselective 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 BOEHRINGER INGELHEIM before starting an MAOI (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of DULOXETINE BOEHRINGER INGELHEIM with selective, reversible MAOIs is not recommended (see section 4.4).

*Serotonin syndrome:* in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if DULOXETINE BOEHRINGER INGELHEIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (Hypericum perforatum), venlafaxine or triptans, tramadol, pethidine and tryptophan.

*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 BOEHRINGER INGELHEIM 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 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.

*Inhibitors of CYP 1A2:* 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 $AUC_{o-t}$ 6-fold. Therefore DULOXETINE BOEHRINGER INGELHEIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

*Inducers of CYP1A2:* Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

## 4.6 Pregnancy and lactation

*Pregnancy*
There are no 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 (see section 5.3).
The potential risk for humans is unknown. As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term.
DULOXETINE BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM 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

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 6828 patients, 4199 on duloxetine and 2629 on placebo).
The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with DULOXETINE BOEHRINGER INGELHEIM were: nausea; headache, dry mouth and somnolence and dizziness.

*Table 1: Adverse reactions*
Frequency estimate: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥ 1/10,000 and <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 | Frequency not known |
|---|---|---|---|---|---|
| *Investigations* | | | | | |
| | Weight decrease | Weight increase<br>Creatine phosphokinase increased | Blood cholesterol increased | | |
| *Cardiac Disorders* | | | | | |
| | Palpitations | Tachycardia<br>Supra-ventricular arrhythmia, mainly atrial fibrillation | | | |
| *Nervous System Disorders* | | | | | |
| Headache (14.3%)<br>Somnolence | Tremor<br>Paraesthesia | Myoclonus<br>Nervousness<br>Disturbance in | Convulsion[1] | | Serotonin syndrome<br>Extra-pyramidal |

| Very common | Common | Uncommon | Rare | Very Rare | Frequency not known |
|---|---|---|---|---|---|
| (10.7%)<br>Dizziness (10.2%) | | attention<br>Lethargy<br>Dysgeusia<br>Dyskinesia<br>Restless legs syndrome<br>Poor quality sleep | | | symptoms<br>Akathisia<br>Psychomotor restlessness |
| *Eye Disorders* | | | | | |
| | Blurred vision | Mydriasis<br>Visual disturbance | Glaucoma | | |
| *Ear and Labyrinth Disorders* | | | | | |
| | Tinnitus[1] | Vertigo<br>Ear pain | | | |
| *Respiratory, thoracic and mediastinal disorders* | | | | | |
| | Yawning | Throat tightness<br>Epistaxis | | | |
| *Gastrointestinal Disorders* | | | | | |
| Nausea (24.3%)<br>Dry mouth (12.8%) | Constipation<br>Diarrhoea<br>Vomiting<br>Dyspepsia<br>Flatulence | Gastroenteritis<br>Eructation<br>Gastritis | Stomatitis<br>Breath odour<br>Haematochezia | | Gastrointestina-l haemorrhage |
| *Renal and Urinary Disorders* | | | | | |
| | | Urinary Retention<br>Dysuria<br>Urinary hesitation<br>Nocturia<br>Polyuria<br>Urine flow decreased | Urine odour abnormal | | |
| *Skin and Subcutaneous Tissue Disorders* | | | | | |
| | Sweating increased<br>Rash | Night sweats<br>Urticaria<br>Dermatitis contact<br>Cold sweat<br>Photo-sensitivity reactions<br>Increased tendency to bruise | | | Angio-neurotic oedema<br>Stevens-Johnson Syndrome |
| *Musculoskeletal and connective tissue disorders* | | | | | |
| | Musculo-skeletal pain<br>Muscle | Muscle twitching | Trismus | | |

| Very common | Common | Uncommon | Rare | Very Rare | Frequency not known |
|---|---|---|---|---|---|
| | tightness<br>Muscle spasm | | | | |
| *Endocrine disorders* | | | | | |
| | | | Hypo-thyroidism | | |
| *Metabolism and Nutrition Disorders* | | | | | |
| | Decreased Appetite | Hyperglycemia (reported especially in diabetic patients) | Dehydration<br>Hyponatremia | | SIADH |
| *Infections and infestations* | | | | | |
| | | Laryngitis | | | |
| *Vascular Disorders* | | | | | |
| | Flushing | Blood pressure increase<br>Peripheral coldness<br>Orthostatic hypotension[2]<br>Syncope[2] | | | Hypertension<br>Hypertensive crisis |
| *General Disorders and Administration Site Conditions* | | | | | |
| | Fatigue<br>Abdominal pain | Feeling abnormal<br>Feeling cold<br>Thirst<br>Chills<br>Malaise<br>Feeling hot<br>Gait disturbance | | | Chest pain |
| *Immune system disorders* | | | | | |
| | | | Hyper-sensitivity disorder<br>Anaphylactic reaction | | |
| *Hepato-biliary disorders* | | | | | |
| | | Elevated liver enzymes (ALT, AST, alkaline phosphatase)<br>Hepatitis[3]<br>Acute liver injury | | | Jaundice<br>Hepatic failure |
| *Reproductive System and Breast Disorders* | | | | | |
| | Erectile dysfunction | Ejaculation disorder<br>Ejaculation delayed<br>Sexual | Menopausal symptoms | | |

| Very common | Common | Uncommon | Rare | Very Rare | Frequency not known |
|---|---|---|---|---|---|
| | | dysfunction<br>Gynaecological haemorrhage | | | |
| *Psychiatric Disorders* | | | | | |
| | Insomnia<br>Agitation<br>Libido decreased<br>Anxiety<br>Orgasm abnormal<br>Abnormal dreams | Sleep disorder<br>Bruxism<br>Disorientation<br>Apathy | Mania<br>Hallucinations<br>Aggression and anger[4] | | Suicidal ideation [5]<br>Suicidal[5] behaviour |

[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 of 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)

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, 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.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. 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.

### 4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400mg 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.

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.

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.

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% 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 8-weeks of acute treatment of DULOXETINE BOEHRINGER INGELHEIM 60 mg once daily was maintained for a further 6-months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item.

### 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.
Duloxetine is well absorbed after oral administration with a Cmax 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. 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.

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 5hydroxy,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.

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 approximatively 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 Cmax 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.

*Nursing 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 (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).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Capsule content:**
Hypromellose.
Hypromellose Acetate Succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate.

**Capsule shell:**
60 mg:
Gelatin
Sodium Lauryl Sulfate
Titanium Dioxide (E171)
Indigo Carmine (E132)
Yellow Iron Oxide (E172)
Edible White Ink

Edible White Ink contains:
Titanium Dioxide (E171)
Propylene glycol
Shellac
Povidone.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30 C.

### 6.5 Nature and contents of container

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

DULOXETINE BOEHRINGER INGELHEIM 60 mg is available in packs of 28 and 98 capsules.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany.

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/471/011-012

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8th October 2008

## 10. DATE OF REVISION OF THE TEXT

# ANNEX II

**A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

## A MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly S.A.
Avda. de la Industria Nº 30,
28108 Alcobendas
Madrid
Spain

## B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

*Pharmacovigilance system*
The MAH must ensure that the system of pharmacovigilance, as described in Edition 5.2 dated April 2009 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

*Risk Management Plan*
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in Revision 0 of 24 April 2008 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

*PSURs*

The PSUR cycle of Duloxetine Boehringer Ingelheim will correspond to the one attributed to the cross-referred product, Ariclaim, until otherwise specified.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTONS FOR 30 MG HARD GASTRO-RESISTANT CAPSULES**

**1. NAME OF THE MEDICINAL PRODUCT**

DULOXETINE BOEHRINGER INGELHEIM 30 mg, hard gastro-resistant capsules.
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 30 mg of duloxetine (as hydrochloride)

**3. LIST OF EXCIPIENTS**

Contains sucrose
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

7 hard gastro-resistant capsules,
28 hard gastro-resistant capsules
98 hard gastro-resistant capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30°C

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany.

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/471/003
EU/1/08/471/004
EU/1/08/471/005

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

DULOXETINE BOEHRINGER INGELHEIM 30 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**
**30 mg hard gastro-resistant capsules**

## 1. NAME OF THE MEDICINAL PRODUCT

DULOXETINE BOEHRINGER INGELHEIM 30 mg hard gastro-resistant capsules
Duloxetine

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot:

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTONS FOR 60 MG HARD GASTRO-RESISTANT CAPSULES**

**1. NAME OF THE MEDICINAL PRODUCT**

DULOXETINE BOEHRINGER INGELHEIM 60 mg, hard gastro-resistant capsules.
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 60 mg of duloxetine (as hydrochloride)

**3. LIST OF EXCIPIENTS**

Contains sucrose
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

28, hard gastro-resistant capsules
98, hard gastro-resistant capsules.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.
Read the leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30°C

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF**

**APPROPRIATE**

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany.

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/471/011
EU/1/08/471/012

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

DULOXETINE BOEHRINGER INGELHEIM 60 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**
**60 mg hard gastro-resistant capsules**

**1. NAME OF THE MEDICINAL PRODUCT**

DULOXETINE BOEHRINGER INGELHEIM 60 mg hard gastro-resistant capsules
Duloxetine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot:

**5. OTHER**

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**DULOXETINE BOEHRINGER INGELHEIM 30 mg hard gastro-resistant capsules**
**DULOXETINE BOEHRINGER INGELHEIM 60 mg hard gastro-resistant capsules**
Duloxetine (as hydrochloride)

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

**In this leaflet**:




## 1. WHAT DULOXETINE BOEHRINGER INGELHEIM IS AND WHAT IT IS USED FOR

DULOXETINE BOEHRINGER INGELHEIM increases the levels of serotonin and noradrenaline in the nervous system.

DULOXETINE BOEHRINGER INGELHEIM is used in adults to treat a condition called diabetic neuropathic pain (often described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain).

The effect of DULOXETINE BOEHRINGER INGELHEIM may be noticeable in many patients with diabetic neuropathic pain within 1 week of treatment.

## 2. BEFORE YOU TAKE DULOXETINE BOEHRINGER INGELHEIM

**DO NOT take DULOXETINE BOEHRINGER INGELHEIM if you:**
- are allergic (hypersensitive) to duloxetine or any of the other ingredients of DULOXETINE BOEHRINGER INGELHEIM
- have liver disease
- have severe kidney disease are taking or have recently taken within the last 14 days, another antidepressant medicine called a monoamine oxidase inhibitor (MAOI) (see also below in section: ‘Taking other medicines’)
-
- are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacine which are used to treat some infections

Talk to your doctor if you have high blood pressure. Your doctor will tell you if you should be taking DULOXETINE BOEHRINGER INGELHEIM.

**Take special care with DULOXETINE BOEHRINGER INGELHEIM**

The following are reasons why DULOXETINE BOEHRINGER INGELHEIM may not be suitable for you. Talk to your doctor before you take the medicine if you:

- are taking other medicines to treat depression(see 'Taking other medicines')
- are taking St. John's Wort, a herbal treatment (Hypericum perforatum)
- have kidney disease
- have had seizures (fits)
- have had mania
- suffer from bipolar disorder
- have eye problems, such as certain kinds of glaucoma (increased pressure in the eye)
- have a history of bleeding disorders (tendency to develop bruises)
- are at risk of low sodium levels
- are currently being treated with another medicine which may cause liver damage
- are taking other medicines containing duloxetine
- have intolerance to some sugars (see end of Section 2)
- are considering stopping DULOXETINE BOEHRINGER INGELHEIM (see section 3)

DULOXETINE BOEHRINGER INGELHEIM may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

***Thoughts of suicide and worsening of your depression or anxiety disorder***
If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this if you:
- have previously had thoughts about killing or harming yourself.
- are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

**If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.**
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

***Use in children and adolescents under 18 years of age***
DULOXETINE BOEHRINGER INGELHEIM should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe DULOXETINE BOEHRINGER INGELHEIM for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed DULOXETINE BOEHRINGER INGELHEIM for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking DULOXETINE BOEHRINGER INGELHEIM. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioural development of DULOXETINE BOEHRINGER INGELHEIM in this age group have not yet been demonstrated.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The main ingredient of DULOXETINE BOEHRINGER INGELHEIM, duloxetine, is used in other medicines for other conditions:
- depression, anxiety and urinary incontinence.

Using more than one of these medicines at the same time should be avoided. Check with your doctor if you are already taking other medicines containing duloxetine.

Your doctor should decide whether you can take DULOXETINE BOEHRINGER INGELHEIM with other medicines. **Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.**

You should also tell your doctor if you are taking any of the following:

***Monoamine Oxidase Inhibitors (MAOIs):*** You should not take DULOXETINE BOEHRINGER INGELHEIM if you are taking, or have recently taken within the last 14 days, another antidepressant medicine called a monoamine oxidase inhibitor (MAOI). Taking a MAOI together with many prescription medicines, including DULOXETINE BOEHRINGER INGELHEIM, can cause serious or even life-threatening side effects. You must wait at least 14 days after you have stopped taking an MAOI before you can take DULOXETINE BOEHRINGER INGELHEIM. Also, you need to wait at least 5 days after you stop taking DULOXETINE BOEHRINGER INGELHEIM before you take a MAOI.

***Medicines that cause sleepiness:*** These include medicines prescribed by your doctor including benzodiazepines, strong painkillers, antipsychotics, phenobarbital, antihistamines.

***Medicines that increase the level of serotonin:*** triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with DULOXETINE BOEHRINGER INGELHEIM, you should see your doctor.

***Oral anticoagulants*****:** medicines which thin the blood. These medicines might increase the risk of bleeding.

**Taking DULOXETINE BOEHRINGER INGELHEIM with food and drink**
DULOXETINE BOEHRINGER INGELHEIM may be taken with or without food. Care should be taken if you drink alcohol while you are being treated with DULOXETINE BOEHRINGER INGELHEIM.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.
Tell your doctor if you

- become pregnant, or you are trying to become pregnant, while you are taking DULOXETINE BOEHRINGER INGELHEIM. You should use DULOXETINE BOEHRINGER INGELHEIM only after discussing the potential benefits and any potential risks to your unborn child with your doctor.

- are breast-feeding. The use of DULOXETINE BOEHRINGER INGELHEIM while breastfeeding is not recommended. You should ask your doctor or pharmacist for advice.

**Driving and using machines**
DULOXETINE BOEHRINGER INGELHEIM may make you feel sleepy of dizzy. Do not drive or use any tools or machines until you know how DULOXETINE BOEHRINGER INGELHEIM affects you.

**Important information about some of the ingredients of DULOXETINE BOEHRINGER INGELHEIM**
DULOXETINE BOEHRINGER INGELHEIM contains **sucrose.** If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 3. HOW TO TAKE DULOXETINE BOEHRINGER INGELHEIM

Always take DULOXETINE BOEHRINGER INGELHEIM exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**The usual dose** of DULOXETINE BOEHRINGER INGELHEIM is 1 capsule (60 mg) once a day, but your doctor will prescribe the dose that is right for you.

DULOXETINE BOEHRINGER INGELHEIM is for oral use. You should swallow your capsule whole with a drink of water.

To help you remember to take DULOXETINE BOEHRINGER INGELHEIM, you may find it easier to take it at the same times every day.

Talk with your doctor about how long you should keep taking DULOXETINE BOEHRINGER INGELHEIM. Do not stop taking DULOXETINE BOEHRINGER INGELHEIM without talking to your doctor.

**If you take more DULOXETINE BOEHRINGER INGELHEIM than you should**
Call your doctor or pharmacist immediately if you take more than the amount of DULOXETINE BOEHRINGER INGELHEIM prescribed by your doctor.

**If you forget to take DULOXETINE BOEHRINGER INGELHEIM**
If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take a double dose to make up for a forgotten dose. Do not take more than the daily amount of DULOXETINE BOEHRINGER INGELHEIM that has been prescribed for you in one day.

**If you stop taking DULOXETINE BOEHRINGER INGELHEIM**
DO NOT stop taking your capsules without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need DULOXETINE BOEHRINGER INGELHEIM he or she will ask you to reduce your dose over at least 2 weeks before stopping treatment altogether.
Some patients who stop taking DULOXETINE BOEHRINGER INGELHEIM suddenly have had symptoms such as :

- dizziness, tingling feelings like pins and needles, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling restless or agitated, feeling anxious, feeling sick (nausea) or being sick (vomiting), tremor (shakiness), headaches, feeling irritable, diarrhoea, excessive sweating or vertigo. These symptoms are usually not serious and disappear within a few days, but if you have symptoms that are troublesome you should ask your doctor for advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.



## 4. POSSIBLE SIDE EFFECTS

Like all medicines, DULOXETINE BOEHRINGER INGELHEIM can cause side effects, although not everybody gets them. These effects are normally mild to moderate and often disappear after a few weeks.

**Very common side effects (these can affect more than 10 in 100 patients treated)**

- feeling sick (nausea), somnolence, headache, dizziness and dry mouth

**Common side effects (these can affect from 1 to 10 users in 100 patients treated)**

- tiredness, trouble sleeping, anxiety, feeling agitated or having abnormal dreams
- tremor or numbness, including numbness or tingling of the skin
- diarrhoea, constipation, being sick (vomiting), heartburn, breaking wind, stomach pain

- tinnitus (perception of sound in the ear when there is no external sound)
- blurred eyesight
- feeling the heart pumping in the chest, flushing, increased sweating, night sweats
- problems getting an erection, less sex drive
- (itchy) rash
- muscle pain, muscle tightness, muscle spasm
- increased yawning
- lack of appetite, weight loss

**Uncommon side effects (these can affect from 1 to 10 users in 1,000 patients treated)**
- throat inflammation
- feeling disorientated, feeling sleepy, lack of motivation
- tasting things differently than usual, disturbance in attention, stiffness, spasms and involuntary movements of the muscles, muscle twitching, abnormal manner of walking
- poor sleep quality
- restless legs syndrome
- burping, indigestion, gastroenteritis
- vertigo, ear pain
- inflammation of the liver that may cause abdominal pain
- large pupils (the dark centre of the eye), visual disturbance
- fast or irregular heart beat
- sexual problems, including changes in ejaculation and abnormal orgasm
- abnormal periods, including heavy or prolonged periods
- allergic reactions, increased tendency to bruise, blisters or sensitivity to sunlight
- increase in blood pressure, feeling cold in your fingers and/or toes, feeling dizzy (particularly when standing up too quickly), cold sweats, shivering or fainting
- an increased level of sugar in the blood
- need to pass more urine than normal, need to pass urine during the night, difficulty or inability to pass urine or having an urine flow decreased
- grinding of teeth, feeling hot/cold, thirst, throat tightness, nose bleeds
- weight gain

**Rare side effects (these can affect from 1 to 10 users in 10,000 patients treated)**
- decreased thyroid gland activity
- dehydration
- mania (over activity, racing thoughts and decrease need for sleep)
- bad breath
- increased pressure in the eye (glaucoma)
- menopausal symptoms
- contraction of the jaw muscle
- increased level of cholesterol in the blood, low levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused),
- serious allergic reaction which causes difficulty in breathing or dizziness or hives
- fits

**Other possible side effects**
- hallucinations, suicidal thoughts, behaviour aggression and anger
- a sensation of restlessness or an inability to sit or stand still or “Serotonin syndrome” (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles)
- passing bright red blood in your stools, vomiting blood, or black tarry stools (faeces)
- having abnormal urine odour
- syndrome of inadequate secretion of anti-diuretic hormone (SIADH)
- chest pain

- yellow colouration of the skin (jaundice), hepatic failure, Stevens-Johnson syndrome, sudden swelling of skin or mucosa (angioedema)

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.**

## 5. HOW TO STORE DULOXETINE BOEHRINGER INGELHEIM

**Keep out of the reach and sight of children**

Do not use DULOXETINE BOEHRINGER INGELHEIM after the expiry date which is stated on the carton.

Store in the original package. Do not store above 30°C.

## 6. FURTHER INFORMATION

**What DULOXETINE BOEHRINGER INGELHEIM contains**
The **active** substance is duloxetine.
Each capsule contains 30 or 60 mg of duloxetine (as hydrochloride).

The **other** ingredients are:
*Capsule content:* hypromellose, Hypromellose Acetate Succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate.
*(See end of Section 2 for further information on sucrose)*
*Capsule shell:* gelatin, sodium lauryl sulphate, titanium dioxide (E171), indigo carmine (E132), iron oxide yellow (E172) (60 mg only) and edible green ink (30 mg) or edible white ink (60 mg).
*Edible green ink:* black iron oxide-synthetic (E172), yellow iron oxide- synthetic (E172), propylene glycol, shellac.
*Edible White Ink:* titanium dioxide (E171), propylene glycol, shellac, povidone.

**What DULOXETINE BOEHRINGER INGELHEIM looks like and contents of the pack**
DULOXETINE BOEHRINGER INGELHEIM is a hard gastro-resistant capsule
Each capsule of DULOXETINE BOEHRINGER INGELHEIM contains pellets of duloxetine hydrochloride with a covering to protect them from stomach acid.

DULOXETINE BOEHRINGER INGELHEIM is available in two strengths: 30 and 60 mg.
The 30 mg capsules has an opaque white body, imprinted with '30 mg' and an opaque blue cap, imprinted with '9543'.
The 60 mg capsules has an opaque green body, imprinted with '60 mg' and an opaque blue cap, imprinted with '9542'.

DULOXETINE BOEHRINGER INGELHEIM 30 mg is available in packs of 7, 28 and 98 capsules.
DULOXETINE BOEHRINGER INGELHEIM 60 mg is available in packs of 28 and 98 capsules.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**
*Marketing Authorisation Holder:* Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany.
*Manufacturer:* Lilly S.A., Avda. De la Industria, 30,28108 Alcobendas, Madrid, Spain.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
S.C.S. Boehringer Ingelheim Comm.V.
Tél/Tel: +32 27 73 33 11

**България**
ТП "Ели Лили Недерланд" Б.В. - България
тел. + 359 2 491 41 40

**Česká republika**
Boehringer Ingelheim spol. s r.o.
Tel.: + 42 02 34 65 51 11

**Danmark**
Boehringer Ingelheim Danmark A/S
Tlf: +45 39 15 88 88

**Deutschland**
Boehringer Ingelheim Pharma GmbH & Co. KG
Tel: +49 (0) 69 50 50 83 09

**Eesti**
Boehringer Ingelheim Pharma GmbH
Tel: + 37 2 60 80 940

**Ελλάδα**
Boehringer Ingelheim Ellas A.E.
Τηλ: +30 2 10 89 06 300

**España**
Boehringer Ingelheim España S.A.
Tel: +34 93 404 58 00

**France**
Boehringer Ingelheim France S.A.S.
Tél: +33 3 26 50 45 33

**Ireland**
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

**Ísland**
Vistor hf.
Tel: +354 535 7000

**Italia**
Boehringer Ingelheim Italia S.p.A.
Tel: +39 02 535 51

**Κύπρος**
Boehringer Ingelheim Ellas A.E.
Τηλ: +30 2 10 89 06 300

**Latvija**
Boehringer Ingelheim Pharma GmbH
Tel: +37 167 24 00 68

**Luxembourg/Luxemburg**
S.C.S. Boehringer Ingelheim Comm.V.
Tél/Tel: +32 2 773 33 11

**Magyarország**
Boehringer Ingelheim Pharma
Tel.: +36 1 224 7120

**Malta**
Boehringer Ingelheim Ltd.
Tel: +44 1344 424 600

**Nederland**
Boehringer Ingelheim b.v.
Tel: +31 30 6 02 59 14

**Norge**
Boehringer Ingelheim Norway KS
Tlf: +47 66 76 13 00

**Österreich**
Boehringer Ingelheim Austria GmbH
Tel: +43 1 80 105 0

**Polska**
Eli Lilly Polska Sp. z o.o.
Tel: + 48 22 4403300

**Portugal**
Boehringer Ingelheim, Lda
Tel: +351 21 313 53 00

**România**
Eli Lilly România S.R.L.
Tel: + 40 21 4023000

**Slovenija**
Boehringer Ingelheim Pharma
Tel.: +386 1 586 40 00

**Slovenská republika**
Boehringer Ingelheim Pharma
Tel.: +421 2  5341 8445

**Suomi/Finland**
Boehringer Ingelheim Finland Ky
Puh/Tel: +358 10 310 2800

**Sverige**
Boehringer Ingelheim AB
Tel: +46 8 721 21 00

**United Kingdom**
Boehringer Ingelheim Ltd.
Tel: +44 (0) 1256 315999

**Lietuva**
Boehringer Ingelheim Pharma Ges mbH
Tel.: +370 37 47 39 22

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