Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Venlablue XL 37.5mg, prolonged release capsules, hard
Venlablue XL 75mg, prolonged release capsules, hard
Venlablue XL 150mg, prolonged release capsules, hard

(venlafaxine hydrochloride)

UK/H/1400/001-003/DC
UK licence numbers: PL 31774/0010-0012

Bluefish Pharmaceuticals AB

LAY SUMMARY

On 11th September 2009, the MHRA granted Bluefish Pharmaceuticals AB Marketing Authorisations (licences) for the medicinal products Venlablue XL 37.5mg, 75mg, and 150mg prolonged-release hard capsules (PL 31774/0010-0012, UK/H/1400/001-003/DC). These are prescription-only medicines (POM).

Venlablue XL is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medicines is used to treat depression and other conditions such as anxiety disorders. It is thought that people who are depressed and/or anxious have lower levels of serotonin and noradrenaline in the brain. It is not fully understood how antidepressants work, but they may help by increasing the levels of serotonin and noradrenaline in the brain.

Venlablue XL is a treatment for adults with depression, and is also used to treat adults with the following anxiety disorders: generalised anxiety disorder, social anxiety disorder (fear or avoidance of social situations) and panic disorder (panic attacks).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Venlablue XL 37.5mg, 75mg, and 150mg prolonged-release hard capsules outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Venlablue XL 37.5mg prolonged-release capsules, hard Venlablue XL 75mg prolonged-release capsules, hard Venlablue XL 150mg prolonged-release capsules, hard
Type of Application	PL 31774/0010 (37.5mg) - Hybrid, Article 10.3 PL 31774/0011-0012 (75mg and 150mg) - Generic, Article 10.1
Active Substance	Venlafaxine hydrochloride
Form	Hard capsules, prolonged release
Strength	37.5mg, 75mg, and 150mg
MA Holder	Bluefish Pharmaceuticals AB Torsgatan 11 SE-111 23 Stockholm Sweden
Reference Member State (RMS)	UK
Concerned Member State / s (CMS)	UK/H/1400/01/DC (37.5mg): FR, NL SE UK/H/1400/02-03/DC (75mg & 150mg): AT, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, NL, NO, PL, PT, SE, SK
Procedure Number	UK/H/1400/001-003/DC
Timetable	Day 210 – 2nd August 2009

Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Venlablue XL 37.5mg, 75mg and 150mg prolonged-release capsules, hard (PL 31774/0010-0012) is as follows – Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Venlablue XL 37.5 mg, prolonged-release capsules, hard
Venlablue XL 75 mg, prolonged-release capsules, hard
Venlablue XL 150 mg, prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

For 37.5mg: *37.5 mg:* Each capsule contains: Venlafaxine hydrochloride, corresponding to 37.5 mg Venlafaxine.

For 75mg: *75 mg:* Each capsule contains: Venlafaxine hydrochloride, corresponding to 75 mg Venlafaxine.

For 150mg: *150 mg:* Each capsule contains: Venlafaxine hydrochloride, corresponding to 150 mg Venlafaxine.

Excipients: allura red (E129) 0.198 mg and sunset yellow (E110) 0.396 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

For 37.5mg: *37,5 mg*: Light grey opaque / peach opaque, size '3' hard gelatin capsules having thick and thin radial circular band on the body in red ink and thick and thin radial circular band on the cap in red ink. The capsule is filled with 3 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

For 75mg: *75 mg:* Peach opaque / peach opaque, size '1' hard gelatin capsules having thick and thin radial circular band on the body in red ink and thick and thin radial circular band on the cap in red ink. The capsule is filled with 6 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

For 150mg: *150 mg:* Dark orange / dark orange opaque, size '0' hard gelatin capsules having thick and thin radial circular band on the body in white ink and thick and thin radial circular band on the cap in white ink. The capsule is filled with 12 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.
For prevention of recurrence of major depressive episodes
Treatment of generalised anxiety disorder
Treatment of social anxiety disorder
Treatment of panic disorder, with or without agoraphobia

4.2 Posology and method of administration

Major depressive episodes

The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly on a case-by-case basis. Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during the current episode.

Antidepressive medicinal products should continue for at least six months following remission.

Generalised Anxiety Disorder (GAD):

The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 225 mg/day. Dosage increases can be made at intervals of 2 weeks or more.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis.

Social anxiety disorder

The recommended dose for prolonged-release venlafaxine is 75 mg given once daily. There is no evidence that higher doses confer any additional benefit.

However, in individual patients not responding to the initial 75 mg/day, increases up to a maximum dose of 225 mg/day may be considered. Dosage increases can be made at intervals of 2 weeks or more.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis.

Panic disorder

It is recommended that a dose of 37.5 mg/day of prolonged-release venlafaxine be used for 7 days. Dosage should then be increased to 75 mg/day. Patients not responding to the 75 mg/day dose may benefit from dose increases up to a maximum dose of 225 mg/day. Dosage increases can be made at intervals of 2 weeks or more.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis.

Use in elderly patients:

No specific dose adjustments of venlafaxine are considered necessary based on patient age alone. However, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment, the potential for changes in neurotransmitter sensitivity and affinity occurring with aging). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

Use in children and adolescents under the age of 18 years

Venlablue XL is not recommended for use in children and adolescents.

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.4 and 4.8).

The efficacy and safety of Venlablue XL for other indications in children and adolescents under the age of 18 have not yet been established.

Use in patients with hepatic impairment

In patients with mild and moderate hepatic impairment, in general a 50% dose reduction should be considered. However, due to inter-individual variability in clearance, individualisation of dosage may be desirable.

There are limited data in patients with severe hepatic impairment. Caution is advised, and a dose reduction by more than 50% should be considered. The potential benefit should be weighed against the risk in the treatment of patients with severe hepatic impairment.

Use in patients with renal impairment

Although no change in dosage is necessary for patients with glomerular filtration rate (GFR) between 30-70 ml/minute, caution is advised. For patients that require haemodialysis and in patients with severe renal impairment (GFR < 30 ml/min), the dose should be reduced by 50%. Because of inter-individual variability in clearance in these patients, individualisation of dosage may be desirable.

Withdrawal symptoms seen on discontinuation of venlafaxine

Abrupt discontinuation should be avoided. When stopping treatment with venlafaxine, 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.

For oral use.

It is recommended that Venlablue XL prolonged-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

Patients treated with venlafaxine immediate-release tablets may be switched to venlafaxine prolonged-release capsules at the nearest equivalent daily dosage. For example, venlafaxine immediate-release tablets 37.5 mg twice daily may be switched to venlafaxine prolonged-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

Venlablue XL prolonged-release capsules contain spheroids, which release the active substance slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in faeces.

4.3 Contraindications

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

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia.

Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI.

Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age

Venlablue XL should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt 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.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents, such as MAO-inhibitors, that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

Narrow-angle glaucoma

Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) be closely monitored.

Blood pressure

Dose-related increases in blood pressure have been commonly reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in postmarketing experience. All patients should be carefully screened for high blood pressure and preexisting hypertension should be controlled before initation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function.

Heart rate
Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

Cardiac disease and risk of arrhythmia

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

In postmarketing experience, fatal cardiac arrhythmias have been reported with the use of venlafaxine, especially in overdose. The balance of risks and benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia.

Convulsions

Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions, and concerned patients should be closely monitored. Treatment should be discontinued in any patient who develops seizures.

Hyponatraemia

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

Abnormal bleeding

Medicinal products that inhibit serotonin uptake may lead to reduced platelet function. The risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased in patients taking venlafaxine. As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

Serum cholesterol

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

Co-administration with weight loss agents

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of venlafaxine and weight loss agents is not recommended. Venlafaxine is not indicated for weight loss alone or in combination with other products.

Mania/hypomania

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression

Aggression may occur in a small number of patients who have received antidepressants, including venlafaxine. This has been reported under initiation, dose changes and discontinuation of treatment.

As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

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 treatment discontinuation (tapering and post-tapering) occurred in approximately 31% of patients treated with venlafaxine and 17% of patients taking placebo.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (includingparaesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. 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 venlafaxine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

Akathisia/psychomotor restlessness

The use of venlafaxine 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.

Dry mouth
Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOI)

Irreversible non-selective MAOIs
Venlafaxine must not be used in combination with irreversible non-selective MAOIs. Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible nonselective MAOI. Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible non-selective MAOI (see sections 4.3 and 4.4).

Reversible, selective MAO-A inhibitor (moclobemide)
Due to the risk of serotonin syndrome, the combination of venlafaxine with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of venlafaxine treatment. It is recommended that venlafaxine should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.4).

Reversible, non-selective MAOI (linezolid)
The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with venlafaxine (see section 4.4).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome may occur with venlafaxine treatment,particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), with medicinal agents which impair metabolism of serotonin (including MAOIs), or with serotonin precursors (such as tryptophan supplements).

If concomitant treatment of venlafaxine with an SSRI, an SNRI or a serotonin receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

CNS-active substances

The risk of using venlafaxine in combination with other CNS-active substances has not been systematically evaluated. Consequently, caution is advised when venlafaxine is taken in combination with other CNS-active substances.

Ethanol

Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active substances, patients should be advised to avoid alcohol consumption.

Effect of other medicinal products on venlafaxine

Ketoconazole (CYP3A4 inhibitor)
A pharmacokinetic study with ketoconazole in CYP2D6 extensive (EM) and poor metabolisers (PM) resulted in higher AUC of venlafaxine (70% and 21% in CYP2D6 PM and EM subjects, respectively) and O-desmethylvenlafaxine (33% and 23% in CYP2D6 PM and EM subjects, respectively) following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and venlafaxine may increase levels of venlafaxine and O-desmethylvenlafaxine. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

Effect of venlafaxine on other medicinal products

Lithium
Serotonin syndrome may occur with the concomitant use of venlafaxine and lithium (see Serotonin syndrome).

Diazepam
Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam. Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine. It is unknown whether a pharmacokinetic and/or pharmacodynamic interaction with other benzodiazepines exists.

Imipramine
Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. There was a dose-dependent increase of 2-OH-desipramine AUC by 2.5 to 4.5-fold when venlafaxine 75 mg to 150 mg daily was administered. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown. Caution should be exercised with co-administration of venlafaxine and imipramine.

Haloperidol
A pharmacokinetic study with haloperidol has shown a 42% decrease in total oral clearance, a 70% increase in AUC, an 88% increase in C_{max}, but no change in half-life for haloperidol. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly. The clinical significance of this interaction is unknown.

Risperidone
Venlafaxine increased the risperidone AUC by 50%, but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.

Metoprolol
Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic interaction study for both medicinal products resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite,

O-desmethylvenlafaxine. Caution should be exercised with co-administration of venlafaxine and metoprolol.

Indinavir
A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in Cmax for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of venlafaxine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh any possible risk.

As with other serotonin reuptake inhibitors (SSRIs/SNRIs), discontinuation symptoms may occur in the newborns if venlafaxine is used until or shortly before birth. Some newborns exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalisation. Such complications can arise immediately upon delivery.

The following symptoms may be observed in neonates if the mother has used an SSRI/SNRI late in pregnancy: irritability, tremor, hypotonia, persistent crying, and difficulty in sucking or in sleeping.

These symptoms may be due to either serotonergic effects or exposure symptoms. In the majority of cases, these complications are observed immediately or within 24 hours after partus.

Lactation

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are excreted in breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision to continue/discontinue breast-feeding or to continue/discontinue therapy with Venlablue XL should be made, taking into account the benefit of breast-feeding to the child and the benefit of Venlablue XL therapy to the woman.

4.7 Effects on ability to drive and use machines

Any psychoactive medicinal product may impair judgment, thinking, and motor skills. Therefore, any patient receiving venlafaxine should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Adverse reactions are listed below by system organ class and frequency.

Frequencies are defined as: very common ≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); not known (cannot be estimated from the available data).

Body system	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			Ecchymosis, Gastrointestinal haemorrhage		Mucous membrane bleeding, Prolonged bleeding time, Thrombocytopaenia , Blood dyscrasias, (including agranulocytosis, aplastic anaemia, neutropaenia and pancytopaenia)
Immune system disorders			Photosensitivity reaction		Anaphylaxis

Metabolism and nutrition disorders		Serum cholesterol increased, Weight loss	Weight gain		Abnormal liver function tests, Hyponatraemia, Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Prolactin increased
Nervous system disorder	Dry mouth (10.0%), Headache (30.3%)*	Abnormal dreams, Decreased libido, Dizziness, Increased muscle tonus (hypertonia), Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Depersonalisation	Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance	Akathisia/ Psycho-motor restlessness, Convulsion, Manic reaction	Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Delirium, Extrapyramidal reactions (including dystonia and dyskinaesia), Tardive dyskinaesia, Suicidal ideation and behaviours**
Eye disorders		Abnormality of accommodation, mydriasis, visual disturbance.			Angle-closure glaucoma
Ear and labyrinth disorders			Tinnitus		
Cardiac disorder		Hypertension, Vasodilatation (mostly hot flashes/flushes), Palpitations	Postural hypotension, Syncope, Tachycardia		Hypotension, QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)
Respiratory, thoracic and mediastinal disoreder		Yawning			Pulmonary eosinophilia
Gastrointestinal disorders	Nausea (20.0%)	Appetite decreased (anorexia), Constipation, Vomiting	Altered taste sensation, Bruxism, Diarrhoea		Pancreatitis
Skin and subcutaneous tissue disorders	Sweating (including night sweats) [12.2%]	Chills	Rash, Alopecia		Erythema multiforme, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus, Urticaria
Musculoskeletal and connective tissue disorders					Rhabdomyolysis
Renal and urinary disorders		Urination impaired (mostly hesitancy), Pollakiuria	Urinary retention		
Reproductive system and breast disorder		Abnormal ejaculation/ orgasm (males),	Abnormal orgasm (females)		

		Anorgasmia, Erectile dysfunction (impotence), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia)			
General disorders and administra-tion site conditions		Asthenia (fatigue)			

*In pooled clinical trials, the incidence of headache was 30.3% with venlafaxine versus 31.3% with placebo.

**Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 4.4).

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache and flu syndrome are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Paediatric patients
In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see section 4.4).

In paediatric clinical trials the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

Particularly, the following adverse reactions were observed in paediatric patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

4.9 Overdose

In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other reported events include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxinetreated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear. Prescriptions for venlafaxine should be written for the smallest quantity of the medicinal product consistent with good patient management in order to reduce the risk of overdose.

Recommended treatment

General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored. When there is a risk of aspiration, induction of emesis is not recommended. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit absorption of the active substance. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants
ATC code: N06AX16

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline re-uptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H_1-histaminergic or α_1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicinal products, such as anticholinergic, sedative and cardiovascular side effects.

Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

In vitro studies revealed that venlafaxine has virtually no affinity for opiate or benzodiazepine sensitive receptors.

Major depressive episodes

The efficacy of venlafaxine immediate-release as a treatment for major depressive episodes was demonstrated in five randomised, double-blind, placebo-controlled, short-term trials ranging from 4 to 6 weeks duration, for doses up to 375 mg/day. The efficacy of venlafaxine prolonged-release as a treatment for major depressive episodes was established in two placebo-controlled, short-term studies for 8 and 12 weeks duration, which included a dose range of 75 to 225 mg/day.

In one longer-term study, adult outpatients who had responded during an 8-week open trial on venlafaxine prolonged-release (75, 150, or 225 mg) were randomised to continuation of their same venlafaxine prolonged-release dose or to placebo, for up to 26 weeks of observation for relapse.

In a second longer-term study, the efficacy of venlafaxine in prevention of recurrent depressive episodes for a 12-month period was established in a placebo-controlled double-blind clinical trial in adult outpatients with recurrent major depressive episodes who had responded to venlafaxine treatment (100 to 200 mg/day, on a b.i.d. schedule) on the last episode of depression.

Generalised anxiety disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for generalised anxiety disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies (75 to 225 mg/day), one 6-month, placebo-controlled, fixed-dose study (75 to 225 mg/day), and one 6-month, placebo-controlled, flexible-dose study (37.5, 75, and 150 mg/day) in adult outpatients.

While there was also evidence for superiority over placebo for the 37.5 mg/day dose, this dose was not as consistently effective as the higher doses.

Social anxiety disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for social anxiety disorder was established in four double-blind, parallel-group, 12-week, multi-center, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study in adult outpatients. Patients received doses in a range of 75 to 225 mg/day. There was no evidence for any greater effectiveness of the 150 to 225 mg/day group compared to the 75 mg/day group in the 6-month study.

Panic disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for panic disorder was established in two double-blind, 12-week, multi-center, placebo-controlled studies in adult outpatients with panic disorder, with or without agoraphobia. The initial dose in panic disorder studies was 37.5 mg/day for 7 days. Patients then received fixed doses of 75 or 150 mg/day in one study and 75 or 225 mg/day in the other study.

Efficacy was also established in one long-term double-blind, placebo-controlled, parallel-group study of the long-term safety, efficacy, and prevention of relapse in adult outpatients who responded to open-label treatment. Patients continued to receive the same dose of venlafaxine prolonged-release that they had taken at the end of the open-label phase (75, 150, or 225 mg).

5.2 Pharmacokinetic properties

Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). Mean ± SD plasma half-lives of venlafaxine and ODV are 5±2 hours and 11±2 hours, respectively. Steady-state concentrations of venlafaxine and ODV are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Absorption

At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of venlafaxine and ODV.

Distribution

Venlafaxine and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27% and 30%, respectively). The volume of distribution for venlafaxine at steady-state is 4.4±1.6 L/kg following intravenous administration.

Metabolism

Venlafaxine undergoes extensive hepatic metabolism. *In vitro* and in vivo studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. *In vitro* and *in vivo* studies indicate that venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9, or CYP3A4.

Elimination

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%).

Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1.3±0.6 L/h/kg and 0.4±0.2 L/h/kg, respectively.

Special populations

Age and gender
Subject age and gender do not significantly affect the pharmacokinetics of venlafaxine and ODV.

CYP2D6 extensive/poor metabolisers
Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

Patients with hepatic impairment
In Child-Pugh A (mildly hepatically impaired) and Child-Pugh B (moderately hepatically impaired) subjects, venlafaxine and ODV half-lives were prolonged compared to normal subjects. The oral clearance of both venlafaxine and ODV was reduced. A large degree of intersubject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).

Patients with renal impairment
In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance reduced by about 57% compared to normal subjects, while ODV elimination half-life was prolonged by about 142% and clearance reduced by about 56%. Dosage adjustment is necessary in patients with severe renal impairment and in patients that require haemodialysis (see section 4.2).

5.3 Preclinical safety data

Studies with venlafaxine in rats and mice revealed no evidence of carcinogenesis. Venlafaxine was not mutagenic in a wide range of *in vitro* and *in vivo* tests.

Animal studies regarding reproductive toxicity have found in rats a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation. The cause of these deaths is unknown. These effects occurred at 30 mg/kg/day, 4 times the human daily dose of 375 mg of venlafaxine (on an mg/kg basis). The no-effect dose for these findings was 1.3 times the human dose. The potential risk for humans is unknown.

Reduced fertility was observed in a study in which both male and female rats were exposed to ODV. This exposure was approximately 1 to 2 times that of a human dose of 375mg/day. The human relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: **For all strengths**
microcrystalline cellulose
povidone
talc
silica, colloidal anhydrous
magnesium stearate

Tablet film coat: **For all strengths**
ethyl cellulose
copovidone

Capsule:

For 37.5mg:
black iron oxide (E172)
red iron oxide (E172)
yellow iron oxide (E172)
titanium dioxide (E171)
gelatin

For 75mg:
black iron oxide (E172)
red iron oxide (E172)
titanium dioxide (E171)
gelatin

For 150mg:
allura red (E129)
sunset yellow FCF (E110)
brilliant blue FCF (E133)
titanium dioxide (E171)
gelatin

Printing Inks:

For 37.5 and 75mg:
Shellac
Red Iron Oxide

For 150mg:
Shellac
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of opaque, white PVC/Aclar film and aluminium foil; 10, 14, 28, 30, 50& 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
Torsgatan 11
SE-111 23 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

PL31774/0010

PL31774/0011

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/09/2009

10 DATE OF REVISION OF THE TEXT

11/09/2009

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Venlablue XL 37.5 mg, prolonged-release capsules
Venlablue XL 75 mg, prolonged-release capsules
Venlablue XL 150 mg, prolonged-release capsules
Venlafaxine

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 Venlablue XL is and what it is used for
2. Before you take Venlablue XL
3. How to take Venlablue XL
4. Possible side effects
5. How to store Venlablue XL
6. Further information

1. WHAT VENLABLUE XL IS AND WHAT IT IS USED FOR

Venlablue XL is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medicines is used to treat depression and other conditions such as anxiety disorders. It is thought that people who are depressed and/or anxious have lower levels of serotonin and noradrenaline in the brain. It is not fully understood how antidepressants work, but they may help by increasing the levels of serotonin and noradrenaline in the brain.

Venlablue XL is a treatment for adults with depression. Venlablue XL is also a treatment for adults with the following anxiety disorders: generalised anxiety disorder, social anxiety disorder (fear or avoidance of social situations) and panic disorder (panic attacks). Treating depression or anxiety disorders properly is important to help you get better. If it is not treated, your condition may not go away and may become more serious and more difficult to treat.

2. BEFORE YOU TAKE VENLABLUE XL

Do not take Venlablue XL

- if you are allergic to venlafaxine or any of the other ingredients of Venlablue XL.
- If you are also taking or have taken any time within the last 14 days any medicines known as irreversible monoamine oxidase inhibitors (MAOIs), used to treat depression or Parkinson's disease. Taking an irreversible MAOI together with other medicines, including Venlablue XL, can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Venlablue XL before you take any MAOI (see also the sections "Serotonin syndrome" and "Taking other medicines").

Take special care with Venlablue XL

- If you use other medicines that taken concomitantly with Venlablue XL could increase the risk of developing serotonin syndrome (see the section "Taking other medicines").
- If you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- If you have a history of high blood pressure.
- If you have a history of heart problems.
- If you have a history of fits (seizures).

Do not start or stop taking any medicines, including those bought without a prescription, natural and herbal remedies, before checking with your doctor or pharmacist.

- Monoamine oxidase inhibitors (MAOIs: see the section "Before you take Venlablue XL").
- Serotonin syndrome:
- Serotonin syndrome, a potentially life-threatening condition (see the section "Possible Side Effects"), may occur with venlafaxine treatment, particularly when taken with other medicines.
  Examples of these medicines include:
- Triptans (used for migraine)
- Medicines to treat depression, for instance SNRI, SSRIs, tricyclics, or medicines containing lithium
- Medicines containing linezolid, an antibiotic (used to treat infections)
- Medicines containing moclobemide, a reversible MAOI (used to treat depression)
- Medicines containing sibutramine (used for weight loss)
- Medicines containing tramadol (a pain-killer)
- Products containing St. John's Wort (also called Hypericum perforatum, a natural or herbal remedy used to treat mild depression)
- Products containing tryptophan (used for problems such as sleep and depression)

Signs and symptoms of serotonin syndrome may include a combination of the following:
restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhoea, coma, nausea, vomiting. Get medical care right away if you think serotonin syndrome is happening to you.

The following medicines may also interact with Venlablue XL and should be used with caution. It is especially important to mention to your doctor or pharmacist if you are taking medicines containing:

- Ketoconazole (an antifungal medicine)
- Haloperidol or risperidone (to treat psychiatric conditions)
- Metoprolol (a beta blocker to treat high blood pressure and heart problems)

Taking Venlablue XL with food and drink

Venlablue XL should be taken with food (See section 3). You should avoid alcohol while you are taking Venlablue XL.

Pregnancy and breast-feeding

Tell your doctor if you become pregnant, or you are trying to become pregnant. You should use Venlablue XL only after discussing the potential benefits and the potential risks to your unborn child with your doctor.

If you are taking Venlablue XL during pregnancy, let your midwife and/or doctor know, as your baby might have some symptoms when it is born. These symptoms usually begin during the first 24 hours after the baby is born. They include not feeding properly and trouble with breathing. If your baby has these symptoms when it is born and you are concerned, contact your doctor and/or midwife who will be able to advise you.

Venlablue XL passes into breast milk. There is a risk of an effect on the baby. Therefore, you should discuss the matter with your doctor, and he/she will decide whether you should stop breast-feeding or stop the therapy with Venlablue XL.

- If you have a history of low sodium levels in your blood (hyponatraemia).
- If you have a tendency to develop bruises or a tendency to bleed easily (history of bleeding disorders), or if you are taking other medicines that may increase the risk of bleeding.
- If your cholesterol levels get higher.
- If you have a history of, or if someone in your family has had, mania or bipolar disorder (feeling over-excited or euphoric).
- If you have a history of aggressive behaviour.

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

If any of these conditions apply to you, please talk with your doctor before taking Venlablue XL.

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 you 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.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults(less than 25 years old) 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.

Dry mouth

Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries. Therefore, you should take special care in your dental hygiene.

Use in children and adolescents under 18 years of age

Venlablue XL 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 Venlablue XL for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Venlablue XL 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 Venlablue XL. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Venlablue XL in this age group has not yet been demostrated.

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.

Your doctor should decide whether you can take Venlablue XL with other medicines.

Driving and using machines

Do not drive or use any tools or machines until you know how Venlablue XL affects you.

Important information about some of the ingredients of Venlablue XL
Venlablue XL 150 mg contains the colouring agents allura red and sunset yellow which may cause allergic reactions.

3. HOW TO TAKE VENLABLUE XL

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

The usual recommended starting dose for treatment of depression, generalised anxiety disorder and social anxiety disorder is 75 mg per day. The dose can be raised by your doctor gradually, and if needed, even up to a maximum dose of 375 mg daily for depression. If you are being treated for panic disorder, your doctor will start with a lower dose (37.5 mg) and then increase the dose gradually. The maximum dose for generalised anxiety disorder, social anxiety disorder and panic disorder is 225 mg/day.

Take Venlablue XL at approximately the same time each day, either in the morning or in the evening. Capsules must be swallowed whole with fluid and not opened, crushed, chewed or dissolved. Chewing, crushing or dissolving the content of the capsule may damage the film coating that modifies the release of the drug.

Venlablue XL should be taken with food.

Do not be concerned if you see small white granules or balls in your stools after taking Venlablue XL. Inside Venlablue XL capsules are spheroids or small white balls that contain the venlafaxine active ingredient. These spheroids are released from the capsule into your gastrointestinal tract. As the spheroids travel the length of your gastrointestinal tract, venlafaxine is slowly released. The spheroid "shell" remains undissolved and is eliminated in your stools. Therefore, even though you may see spheroids in your stools, your dose of venlafaxine has been absorbed.

If you have liver or kidney problems, talk to your doctor, since your dose of Venlablue XL may need to be different.

Do not stop taking Venlablue XL without talking to your doctor (see the section "If you stop taking Venlablue XL").

If you take more Venlablue XL than you should

Call your doctor or pharmacist immediately if you take more than the amount of Venlablue XL prescribed by your doctor.

The symptoms of a possible overdose may include a rapid heartbeat, changes in level of alertness (ranging from sleepiness to coma), blurred vision, seizures or fits, and vomiting.

If you forget to take Venlablue XL

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 more than the daily amount of Venlablue XL that has been prescribed for you in one day.

If you stop taking Venlablue XL

Do not stop taking your treament or reduce the dose without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Venlablue XL he/she will ask you to reduce your dose slowly before stopping treatment altogether. Side effects are known to occur when people stop using venlafaxine Bluefish, especially when

Venlablue XL is stopped suddenly or the dose reduced too quickly. Some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, dry mouth, loss of appetite, nausea, diarrhoea, nervousness, agitation, confusion, ringing in the ears, tingling or rarely electric shock sensations, weakness, sweating, seizures, or flu-like symptoms.

Your doctor will advise you on how you should gradually discontinue Venlablue XL treatment. If you experience any of these or other symptoms that are troublesome, ask your doctor for further 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, Venlablue XL can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not take more Venlablue XL. Tell your doctor immediately, or go to the casualty department at your nearest hospital:
- Chest tightness, wheezing, trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, dizziness, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious side effects

If you notice any signs of the following, you may need urgent medical attention:
- Heart problems, such as fast or irregular heart rate, increased blood pressure
- Eye problems, such as blurred vision, dilated pupils
- Nerve problems, such as dizziness, pins and needles, movement disorder, seizures or fits
- Psychiatric problems, such as hyperactivity and euphoria
- Treatment withdrawal (see the section "How to take Venlablue XL, if you stop taking Venlablue XL").

Complete side effect listing

The frequency (likelihood of occurring) of side effects is classified as follows:

Very common	Affects more than 1 user in 10
Common	Affects 1 to 10 users in 100
Uncommon	Affects 1 to 10 users in 1,000
Rare	Affects 1 to 10 users in 10,000
Not known	Frequency cannot be estimated from the available data

- **Blood and lymphatic system disorders**
  Uncommon: bruising; black tarry stools (faeces) or blood in stools, which can be a sign of internal bleeding
  Not known: reduced number of platelets in your blood, leading to an increased risk of bruising or bleeding; blood disorders which may lead to an increased risk of infection

- **Immune system disorders**
  Uncommon: Photosensitivity reaction
  Not known: Anaphylaxis

- **Metabolism and nutrition disorders**
  Common: weight loss; increased cholesterol
  Uncommon: weight gain
  Not known: slight changes in blood levels of liver enzymes; decrease in blood sodium levels; itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis); confusion, excessive water intake (known as SIADH); abnormal breast milk production

- **General disorders and administration site conditions**
  Common: weakness (asthenia)
  Uncommon: sensitivity to sunlight
  Not known: swollen face or tongue, shortness of breath or difficulty breathing, often with skin rashes (this may be a serious allergic reaction)

Venlablue XL sometimes causes unwanted effects that you may not be aware of, such as increases in blood pressure or abnormal heart beat; slight changes in blood levels or liver enzymes, sodium or cholesterol. More rarely, Venlablue XL may reduce the function of platelets in your blood, leading to an increased risk of bruising or bleeding. Therefore, your doctor may wish to do blood tests occasionally, particularly if you have been taking Venlablue XL for a long time.

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.

5. HOW TO STORE VENLABLUE XL

Do not store above 30°C.

Keep out of the reach and sight of children.

Do not use Venlablue XL after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not use Venlablue XL if you notice that the capsules are sticky.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Venlablue XL contains

The active substance is venlafaxine .

Each capsule contains: Venlafaxine hydrochloride, corresponding to 37,5 mg Venlafaxine.
Each capsule contains: Venlafaxine hydrochloride, corresponding to 75 mg Venlafaxine.
Each capsule contains: Venlafaxine hydrochloride, corresponding to 150 mg Venlafaxine.

The other ingredients are
Tablet core:
microcrystalline cellulose, povidone, talc, silica, colloidal anhydrous, magnesium stearate

Tablet film coat:
ethyl cellulose, copovidone

37.5 mg
Capsule:
black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), gelatin

Printing Inks:
Shellac, red iron oxide

75 mg:
Capsule:
black iron oxide (E172), red iron oxide (E172), titanium dioxide (E171), gelatin

Printing Inks:
Shellac, red iron oxide

150 mg:
Capsule:
allura red (E129), sunset yellow FCF (E110), brilliant blue FCF (E133), titanium dioxide (E171), gelatin

Printing Inks:
Shellac, titanium dioxide

- **Nervous system disorders**
  Very common: dry mouth; headache
  Common: abnormal dreams; decreased libido; dizziness; increased muscle tonus; insomnia; nervousness; pins and needles; sedation; tremor; confusion; feeling separated (or detached) from yourself and reality
  Uncommon: lack of feeling or emotion; hallucinations; involuntary movement of the muscles; agitation; impaired coordination and balance
  Rare: a sensation of restlessness or an inability to sit or stand still; seizures or fits; feeling overexcited or euphoric
  Not known: a high temperature with rigid muscles, confusion or agitation, and sweating, or if you experience jerky muscle movements which you can't control, these may be symptoms of serious conditions known as neuroleptic malignant syndrome; euphoric feelings, drowsiness, sustained rapid eye movement, clumsiness, restlessness, feeling of being drunk, sweating or rigid muscles, which are symptoms of serotonergic syndrome; disorientation and confusion often accompanied by hallucination (delirium); stiffness, spasms and involuntary movements of the muscles; thoughts of harming or killing yourself

- **Eye disorders**
  Common: blurred vision
  Not known: severe eye pain and decreased or blurred vision

- **Ear and labyrinth disorders**
  Uncommon: ringing in the ears (tinnitus)

- **Cardiac disorder**
  Common: increase in blood pressure; flushing; palpitations
  Uncommon: feeling dizzy (particularly when standing up too quickly), fainting, fast heartbeat
  Not known: decrease in blood pressure; abnormal, rapid or irregular heart beat, which could lead to fainting

- **Respiratory, thoracic and mediastinal disoreder**
  Common: yawning
  Not known: coughing, wheezing, shortness of breath and a high temperature, which are symptoms of inflammation of the lungs associated with an increase in white blood cells (pulmonary eosinophilia)

- **Gastrointestinal disorders**
  Very common: nausea
  Common: appetite decreased; constipation; vomiting
  Uncommon: grinding of the teeth; diarrhoea, altered taste sensation
  Not known: severe abdominal or back pains (which could indicate a serious problem in the gut, liver or pancreas)

- **Skin and subcutaneous tissue disorders**
  Very common: sweating (including night sweats)
  Common: chills
  Uncommon: rash; abnormal hair loss
  Not known: skin rash, which may lead to severe blistering and peeling of the skin; itching; mild rash

- **Musculoskeletal and connective tissue disorders**
  Not known: unexplained muscle pain, tenderness or weakness (rhabdomyolysis)

- **Renal and urinary disorders**
  Common: difficulties passing urine; increased frequency in urination
  Uncommon: inability to pass urine

- **Reproductive system and breast disorder**
  Common: abnormal ejaculation/orgasm (males); lack of orgasm; erectile dysfunction (impotence); menstrual irregularities such as increased bleeding or increased irregular bleeding
  Uncommon: abnormal orgasm (females)

What Venlablue XL looks like and contents of the pack

Prolonged release capsule, hard

37,5 mg: Light grey opaque / peach opaque, size '3' hard gelatin capsules having thick and thin radial circular band on the body in red ink and thick and thin radial circular band on the cap in red ink. The capsule is filled with 3 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

75 mg: Peach opaque / peach opaque, size '1' hard gelatin capsules having thick and thin radial circular band on the body in red ink and thick and thin radial circular band on the cap in red ink. The capsule is filled with 6 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

150 mg: Dark orange / dark orange opaque, size '0' hard gelatin capsules having thick and thin radial circular band on the body in white ink and thick and thin radial circular band on the cap in white ink. The capsule is filled with 12 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

Blister packs of PVC/Aclar film and aluminium foil; 10, 14, 28, 30, 50& 100 capsules

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Bluefish Pharmaceuticals AB
Torsgatan 11
SE-111 23 Stockholm
Sweden.

This medicinal product is authorised in the Member States of the EEA under the following names:

Name of the Member State	Name of the medicinal product
Austria	Venlafaxin Bluefish 75 mg/150 mg Hartkapseln, retardiert
Czech Republic	Venlafaxine Bluefish 75 mg/150 mg Tvrdá tobolka s prodlouženým uvolňováním
Denmark	Venlafaxin Bluefish XR 75 mg/150 mg
Finland	Venlafaxine Bluefish 75 mg/150 mg depotkapseli, kova Venlafaxine Bluefish 75 mg/150 mg depotkapsel, hård
France	Venlafaxine Bluefish LP 37.5 mg/75 mg /150 mg gélules à libération prolongée
Germany	Venlafaxin Bluefish 75/150 mg Hartkapseln, retardiert
Greece	Venlafaxine Bluefish XR 75 mg/150 mg Κάψουλες παρατεταμένης αποδέσμευσης
Hungary	Venlafaxine Bluefish XR 75 mg/150 mg Nyújtott hatóanyagleadású kapszulák
Ireland	Venlablue XL 75 mg/150 mg prolonged -release capsules
Italy	Venlafaxina Bluefish 75 mg/150 mg Capsule a rilascio prolungato
Netherlands	Venlafaxine Bluefish XR 37.5 mg/75 mg/150 mg Capsules met verlengde afgifte
Norway	Venlafaxin Bluefish XR
Poland	Venlafaxine Bluefish XL
Portugal	Venlafaxina Bluefish XR
Slovakia	Venlafaxine Bluefish XR 75 mg/150 mg tvrdé kapsuly s predĺženým uvoľňovaním
Spain	Venlafaxina Bluefish 75 mg/150 mg Cápsulas de liberación prolongada
Sweden	Venlafaxine Bluefish 37.5 mg/75 mg /150 mg depotkaplar, hårda
United Kingdom (RMS)	Venlablue XL 37.5 mg/75 mg/150 mg prolonged release capsules

This leaflet was last approved in {07/2009}.

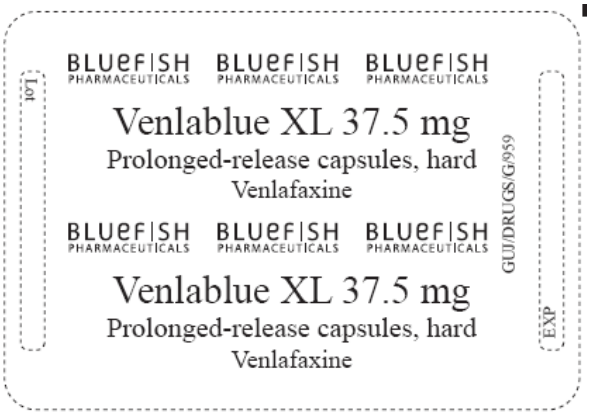
Module 4

Labelling

Venlablue XL 37.5mg prolonged-release capsules, hard

Blister carton with Braille - pack size 10 capsules

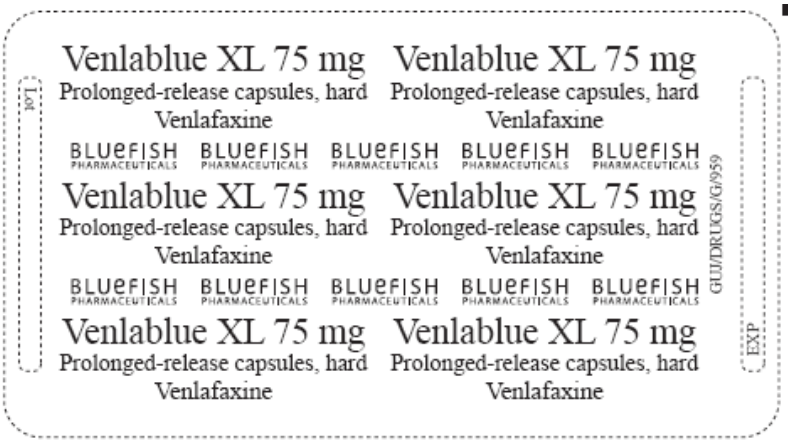
Blister foil



Venlablue XL 75mg prolonged-release capsules, hard

Blister carton with Braille - pack size 28 capsules

Blister foil



Venlablue XL 150mg prolonged-release capsules, hard

Blister carton with Braille - pack size 28 capsules

Blister foil

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bluefish Pharmaceuticals AB Marketing Authorisations for the medicinal products Venlablue XL 37.5mg, 75mg and 150mg prolonged release capsules, hard (PL 31774/0010-0012, UK/H/1400/001-003/DC) on 11th September 2009. The products are prescription-only medicines.

These are abridged applications for Venlablue XL 37.5mg, 75mg and 150mg prolonged release capsules, hard. These are three strengths of venlafaxine in a modified release formulation, submitted under Article 10.1 (75mg and 150mg) and Article 10.3 (37.5mg) of Directive 2001/83 EC, as amended. The UK reference products are Efexor XL 75mg and 150mg Capsules (PL 00011/0223-4), authorised to John Wyeth & Brother Ltd on 5th August 1997. These products have been authorised in the EU for more than 10 years, so the period of data exclusivity has expired.

Venlablue XL prolonged release capsules are indicated in the following:

- Treatment of major depressive episodes, and prevention of recurrence of major depressive episodes
- Treatment of generalised anxiety disorder
- Treatment of social anxiety disorder
- Treatment of panic disorder, with or without agoraphobia

Venlafaxine is a structurally novel antidepressant that is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants. The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major, active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

At least 92% of a single oral dose of venlafaxine is absorbed. After administration of an extended release formulation dose, the peak plasma concentrations of venlafaxine and ODV are attained within 6.0±1.5 and 8.8 ±2.2 hours, respectively. Venlafaxine undergoes extensive first-pass metabolism in the liver, primarily by CYP2D6, to the major metabolite ODV. Venlafaxine is also metabolised to other minor metabolites. Venlafaxine and its metabolites are excreted primarily through the kidneys. Administration of the modified/extended release capsules with food has no effect on the absorption of venlafaxine, or on the subsequent formation of ODV.

No new preclinical or clinical efficacy studies were conducted, which is acceptable given that the applications were for generic versions (hybrid version for the 37.5mg strength) of products that have been licensed for over 10 years.

The applications are supported by three bioequivalence studies presented by the applicant comparing the pharmacokinetic profile of the test product, Venlablue XL 150mg prolonged release capsules, to that of the reference product, Trevilor Retard 150mg (Wyeth Pharma

GmbH, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Venlablue XL 37.5mg prolonged-release capsules, hard Venlablue XL 75mg prolonged-release capsules, hard Venlablue XL 150mg prolonged-release capsules, hard
Name(s) of the active substance(s) (INN)	Venlafaxine hydrochloride
Pharmacotherapeutic classification (ATC code)	Other antidepressants (N06A X16)
Pharmaceutical form and strength(s)	Hard capsules (prolonged release) 37.5mg, 75mg, and 150mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1400/001-003/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/1400/01/DC (37.5mg): FR, NL SE UK/H/1400/02-03/DC (75mg & 150mg): AT, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, NL, NO, PL, PT, SE, SK
Marketing Authorisation Number(s)	PL 31774/0010-0012
Name and address of the authorisation holder	Bluefish Pharmaceuticals AB Torsgatan 11 SE-111 23 Stockholm Sweden

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

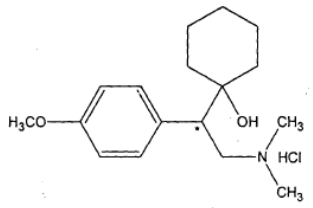
Venlafaxine hydrochloride

Nomenclature:

INN: Venlafaxine hydrochloride

Chemical name: 1-[(1RS)-2-Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride

Structure:



Molecular formula: $C_{17}H_{27}NO_2$, HCl

Molecular weight: 313.9

CAS No: 99300-78-4

Physical form: White or almost white powder

Solubility: Freely soluble in methanol and water, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone

Stereochemistry: It displays polymorphism

The active substance, venlafaxine hydrochloride, is the subject of a European Pharmacopeia (Ph Eur) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. The primary packaging is double low-density polyethylene (LDPE) food grade containers, transparent and black; these are placed into high-density polyethylene (HDPE) drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The LDPE containers in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 2 years, with the storage conditions 'Keep the container tightly closed'.

DRUG PRODUCT

Description and Composition

The drug products are presented as hard gelatin capsules with different sizes, colours, and markings (see individual SmPCs / patient information leaflets for full descriptions of capsules). Each capsule contains venlafaxine hydrochloride equivalent to 37.5mg, 75mg or 150mg of venlafaxine free base, in an extended release formulation. The capsules are filled with 3, 6 and 12 (respectively) white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, povidone, talc, colloidal anhydrous silica, magnesium stearate, ethylcellulose, and copovidone comprising the mini film-coated tablets contained in the capsules; and gelatin and titanium dioxide (E171) making up the capsule shell. In addition, in the capsule shell, the 37.5mg strength capsules contain the colour agents black, red, and yellow iron oxide (E172); the 75mg strength capsules contain the colour agents black and red iron oxide (E172); and the 150mg strength capsules contain the colour agents brilliant blue (E133), allura red (E129), and sunset yellow (E110). The printing ink used for the markings on the capsules is comprised of shellac (E904) and red iron oxide (E172) for the 37.5mg and 75mg strength capsules; and shellac and titanium dioxide (E171) for the 150mg strength capsules. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs or the relevant EEC specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is gelatine. Certificates of Suitability have been provided by all the gelatine suppliers stating that the gelatine they provide meets the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'.

There were no novel excipients used and no overages.

Dissolution profiles

Comparative dissolution data were provided for each strength of the generic venlafaxine capsules against the corresponding innovator products. The dissolution profiles were found to be similar.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on three commercial scale batches for each of the strengths.

Finished product specification

The finished product specifications include tests and criteria to apply for both release and end of shelf life testing and are satisfactory; they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in PVC (polyvinylchloride) - ACLAR/aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The capsules are packaged in pack sizes of 10, 14, 28, 30, 50 and 100 capsules. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are ‘Do not store above 30°C’.

Bioequivalence Study

Three bioequivalence studies were presented by the applicant, comparing the pharmacokinetic profile of the test product, Venlablue XL 150mg prolonged release capsules, to that of the reference product, Trevilor Retard 150mg (Wyeth Pharma GmbH, Germany).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Venlablue XL

150mg prolonged release capsules is a generic medicinal product of Efexor XL 150mg Capsules (John Wyeth & Brother Ltd) appears justified.

As the test products, Venlablue XL 37.5mg, 75mg and 150mg prolonged release capsules meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 150mg strength were extrapolated to the 37.5mg and 75mg strength capsules.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic / hybrid versions of products that have been licensed for over 10 years. The non-clinical overview has been prepared by an appropriately qualified expert and provides a satisfactory review of the pharmacological and toxicological properties of venlafaxine, which is a widely used and well-known active substance.

III.3 CLINICAL ASPECTS

INDICATIONS

Venlablue XL prolonged release capsules are indicated in the following:

- Treatment of major depressive episodes, and prevention of recurrence of major depressive episodes
- Treatment of generalised anxiety disorder
- Treatment of social anxiety disorder
- Treatment of panic disorder, with or without agoraphobia

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The capsules should be taken with food. Each capsule should be swallowed whole with fluid. The dose of Venlablue XL prolonged release capsules should be taken once daily, at approximately the same time each day, either in the morning or in the evening. Full details concerning the posology are provided in the SmPCs.

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of venlafaxine is well known. No novel pharmacodynamic data are supplied or required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by three bioequivalence studies presented by the applicant comparing the pharmacokinetic profile of the test product, Venlablue XL 150mg prolonged release capsules, to that of the reference product, Trevilor Retard 150mg (Wyeth Pharma GmbH, Germany). The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP).

There was a single dose fasting study (Study 059-06); a single dose fed study (Study 060-06) and a multiple dose (steady state) fed study (Study 088-06). In both single dose studies, a satisfactory washout period of 19 days was maintained between the two dosing days in each group; in the multiple dose study it was 10 days. Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours (24 hours for the multiple dose study) after administration of test or reference product. Plasma levels of venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), were detected by a validated LC/MS/MS bioanalytical method.

The primary pharmacokinetic parameters for the studies were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Study 059-06

This was a randomised, two-way, two-period, single dose crossover study performed in fasting subjects. 44 healthy fasting male volunteers were randomised to receive a single oral dose of 150mg of either the applicant's test product or the reference product.

42 of the volunteers completed the study; 2 subjects were withdrawn. The results for the main pharmacokinetic parameters are reported below.

Pharmacokinetic results (log-transformed) for venlafaxine for a randomised, two-treatment, two-period, single dose crossover study. n=42 healthy subjects, dosed fasted. Wash-out period: 19 days

PK Parameters	Anti Log Least Square Mean		Ratio% T/R	90% Confidence Intervals
	Test (T)	Reference (R)		
C_{max} (ng/mL)	201.4738	197.1465	102.19	95.98 – 108.81
AUC_{0-t} (ng*hr/mL)	3820.7336	3514.7576	108.71	102.33 - 115.47
AUC_{0-INF}(ng*hr/mL)	3920.5730	3615.5512	108.44	102.15 – 115.12

Pharmacokinetic results (log-transformed) for O-Desmethyl venlafaxine for a randomised, two-treatment, two-period, single dose crossover study. n=42 healthy subjects, dosed fasted. Wash-out period: 19 days

PK Parameters	Anti Log Least Square Mean		Ratio% T/R	90% Confidence Intervals
	Test (T)	Reference (R)		
C_{max} (ng/mL)	277.5307	251.6119	110.30	105.42 – 115.41
AUC_{0-t} (ng*hr/mL)	7557.0938	6813.3067	110.92	105.14 – 117.01
AUC_{0-INF}(ng*hr/mL)	7970.5550	7147.0234	111.52	105.63 – 117.74

The 90% confidence intervals for the log-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0 – 125.0%, such that the test and reference products may be considered bioequivalent after a single dose under fasted conditions.

Study 060-06

This was a randomised, two-way, two-period, single dose crossover study performed in fed subjects. 44 healthy male volunteers were randomised to receive a single oral dose of 150mg of either the applicant's test product or the reference product, following a standardised high fat meal (approx. 1000 cal).

43 of the volunteers completed the study; 1 subject was withdrawn. The results for the main pharmacokinetic parameters are reported below.

Pharmacokinetic results (log-transformed) for venlafaxine for a randomised, two-treatment, two-period, single dose crossover study. n=43 healthy subjects, dosed fed. Wash-out period: 19 days

PK Parameters	Anti Log Least Square Mean		Ratio% T/R	90% Confidence Intervals
	Test (T)	Reference (R)		
C_{max} (ng/mL)	143.3329	159.3208	89.96	82.68 – 97.90
AUC_{0-t} (ng*hr/mL)	2620.6612	2782.0710	94.20	87.81 – 101.06
AUC_{0-INF}(ng*hr/mL)	2977.7268	2970.6391	100.24	93.70 – 107.23

Pharmacokinetic results (log-transformed) for O-Desmethyl venlafaxine for a randomised, two-treatment, two-period, single dose crossover study. n=43 healthy subjects, dosed fed. Wash-out period: 19 days

PK Parameters	Anti Log Least Square Mean		Ratio% T/R	90% Confidence Intervals
	Test (T)	Reference (R)		
C_{max} (ng/mL)	178.5344	194.9144	91.60	87.02 – 96.42
AUC_{0-t} (ng*hr/mL)	4869.3620	5032.5361	96.76	91.63 – 102.18
AUC_{0-INF}(ng*hr/mL)	5489.6723	5476.4478	100.24	94.68 – 106.13

The 90% confidence intervals for the log-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0 – 125.0%, such that the test and reference products may be considered bioequivalent after a single dose under fed conditions.

Study 088-06

This was a randomised, two-way, two-period, multiple dose crossover study performed in fed subjects. 36 healthy male volunteers were randomised to receive a multiple oral dose of 150mg of either the applicant's test product or the reference product, following a standardised high fat meal (approx. 1000 cal).

34 of the volunteers completed the study; 2 subjects were withdrawn**.** The results for the main pharmacokinetic parameters are reported below.

Pharmacokinetic results (log-transformed) for venlafaxine for a randomised, two-treatment, two-period, multiple dose crossover study. n=34 healthy subjects, dosed fed. Wash-out period: 10 days

PK Parameters	Anti Log Least Square Mean		Ratio% T/R	90% Confidence Intervals
	Test (T)	Reference (R)		
$(C_{max})_{ss}$ (ng/mL)	198.8035	206.7689	96.15	85.65 – 107.93
$(AUC_{0-t})_{ss}$ (ng*hr/mL)	2654.4596	2755.9130	96.32	90.93 – 102.03

Pharmacokinetic results (log-transformed) for O-Desmethyl venlafaxine for a randomised, two-treatment, two-period, multiple dose crossover study. n=34 healthy subjects, dosed fed. Wash-out period: 10 days

PK Parameters	Anti Log Least Square Mean		Ratio% T/R	90% Confidence Intervals
	Test (T)	Reference (R)		
$(C_{max})_{ss}$ (ng/mL)	345.7923	357.0541	96.85	90.91 – 103.16
$(AUC_{0-t})_{ss}$ (ng*hr/mL)	6209.1936	6277.3267	98.91	94.67 – 103.34

The 90% confidence intervals for the log-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0 – 125.0%, such that the test and reference products may be considered bioequivalent after a multiple dose under fed conditions.

Conclusion on Bioequivalence

The results of the bioequivalence studies show that the test product and reference product are bioequivalent, under both fasting and fed conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Venlablue XL 37.5mg and 75mg prolonged release capsules. As Venlablue XL 37.5mg, 75mg, and 150mg prolonged release capsules meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 150mg strength were extrapolated to the 37.5mg and 75mg strength products.

Clinical efficacy

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of venlafaxine is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of venlafaxine is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Venlablue XL 150mg prolonged release capsules, Bluefish Pharmaceuticals AB) and reference (Trevilor Retard 150mg, Wyeth Pharma GmbH, Germany) products within acceptance limits. The results and conclusions of the bioequivalence study on the 150mg strength were extrapolated to the 37.5mg and 75mg strength products.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Venlablue XL 37.5mg, 75mg, and 150mg prolonged release capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Venlablue XL 150mg prolonged release capsules, hard, and the reference product, Trevilor Retard 150mg (Wyeth Pharma GmbH, Germany).

As Venlablue XL 37.5mg, 75mg, and 150mg prolonged release capsules, hard were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 150mg strength were extrapolated to the 37.5mg and 75mg strength products, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that the patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claims that the applicant's products and their respective reference products are interchangeable (for the 75mg and 150mg strengths); and that the 37.5mg strength capsules are a hybrid version of the 75mg strength reference product. Extensive clinical experience with venlafaxine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome