European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT
FOR

ELLEFORE

International Nonproprietary Name:

DESVENLAFAXINE

Procedure No. EMEA/H/C/932

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Ellefore in the treatment of major depressive disorder is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.
The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Efficacy and safety
The benefit-risk of desvenlafaxine is not positive. The overall efficacy documentation is not convincing. Relative to the mother compound venlafaxine, desvenlafaxine appears less effective with a similar safety and tolerability profile. The clinical value of such a product is questioned:

- Evidence with respect to short-term efficacy is considered insufficient as only two of the fixed dose studies employed a dose range that is consistent with the proposed dose (studies 332 and 333) and as the results of these studies are mixed.
- Maintenance of effect was not demonstrated in the dose range that is proposed.
- The number of elderly included in the studies is not sufficient for demonstrating efficacy and safety in patients 65 years or older and is not sufficient for determining the adequate dose in this age group.

Proposal for Questions to be posed to additional Experts
None, at present.

Proposal for Inspection.
A request for a GCP inspection has been issued by the EMEA after a request by the CHMP. This inspection concerns the clinical study 3151A1-302-EU/WW and two study sites are to be inspected. The inspection is a routine GCP inspection and no specific concerns have been identified at the time of adoption of the inspection request.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Wyeth Europa Limited filed a full application for a medical product using the Centralised Procedure containing a new active substance: desvenlafaxine succinate (DVS). The intended trade name is Ellefore.

The proposed therapeutic **indication** for Ellefore is:

Treatment of major depressive disorder.

The recommended usual and maintenance dose for Ellefore is 50 mg once daily, with or without food. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur gradually and at intervals of not less than 7 days. The maximum dose should not exceed 200 mg/day (see section 5.1).

Depression is characterized by a persistent lowering of mood, loss of interest in usual activities and diminished ability to experience pleasure. In order to meet the criteria for Major Depressive Disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), an individual must experience at least 5 of the following symptoms for at least 2 weeks: decreased mood or loss of interest, changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. Symptoms must persist for most of the day, nearly every day, and be accompanied by clinically important impairment in social or occupational functioning.

A large proportion of depressed patients have comorbid disorders with the most common comorbid disorder being anxiety. Other comorbid disorders are alcohol dependence and other substance related disorders, PTSD, and medical conditions, especially in the elderly. Depression has an episodic nature with a high risk for relapse and recurrence.

Depression is a common psychiatric disorder with a lifetime prevalence of about 15% and as high as 25% in women.

II.2 About the product

DVS is the succinate salt of the major metabolite O-desmethylvenlafaxine (i.e. desvenlafaxine) of venlafaxine, a well-known antidepressant marketed as Effexor/Efexor. The formation of desmethylvenlafaxine from venlafaxine is mediated by CYP2D6. Both the parent drug venlafaxine and the metabolite are biologically active. In patients with a poor metabolizing capacity of CYP2D6, high Cmax levels of the parent drug may occur in clinical practice. As venlafaxine is the biologically active parent drug, side effect may occur because of high peak levels in poor metabolisers. Poor metabolizing capacity for CYP2D6 is rather common in Caucasians (estimated prevalence 10-20%).

By dosing the active metabolite DVS instead of the parent drug venlafaxine, unpredictable high concentrations of venlafaxine due to CYP2D6 metabolism are avoided, and interactions at the CYP2D6 levels are avoided. After administration of an Effexor (venlafaxine) XR tablet or a DVS SR tablet of the same strength, the sum of active moiety (i.e. venlafaxine + O-desmethylvenlafaxine) in plasma was similar, though higher variability was indeed observed for venlafaxine peak levels.
Non-clinical studies have shown that desvenlafaxine (O-desmethylvenlafaxine, ODV) is a serotonin and norepinephrine reuptake inhibitor (SNRI). Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H_1-histaminergic, or α_1-adrenergic receptors in vitro. Desvenlafaxine also showed lack of significant affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels and also lacked monoamine oxidase (MAO) inhibitory activity. Desvenlafaxine lacked significant activity in the in vitro cardiac potassium channel (hERG) assay.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

Nineteen phase I studies were conducted to support the development programs for both the vasomotor symptoms (VMS) and major depression disorder (MDD) indications.

Efficacy in the treatment of patients with Major Depressive Disorder (MDD) was investigated in 10 trials in adult outpatients (18-75) with MDD. All were randomized, multicenter, double-blind (DB), placebo-controlled, and parallel-group. Five of theses trials were short-term fixed dose studies (223, 306, 308, 332, and 333), four were flexible-dose studies (304, 309, 317, and 320) and one was a randomised withdrawal study (302). Two of the flexible dose studies (309, 317) included an active control arm (Venlafaxine ER) in addition to placebo.

The applicant sought advice from regulatory agencies, including those in the Netherlands, United Kingdom, France, Sweden, and the United States, and from the European Medicines Agency (EMEA). In a scientific advice that was given in 2003 the applicant was advised to include a sufficient number of elderly in the studies to allow a subgroup analysis across all the studies.

II.4 General comments on compliance with GMP, GLP, GCP

Inspection of the active ingredient manufacturing site, the finished product manufacturing site and/or the batch release site is not recommended.

According to the applicant, most of the toxicology studies, including the toxicokinetic studies were performed under GLP. Although many study reports of studies performed at Wyeth did not contain GLP

statements, most of them were audited by QA, and sometimes it was stated in the protocol that the study was to be conducted under GLP. Also on review of the reports and the protocols, the general impression is that the studies are of sufficient quality. For these reasons the studies have been accepted.

According to the applicant, the clinical trials used to support this marketing authorization application were designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations. All studies were conducted in accordance with the Declaration of Helsinki and recent revisions.

A routine GCP inspection of two investigator sites has been planned.

II.5 Type of application and other comments on the submitted dossier

This application is a complete and independent/stand-alone Marketing Authorization Application, i.e. a complete dossier with administrative, quality, pre-clinical and clinical data, in accordance with Directive 2001/83/EC, as amended.

In general, the submitted dossier was of adequate quality. However some of the tables were presented without a relevant analysis.

A risk-management plan is included in the application.

In the cover letter, the applicant states that in accordance with Article 7 of the Paediatric Regulation (EC) No 1901/2006, as amended by Regulation (EC) No 1902/2006, Wyeth intends to submit an application for a Paediatric Investigation Plan (PIP) for desvenlafaxine, for the treatment of MDD, during 2008. The PIP application will address (a) comments from the assessment of the Ellefore (desvenlafaxine) MAA regarding the use of desvenlafaxine for the depression indication in children and adolescents, and (b) draft guidance provided by the Paediatric Working Party to identify the paediatric needs for psychiatric products ("Assessment of the Paediatric Needs – Psychiatry" [Ref. EMEA/288917/2007], issued for consultation 19 July 2007).

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Desvenlafaxine succinate monohydrate
For this drug substance the EDMF-procedure was followed.

- Manufacture

The manufacture of desvenlafaxine succinate monohydrate comprises three main steps using commercially available starting materials.

- Specification

The drug substance is adequately characterized and the proposed specification is acceptable in view of the concerning route of synthesis and the various ICH guidelines. The impurity profile for the starting material as well as for the drug substance has been satisfactorily accounted for. Desvenlafaxine succinate monohydrate drug substance consistently contains low levels of related substances, venlafaxine is the only compound found above the detection limit.
Relevant validation data for the HPLC methods (identification, assay, related substances) and particle size have been included in the dossier.

- Stability

Stability studies reveal the absence of degradation at the conditions studied (25°C/60%RH and 40°C/75%RH) and in addition forced degradation studies also confirm the stability of the drug substance.

Drug Product

- Pharmaceutical development

The aim of the pharmaceutical development was to produce a prolonged release oral formulation of desvenlafaxine
The development of the product is satisfactorily performed and explained. The excipients are common for oral immediate release products.

- Manufacture of the product

Adequate descriptions of the manufacturing steps and a concerning flow-chart are presented.

- Product specification

The specification for the drug product is in general satisfactory.

- Stability

Stability studies demonstrated that the product is very stable; and support the proposed shelf life of 2 years without any specific storage condition.

III.2 Non clinical aspects

Pharmacology
Characterization of the activity of desvenlafaxine for the human 5-HT and NE transporters was performed in cells expressing these human protein transporters. In addition, neurochemical and physiological studies were performed to support the mechanism of actions of desvenlafaxine to inhibit the re-uptake of 5-HT and NE by the monoamine transporters resulting in the extracellular increase of 5-HT and NE levels in vivo. Various other assays were employed, including a broad receptor binding profile, to determine the selectivity of action of desvenlafaxine. Desvenlafaxine is devoid of monoamine oxidase (MAO) inhibitory

activity and shows virtually no affinity for muscarinic, cholinergic, H1-histaminergic, or α1-adrenergic receptors, and lacks significant affinity for various ion channels including calcium, chloride, potassium, and sodium. Based on the supporting data mentioned above, desvenlafaxine is appropriately classified as a selective novel serotonin and norepinephrine re-uptake inhibitor (SNRI).
Desvenlafaxine is being developed as an approximate 50/50 racemic mixture of the R(-) and S(+) enantiomers. Based on results from in vitro and in vivo assays, the R(-) enantiomer was more potent than the S(+) enantiomer at inhibiting NE re-uptake, whereas the S(+) and R(-) enantiomers have similar activities at inhibiting 5-HT re-uptake by the 5-HT transporter.
Desvenlafaxine is active in various animal models of depression including: reversal of reserpine-induced hypothermia, reduction in immobility time in a mouse tail-suspension test and reduced aggressive behavior in the acute phase of the rat resident intruder paradigm.
As part of the secondary pharmacology, desvenlafaxine was evaluated in various animal models where changes in 5-HT and NE levels play a role in dysfunction. These animal models included evaluation on efficacy measures of temperature regulation i.e. changes in tail skin temperature (TST) in ovariectomized (OVX) rats, pain modulation, contractile responsiveness in the bladder, and antidepressant and antinociceptive activity.
In a rat safety pharmacology study desvenlafaxine did not show a risk of an adverse effect upon respiratory or CNS functions at exposures up to at least 54 times the calculated Cmax value in humans. However, in dogs and mice, convulsions were seen in toxicology and safety pharmacology studies, albeit at comparatively high systemic exposures (Cmax>18x).
In two studies on the effects of desvenlafaxine on the cardiovascular system of dogs, desvenlafaxine increased arterial blood pressure and heart rate at exposures of 6 to 45 times the calculated Cmax value in humans.
Based on the calculated IC50 (>195 μM) for desvenlafaxine and lack of inhibition for its metabolite NODV (IC50 > 10 μM) in the hERG assay, it is unlikely that desvenlafaxine or its metabolite NODV will prolong the QT interval of the surface ECG at high therapeutic plasma concentrations (humans treated with 200 mg desvenlafaxine slow release tablets).

Pharmacokinetics
Pharmacokinetic ADME investigations were carried out in the rat and the dog, the main rodent and non-rodent species. In addition, *in vivo* metabolism and excretion studies were also performed in mice and *in vivo* toxicokinetics were also carried out in mice and rabbits. The preclinical studies were performed in the correct species and were in general studied sufficiently, except that the kinetics were mainly studied in male animals.
Analytical methods were developed and validated for the quantitation of desvenlafaxine and its enantiomers in plasma, and for the N-desmethyl metabolite of desvenlafaxine in plasma. In all the analytical methods, desvenlafaxine free base was measured regardless of whether animals were dosed with desvenlafaxine free base or desvenlafaxine succinate. Desvenlafaxine was stable in rat and dog plasma (25 and 250 μg/ml) for 182 days when stored at -20°C and stable in mouse and rabbit plasma (15, 300, and 3800 ng/ml) for at least 37 and 38 months, respectively, when stored at -70°C.
The AUC/dose is not dose proportional, it increases with increasing dose Furthermore, the S(+) and R(-) enantiomers show different pharmacokinetics in rat and dog, but not in humans. The absolute oral bioavailability of desvenlafaxine succinate salt SR in humans was found to be 80.5% and 31 ± 7.4% in dog studies. The plasma protein binding was low and changes in protein binding would not be expected to affect the pharmacokinetics of desvenlafaxine. No blood to plasma distribution data was provided by the applicant, but based on study RPT-58687 and RPT-55853 a blood to plasma ratio could be calculated and this indicated that desvenlafaxine does not bind to erythrocytes.
The radioactivity tissue:plasma ratios were highest in the urinary bladder, liver, kidney, and the gastrointestinal tract, while the radioactivity tissue:plasma ratio was low in the brain. The pattern of radioactivity distribution was consistent with the preferential uptake of [^{14}C] desvenlafaxine succinate salt by tissues involved in the oral absorption, metabolism, and excretion of desvenlafaxine. The brain:plasma ratios in two brain penetration studies were higher than in the tissue distribution study. In the brain penetration studies, tissue (brain and hypothalamus) and plasma concentrations of unchanged

desvenlafaxine were measured, whereas in the tissue distribution study, radioactivity associated with desvenlafaxine and its metabolites was measured. The majority of radioactivity in plasma as measured in the tissue distribution study could be attributed to desvenlafaxine metabolites, particularly the O-glucuronide, which had been shown to be the predominant circulating radioactive entity in the excretion and mass balance studies conducted in rats. The difference in brain:plasma ratios as measured by [^{14}C] desvenlafaxine succinate salt derived radioactivity versus direct measurement of desvenlafaxine also suggests that the major metabolites of desvenlafaxine do not partition into brain tissues.
The metabolism of desvenlafaxine in humans was similar to that in mice, rats, and dogs, with O-glucuronidation as the major pathway and oxidative metabolism (N-demethylation, hydroxylation, and the formation of N-oxide) as a minor pathway. In mice, rats, and dogs given a single oral dose of [^{14}C]desvenlafaxine succinate salt, recovery of radioactivity was rapid and nearly complete. Urine was the predominant route of excretion in all 3 species. In humans given a single 100 mg oral dose of desvenlafaxine succinate salt, urinary recovery of conjugated and unconjugated desvenlafaxine and N-desmethyl metabolite accounted for 69% of the dose (46% as unchanged desvenlafaxine, 19% as desvenlafaxine-O-glucuronide, and 3.5% as conjugated and unconjugated N-desmethyl metabolite). The excretion of desvenlafaxine in humans is similar to that in mice, rats, and dogs, with urine the predominate route of excretion. Desvenlafaxine metabolites excreted in urine were similar in humans and in all animal species tested. [^{14}C]desvenlafaxine succinate salt showed limited distribution to the foetus and foetal environment. Furthermore, radioactivity was excreted readily into the milk of lactating rats; however, systemic exposure to [^{14}C]desvenlafaxine succinate salt-derived radioactivity in the nursing pups as a result of exposure via the maternal milk supply was very low.
The two primary oxidative metabolites of desvenlafaxine in human liver microsomes were formed by N-demethylation and hydroxylation on the benzyl ring of the molecule; CYP2C9 and CYP3A4 produced these metabolites *in vitro*. Based on the relative amounts of CYP isozymes in liver microsomes, the major isozyme involved in the oxidative metabolism of desvenlafaxine was determined to be CYP3A4. Multiple human UGT isoforms were shown to be involved in the metabolism of desvenlafaxine to desvenlafaxine-O-glucuronide, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17. In CYP enzyme inhibition studies with desvenlafaxine succinate salt using human liver microsomes, no significant inhibition (IC_{50} values > 100 μM) was seen on the activities of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. However, desvenlafaxine is a weak inhibitor of CYP2D6 isozyme, and therefore, has low potential for clinically significant drug-drug interaction with compounds that are metabolised by CYP2D6. Desvenlafaxine itself is no substrate for or inhibitor of P-glycoprotein. These results indicate that desvenlafaxine has low potential for significant drug-drug interactions with compounds metabolised by CYP3A4 or transported by the P-glycoprotein pathways. However, no drug-drug interaction studies were performed for UGT metabolism. Drugs like lamividine (HIV treatment), AZT (HIV treatment), lamotrigine (anti-epileptic) and hormones are also specifically glucuronidated and could lead to interactions with desvenlafaxine.

Toxicology

Acute toxicity

Desvenlafaxine-related mortality was observed in mice (≥ 1800 mg/kg) and rats (≥ 2500 mg/kg) following a single oral dose; and in mice (≥ 250 mg/kg) and rats (≥ 700 mg/kg) following a single IP dose. No mortality was observed in dogs following a single oral dosage up to 500 mg/kg. The single-dose studies confirmed the low potential for acute toxicity. The clinical signs of overdosage observed in these studies were ataxia, decreased motor activity, and tremors.

Repeated dose toxicity

The results from repeat-dose toxicity studies of desvenlafaxine administered daily by oral gavage for up to 6 months (rat) or 9 months (dog) produced dose-limiting antemortem observations of CNS toxicity, including severe tremors, convulsions, and death (3-month studies). Although no microscopic target organs were identified in either rats or dogs, the CNS was considered to be the target organ based on the antemortem observations of severe tremors and convulsions.

Incidental increases in ALT en AP suggest transient effects on liver function. In addition in male mice in the carcinogenicity study, diffuse liver hypertrophy has been observed. Although these signs are not very prominent, they could be 'early signs' of a hepatotoxic effect, which should be addressed in the SPC and/or risk management plan.
A decrease in prostate weight was observed in rats. According to the Applicant effects on organ weight were attributable to reduced body weight gain. However, decreased body weight gain was usually only evident at the high dose. Prostate weight was reduced at all doses in rat studies. In a rat fertility study, reduced prostate weight was associated with microscopic pathology observed as a dose-related increase in the incidence of slight prostate atrophy. The mechanism of action for the effects on the prostate and the clinical relevance of prostate atrophy should be further addressed.

Reproductive and developmental toxicity
Desvenlavaxine reduced fertility in female rats and increased the time-to-mating. These effects were attributed primarily to disruption of the estrous cycling, which is considered to be related to the pharmacologic activity of desvenlavaxine. These effects were reversible after cessation of treatment. Decreases in prolactin and estrogen during diestrus most likely caused the alterations of cyclicity. In rats, prolactin controls the duration of the estrous cycle, and plays a major role on embryo implantation and pregnancy maintenance. Prolactin does not play such a central role in humans. Therefore, the effects of desvenlavaxine on female fertility are regarded as rodent-specific and not relevant to humans.
In males desvenlavaxine did not show an effect on male reproduction hormones on the seminal vesicles, epididymides, testis and male fertility. The increased time-to-mating may have been secondary to altered estrous cycling in the females. However, a direct effect on male mating behaviour cannot be excluded. Reduction in prostate weight, followed by prostate atrophy at the next higher dose, was observed. There was no safety margin for this effect, since it was noticed at 0.3 times the maximum therapeutic exposure in human at 200 mg/day.
There were no teratogenic effects in rats and rabbits. Maternal toxicity was seen in rats (lower gestational body weight gain, decreased food consumption, slight increase in gestation length) and in rabbits (reduced number of implantations, reduced litter size) at exposures above 2.5 (rats) and 0.3 times (rabbits) of that at the maximum therapeutic exposure in humans at 200 mg/day. This means that there is no safety margin for maternal and developmental toxicity in human. No effects on the placenta in rats and rabbits were noticed.
In rats, there was a decrease in pup survival up to postnatal day 4 and the body weights remained lower throughout the lactation period. This effect was seen at an exposure which was 2.5 times higher as compared to that in human at the maximum therapeutic dose of 200 mg/day. This effect might be related to the mechanism of action of desvenlafaxine. In rats, desvenlafaxine decreased the prolactin level, which might lead to a suppressed milk production. For venlafaxine, only increases of the prolactin level have been mentioned in human and that only very occasionally. For this reason, no effect of desvenlafaxine on serum prolactin is expected in human.

Genotoxicity
Desvenlafaxine was negative in a battery of *in vitro* mutagenicity, clastogenicity assays. However, results from a series of cell transformation assays are considered equivocal. *In vivo* there was a signal for clastogenicity at a single dose at a single time point in the rat bone marrow chromosomal aberration assay. The same assay in mice was negative. Taken together, and also taking into account the negative cacinogenicity data, it is considered that the weight of evidence indicates that desvenlafaxine is not a genotoxic compound.

Carcinogenicity
Two-year carcinogenicity bioassays in rats and mice, revealed no carcinogenic potential of desvenlafaxine. An increased incidence of fibro-osseous lesions in female mice in the carcinogenicity study was observed, which was most likely related pharmacologically mediated changes in hormone balance, although a direct effect of desvenlafaxine on bone metabolism cannot be excluded. An increased incidence of ovarian atrophy is most likely also related to hormonal changes following desvenlafaxine

exposure for extended periods of time. It is noted that the species differences in effects of desvenlafaxine on hormonal balance and sensitivity of tissues for hormonal disturbances may exist. The relevance of the animal findings for the human situation is unclear.

Dependence potential of desvenlafaxine has not been studied in specifically designed non-clinical in vivo models. However, receptor-binding data do not indicate abuse potential. The potential to cause withdrawal phenomena has been addressed clinically.

Based on the provided information, the Environmental Risk Assessment cannot be completed Additional studies are required.
Based on the provided information for desvenlafaxine, the risk posed by the drug substance desvenlafaxine for surface water, sewage treatment, and groundwater is acceptable.

Desvenlafaxine (CAS 386750-22-7) is not PBT nor vPvB.

Desvenlafaxine succinate has two dissociation constants: 8.34 and 10.11, and has a molar mass of 399.5 g/mol for the base. Desfenlafaxine succinate (DVS) has a water solubility of 13.6-65.5 g/L over the pH range of 2.8 tot 7.3. Above pH 8, the aqueous solibility decreases rapidly to less than 1 g/L. The octonal/water partition coefficient ranges from -2.04 to 2.02 for the pH 1.2 to pH 10. At neutral pH, log K_{OW} was 0.33. Log K_{OC}, calculated using QSARs, was 1.8 and thus DVS does not show strong sorption behaviour.
Desvenlafaxine succinate is assumed to be not readily biodegradable. Model calculations show that significant shifting to the sediment may occur.
The 96h NOEC for growth for the algae P. *subcapitata* is 20 mg/L, with a 96h EC_{50} of 43 mg/L. The 48h LC_{50} for Daphnia *magna* was 33.0 mg/L. The 21d NOEC for reproduction for Daphnia *magna* was 8.2 mg/L. The 96h LC_{50} for Pimephales *promelas* is 9.4 mg/L. The NOEC for the Early Life Stage of Pimephales *promelas* is 2.1 mg/L. The EC_{50} for activated sludge was above 100 mg/L.

III.3 Clinical aspects

Pharmacokinetics

The Applicant provided a full dossier on the pharmacokinetic (PK) characteristics of DVS, the succinate-salt of O-desmethylvenlafaxine (ODV), the active metabolite of venlafaxine.
The Applicant performed 5 bioavailability and bioequivalence studies (including food interaction studies) and 5 dose-proportionality studies in healthy volunteers. In one study, PK of venlafaxine and DVS were compared head-to-head. In addition, the Applicant performed several studies on the influence of intrinsic factors (renal and hepatic function, age /gender, CYP2D6 polymorphism), and several clinical interaction studies with desipramine (CYP2D6 substrate), ketoconazole (CYP3A4/UGT inhibitor), and midazolam (CYP3A4 substrate).

DVS is a racemic mixture of R- and S-metabolite. Both enantiomers differ in potency. The pharmacokinetic profile of both enantiomers are however the same. Interconversion was not observed.

Absorption
Absolute bioavailability of DVS is approximately 80%. The absorption of the SR formulation is slow and gradually (tmax may vary between 5-10 h).
Food has little influence on the pharmacokinetics of the active compound ODV. In multiple dosing, 50% accumulation was observed after 15 daily doses. Based on estimates of half-life (9-11 hr), it is expected that steady state will be achieved within two days. Peak-to-trough ratios were 200%.
The desvenlafaxine Cmax and AUC values increased in a linear dose-proportional manner after single doses of 100- to 600-mg of DVS and after multiple doses of 300- to 450-mg of DVS per 24 hours.

Efexor and DVS modified release tablets were compared to each other, and the sum of the active moieties (i.e. venlafaxine + ODV) in plasma is similar after an equal dose of parent drug venlafaxine and DVS. The inter-individual variability in venlafaxine Cmax was higher (110%) compared to ODV Cmax (30%). A low Cmax may improve tolerability. When DVS SR (slow-release) formulation (with low Cmax) was compared to Efexor and a DVS immediate-release Test formulation (with high Cmax), nausea scores were significantly lower for the DVS SR tablet.

Distribution
Binding to plasma proteins is low (30%), indicating that no significant interactions are expected at protein-binding level. Distribution volume is rather large (200-300 L), indicating that ODV is widely distributed. In animals, active agent ODV is excreted into milk and passes the placenta.

Metabolism & Elimination
The terminal half-life varied between 9-11 hrs in different studies. In healthy young subjects, clearance is approximately 0.3 L/hr/kg. Clearance capacity remained constant over time.
Mean renal clearance of free ODV after IV administration was 12.1 L/h (202 mL/min) and accounted for 54% of the total clearance of DVS from plasma. Urinary excretion exceeded intrinsic creatinine clearance capacity, indicating that active renal excretion occurs. It is unlikely that the active excretion is mediated by P-glycoprotein, as ODV is not a substrate for P-gp *in-vitro*.

The other major pathway is conjugation to glucuronides, mediated by UGT1A1, 1A3, 2B4, 2B15 and 2B17. Approximately 20% of the total dose is metabolised by glucuronidation. Like the free drug, the glucuronides are excreted into urine (and not into faeces). N-demethylation products (NODV and NODV-O-glucuronide) were present at concentrations typically less than 3% in urine and plasma. Oxidation to N-demethyl-metabolites is mainly mediated by CYP3A4. The exposure to ODV was similar in rapid and slow metabolizers of CYP2D6 after the same dose of DVS, indicating that CYP2D6 is not involved in the metabolism of DVS, in contrast to "parent drug" venlafaxine.

There were some technical problems with the *in-vitro* study on UGT-isoenzymes. The Applicant committed to provide more specific information about the relative contribution of the different UGT isotypes. These data will be useful for further evaluation of possible consequences of genetic variability in UGT-expression.

Special populations
Though the PK-PD relationship may be less evident for the clinical efficacy, there is a clear relationship between plasma exposure/dose and adverse events like hypertension. tachycardia, postural hypotension and nausea/vomiting. This should be kept in mind in prescribing desvenlafaxine in a patient with decreased clearance capacity.

Renal patients
As could be expected from a drug that is almost exclusively cleared by the kidney, plasma exposure of DVS and its conjugates increased significantly in renal patients. After a 100 mg single dose, the desmethylvenlafaxine plasma levels were doubled in patients with severe impairment and ESRD (end-stage renal disease), ~60% higher in patients with moderate renal impairment, and ~40% higher in patients with mild renal dysfunction compared to the healthy reference population. The plasma exposure may increase even more after multiple dosing, as half-life increased till 30 hrs in renal patients.
Simulation data showed that no dose adjustments are indicated for patients with mild renal dysfunction. For patients with moderate renal dysfunction, a 50 mg starting dose seems feasible. As the variability in clearance capacity was highly variable in renal patients, it should be evaluated on a case by case basis whether further uptitration to 100 mg dose would be possible for individual patients. It should be reflected in the SPC under what conditions dose extensions are possible in this specific group of patients, e.g. under monitoring of the blood pressure.

The Applicant proposes an every day dosing schedule for patients with severe or end-stage renal impairment. This proposal needs further evaluation by means of simulated data.

Hepatic patients
Accumulation was moderate in patients with hepatic disease. On average, AUC levels increased with 40% in patients classified Child-Pugh B and C (i.e. moderate to severe hepatic dysfunction). In individual patients however, plasma exposure was twice as high as in healthy subjects, and this could not be explained by low renal function. There was no relationship between different elements of the Child-Pugh score (such as albumin and bilirubin) and plasma exposure.

Elderly
As renal function declines with age, and renal clearance is the main metabolic pathway, it is expected that accumulation of the drug may occur in the elderly. In elderly > 75 years, plasma exposure was on average 50% higher compared to younger adults (aged 18-45 years). Moreover, tolerability was lower in healthy elderly than in younger adults in a Phase I study (no 175). As only a limited number of elderly patients were included in Phase III studies, and even less older patients received dosages according to the current posology, it is difficult to evaluate whether the proposed dose regimen of 50-200 QD for adults is indeed also feasible for elderly. The Applicant should discuss the need for dose adjustments in elderly patients. Moreover, safety in elderly should be addressed in the post-marketing RMP.

Body weight, gender and race
Plasma concentrations are reverse related to bodyweight. The Applicant is requested to evaluate in more detail the relationship between AEs like nausea, dizziness, hypertension and tachycardia low body weight/high Cmax, and to discuss whether dose adjustments are necessary.
Females had slightly higher DVS plasma levels than males. The differences may be explained by differences in bodyweight between men and women. There were no ethnic differences in pharmacokinetics, though the number of Asians was low in the studies. As the metabolism of DVS is CYP2D6 independent, no major differences are expected for different ethnic groups, except maybe for differences in body weight.

Drug-drug Interactions
Cytochrome-P
DVS did not inhibit significantly the metabolism of substrates of CYP3A4, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1 *in-vitro*.
Mixed results were seen in several human liver microsomes studies on the effect of DVS on CYP2D6. Though it was not expected based on the in-vitro studies, DVS acted as a CYP2D6 inhibitor in the in-vivo interaction study with 2D6 substrate desipramine, at higher doses. When DVS 400 mg dose was applied, the AUC of desipramine increased with 90%, whereas at a dose of 100 mg DVS , a mild interaction effect of 17-36% was observed. This kind of dose-dependency in interaction effect may be due to the limited CYP2D6 enzyme capacity in humans.

The plasma levels of CYP3A4 substrate midazolam decreased with ± 30% after a 8-day period of co-administration of DVS. Whether this is also the case for other CYP3A4 substrates is unclear. It may not be excluded that the reduced midazolam exposure was caused by induction, but the study was too short for a proper evaluation of any induction effect. In the *in-vitro* induction study in cultured hepatocytes, induction was observed in the hepatocytes from the only donor studied at this concentration (20 uM). Of note, venlafaxine is known to act as an inducer of MDR and MRP gene 3A4 in-vitro, and the same may apply to DVS (Ehret, Hum. Psychopharmacol Clin Exp 2007; 22: 49–53). As it is important to know whether the reduced levels are caused by induction for predicting other interactions, an additional *in vivo* study will be performed with a probe appropriate for CYP3A4 intestinal and hepatic metabolism, as a FUM. The study should be of sufficient duration for detection of the full induction to be possible (at least 14 days). If induction is found, the effect on other enzyme systems (like UGT or other CYP enzymes with limited

capacity like 2D6 and 1A2) may need to be further studied in vivo. These could be performed post-approval.

DVS levels increased with on average 40% after co-administration of ketoconazole, a CYP3A4 inhibitor. This is an unexpected finding as CYP3A4 constitutes only a minor pathway. This might be partly due to the fact that ketoconazole may act as an UGT-inhibitor besides a major CYP3A4-inhibitor.

Glucuronidation
There are no studies performed on the effect of DVS on UGT activity, neither in-vitro nor in-vivo.

Pharmacodynamics
Like Venlafaxine, Desvenlafaxine belongs to the class of SNRIs, a class of compound that increase the number of, of serotonine and norepinephrine neurotransmitters active in the synapse, thereby enhancing neuronal activity downstream. This in turn causes neuronal growth and synapse formation which have been shown in animal models to correlate with depression. The bioequivalence of desvenlafaxine with venlafaxine was supported by showing similar effects on sleep and daytime EEGs and other peripheral biomarkers.

As with venlafaxine and other antidepressants, no dose-response relationship could be demonstrated for clinical efficacy, but may be more clear for safety. The Applicant is requested to further evaluate the relationships between dose/plasma concentration and safety, as this may be relevant for dosing recommendations in special populations with a relative high plasma exposure, such as elderly, renal patients, hepatic patients, and subjects with low bodyweight.

The effect of DVS SR on QTc was addressed in a so-called "thorough QT/QTc study". Results indicate no significant prolongation of QTc, but further analysis of the results using 95 % CI according to the relevant guideline are needed before a final assessment can be made.

The clinical relevance of the effects on vigilance (reaction time) and psychomotor performance is difficult to estimate as the external validity of the tests has not been established or at least not presented (i.e. it is not clear what the implication is of a reduction of e.g. 2 m/sec in reaction time on e.g. safety in driving). Without further information, it is tentatively concluded that an effect on vigilance and psychomotor performance cannot be ruled out.

Clinical efficacy
The efficacy of desvenlafaxine succinate sustained-release tablets (DVS SR) in the treatment of patients with Major Depressive Disorder (MDD) was investigated in 10 trials in adult outpatients (18-75) with MDD. All were randomized, multicenter, double-blind (DB), placebo-controlled, and parallel-group. Five of theses trials were short-term fixed dose studies (223, 306, 308, 332, and 333), four were flexible-dose studies (304, 309, 317, and 320) and one was a randomised withdrawal study (302). Two of the flexible dose studies (309, 317) included an active control arm (Venlafaxine ER) in addition to placebo.

An overview of the clinical studies is presented in table 1. The only two studies with dose ranges that are consistent with the proposed dose (studies 332 and 333), are highlighted in the table.

Table 1. Design of Ellefore studies

Study ID	Locations	Double blind treatment duration	DVS Dose in mg	Ns randomised	age range	Dx Incl. criteria	Primary Endpoint
Phase 2 study							
223	FR/PL/US/ZA	8 weeks	200 400 Placebo	72 77 80	18-65	MDD (DSM-IV) MADRS>= 24	Change from baseline on the HAM-D17
Phase 3 fixed-dose studies							
306	US	8 weeks	100 200 400	120 120 119	18-75	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2	Change from baseline on the HAM-D17

Table 1. Design of Ellefore studies

Study ID	Locations	Double blind treatment duration	DVS Dose in mg	Ns randomised	age range	Dx Incl. criteria	Primary Endpoint
			Placebo	121		CGI>=4	
308	EU/WW	8 weeks	200 400 Placebo	124 125 126	18-75	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
332	US	8 weeks	50 100 Placebo	158 157 159	18+	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
333	EU	8 weeks	50 100 Placebo	166 158 161	18+	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
	Phase 3 flexible-dose studies						
304	US	8 weeks	100 to 200 Placebo	125 122	18-75	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
320	US	8 weeks	200 to 400 Placebo	123 121	18+	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
309	EU	8 weeks	200 to 400 Ven ER 75-150 Placebo	118 128 123	18-75	MDD (DSM-IV) HAMD>= 22 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
317	US	8 weeks	200 to 400 Ven ER 150-225 Placebo	121 121 127	18-75	MDD (DSM-IV) HAMD>= 22 HAMD (item1)>=2 CGI>=4	Change from baseline on the HAM-D17
Randomised withdrawal study							
302	EU/WW	6 month	200 to 400 Placebo	191 185	18-75	MDD (DSM-IV) HAMD>= 20 HAMD (item1)>=2 CGI>=4	Time to relapse

Abbreviations: EU=Europe; FR=France; MDD= major depressive disorder; PL=Poland; US=United States; Ven ER=venlafaxine extended-release formulation; WW=worldwide; ZA=South Africa.

Methods

- **Study Participants**

To be included in the studies patients had to meet the diagnostic criteria according to DSM-IV, to be in a depressive episode (single or recurrent) without psychotic symptoms and with depressive symptoms that were present at least 30 days prior to screening. Minimum severity for inclusion on the MADRS or the HAMD is indicated in table 1 below. These criteria had to be met at both screening and baseline. In addition, to avoid predominance of anxiety symptoms, subjects were excluded if their Covi Anxiety Scale total score was greater than the Raskin Depression Scale total score, or the Covi Anxiety Scale score was >3 on any single item or the total Covi score was >9.
In study 223 (a phase II study), only postmenopausal or surgically sterile women were eligible.
To be included in the 6 month double-blind phase of the randomised withdrawal study (302), patient had to meet response criteria at the end of week 12 (study day 84) of the open label phase. Response was defined as a HAM-D17 total score <= 11 and still meeting eligibility criteria.

Inclusion of elderly patients was permitted in all studies except for the phase II study (study 223). However, although elderly patients were permitted in all studies, the number of patients aged 65+ that were in fact included was small:

- The short term phase 3 studies included in total 128 patients aged 65+ (78 in DVS SR, 37 in placebo, 13 in venlafaxine) of whom only 14 were 75+ (11 DVS SR, 3 placebo).
- The relapse prevention study included only 13 patients aged 65+ (7 DVS SR, 6 placebo) in the randomised withdrawal phase.

- A 6-month open-label study (study 307) included 52 elderly (65+).

This small number of exposed elderly will not allow for an adequate estimation of efficacy or safety in the elderly i.e. in relation to dose and the question whether a lower dose would be more suitable for elderly patients.

- **Treatments**

The short-term trials had a screening period that lasted between 6 and 14 days, followed by a DB treatment period of 8 weeks, followed by a 1-week (223, 304, 332, and 333) or up to a 2-week taper period (306, 308, 309, 317, and 320).

The doses used in the various studies are indicated in table 1.

Subjects in the fixed dose studies were titrated up to their target dose (50, 100, 200, or 400mg) during the first week of double blind treatment. Those assigned to the lowest dose (50mg in studies 332 and 333; 100mg in study 306, 200 mg in study 308) received their target dose starting from day 1.

In fact, only patients in studies 332 and 333 received doses that would support the proposed posology in the SPC of Ellefore. In this sense, this is a curious research program in that only two of the short-term studies support the SPC proposed dose.

Results from phase 1 studies indicated that 400 mg was not well tolerated by elderly patients and it is not clear why such high doses were used in studies that included elderly patients.
Furthermore, the dose ranges and the titration schemes used in the DVS SR studies differ from those indicated in the proposed product information and from the dosing recommended in the Efexor SPC. The rational for this deviation is not clear.
The recommended dose of Efexor is between 75 mg and 375 mg (lower than 375 mg in some EU countries). This is in contrast to the doses used in the fixed dose studies (50- 400 mg). In addition, dosing instruction for both Efexor and DVS SR indicate that dosing should start with the lowest recommended dose while much higher initial doses were used in some of the DVS SR studies (e.g. initial dose in studies 320, 309, and 317 was 200 mg).

Subjects in the flexible dose studies received the lowest dose during the first two weeks of double-blind treatment (4 weeks in the two active controlled studies). Thereafter the dose was increased and could be decreased to the original dosage only for safety and tolerability reasons.

In the randomised withdrawal study (302), responders to the 12-week open-label treatment with DVS SR 200 to 400 mg/day were randomly assigned to either DVS SR 200 or 400 mg (whichever dose they responded to during the open label phase) or placebo for a 6-month double blind period followed by a 7 to 14 days taper phase.
The dose range used in the randomised withdrawal study (200-400 mg) does not correspond to the 50 mg recommended dose for maintenance of efficacy in the product information (section 4.2 Posology).

- **Outcomes/endpoints**

The primary efficacy variable in all short-term trials was the change from baseline to week 8 on the HAM-D17 total score. In addition, response was defined as at least 50% reduction in HAM-D17.

In the randomised withdrawal study, the primary efficacy variable was the time to relapse, with relapse defined as meeting at least 1 of the following criteria:

1. a HAM-D17 total score >= 16 at any office visit.
2. a clinical deterioration as defined by a CGI-I score >= 6 compared with the study day 84 assessment (baseline visit for the DB treatment phase) at any office visit.

3. a discontinuation from the study because of an unsatisfactory response (primary or secondary reason).

In addition, subjects who were withdrawn from the study were considered to have relapsed on the date of the last dose of study medication.

An amendment to the protocol changed the relapse definition. According to the new definition a relapse was defined as meeting at least one of the following criteria:

1. a HAM-D17 total score >=16 at 2 consecutive office visits.
2. a clinical deterioration as defined by a CGI-I score >=6 as compared with the study day 84 assessment (baseline visit for the DB treatment phase) at any office visit.

The study report of the randomised withdrawal trial does not indicated how "unsatisfactory response" was defined and by whom, but it seems likely that this was by the investigator. This part of the relapse definition is thus subjective as it is not related to documented deterioration on a depression scale (see depression guidelines). The definition introduced by protocol amendment 2 is an improvement on the original definition, but still contains a non-specific deterioration in the form of the CGI.

- **Statistical methods**

The primary analysis used an intent-to-treat (ITT) population, which included all subjects who were randomly assigned to treatment and who had: a baseline primary efficacy evaluation, took at least 1 dose of study medication, and had at least 1 primary efficacy evaluation after the first dose of double blind treatment. The analysis of covariance (ANCOVA) used the last observation carried forward (LOCF) to estimate missing values.

- **Sample size**

The sample size estimates in the different studies were based on the HAM-D17 total score as the primary outcome. Based on experience with venlafaxine ER, a standard deviation of 8 units was assumed for the power calculations. The difference between active arm (DVS) and placebo was chosen to be 3-3.5 points on the HAMD17 (varying between studies). A type I error of 5% and a power of 90% were chosen. In addition, the calculations took into account that 5% of subjects would not qualify for the ITT analysis.
The power calculations seem adequate.

Results

- **Participant flow**

Table 2 below presents the number of patients who were randomised and the number who dropped out due to lack of efficacy and due to AEs in the different studies.

Table 2. Dropouts in Ellefore studies

Study ID	Study arms (DVS SR dose)	Randomised	Dropouts N (%)	Due to Lack of efficacy N (%)	Due to AEs N (%)
Phase 2 study					
223	200	72	20 (29)	2 (3)	9 (13)
	400	77	19 (25)	1 (1)	11 (14)
	Placebo	80	20 (26)	5 (6)	4 (5)
Phase 3 fixed-dose studies					
306	100	120	27 (23)	0	15 (13)
	200	120	26 (22)	1 (<1)	12 (10)
	400	119	35 (30)	2 (2)	19 (16)
	Placebo	121	22 (18)	5 (4)	4 (3)
308	200	124	33 (27)	4 (3)	25 (20)
	400	125	33 (26)	2 (2)	26 (21)
	Placebo	126	27 (22)	15 (12)	7 (6)
332	50	158	34 (26)	0	5 (3.3)
	100	157	31 (21)	1 (0.7)	11 (7.4)
	Placebo	159	25 (16)	5 (3.3)	4 (2.6)
333	50	166	17 (10)	2 (1.2)	8 (4.8)
	100	158	20 (13)	1 (0.6)	11 (7.0)
	Placebo	161	13 (8)	5 (3.1)	5 (3.1)
	Phase 3 flexible-dose studies				
304	100 to 200 Placebo	125	31 (26)	1 (<1)	13 (11)
		122	24 (21)	3 (3)	3 (3)
320	200 to 400	123	29 (25)	1 (<1)	15 (13)
	Placebo	121	15 (13)	1 (<1)	4 (3)
309	200 to 400	118	25 (21)	2 (2)	19 (16)
	Ven ER 75-150	128	16 (13)	3 (2)	7 (6)
	Placebo	123	13 (11)	6 (5)	1 (<1)
317	200 to 400	121	35 (31)	0	19 (17)
	Ven ER 150-225	121	25 (21)	2 (2)	10 (9)
	Placebo	127	17 (14)	3 (2)	6 (5)
Randomised withdrawal study					
302	200 to 400	191	58 (31)	28 (15)	10 (5)
	Placebo	185	101 (55)	60 (32)	14 (8)

Roughly one quarter of patients dropped out. This is not unusual in this setting. In the active arm about half of the dropouts were due to AEs. Higher dropouts due to lack of efficacy are seen in the placebo group. These are expected results.

- **Outcomes and estimation**

Results of the primary analyses are presented in table 3 below.

Table 3. Primary efficacy results in Ellefore studies

Study/ Treatment Group	Least Squares Means (SD) Baseline	Change from baseline (SE)	Treatment Comparisons Diff. from placebo (95% CI)	P-value[c]	N (%) Responders	OR (95% CI)
Phase 2 study						
223						
200mg (63)	22.7 (4.2)	-9.2 (1.1)	0.7 (-1.9 , 3.2)	0.600	32 (51)	1.5 (0.75 , 2.97)
400mg (72)	22.0 (3.9)	-9.3 (0.9)	0.7 (-1.7 , 3.2)	0.560	32 (44)	1.2 (0.59 , 2.23)
Placebo (78)	21.9 (4.1)	-8.5 (0.8)			33 (42)	
Phase 3 fixed-dose studies						
306						
100mg (114)	23.2 (2.5)	-10.6 (0.7)	2.9 (0.8, 5.1)	0.004	57 (50)	2.2 (1.27, 3.80)
200mg (116)	22.9 (2.4)	-9.6 (0.7)	2.0 (-0.2, 4.1)	0.076	50 (43)	1.6 (0.92, 2.73)
400mg (113)	23.0 (2.2)	-10.7 (0.7)	3.1 (0.9, 5.2)	0.002	54 (48)	2.1 (1.19, 3.57)
placebo (118)	23.1 (2.5)	-7.7 (0.6)			39 (33)	
308						
200mg (121)	24.8 (2.9)	-12.6 (0.8)	3.3 (1.2, 5.3)	0.002	70 (58)	2.3 (1.37, 3.89)
400mg (124)	25.2 (3.2)	-12.1 (0.7)	2.8 (0.7, 4.8)	0.008	70 (57)	2.2 (1.32, 3.73)
placebo (124)	25.3 (3.3)	-9.3 (0.7)			46 (37)	
332						
50mg (150)	23.4 (2.6)	-11.5 (0.6)	1.9 (0.3, 3.5)	0.018	81 (54)	1.7 (1.04, 2.62)
100mg (147)	23.4 (2.6)	-11.0 (0.6)	1.5 (-0.1, 3.1)	0.065	74 (50)	1.4 (0.90, 2.28)
Placebo (150)	23.0 (2.6)	-9.53 (0.6)			63 (42)	
333						
50mg (164)	24.3 (2.6)	-13.2 (0.6)	2.5 (0.9, 4.1)	0.002	107 (65)	2.0 (1.27, 3.13)
100mg (158)	24.3 (2.4)	-13.7 (0.6)	3.0 (1.4, 4.7)	<0.001	100 (63)	1.8 (1.17, 2.90)
Placebo (161)	24.4 (2.7)	-10.7 (0.6)			79 (49)	
Phase 3 flexible-dose studies						
304						
100 to 200mg (120)	23.7 (3.3)	-9.7 (0.7)	1.1 (-0.8 , 3.0)	0.256	52 (43)	1.5 (0.83, 2.54)
Placebo (114)	23.7 (2.5)	-8.6 (0.8)			40 (35)	
320						
200 to 400mg (117)	23.3 (2.9)	-9.11 (0.7)	1.6 (-0.2, 3.4)	0.082	46 (39)	1.4 (0.82, 2.43)
Placebo (118)	23.1 (2.7)	-7.52 (0.7)			36 (31)	
309						
200 to 400mg (116)	25.9 (3.1)	-13.4 (0.7)	0.9 (-1.1, 2.8)	0.275	69 (60)	1.5 (0.89, 2.55)
Ven ER 75-150 (127)	25.8 (3.0)	-13.8 (0.7)	1.3 (-0.6, 3.2)	0.121	81 (64)	1.8 (1.06, 2.97)
Placebo (120)	26.0 (3.2)	-12.5 (0.7)			60 (50)	
317						
200 to 400mg (110)	25.0 (2.6)	-10.5 (0.8)	0.7 (-1.3, 2.7)	0.488	55 (50)	1.2 (0.71 , 2.04)
Ven ER 150-225 (121)	25.1 (2.4)	-12.6 (0.8)	2.9 (0.9, 4.9)	0.005	62 (54)	1.5 (0.87 , 2.45)
Placebo (125)	25.0 (2.3)	-9.78 (0.7)			56 (45)	
	Randomised withdrawal study					
302	**Relapse N (%)**		**Diff. from placebo (95% CI)**	**Time to relapse[1] in days (95% CI)**		**Log-Rank Chi-Square Statistics (p-value)**
200 to 400mg (191)	45 (24)			169 (85, ∞)		18.51 (p <0.0001)
Placebo (185)	78 (42)			35 (22 , 55)		

[1] The 25% quantile for time to relapse

Only two of the studies employed a dose range that is consistent with the proposed dose (studies 332 and 333). Statistically significant results were obtained in study 333 and mixed results for study 332. Only the lowest dose group (50 mg) in this latter study showed statistically significant improvement in depression scores compared to placebo. The clinical relevance of these results, especially in study 332 is questionable as well, with percent responders in study 332 only 12% (50 mg group) and 8% (100 mg group) higher than in placebo. In addition, results with respect to CGI responders were also not significant in study 332.

The results for the other two fixed dose studies are positive for one study (308) and mixed for the other (306).

No dose-response relationship is apparent in the results of the fixed dose studies. In some studies, lower doses showed significant benefits while benefits in the higher doses were not significant. An analysis conducted across the four fixed dose studies showed no significant trend in efficacy as measured by improvement on the HAMD17 or the MADRS.

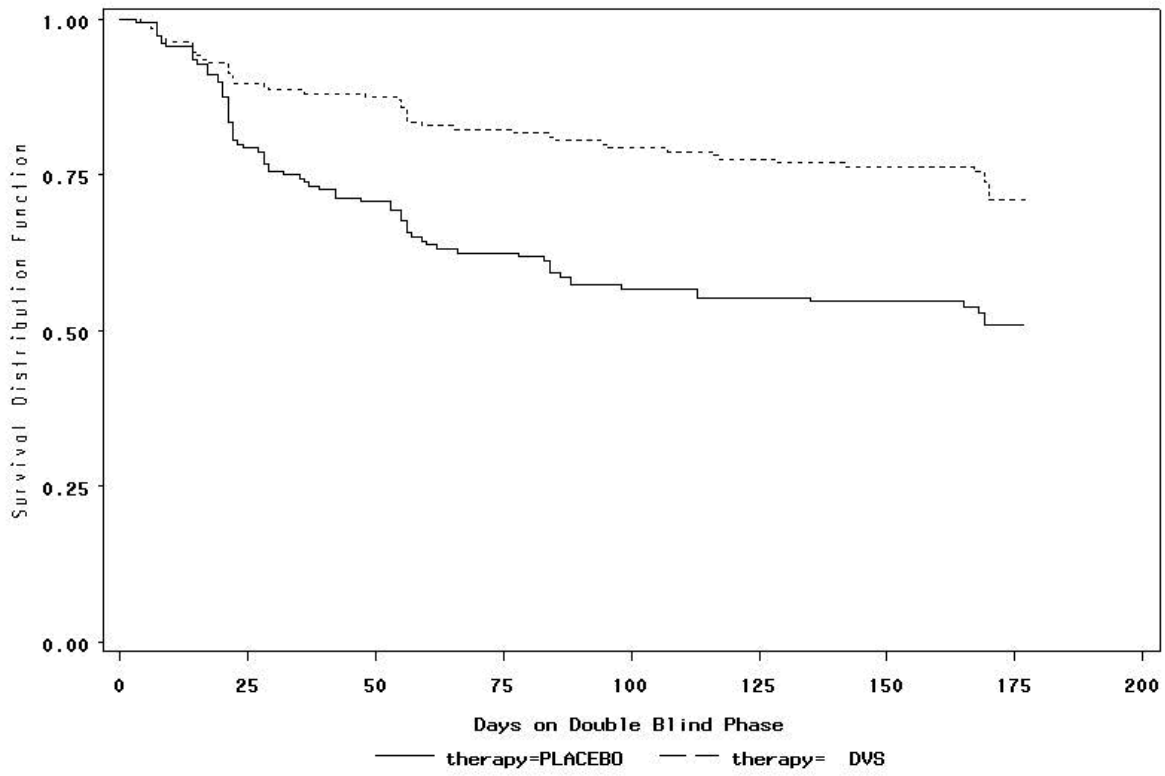
Results of CGI responders are in favour of the active arms in all studies except study 332. The results of the observed cases analyses of improvement in HAMD17 scores were superior to the ITT analyses.

Efficacy results of the flexible dose studies, were smaller compared to the fixed dose studies (ranging between 0.7 and 1.6 points) and not statistically significant. In one of the two three-arm studies (309) the active comparator Venlafaxine did not show a significant effect, albeit the responder analysis shows a significantly larger odds of being a responder in the venlafaxine arm compared to the odds in placebo. In the other three-arm study (317), venlafaxine had a larger and significant effect (amounting to almost 3 points difference from placebo in HAMD17 improvement) compared to the small and non-significant effect of Desvenlafaxine. However, the responder analysis in this study did not confirm the clinical relevance of the effect of venlafaxine, with a responder rate of 54% (in venlafaxine) compared to 50% in placebo.
Given the negative results of the three arm studies and the fact that different dose ranges of DVS SR compared to venlafaxine were used in these studies, there is no way to determine whether the two compounds have similar efficacy.

As the table indicates, the phase II study did not achieve significant results with a difference of 0.7 points between active arms and placebo.
It is curious that the results of all flexible dose studies show a small and non-significant difference from placebo. One would expect the flexible dose studies to produce more positive results, because doses are suited to individual needs rather than being forced, as they are, in the fixed dose studies. Furthermore, flexible dose study mirror to a greater extent the clinical situation. The applicant attributes the failure of the flexible dose studies to the high proportion of failed studies that is usually seen in depression studies but does not address the systematic nature of the difference in study results between the fixed and the flexible dose studies.

Relapse prevention study
Results of the relapse prevention study show that patients treated with DVS SR had a lower risk of relapsing and an average longer relapse-free survival compared to patients receiving placebo during the double blind period. These results are depicted in the figure below.

Figure 9.1.1-1: Survival Function Estimates, ITT Population



The results of the survival analysis with relapse defined, according to protocol amendment 2, as a score on the HAM-D17 >= 16 at 2 consecutive office visits or CGI-I >= 6, showed that the percentage of patients with relapse in the DVS SR group was 16% (30/189) compared to 38% (71/185) in the placebo group (a difference of 22% with a 95% CI: 13 , 31) and patients in the DVS SR group had on average a significantly longer relapse-free survival time (169 days; 95% 85-∞) compared to patients receiving placebo during the double blind period (35 days; 95% CI 22-55; log-rank test chi square value 30.44; p-value <0.0001).
As indicated earlier, the evidence for maintenance of effect is with doses (200-400 mg) that are much higher than the proposed dose in the SPC (50 mg) and there is no evidence supporting maintenance of effect with a 50 mg dose.
In addition, the relapse definition used includes relapses based on CGI deterioration, which might be due to deterioration not due to depression. An additional analysis should therefore be performed which takes into account only relapses defined based on the criterion of HAMD >=16.

Two additional analyses were performed on the data from the relapse prevention study. One excluded relapses that occurred in the first 2 weeks of double blind treatment in order to account for the potential confounding of discontinuation effects with relapse. The results of this analysis show that the 20% (35/175) of patients in the DVS SR group relapsed compared to 41% (66/161) in the placebo group (a difference of 21% with a 95% CI: 11% , 30%). The conclusion from this analysis is that potential discontinuation effect in the placebo group have not confounded the results of the relapse prevention study.

An additional analysis examined the difference in relapse rates between patients who received 200 mg and those who received 400 mg of DVS SR. Of the 189 DVS SR-treated subjects at entry in the double-blind period, 53 receiving DVS SR 200 mg and 136 receiving DVS SR 400 mg. The analysis stratified by dose

showed that both dose groups had relapse rates that were significantly lower than those in placebo, and that there was no statistically significant difference between the two dose groups (relapse rates in the 200 mg group was 19%; in 400 mg group 26%; in placebo 42%).

Clinical safety

The safety evaluation is based on 13 phase 2 and 3 studies. These include:

- 9 controlled short-term trials with 1,834 patients exposed to DVS SR
- one randomised withdrawal trial with 190 patients exposed to DVS SR
- 3 open label safety studies ranging between 6 and 12 month in which 1,437 patients were exposed to DVS SR, of whom 684 were exposed for more than 6 month and 274 for one year.

Altogether 148 elderly were included in the various studies and this number is considered insufficient to establish efficacy and safety in this age group. The need for adjusted doses in the elderly is supported by the results of a pharmacokinetic and safety study (study 175, see PD section) demonstrating that high doses of DVS SR were not well tolerated by elderly, probably due to compromised clearance and consequent accumulation in elderly leading to higher exposure.

In the short-term placebo/active controlled studies, 1,582 (86%) patients in the DVS SR treatment groups experienced at least one adverse event (AE) compared to 204 (84%) of the patients in the venlafaxine ER treatment groups and 831 (75%) patients in the placebo groups.
Most AEs were dose related.

The most common AEs in the short term trials with an incidence >= 5% and at least 2 times greater with DVS SR (all doses combined) than with placebo were nausea (32% vs. 11%), dry mouth (20% vs. 8%), hyperhidrosis (15% vs. 4%), dizziness (13% vs. 6%), constipation (11% vs. 4%), decreased appetite (9% vs. 2%), somnolence (9% vs. 4%), vomiting (6% vs. 2%), and tremor (6% vs. 2%).

All these AEs have similar frequencies in the venlafaxine ER comparison group and are known AEs from the SPC of venlafaxine (Efexor).

For most of the common AEs there was a dose response relationship, with higher rates of AEs in the higher doses. This was the case as well for the SPC proposed dose range of 50 mg to 200 mg.

AEs in the randomised withdrawal study with higher frequency in the DVS SR group compared to placebo are: influenza, increased weight, back pain, somnolence and hot flushes.

Most AEs in the long-term studies that are more frequent in the DVS SR (and in the group venlafaxine ER comparison group) have been noted in the short-term studies and/or are known AEs from the SPC of venlafaxine (Efexor).

Serious adverse events and deaths. One (1) death occurred in the phase 1 studies and one in the phase 2 and 3 studies. The death in the phase 1 studies occurred in a 40-year-old man 25 days after receiving the last dose of DVS SR. Following an autopsy and toxicology findings, the medical examiner concluded that the death was due to dilated cardiomyopathy with cocaine use as a contributory cause.
The death in the phase 2 and 3 studies (fixed dose study 306) was due to a suicide. The investigator and the applicant's medical monitor independently considered the event to be unrelated to treatment but related to the patient's depression.

The description seems to support the assessment that the patients' depression contributed to the suicide of this patient. However, contribution of the treatment with DVS SR to this completed suicide can not be fully ruled out.

Discontinuation due to AEs. AEs were the reason for withdrawal in 12% of DVS SR treated patients in the short-term studies compared to 3% in placebo and 7% in the venlafaxine treated groups. Nausea, vomiting, dizziness, insomnia, headache, and hyperhidrosis were the most frequent (>=1%) AEs cited as reasons for withdrawal in the DVS SR group. Together these AEs were responsible for 94% of the withdrawals in the DVS SR groups. The incidence of subjects withdrawing due to AEs was dose related (in the fixed dose studies 4, 9, 15, and 18% withdrew due to AEs in the 50, 100, 200, and 400mg treated groups, respectively). Most withdrawals occurred during the first week of therapy.

AEs were the reason for withdrawal in 6% of DVS SR treated patients in the long-term (>=6 month) studies. As with short-term studies, withdrawals due to AEs were most frequent in the first week of therapy.
In the randomised withdrawal trial, more patients who were randomised to placebo withdrew than patients who were randomised to DVS SR (18% vs. 11%). However, this was largely due to depression as an AE (8% in placebo and 4% in DVS SR).

AEs related to cardiovascular, seizures, suicidality, and manic reactionsare discussed in more detail below. With respect to other serious AEs – no consistent pattern could be detected and the number of such events in each category was too small to reach any conclusions.

Cardiovascular AEs. Cardiovascular AEs are of special interest due to the noradrenergic effect of DVS SR. In the short-term placebo-controlled studies 20% of patients in the DVS SR group had cardiovascular-related AEs compared to 11% in the placebo group and 18% in the venlafaxine comparison group. Specifically, dizziness (14%), hypertension (3.5%), tachycardia (2.2%), and orthostatic hypotension (0.5%) occurred more frequently in DVS SR treated group than in placebo. There is some indication for a dose-response relationship (i.e. increased frequency of AEs in higher doses) for tachycardia and dizziness.
In addition, 6 cardiac ischemic events, including 3 myocardial infarctions and 3 coronary occlusions, were reported in 5 patients who took DVS SR in the year-long vasomotor symptoms (VMS) clinical study 315. In each case, multiple risk factors for coronary artery disease were present prior to the start of the treatment with DVS SR. The patients' ages ranged from 50 to 70 years. The events occurred at DVS SR doses ranging from 50 mg to 200 mg daily and are too few to assess dose relationship.
Safety results with respect to cardiovascular risks would call for caution in use with elderly and cardiovascular compromised individuals, similar to venlafaxine (Efexor). A warning regarding this issue was taken up in the proposed SPC (section 4.4 Special Warnings). The cardiovascular risk is taken up as a potential risk in the RMP.

Seizures. Antidepressant may lower the threshold for seizure. Therefore patietns with a history of seizure disorder were excluded from the studies. In all the phase 2/3 studies there were 3 patients (in long-term studies) who experienced SAEs of convulsion (seizure or seizure disorder). These events were assessed by the investigators as possibly related to study medication.
An additional seizure which was defined as a SAE was reported in a phase 1 study (study 401) on the second day of DVS SR administration.
The (known) risk of seizure is reported in the product information similarly to venlafaxine.

Discontinuation symptoms. Patients had their doses tapered at the end of the studies in order to address the possibility of discontinuation or rebound effects. Taper/poststudy-emergent adverse events (TPAEs) were defined as AEs that were not present during the 7 days before the dosage-tapering period or AEs that were present but became more severe during the taper/poststudy period.
The most common (>5% and at least 2 times greater with DVS SR than with placebo) TPAEs for subjects treated with DVS SR in the short-term studies were dizziness and nausea.
No dose-response relationship was observed for any of the most common TPAEs in the fixed dose studies.

In long-term studies, the most common (>5%) TPAEs for subjects treated with DVS SR were dizziness, nausea, headache, irritability, drug withdrawal syndrome, and depression. TPAEs were reported by 29% of subjects who received placebo and 53% of subjects who received DVS SR.
Withdrawal symptoms are a known risk with all SSRIs and NSRIs. These symptoms are reported in the proposed SPC and are taken up as an identified risk in the risk management plan. These measures are considered sufficient to address this issue.

Suicide related AEs. Suicide and suicide related behaviours and thought have been associated with antidepressants. The applicant presents three methods of examining the issue of suicidality. Altogether, the evidence in the DVS SR dossier does not suggest an increased risk associated with DVS SR, although, an increased suicidality risk cannot be ruled out given the small number of events. The rate of such events in the venlafaxine treated subjects seems higher, but again, due to the small number of patients (especially those exposed to venlafaxine), the possibility that this is due to methodological issues or has resulted from chance cannot be ruled out with any degree of certainty.
A warning about the risk of suicidality was included in the proposed SPC (as with all other antidepressants). In addition, this is included as an identified risk in the RMP. For now, this issue seems to be sufficiently addressed.

Overdoses. Four overdoses with large doses>800 mg of DVS SR (1800, 5200, 4000, and 900 mg) occurred in the clinical trials. All 4 patients recovered and did not have adverse events that were different from those for subjects who had taken DVS SR at therapeutic doses.

Manic reactions. Switch to manic episodes is a risk of all antidepressive agents particularly when patients with (underlying) bipolar disorder are treated. In all the phase 2 and 3 studies there were 4 out of a total of 3292 (0.1 %) patients who were treated with DVS SR and experience manic (1) or hypomanic (3) reactions while on therapy. The manic reaction was assessed by the investigator as possibly related to study medication and the patient was withdrawn from the study.
The report does not indicate whether these events occurred in patients with a history of manic episodes. The (known) risk of switching from depression to mania/hypomania is reported in the product information, similarly to venlafaxine.

Laboratory findings

Lipids. Compared to placebo, DVS SR treated patients in the short-term studies experienced significantly higher increases (from baseline) in mean serum total cholesterol (an increase of 0.11 mmol/L in DVS SR vs. a decrease of 0.13 in placebo), LDL cholesterol (an increase of 0.07 mmol/L in DVS SR vs. a decrease of 0.11 in placebo) and HDL cholesterol (an increase of 0.03 in DVS SR vs. a decrease of 0.01 in placebo). In the fixed-dose studies these increases were dose related.
In addition, compared to placebo, a higher percentage of DVS SR treated patients had clinically relevant changes on total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides values.
The table below present the number (%) of patients with clinically important changes in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.
Increases in serum cholesterol are noted in the SPC of venlafaxine, but then after a longer duration of exposure (>=3 months). The short-term increase of LDL cholesterol is noted in the product information of DVS SR, similarly to venlafaxine, with a recommendation to switch to another antidepressant if hypercholesterolemia occurs or to treat it. This issue has been designated as an identified risk in the RMP. These measures are considered sufficient to address this risk.

Liver function tests. Statistically significant increases from baseline in mean aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase values were observed in the DVS SR treated groups of the short term studies compared with baseline and compared with placebo. There were no increases in mean total bilirubin values (in fact

decreases were seen in the DVS SR treated patients). In the DVS SR group, mean increases from baseline were 1.4 mU/mL for AST, 2.0 mU/mL for ALT, 5.8 mU/mL for GGT, and 5.2 mU/mL for alkaline phosphatase.
To investigate whether these mean increases are clinically meaningful, the percentage of patients with changes that were defined as potentially clinical meaningful were determined. The results indicate that compared to placebo, a higher percentage of patients in the DVS SR group had potentially clinically relevant changes defined as ALT/SGPT>= 3xULN (0.7% compared to 0.2% in placebo). However, when the increases in aminotransferase values were examined in relation to Hy's law[1] in order to determine the clinical relevance of these change, none of the patient met Hy's law criteria. The criteria for Hy's law were operationalized as AST or ALT level more than 3 times the upper limit of normal, total bilirubin levels >34 mmol/L, and alkaline phosphatase level within normal limits.

Results in the long-term studies were consistent with those of the short-term studies.
Although changes in liver function parameters were not clinically relevant according to Hy's law criteria, and although the difference between 0.7% and 0.2% does not seem large, there is no assurance that longer-term exposure (longer than that available in the current dossier) might not be harmful. This issue has been designated as an identified risk in the RMP. Furthermore, abnormal liver function test is indicated in the proposed SPC (section 4.8) as an uncommon AE (0.1% to 1%). Abnormal liver function test are also listed in the SPC of venlafaxine as an uncommon AE. Nevertheless, the applicant should address this clinical relevance of this result.

Renal Tests. A significantly higher percentage of patients in the DVS-SR group had clinically relevant proteinuria compared to placebo. The applicant argues that the protein excretion is mild, transient, and not associated with azotemia. In addition, it is indicated that proteinuria has been designated as an adverse reaction and is included in section 4.8, Undesirable Effects of the proposed SPC.
The applicant should examine effects on renal function including creatinine clearance and plasma glucose levels.

Blood pressure. The effects of DVS SR on blood pressure in the phase 1 studies defined the maximum tolerated dose. In study 171, the maximum tolerated dose was 450 mg/day, based on symptomatic orthostatic hypotension observed after 5 to 7 days of DVS SR (600 mg) administration. In study 175, single doses of 300 mg of DVS SR were initially used to evaluate the pharmacokinetics and safety in various age groups. However, because intolerable symptomatic orthostatic hypotension and clinically relevant increases in supine blood pressure occurred in several elderly, the dose was reduced to 200 mg, which was well-tolerated.
Given these results, it is strange that doses higher than 200 mg were used in the phase 2 and 3 studies, i.e. studies that included elderly patients. One would expect doses, at least for the elderly, not to exceed 200mg.
The SPC should contain a warning not to use doses higher than 200 mg in the elderly.

Effects on systolic and diastolic blood pressure were seen in the phase 2 and 3 studies. Mean increases from baseline in the DVS SR groups were statistically significant higher than in placebo (systolic BP in DVS increased by 2.24 mm Hg, in the venlafaxine group by 2.50 mm Hg, while in placebo it decreased by 1.08 mm Hg; diastolic BP in DVS increased by 1.60 mm Hg, in the venlafaxine group by 1.12 mm Hg, while in placebo it decreased by 0.40 mm Hg). In the fixed dose studies, the changes in BP were dose related.
The percentage of patients with diastolic BP increases that were defined as being of potential clinical interest were 1.3% (22/1734) in the DVS SR group, 0.8% (2/242) in the venlafaxine group, compared to 0.9% (10/1098) in the placebo group. Criteria for sustained increase in diastolic BP were met by 1% of the patients in the DVS SR and by 1.2% in the venlafaxine group compared to 0.4% in placebo group.

[1] Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006; 354:731-739.

A higher percentage of patients in the DVS SR group experienced changes in postural BP that were defined as clinically important (1.4% systolic and 2.8% diastolic) compared to placebo (0.7% and 2% respectively).
Long-term effects on BP were shown to be of a similar magnitude as in the short-term studies. The effects were shown to subside during the taper period.
The effects on BP are known from and similar to the experience with venlafaxine and the SPC of venlafaxine recommends checking the BP during treatment.

Pulse Rate. Mean increases (from baseline) in pulse rates were seen in the DVS SR treated groups in the short-term and in the long-term studies (2.1 beats per minutes in the short-term studies; 3.3 in the long-term studies). These increases were significantly larger than in placebo. In the fixed dose studies, the mean increase in pulse rate was largest in the 400mg group (4.1 beats per minute). In the short-term studies there were 0.1% of the patients treated with DVS SR with changes in pulse rates that were of potential clinical importance (increase >=15 bpm and >= 120 bpm) compared to 0 in placebo.
The effects on pulse rate, specifically associated with higher doses, are noted in the SPC of venlafaxine. The SPC calls for caution in the use of venlafaxine in patients with underlying illnesses where increases in pulse rate could cause problems. A similar call for caution seems indicated for DVS SR.

ECG. The proportion of patients with relevant QTcB prolongation (Bazett's correction) is higher in the DVS SR group compared to placebo. However, when Fridericia's correction is applied (QTcF) there is no difference between the DVS SR and placebo. Results for the fixed dose studies show no dose response relationship with QT prolongation as the outcome. The guideline on the clinical Evaluation of QT/ QTc Interval prolongation (ICH Topic E14; CHMP/ICH/2/0) indicates that Fridericia's correction is more accurate than Bazett's correction in subjects with altered heart rates, as is the case with DVS SR treated patients.
Altogether, these results do not indicate a strong signal for QT prolongation but such a risk cannot completely be ruled out, especially given the AEs results showing an increases rte of various cardiovascular events in the DVS SR groups. A warning regarding this issue was taken up in the SPC (section 4.4 Special Warnings). In addition, QT prolongation should be added to section 4.8 of the SPC, especially given the fact that this is indicated in the SPC of Efexor as well. The cardiovascular risk is taken up as a potential risk in the RMP.

In addition, the applicant should present data regarding QT prolongation for cardiac compromised patients.

Safety in special populations. Subgroup analyses by gender, age and ethnicity revealed no differences in the association between DVS SR and the most common AEs, with the exception of vomiting where the relationship with DVS SR was stronger in women than in men.
However, very few elderly were included in the DVS SR studies and, therefore, the effect of age is difficult to evaluate. More data are clearly necessary.

Furthermore, no clinical evidence is provided regarding safety in special population i.e. patients with compromised kidney or liver function. Kinetic studies indicate increased exposure in such patients. Therefore any available clinical evidence should be submitted.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

Risk Management Plan

Identified risks were lipid effects, hepatic effects and withdrawal syndrome effects. Potential risks were ischaemic cardiac events, suicidality and risk of fracture. And important mission information was used in elderly patients, paediatric patients, hepatic impaired patients, renal impaired patients, pregnant and lactating women, patients with malignancy, hypertensive patients, patients with history of cardiac arrhythmia and patients with history of MI within 6 months.

In general the applicant will perform routine pharmacovigilance activities as surveillance of post-marketing adverse reactions and discussion of report of identified and potential risks in the PSURs. Active surveillance will also take place for identified and potential risks being systematic collection and analysis of these cases in ongoing and future clinical trials.

For ischaemic cardiac events the applicant proposed a pre-marketing safety study in the US.

Risk Minimisation Plan
Risk minimisation activities for desvenlafaxine proposed by the applicant include: product labelling, and small (14 day) pack sizes. The latter was specifically for the potential risk of suicidality.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Clinical context

V.2 Benefits

Desvenlafaxine is the main metabolite of venlafaxine. As venlafaxine is already approved for the treatment of MDD and as venlafaxine is almost entirely transformed into desvenlafaxine, it would be expected that efficacy and safety of desvenlafaxine in the treatment of MDD would be very similar to that of venlafaxine.

Short-term efficacy
Short-term efficacy of DVS SR was examined in 8 phase 3 studies, 4 of which were fixed dose studies with doses ranging between 50 and 400 mg, the other 4 studies used flexible doses ranging between 100 and 400 mg. Two of these studies included venlafaxine ER as an active comparator.

The choice of doses in the short-term studies (50 mg-400 mg) is curious as these do not correspond to the dose proposed (the recommended usual and maintenance dose is 50mg with 200mg being the maximum dose). In fact, only studies 332 and 333 provide evidence for short-term efficacy in the dose range that is consistent with the posology in the SPC of Ellefore.

In addition, these doses do not correspond to the SPC recommended doses of venlafaxine (75 mg- 375 mg). Based on PK data and the fact that venlafaxine is almost entirely (80%) transformed into desvenlafaxine, it would have been expected that similar doses of desvenlafaxine would be used in the studies and recommended in the SPC.

Furthermore, doses higher than 200 mg were shown in phase 1 studies to be not well tolerated by elderly and, therefore, it is curious that studies that include elderly patients used doses as high as 400 mg. Altogether, evidence relevant to the elderly population is insufficient as too few elderly patients were

included in the studies, this contrary to the scientific advice given to the applicant in 2003 in which it was recommended that to include a sufficient number of elderly in the studies in order to allow a subgroup analysis across all the studies.

Only two of the fixed-dose studies employed a dose range that is consistent with the proposed dose (studies 332 and 333). Statistically significant results were obtained in study 333 and mixed results for study 332. Only the lowest dose group (50 mg) in this latter study showed statistically significant improvement in depression scores compared to placebo. The clinical relevance of these results, especially in study 332 is questionable as well, with percent responders in study 332 only 12% (50mg group) and 8% (100 mg group) higher than in placebo.
The other 2 fixed dose studies were conducted with doses that are higher than the proposed dose and the results of these studies can be seen as only supportive to short-term efficacy.
The results of the flexible dose studies showed smaller differences between the active arms and placebo (ranging between 0.7 and 1.6 points) and these differences did not reach statistical significance. In one of the two three-arm studies (309), the active comparator, Venlafaxine, did show a larger (3 points) difference from placebo which was statistically significant. However, responders analysis did not support the clinical relevance of this effect (rate of responders in the venlafaxine arm was 54% compared to 45% responders in placebo.

The applicant argues that 50% negative studies are common in outpatient depression studies and that this is, at least partly, due to the high placebo response in this patient population. However, this explanation fails to address the fact that in the DSV SR dossier the negative/failed studies were all flexible-dose studies. One would expect the flexible dose studies to produce more positive results because doses are suited to individual needs and response rather than being forced, as they are, in the fixed dose studies. Furthermore, flexible dose study mirror to a greater extent the clinical situation where doses are indeed adapted according to individual responses. Altogether, the results of the short-term studies do not provide sufficient support for short-term efficacy in the dose range that is proposed. In addition, the three arm studies seem to suggest reduced efficacy compared to venlafaxine. Finally, there is no sufficient evidence for short-term efficacy in elderly patients.

Maintenance of effect
The dose range used in the relapse prevention study (200-400 mg), does not correspond to the proposed dose for maintenance treatment (50 mg). There is, therefore no evidence to support maintenance of effect with the recommended dose.

The relapse prevention study demonstrates maintenance of effect over a period of 6 months for DVS SR in doses ranging between 200 and 400 mg. However, the definition of relapse included deterioration in CGI scores that is not necessarily specific for depression. Therefore, the results would need to be re-analysed with relapse adequately defined. Therefore, it is considered that there is no evidence to support maintenance of effect in the dose recommended by the SPC. This was a major objection.

An additional major objection concerns the lack of evidence to support a safe and effective dose in the elderly. Results of kinetic studies show that plasma exposure was on average 50% higher in elderly >75 compared to younger adults (aged 18-45 years). However, the small number of elderly included in the studies does not allow an assessment of the adequate dose for this important segment of the population with major depression.

V.3 Risks
The safety evaluation is based on more than 3,000 patients exposed to at least one dose of DVS SR in 13 phase 2 and 3 studies and additional specific safety studies, including 1070 patients who were exposed for at least 6 months and 274 exposed for at least one year. Although a smaller number of patients were exposed to the SPC recommended dose, this could only lead to an over rather than under-estimation of safety problems, given the dose-response relationship of safety problems with dose.

Although this number is in general sufficient, the number of elderly patients exposed is very small, especially since the metabolism (clearance) of DVS SR is slower in the elderly, which makes it necessary to adjust the dose. However, there is no sufficient data with respect to safety and efficacy in the elderly upon which dose recommendation can be based. The SPC of venlafaxine (Efexor), provided only general instructions in this respect by calling for caution in increasing the dose beyond the minimal recommended dose in elderly (75mg).

Two deaths occurred during the development program. One is not likely to be related to DVS SR. The other death resulted from suicide in a depressed patient on DVS SR on the 5th study day. The death was assessed by the medical evaluator as related to the patients' depression and not to study medication. However, there is no way to rule out the possibility of DVS SR contributing to this suicide.
The frequency of other suicide related events does not reveal a signal of increased suicidality associated with DVS SR. Altogether, it is concluded that the available evidence in this dossier does not support an increased suicidality risk with DVS SR, although such risk cannot be completely ruled out given the relatively small dataset in relationship to the rarity of the event.

Altogether, as can be expected, the AEs profile in the DVS SR studies is similar to the one known from the experience with venlafaxine. This includes cardiovascular risks calling for caution in the use of DVS SR in cardiovascular compromised individuals and elderly, risk of switching to mania, risk of seizures, increases in levels of LDL cholesterol, and increases in blood pressure and pulse rate. Although from a kinetic perspective there is an expectation for a better safety profile of DVS SR compared to venlafaxine due to more stable Cmax levels, this potential advantage was not demonstrated in this dossier.

Therefore it is concluded that with respect to safety no alarming signals have been uncovered and the safety of DVS SR seems to be similar to that of venlafaxine.

V.4 Balance

Only two of the fixed-dose studies employed a dose range that is consistent with the SPC recommended dose (studies 332 and 333). Statistically significant results were obtained in study 333 and mixed results for study 332. Only the lowest dose group (50 mg) in this latter study showed statistically significant improvement in depression scores compared to placebo. The clinical relevance of these results, especially in study 332 is questionable as well, with percent responders in study 332 only 12% (50 mg group) and 8% (100 mg group) higher than in placebo.
In addition, the negative results that were obtained for the flexible dose studies contribute to the conclusion that not sufficient evidence was obtained to support short-term efficacy.
Efficacy of desvenlafaxine would be expected based on the fact that venlafaxine is an antidepressant with established efficacy and the fact that desvenlafaxine is the active metabolite of venlafaxine. However the efficacy results are far from impressive.
The evidence with respect to long-term efficacy is considered lacking. The dose used in the randomised withdrawal study does not support long-term efficacy in the doses that are indicated in the SPC (50 mg).
In addition, the definition of relapse that was used in the long-term study allows for relapses that might be due to deteriorations that are not related to depression. Therefore, the data of the long-term study need to be re-analysed with an acceptable definition of relapse.

With respect to safety and efficacy, an additional major fault of this dossier is the lack of evidence to support a safe and effective dose for the elderly. The presented evidence suggests that tolerability issues in elderly due to slower elimination and therefore higher exposure. However, the small number of elderly included in this dossier does not provide sufficient evidence to establish what would be safe and effective dose in elderly patients. This is contrary to a recommended during a scientific advice in 2003 to include a sufficient number of elderly in the studies in order to allow a subgroup analysis across all the studies.

Altogether, given the insufficient and inconsistent data to support short- and long-term efficacy in the recommended dose range, the potentially reduced efficacy compared to venlafaxine, and the lacking evidence to support a safe and effective treatment in the elderly, it is considered that the benefit/risk balance of DVS SR for the indication of major Depressive Disorder is negative.

V.5 Conclusions

The overall B/R of Ellefore is negative.