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

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WITHDRAWAL ASSESSMENT REPORT
FOR

PRISTIQS

International Nonproprietary Name:

DESVENLAFAXINE

Procedure No. EMEA/H/C/794

Day 180 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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LIST OF ABBREVIATIONS

5-HT	serotonin
ADME	absorption, distribution, metabolism and excretion
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AR	assessment report
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	total area under the concentration-time curve
BMI	body mass index
CHMP	Committee on Human Medicinal Products (formerly CPMP)
C_{max}	peak concentration
COSTART	coding symbols for a thesaurus of adverse reaction terms
CPMP	Committee on Proprietary Medicinal Products
CNS	central nervous system
CO	Cross-over
CSR	clinical study report
CYP	cytochrome P450
DA	dopamine
DMSO	dimethylsulfoxide
DVS	desvenlafaxine free base
DVS-233	desvenlafaxine succinate salt
DVS MR	desvenlafaxine succinate salt modified-release tablet (a prototype of the SR)
DVS SR	desvenlafaxine succinate sustained release
ECG	electrocardiogram
ED50	effective dose of 50%
EEG	electroencephalogram
E_{max}	maximum increase in QTc resulting from drug concentrations
EMEA	European Medicines Agency
ER	extended release
ERA	environmental risk assessment
ESRD	end-stage renal disease
FDA	Food and Drug Administration (US)
GCS	Greene Climacteric Scale
GD	gestational day
GLP	Good Laboratory Practices
GMR	general medical report (previous name for clinical study reports)
GTR	general technical report (previous name for nonclinical reports, now RPT)
hDAT	human dopamine transporter
HDL	high-density lipoprotein
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HPGRT	hypoxanthine-guanine phosphoribosyl transferase
HPLC	high pressure liquid chromatography
IC50	concentration that inhibits 50%
ICH	International Conference on Harmonisation
Ikr	rapidly activating, delayed rectifier cardiac potassium ion current
IP	intraperitoneal
IR	immediate release
ITT	intent-to-treat
IV	intravenous
IVIVC	*in vitro*/*in vivo* correlation
LC50	concentration that produced 50% lethality
LC/MS/MS	HPLC with tandem mass spectrometry

LDL	low-density lipoprotein
LFT	liver function test
LH	lutenizing hormone
LOAEL	Lowest Observed Adverse Effect Level
LOCF	last observation carried forward
MAA	marketing authorisation application
MABP	mean arterial blood pressure
MAO	monoamine oxidase
MDD	major depressive disorder
MTD	maximum tolerable dose
N/A	not applicable
NA	not available
NDA	New Drug Application
NDV	N-desmethylvenlafaxine
NE	norepinephrine
NOAEL	No Observed Adverse Effect Level
NODV	N-oxide desvenlavaxine
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
ODV	O-desmethylvenlafaxine
OECD	Organisation for Economic Co-operation and Development
OL	Open label
OVX	ovariectomized
PCI	potential clinical importance
PEC	predicted environmental concentration
P-gp	P-glycoprotein
PNEC	predicted no effect concentration
POMS	Profile of Mood States
QA	Quality Assurance
QTc	corrected QT interval
QTcF	QT interval based on Fridericia's correction
QTcN	population-corrected QT interval
R	Randomised
REM	rapid eye movement
RPT	report of nonclinical study results
SCS	Summary of Clinical Safety
SR	sustained release
SNRI	serotonin and norepinephrine reuptake inhibitor
SPC	summary of product characteristics
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TST	tail skin temperature
UDP	uridinediphosphate
UGT	UDP-glucuronosyltransferase
UV	ultraviolet
VMS	vasomotor symptoms (associated with menopause)
WHI	Women's Health Initiative study
WLQ	Work Limitations Questionnaire

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP consider that the application for Pristiqs, in the treatment of vasomotor symptoms (VMS) associated with the menopause,

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Clinical efficacy and safety
The current number of clinical studies includes 1 dose-response study (315), and 3 main efficacy/safety studies (319, 321, 337).

100 mg dose
Re-analysis of the effect size based on the population that approached most the ITT population requested (S3 analysis) resulted in further reduction in the already small effect size previously calculated in the original file based on the unaccepted modified ITT population.

The reduction in the mean daily number of hot flushes in post-menopausal women remained significant, but due to the new analysis, dropped to borderline significance ($p<0.05$) in the one dose-response study and in two out of three main clinical studies. In the third active- and placebo-controlled study the effect of Pristiqs remained similar to that of placebo whereas the active comparator tibolone showed both statistically and clinically significant effects that were not influenced by the new analyses applied. This latter study was the only non-US study whereas the other positive studies were conducted in US, which questions whether extrapolation of data between these two different populations is justified.

Further, in all 3 main studies (319, 321, 337) a decrease in effect size is noted from week 4 to week 12. This trend is not observed in the tibolone arm of study 321, which outcome seriously questions the maintenance of effect size.

Subsequently, the decrease in the already marginal effect size noted together with the decrease in effect size noted from week 4 to week 12 seriously questions the clinical relevance. This is also reflected in the percentage of responders.

150 mg dose:
Applying the S3 analysis to the results of the 150 mg dose, the difference versus placebo is no longer statistically significant in two of the three US-studies, indicating that no additional increase in effect size can be obtained by increasing the dose. Although no argumentation has been given, the 150 mg dose is no longer included in the dose recommendation.

Dose titration
In the newly submitted study 337 which applied dose-titration and tapering, dose titration did not significantly reduce the incidence of SNRI-like adverse effects such as nausea nevertheless the rate of drop-outs noted in the fixed-dose studies at week 1 decreased. Dose tapering did not significantly decrease the withdrawal symptoms (dizziness, nausea, hostility, and vertigo) either.

Safety
Although the reported SNRI-like adverse events and the occurrence of withdrawal symptoms are consistent with the known AE profile of venlafaxine in the treatment of major depression disorders, it is doubtful if such adverse events could also be acceptable for an indication such as VMS. Regarding cardiovascular safety, the current data show that Pristiqs poses extra burden on the cardio-vascular compromised patients and accordingly these patients should be contraindicated. Recent reports have observed an increased risk in clinical fragility fractures in elderly (>50 years) depressive patients using SSRIs. Although no information on this point is available for SNRIs it is recommended that bone safety should be assessed. Current available data on bone safety in this file, i.e. measurement of serum bone-specific alkaline phosphatase and CTX were used as bone turnover markers over a period of 3

months in study 337, are insufficient to conclude that DVS has no effect on bone. Taking into account the target population of postmenopausal women, both (long-term) cardiovascular safety and bone safety are of serious concern.

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 tradename is Pristiqs. The CHMP appointed Dr. B. Van Zwieten-Boot from the Netherlands as rapporteur and Dr. Tomas Salmonson from Sweden as co-rapporteur.

The proposed therapeutic **indication** for Pristiqs is:
"Treatment of vasomotor symptoms associated with the menopause".

Menopause may be associated with vasomotor symptoms (hot flushes and night sweats), vulvovaginal atrophy and osteoporosis, as well as difficulties with sleep, mood, and sexual complaints. These symptoms may have significant impact on women's lives and their ability to function.
Vasomotor symptoms (hot flushes) occur in 30-80% of women after menopause. Hot flushes usually occur several times per day, although the range may vary from only 1-2/day to as many as 1/hour during the day and night. They cause arousal from sleep, leading to sleep disturbances. In addition, many women have profuse perspiration which can be embarrassing in social situations.
The exact cause of hot flushes is unknown but they are thought to result from thermoregulatory dysfunction, initiated at the level of the hypothalamus due to oestrogen withdrawal. Oestrogen withdrawal is thought to influence the function of the neurotransmitters: serotonin (5-HT) and norepinephrine (NE). These neurotransmitters are hypothesized to play an important role in the maintenance of temperature homeostasis. DVS blocks the reuptake of both 5-HT and NE in the brain causing an increase in their levels in the extracellular spaces in the brain.

Oestrogen, i.e. hormone replacement therapy (HRT) is recognized to be the most effective medication for the treatment of hot flushes, providing greater than 95% efficacy for relief of vasomotor symptoms. However, on the basis of results of several recent large placebo-controlled and epidemiological studies, the opinion on the long-term safety of HRT has changed. The benefit/risk balance of long-term treatment with HRT is considered negative specially due to the duration-dependent increased risk of breast cancer. Currently, the European Medicines Agency therefore recommends that "*For the initiation and the continuation of treatment, the minimum effective dose for the shortest duration should be used. And in all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk (core SmPC for HRT).*"
Tibolone, a synthetic steroid with oestrogenic, progestagenic and androgenic properties is very effective in the treatment of hot flushes but its efficacy is slightly less than that noted with oestrogens. Also the long-term safety of this drug is considered negative in view of a possible increased risk of breast cancer and recently reported increased risk of stroke.

Non-hormonal options
Because hormone replacement therapy is contraindicated in some women, and some others are anxious about the use of hormones and prefer alternative approaches, there is a need to find alternative non-hormonal options. Many off-label compounds, including centrally acting antihypertensive medications (such as clonidine and methyldopa), veralipride, gabapentin, bellergal and selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) including venlafaxine, have been investigated in clinical trials for their potential effects on vasomotor instability. The results of published clinical trials have indicated variable efficacy, and adverse effects often limit the use of these agents.

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 C_{max} levels of the parent drug a may occur in clinical practice. As venlafaxine is biological 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 Efexor® (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.2 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. Four phase III studies were conducted to evaluate the safety and efficacy of DVS-SR for the treatment of VMS. The submission cut-off date for this registration application was 4 February 2006.

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). According to the applicant, there were no major comments from national agencies or the EMEA.
The exception was the Netherlands, which requested that results of a study with a hormonal active comparator be made available during review of the Marketing Authorization Application.

II.3 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.

II.4 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.

According to the application form, there is no paediatric development plan. The indication applied for concerns menopausal females.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

For the drug substance, desvenlafaxine succinate monohydrate, the ASMF-procedure was followed.

The manufacture of desvenlafaxine succinate monohydrate comprises of three main steps using commercially available starting materials. Outstanding questions on the restricted part of the ASMF have been satisfactorily settled by the ASMF-holder.
The drug substance, desvenlafaxine succinate, 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 materials as well as for the drug substance has been satisfactorily accounted for. At the time of the withdrawal some minor issues regarding one of the analytical methods were still pending.
Stability studies reveal the absence of degradation at the conditions studied (25°C/60%RH and 40°C/75%RH). Forced degradation studies also confirm the stability of the drug substance.

Drug Product

The aim of the pharmaceutical development was to produce a prolonged release oral formulation of desvenlafaxine. The development of the product has been satisfactorily performed and explained. The excipients employed are commonly used for oral formulations.
The specification for the drug product is in general satisfactory.
Stability studies demonstrated that the product is very stable and support the proposed shelf life of 2 years without any specific storage condition. At the time of withdrawal there were still some minor unresolved issues concerning certain acceptance criteria in the shelf-life specification.

III.2 Non clinical aspects

Pharmacology

Desvenlafaxine is a metabolite of venlafaxine, a known noradrenergic and serotonergic re-uptake inihibitor. 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 serotonin and norepinephrine re-uptake inhibitor (SNRI).
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. Historical data using these models demonstrate that chronically administered estrogens can alleviate temperature dysregulation. Venlafaxine has shown efficacy for the treatment of VMS (commonly referred to as hot flushes and night sweats) in clinical trials. Therefore, desvenlafaxine was evaluated in 2 rat models of OVX-induced thermoregulatory dysfunction and was found to be efficacious.
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.
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 71 times the calculated C_{max} value in humans. However, in dogs and mice, convulsions were seen in toxicology and safety pharmacology studies, albeit at comparatively high systemic exposures (C_{max}>23x).
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 8 to 59 times the calculated C_{max} 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 150 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 and the drug is specifically for menopausal vasomotor symptoms which only occurs in females.
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 clinical relevance of this finding for the current indication is obviously very limited. However, when the Applicant intends to include man in the target population in future applications for desvenlafaxine, than 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 0.4 times the maximum therapeutic exposure in human at 150 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 3 (rats) and 0.3 times (rabbits) of that at the maximum therapeutic exposure in humans at 150 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 3-times higher as compared to that in human at the maximum therapeutic dose of 150 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. *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. The weight of evidence indicates that desvenlafaxine is non-genotoxic non-carcinogenic substance.

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. Yet, on the other hand a concern regarding desvenlafaxine therapy and bone markers is expressed in the clinical part of the AR. 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, which could be resolved as a follow-up measure.
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 KOW was 0.33. Log KOC, 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 EC50 of 43 mg/L. The 48h LC50 for Daphnia magna was 33.0 mg/L. The 21d NOEC for reproduction for Daphnia magna was 8.2 mg/L. The 96h LC50 for *Pimephales promelas* is 9.4 mg/L. The NOEC for the Early Life Stage of *Pimephales promelas* is 2.1 mg/L. The EC50 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, besides the fact that the parent drug venlafaxine has been marketed for more than 10 years in several EU countries.
The Applicant performed 7 bioavailability and bioequivalence studies and 3 dose-proportionality studies in healthy volunteers. In addition, the Applicant performed 3 studies on the influence of intrinsic factors (renal and hepatic function, and age /gender), and clinical interaction studies with desipramine, ketoconazole, and midazolam.

Absorption
Absolute bioavailability of DVS is approximately 80%. The absorption of the SR formulation is slow and gradually (t_{max} may vary between 5-10 h). Food has little influence on the pharmacokinetics of O-desmethylvenlafaxine (ODV), although with study formulations not to be marketed significant food effects were observed. 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 C_{max} 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 variability in venlafaxine C_{max} was higher (±100%) compared to ODV C_{max}.

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 DVS is widely distributed. In animals, DVS is excreted into milk and passes the placenta.

Metabolism & Elimination
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. The terminal half-life varied

between 9-11 hrs in different studies. In healthy young subjects, clearance is approximately 0.3 L/hr/kg. Mean renal clearance of unchanged desmethylvenlafaxine after IV administration was 12.1 L/h (202 mL/min) and accounted for 54% of the total clearance of DVS from plasma. Clearance capacity remained constant over time. 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. 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. Hydroxy-metabolites were below detection limits in humans.
There were some technical problems with the *in vitro* study on UGT-isoenzymes. More specific information about the relative contribution of the different UGT isotypes will be provided as a FUM, for further evaluation of the interaction potency and possible consequences of genetic variability in UGT-expression.

Special populations
Though the PK-PD relationship is less clear for the clinical efficacy, there is a clear relationship between dose (ergo plasma exposure) and adverse events like hypertension and nausea. 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. The urinary recovery of desvenlafaxine and the conjugates were relatively low in the study in renal patients (52%).
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 is 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. This should be reflected in the SPC.
The Applicant proposes a once each day dosing schedule for patients with severe or end-stage renal impairment.

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. This should be mentioned in section 4.2 of the SPC. The accumulation of DVS in hepatic patients may be related to different clinical manifestations of hepatic dysfunction, which are not presented by the composite Child-Pugh scale. The Applicant is requested to investigate the relationship between different elements of the Child-Pugh score (such as albumin and bilirubin) and plasma exposure.

Elderly
As renal function declines with age, 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). For indication VMS, it is not expected that very elderly women will be treated, and no specific dosing schedule is therefore indicated for population of VMS patients.

Gender, race and body weight
Females had slightly higher DVS plasma levels than males, but dose adjustment for gender seems not necessary. The differences may be explained by differences in bodyweight and renal capacity between

men and women. Plasma concentrations are reverse related to bodyweight, but dose adjustment for extreme low or high bodyweight do not seem to be necessary in clinical practice. 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
The Applicant tested the influence of DVS on the activity of a range of CYP-enzymes *in vitro*, and no significant interactions are expected with substrates of CYP3A4, 1A2, 2A6, 2C8, 2C9, 2C19 and 3A4. The influence of DVS on CYP2E1 and 2B6 activity will be investigated *in vitro* as well, as these enzymes are known to be involved in clinically relevant interactions to be considered in FUMs.
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, virtual no interaction effect was observed. This may be due to the limited CYP2D6 enzyme capacity in humans.
The plasma levels of CYP3A4 substrate midazolam decreased slightly after 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. The observation of unchanged metabolite levels may be caused by induction of further metabolism of the metabolite. 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). If the mechanism is induction, a rather large inter-individual induction response is foreseen leading to much more than 30% reduced levels in some individuals. 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 *in vivo* study should be performed with another probe for CYP3A4 intestinal and hepatic metabolism. 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 enzymes may need to be further studied *in vivo*. This could be performed post-approval.

DVS levels increased with on average 40% after co-administration of ketoconazole, a CYP3A4 inhibitor. This might be 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*.
Neither studies are performed with UGT inhibitors of inducers. Whether studies with UGT inhibitors would be necessary will be decided after the analyses regarding contribution of individual UGT enzymes to metabolism of DVS would be finalised.
UGT-inducers like rifampicin, phenytoin, or hormones have impact on a broad range of UGT-enzymes, and may therefore be relevant for DVS which is metabolised by different UGT enzymes. As it is not likely that these UGT-inducers would be frequently used in patients with VMS, a warning in the SPC that interactions might occur and a monitoring advice (for efficacy) is deemed sufficient.

Pharmacodynamics

No pharmacodynamic studies were performed to investigate the mechanism of action of DVS in the requested indication. No initial dose response studies were performed to assess the required dosages in the clinical studies. Studies focused mainly on CNS and cardiac effects. Dose response studies to assess the tolerability of DVS were conducted, but only at higher fixed dosages (≥ 200 mg) administered once daily. Two studies determined the maximum tolerated dose to be 450 mg and 750 mg daily respectively based on the occurrence of severe nausea and postural hypotension. The reported adverse events were generally in line with those reported with venlafaxine, and were shown to increase with increasing dose. The pharmacodynamic effects of desvenlafaxine on EEG,

polysomnography, several neurocognitive tests and peripheral biomarkers (serotonin and norepinephrine) were investigated. Similar to venlafaxine, DVS SR increases REM sleep latency and decreases REM sleep duration. As this study was conducted in healthy male volunteers and did not evaluate sleep quality, the results cannot be used to make reliable predictions about the effects of DVS SR on sleep quality in women with VMS as claimed in section 5.1. The claims in section 5.1 are thus based solely on the results of the secondary endpoints.

The applicant addressed the effect of DVS SR on QTc adequately in a so-called "thorough QT/QTc study". Results indicate no significant prolongation of QTc. In addition, the pharmacodynamic interaction between DVS SR and alcohol was examined. No significant interaction was noted between DVS and alcohol, which is already reported with venlafaxine and is adequately described in the submitted SPC of DVS SR (Section 4.5).

As the sum of active moieties of venlafaxine + desvenlafaxine were comparable after administration of the same oral dose of Efexor® (venlafaxine) or DVS, pharmacodynamic features of DVS may be comparable to a same dose of Efexor, except for the fact that variability in peak levels was higher after administration of parent drug venlafaxine.

Clinical efficacy

Dose-response studies and main clinical studies

Four clinical studies were submitted to document the efficacy of DVS SR. The four studies were all outpatient, multi-centre, randomized, double-blind, and placebo-controlled trials. Additionally, study 321 was actively-controlled versus tibolone (table 1). Studies 315, 319 and 337 were conducted in the USA while study 321 was conducted in Europe, Mexico and South Africa. Studies 315, 319 and 321 were the studies initially submitted while study 337 is currently submitted with the 120 day responses of the applicant.

Table 1: Efficacy and Safety Studies of DVS SR for Vasomotor Symptoms.

		DVS SR				
Type of Study Study Number, CSR Number	**Treatment Duration**	**No. of Subjects in Each Study**	**Dose (mg/day)**	**No. of Subjects in Each Dose Group**	**Tibolone**	**Placebo**
			Completed Studies			
Double-Blind						
3151A2-315-US, CSR-60178	12 months	612	50	149	NA	77
			100	155		
			150	157		
			200	151		
3151A2-319-US, CSR-60332	6 months	361	100	182	NA	180
			150	179		
3151A2-321-WW, CSR 63098	3 months	158	100	158	166	152
3151A2-337-US, CSR-67349	3 months	301	100	150	NA	151
			150	151		
Total number of subjects VMS submission		1432			166	560

Dose selection

No separate dose-response studies were conducted. Four dose levels of Pristiqs were chosen by the applicant to be directly investigated in study 315 (the first phase III study). These doses were based on pre-clinical data with DVS SR together with that obtained in a non-sponsored clinical trial studying the effect of venlafaxine on hot flushes in breast cancer survivors (Loprinzi et al., 2000[1]). As the major part of venlafaxine is metabolised into desvenlafaxine, it was assumed that desvenlafaxine exposure would be roughly similar after using venlafaxine and DVS tablets of the same strength and formulation type (SR)[2]. The doses selected by the Applicant in study 315 were **50** mg**, 100** mg**, 150** mg and **200** mg DVS SR once daily. The 75 mg dose was not tested clinically. This decision was based on *in vitro* results showing a 45% and 72% inhibition of norepinephrine with the 50 mg and 100 mg doses, respectively, suggesting that the 75 mg dose would not have caused adequate inhibition. The overlap in exposure between each consecutive dose also does not allow for clear conclusions for dose recommendations.

The DVS SR doses selected in the subsequent clinical trials (study 319: **100** and **150** mg, study 321: **100** mg) were based on the interim efficacy results of study 315 at 4 and 12 weeks of treatment, respectively. While the doses selected in study 337 (100 mg and 150 mg) were based on the results of studies 315 and 319.

Posology

Gradual escalation and tapering of the dose is an established practice when using SSRI/SNRIs in order to increase their tolerability and avoid/lessen withdrawal symptoms respectively. However, this dose scheme was not implemented in any of the initially submitted studies (315, 319 and 321). In the fourth study (337) doses were titrated upward during the first week of treatment, after which subjects were treated for up to 84 days with their assigned dose before the dose was tapered for the last 2 weeks of the study, as shown in Table 2.

Table 2: Daily Dosage of DVS SR Received by Subjects in Study 337

	Titration Days		Maintenance Days	Tapering Days	
Treatment Group	1 to 3	4 to 7	8 to 84	1 to 7	8 to 14
DVS SR 100 mg	50 mg	100 mg	100 mg	50 mg	0 mg
DVS SR 150 mg	50 mg	100 mg	150 mg	100 mg	50 mg
Placebo	0	0	0	0	0

Source: Table 6-2, CSR 67349.

In the initial application, the applicant recommended 2 dose levels: 100 and 150 mg but currently the applicant is recommending only the 100 mg dose.

Main Efficacy Studies

Design

The main studies consist of 2 placebo-controlled US-studies (319 and 337) and one three-armed non-US study (321) including a placebo- and active-control arm (tibolone) (table 1). Because of the interim analysis that was carried on the results at week 4 and 12 in study 315 with partial un-blinding of the data, together with some methodological shortcomings, study 315 can be considered as the dose-finding study and further efficacy data obtained from it are considered supportive. Study 337 is newly submitted with the day 120 responses.

No guidelines have been developed for the investigation of non-hormonal products in the VMS indication. The guideline used in the current development program is the European guideline on Hormone Replacement Therapy (HRT) which is specifically developed to investigate the use of hormonal products to treat post-menopausal symptoms. In this guideline, placebo-controlled trials are

[1] Loprinzi C, Kugler J, Sloan J, Mailliard J, LaVasseur B, Barton D, Novotny P, Dakhil S, Rodger K, Rummans T, Christensen B. Venlafaxine in management of hot flashes in survivors of breast cancer: A randomized controlled trial. *Lancet*. 2000;356:2059-2063.

[2] In the Netherlands, venlafaxine XR is approved for the treatment of major depression (MDD) in a dose of 75 mg to be maximally increased to 375 mg/day. The treatment should start with the lowest dose. The dose can be increased in case of non-response, with 2 week intervals.

considered sufficient to demonstrate the efficacy of HRT in the management of hot flushes, as efficacy of oestrogens is well established. However, as to date no other SNRI is approved for the VMS indication, the applicant was advised to conduct an active controlled study with an HRT as the positive control to assess the relative efficacy of this new product versus an established therapy. Study 321, a three-armed study, was accordingly conducted with tibolone 2.5 mg as the active control. Although the efficacy of tibolone is slightly lower than observed with oestrogen or oestrogen-progestagen therapy, the selection of this comparator is considered acceptable. The duration of efficacy evaluation was 12 weeks in all studies. This duration is again based on the guideline developed for HRT, and it is questionable now whether such a short time would really allow for solid conclusion regarding the long term efficacy of Pritiqs in the VMS indication. Still, there were double-blind continuations up to 1 year and 6 months in studies 315 and 319, respectively. This prolongation would have allowed testing for safety, and maintenance of efficacy but not as the primary analysis.

The recruited women had to have a minimum of 7 moderate to severe hot flushes/day. The chosen primary efficacy endpoint consisted of a combination of 4 co-primary efficacy endpoints, i.e. the reduction in the average daily number of moderate and severe hot flushes and the reduction in the average daily severity score of hot flushes at weeks 4 and 12. These selected endpoints are consistent with the FDA guidelines, whereas the CHMP guideline on HRT (EMEA/CHMP/021/97/Rev 1) accepts women to have at least 5 moderate to severe flushes/day and considers reduction in the frequency of moderate to severe hot flushes after 12 weeks of therapy as sole primary end point for proof of efficacy.

The reduction in number of moderate and severe hot flushes at 12 weeks is therefore considered as the most decisive endpoint in this assessment. Twelve weeks of treatment circumvents the possibility that the maximum effect may take some time to be established or indicates that if the effect is reached earlier, that there is some maintenance of effect provided the effect of the other co-primary endpoints are consistent.
Key secondary efficacy variables included number of awakenings due to VMS, profile of mood states, work limitation questionnaire WLQ, and the Green climacteric scale. Although scheduled under “other secondary end points”, responder rates (75% reduction and 50% reduction in number of moderate and severe hot flushes) are considered to be very valuable in the assessment of the clinical relevance.

Inclusion/Exclusion
The applied exclusion criteria were generally consistent with those employed in a SNRI-trial. The studies excluded patients who had had a malignancy within the previous 2 years. According to the applicant, these patients were excluded because therapy for malignancy can impact compliance and completion of the study. In addition, treatments with selective estrogen receptor modulators such as tamoxifen, were prohibited as these medications can induce hot flushes and may have impacted the assessment of the primary endpoints.

The exclusion criteria applied in study 321 are generally in accordance with those employed in a HRT clinical trial due to the inclusion of the tibolone-arm. Patients with a *myocardial infarction, unstable heart disease, uncontrolled hypertension and uncontrolled diabetes were excluded from the clinical trials.* It is noted that cardiovascular contra-indications are implemented in the SPC of venlafaxine in some countries e.g. UK, while in other countries, including the Netherlands, these are included in the Warnings section. However, due to the older age of the post-menopausal women than the MDD indication with possible cardiovascular risk factors, these contraindications should be implemented with Pristiqs. Existence of depression was ruled out on subject interview only. As no proper psychiatric assessment was conducted in the clinical studies, women with depression could have been recruited. Accordingly, whether the shown effect of DVS SR in the positive studies is totally due to a real effect on hot flushes, or due to an effect on their perception can not be ruled out. Whether this issue can affect the prescribing pattern of DVS SR is not clear.

Statistical Plan
Analysis of covariance (ANCOVA) was used with treatment and study site as factors and baseline value as a covariate. Pair-wise comparisons between the Pristiqs groups and the groups that received placebo were performed using the t-test based on the least squares means and pooled error terms

obtained from the ANCOVA. In the initial submission, the above ANCOVA analyses were done on a modified ITT population with LOCF in case of premature withdrawal. The modified ITT population was defined as the population who were administered at least one dose, had also recorded data for at least 5 days at the baseline week, and had data for at least 5 days during at least 1 week in the first 12 on-therapy weeks after the baseline week. The use of this modified ITT definition was objected to as this excluded most of the subjects who withdrew prematurely during the first week due to adverse events. As the dropout rate during the first week was substantial the modified ITT population would not approach the real ITT population. For CHMP this was a major issue and a new analysis was requested, taking into account all randomised patients.

In the responses the ANCOVA analysis is based on 3 new analyses:

1. *Re-Analysis in ITT Population with Mixed Model (S1)*
   In this analysis the ITT was defined as all subjects randomised and having at least 1 day of post-randomization data. This corresponds to 99% of all randomized and dosed subjects for the 50-mg DVS SR dose, 99% for the 100-mg DVS SR dose, 96% for the 150-mg DVS SR dose, and 93% for the 200-mg DVS SR dose (see table above). According to ICH guideline E9, it was reasonable to exclude subjects who did not ever receive study drug because they were lost randomly with no relationship to their treatment assignment.
   The mixed effect model change from baseline in the number and severity of hot flushes was analyzed as response, with treatment, week, baseline scores, and a term for interaction between treatment and week of therapy as exploratory variables. A first order autoregressive of covariance structure was used to take into account the correlation between observations.

2. *Re-Analysis in ITT Population with LOCF Approach (S2)*
   In this second sensitivity analysis the LOCF procedure for all subjects randomised and at least 1 day of post-randomization data was applied.

3. *Re-Analysis in All Randomized and Dosed Subjects with LOCF Approach (S3)*
   Data from all 4 VMS studies were analyzed in all randomized and dosed subjects with baseline data carried forward when subjects had no on-therapy data.

The third re-analysis (S3) reflects mostly the analysis that was actually requested and therefore only results of this analysis will be presented in the current overview.

When multiple doses were tested, and in order to control the type I error rate, the comparisons were to be done in a stepwise manner. That is, when the higher doses tested positive against the placebo, only then would the effect of lower doses be investigated. This was also the intention in testing for significance for the secondary endpoints, i.e. their significance would only be tested if the primary endpoints were significant against the placebo. However, this sequential testing was not strictly followed (study 315) which was justified by the applicant by the importance of conducting this efficacy analysis in any case. This reasoning could have been accepted if the applicant has clearly stated that the submitted analysis is done contrary to the pre-specified statistical protocol and accordingly any subsequent results are only exploratory.

In study 315 two interim analyses were performed after 50% of the subjects had completed 4 weeks of treatment and after 50% had completed 12 weeks. The interim analysis at 4 weeks was performed to evaluate whether one or more dose-arms could be dropped in study 315. It was also used to determine the dose-arms of study 319 and the interim analysis of week 12 for determination of the dose in 321. Hence, it can not be excluded that the interim analyses of study 315 may have influenced the results of this study collected after the time points of these interim-analyses due to the partial un-blinding. As a consequence, study 315 may better be considered as supportive instead of decisive in the assessment of efficacy.

Study population

No major differences in demographics were noted, except for some differences that could be attributed to the difference in the study location. The majority of the patients aged between 50-55 years which is the expected population for this indication. Black and Asian patients were underrepresented.

Results

Primary efficacy results (12 weeks)

Major efficacy data are summarized in table 3, showing the absolute baseline values of the primary efficacy endpoints, the absolute changes seen in week 4 and 12, and the difference between the placebo and the treatment arms.

Table 3: Adjusted mean change in average daily number of moderate and severe hot flushes (prepared by assessor)

	Study 315			Study 319			Study 321			Study 337		
n subjects[A]	**Plac**	**DVS100**	**DVS 150**	**Plac**	**DVS100**	**DVS150**	**Plac**	**DVS100**	**Tibolone**	**Plac**	**DVS100**	**DVS150**
Randomised	**78**	**157**	**163**	**188**	**190**	**189**	**158**	**160**	**167**	**153**	**153**	**152**
Original	77	145	137	178	162	144	152	137	164	150	143	143
ITT-S1-S2	77	154	151	179	177	175	152	156	166	151	146	146
ITT-S3	77	155	157	179	182	179	152	158	166	151	150	151
Score[B]												
Baseline	11.0	10.5	11.2	10.6	10.8	10.6	9.6	10.1	10.1	11.0	11.1	10.5
Week 4	-5.22	-6.62	-6.48	-4.23	-6.29	-4.23	-4.38	-4.63	-6.16	-4.8	-6.7	-6.62
Week 12	-5.50	-7.23	-6.91	-4.92	-6.26	-4.92	-5.83	-5.78	-8.21	-5.8	-7.2	-6.96
Difference[C]												
Week 4												
Original	-	**-1.40 ***	**-1.26 ***	-	**-2.06 $**	**-2.45 $**	-	-0.25	**-1.78 $**	-	**-1.77$**	**-1.84$**
Analysis S1	-	**-1.44 #**	**-1.15 ***	-	**-2.18 $**	**-2.26 $**	-	-0.58	**-1.76 $**	-	**-1.80 $**	**-1.90 $**
Analysis S2	-	**-1.16 ***	-0.58	-	**-1.97 $**	**-1.88 $**	-	-0.18	**-1.73 $**	-	**-1.80 $**	**-1.84 $**
Analysis S3	-	-1.14	-0.66	-	**-1.83 $**	**-1.74 $**	-	-0.12	**-1.73 $**	-	**-1.56 $**	**-1.56 $**
Week 12												
Original		**-1.73 #**	**-1.44 ***		**-1.34 #**	**-2.04 $**		-0.05	**-2.38 $**	-	**-1.31#**	**-1.17***
Analysis S1	-	**-1.88 $**	**-1.36 ***	-	**-1.28 #**	**-1.83 $**	-	-0.42	**-2.61 $**	-	**-1.35 #**	**-1.08 ***
Analysis S2	-	**-1.44 ***	-1.02	-	**-1.25 #**	**-1.41 $**	-	0.23	**-2.32 $**	-	**-1.35 $**	**-1.20 #**
Analysis S3	-	**-1.41 ***	-0.82	-	**-1.11 ***	**-1.28#**	-	0.30	**-2.33 $**	-	**-1.09 ***	-0.92

*** p< 0.05 , # p < 0.01 , $ p <0.001**

[A] Original = mITT is ITT population as defined in original analysis i.e. all randomized subjects who took at least 1 dose and had at least 5 days efficacy evaluation.

ITT-S1-S2 = ITT population definition used in the first and second third sensitivity analysis i.e. all subjects randomised and at least 1 day of on-therapy data.

ITT-S3= ITT population defined in the third sensitivity analysis i.e. all subjects randomised and dosed.

[B] Data from first assessment rapport and study report study 337

[C] Difference versus placebo:

Original: mITT population with last observation carried forward

S1: First sensitivity analysis mixed effect model: change from baseline = treatment + week + treatment*week + baseline.

S2: Second sensitivity analysis: ANCOVA: change from baseline = treatment + site + baseline.

S3: Third sensitivity analysis: All randomised and dosed subjects with LOCF (includes baseline). ANCOVA: change from baseline = treatment + site + baseline.

100 mg DVS:

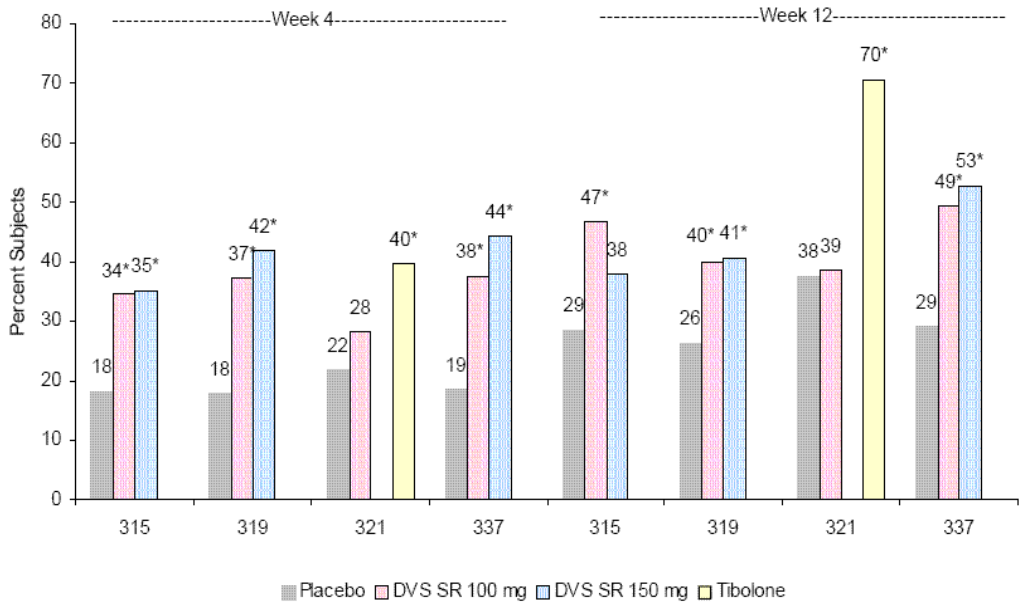
In comparison to the previously submitted mITT analysis, the results of the two US studies 319 and 337 show a borderline significant and marginal effect for Pristiqs in reducing the number of moderate to severe hot flushes compared to placebo. In the actively-controlled non-US study 321 the reduction in hot flushes achieved with the 100 mg dose remained numerically and statistically not different from placebo and apparently less than that of tibolone. These results therefore indicate that efficacy is not consistently shown across the three main studies. There are no apparent differences in population characteristics between studies 319/337 and 321 except that studies 319 and 337 were performed in the USA/Canada while study 321 was performed in Europe, South Africa and Mexico. It is questioned whether extrapolation of results from the USA studies to the non-US population in the presence of a clearly negative study in the latter population is justified.

Regarding the negative results of Pristiqs in the third study, the Applicant attributed these to the high placebo response which negated the efficacy observed with Pristiqs. However, when looking at the mean decrease in daily hot flushes noted at week 12 in all studies, i.e. 5.5 (study 315); 4.92 (study 319); 5.8 (study 321; 5.8 (study 337), there is no indication that the placebo response in study 321 is higher than noted in the other studies. In fact the placebo response is very similar across studies.
Further, in the 3 main efficacy studies there appears to be a decrease in effect size from week 4 to week 12. This trend is not observed in the tibolone arm of study 321. This outcome seriously questions the maintenance of effect size.

150 mg DVS:
Applying the S3 analysis on the results of the 150 mg dose, the difference versus placebo is no longer statistically significant in 2 of the three US-studies (including the dose-response study), indicating that no additional increase in effect size can be obtained by increasing the dose.

Responder rate
The results are illustrated in figure 4-6. This analysis is presented in the clinical overview in which the ***S2 analysis*** was applied.

Figure 4-6: Percentage of Subjects With a 75% Reduction in the Number of Moderate and Severe Hot Flushes From Baseline for the ITT Population, LOCF



*Significantly different from placebo at 0.05 level

The responder rates (defined as the percentage of subjects with at least a 50% or 75% reduction in the number of moderate to severe hot flushes from baseline) were significantly greater with DVS SR than placebo. However, also for this endpoint, in the actively controlled study 321 the results obtained with DVS SR were not significantly different from placebo and much lower than noted for tibolone. The responder rates were not reanalysed as requested for the primary endpoint, therefore any effect of applying the more conventional ITT population (S3) on this parameter is not clear.

Clinical relevance
A mean group difference of at least 2 moderate or severe hot flushes versus placebo is generally accepted as clinically meaningful. The applicant indicated in their sample size description that the power calculations of the dose-response study and the 3 main studies were based on the expectation that the differences between active DVS groups and placebo in the daily mean number of hot flushes would be at least 2. This was not reached in any of the studies performed.

In the one actively-controlled non-US study 321 the reduction in hot flushes achieved with the 100 mg dose remained numerically and statistically not different from placebo and apparently less than that of tibolone. In the 2 main placebo-controlled US-studies the differences between active groups and placebo in the daily mean number of hot flushes were borderline statistically significant, but in terms of clinical relevance the absolute difference in daily hot flushes was only marginal, i.e. less than 2 hot flushes per day (1.11 and 1.09 respectively).

In the context of clinical relevance responder rates are an acknowledged tool. The responder rates (defined as the percentage of subjects with at least a 50% or 75% reduction in the number of moderate to severe hot flushes from baseline) currently submitted were based on the S2 analysis. The responder rates were significantly greater with DVS SR than placebo, but the difference is not large. Also for this endpoint, in the actively controlled study 321 the results obtained with DVS SR were not significantly different from placebo and much lower than noted for tibolone.

Efficacy beyond 12 weeks of treatment
The evaluation of efficacy of DVS SR was continued double-blindly beyond 12 weeks in studies 315 and 319. For efficacy beyond the initial 12 weeks of therapy, only observed data were used to perform these analyses. Therefore, the definition of the mITT population does not affect the results of the analyses previously submitted in the original MAA.

Table 4: Adjusted Mean Change From Baseline in Average Number and Severity of Hot Flushes Beyond Week 12, ITT Population, Observed Cases

			Adjusted Mean Difference From Baseline in Average Number of Moderate and Severe HF			Adjusted Mean Difference From Baseline in Average Severity Score of HF		
Treatment	Weeks	N	Mean	SE	p-Value versus Placebo	Mean	SE	p-Value versus Placebo
315								
DVS SR 50 mg	12	125	-6.06	0.36	0.967	-0.43	0.07	0.288
	25-28	103	-6.85	0.36	0.328	-0.63	0.09	0.575
	49-52	88	-7.51	0.37	0.317	-0.76	0.10	0.913
DVS SR 100 mg	12	121	-7.80	0.36	**0.003**	-0.88	0.07	**0.006**
	25-28	108	-8.01	0.35	**0.003**	-0.90	0.08	0.136
	49-52	83	-8.26	0.37	**0.024**	-0.99	0.10	0.111
DVS SR 150 mg	12	109	-7.00	0.39	0.111	-0.64	0.08	0.466
	25-28	90	-7.45	0.38	0.052	-0.77	0.09	0.639
	49-52	75	-7.81	0.40	0.142	-0.75	0.10	0.937
DVS SR 200 mg	12	97	-6.92	0.41	0.153	-0.80	0.08	**0.040**
	25-28	82	-7.74	0.40	**0.017**	-0.81	0.10	0.148
	49-52	69	-8.16	0.42	**0.042**	-1.08	0.11	**0.035**
Placebo	12	67	-6.04	0.49	-	-0.55	0.10	-
	25-28	58	-6.29	0.47	-	-0.70	0.11	-
	49-52	48	-6.93	0.49	-	-0.74	0.13	-
319								
DVS SR 100 mg	12	129	-6.52	0.35	**0.010**	-0.55	0.07	**0.009**
	25+	111	-6.46	0.40	0.061	-0.59	0.08	0.068
DVS SR 150 mg	12	117	-7.41	0.36	**0.000**	-0.73	0.07	**0.000**
	25+	103	-7.19	0.41	**0. 001**	-0.69	0.09	**0.008**
Placebo	12	147	-5.36	0.32	-	-0.30	0.07	-
	25+	129	-5.48	0.37	-	-0.39	0.08	-

In this analysis the applicant only included '***observed cases'***. Already in the 12 weeks outcome it is clear that the number of women evaluated is less than in any of the analyses on the primary endpoint. Therefore women who discontinued DVS have not been taken into account, i.e. 74 of 157 women randomised discontinued in dose-response study 315 of 1 year duration and 79 of 190 in study 319 of 6 months duration. Subsequently, at the most from the supportive dose-response study these results may only suggest that the efficacy in reduction in hot flushes is maintained in a small subgroup of women. However, in the one main study that lasted 6 months, the reduction in hot flushes at week 25+ was no longer statistically significant. In conclusion, there are no robust data available supporting the long-term efficacy of Pristiqs.

Clinical safety

Patient exposure
The safety data presented summarizes treatment related adverse events and post therapy (15 days after discontinuation) adverse events for all subjects who received at least one dose of DVS SR or placebo

during the four VMS phase III studies, with some reference to the general safety profile from the MDD application.

In the phase III studies, DVS SR was administered in doses of 50 mg, 100 mg, 150 mg and 200 mg, with the majority of subjects receiving the 100 mg dose (the proposed dose).

In the 4 completed VMS studies, 1432 subjects received Pristiqs, 166 received tibolone, and 560 received placebo. Safety data is considered adequate for exposure to Pristiqs for one year, where sufficient numbers of patients are still participating in the studies (doses 100, 150 and 200 mg DVS SR). Subjects were generally healthy postmenopausal women. Significant differences between groups were seen for race, weight, BMI, and years since last natural menstrual period. According to the Applicant, these differences were primarily driven by differences between the US population enrolled in studies 315 and 319 and the populations enrolled in study 321 that additionally applied different exclusion criteria due to the active-control arm of tibolone (Europe, Mexico and South Africa). This explanation can be accepted. Most subjects in each treatment group had undergone natural menopause with an intact uterus. The majority of the recruited subjected were in the age range of 50-55 years which is expected to be the targeted population. Very few patients were recruited in the age group >65 years. Extrapolation of safety information to other racial groups than Caucasians is not possible, due to only minimal (~ <10%) inclusion of such patients.

Among the 2158 subjects who participated in these studies, the overall incidence of the treatment-emergent adverse events (TEAEs) was significantly higher in the Pristiqs treatment groups (91.3%, 87.8%, 91.6%, and 100% for the 50 mg, 100 mg, 150 mg, and 200 mg, respectively) compared to tibolone (65.7%) and placebo (75.4.0%).

The most common adverse drug reactions reported with the DVS SR 100-mg were nausea (37.4%), dizziness (16.9%), dry mouth (16.0%) insomnia (13.2%) and constipation. These adverse events were reported with tibolone in the following frequencies: 8.4%, 6.6%, 3.0%, 1.8%, 1.8% and 3.0% respectively. The reported AEs are conforming to those reported with other SNRIs, including venlafaxine, and are well reflected in section 4.8 of the proposed SPC.

There was a trend for dose-related increases in the incidence of some TEAEs, mainly in the digestive system (nausea and dry mouth) and the nervous system (dizziness, insomnia and somnolence) with most of the TEAEs of mild to moderate in severity.

Discontinuations (fixed dose studies 315, 319 and 321). A total of 578 (33.9%) subjects discontinued the test drug, versus 10.8% in the tibolone and 10% in the placebo groups. Most of the subjects withdrew because of adverse events (nausea, dizziness, asthenia and headache). The majority of discontinuations in the Pristiqs treatment groups occurred in the first week of treatment (up to 17%) versus <1% in the tibolone and placebo groups.
The majority of discontinuations due to adverse events occurred during the first week of drug administration with a significantly higher percent (14%) in all Pristiqs groups compared with placebo and tibolone (1%). The dropout rates amounted to 6%, 12%, 17% and 22% for the 50 mg, 100 mg, 150 mg and 200 mg Pristiqs in the first week respectively. After that, there was no clinically important difference between groups in safety-related discontinuations. On the other hand, withdrawals for unsatisfactory response were more frequent for subjects in the placebo and Pristiqs 50-mg groups than in Pristiqs 100-mg and Pristiqs 150-mg groups.

Effect of dose titration: In study 337, the discontinuation rate did not differ among groups at any time point during the study, including the first week. However, this was not accompanied by a parallel decrease in the incidence of nausea. The results as such probably point to better patient counselling regarding the incidence of nausea in the beginning of the study 337, rather than an effect of dose titration per se. The importance of patient counselling regarding nausea should be implemented in the SPC.

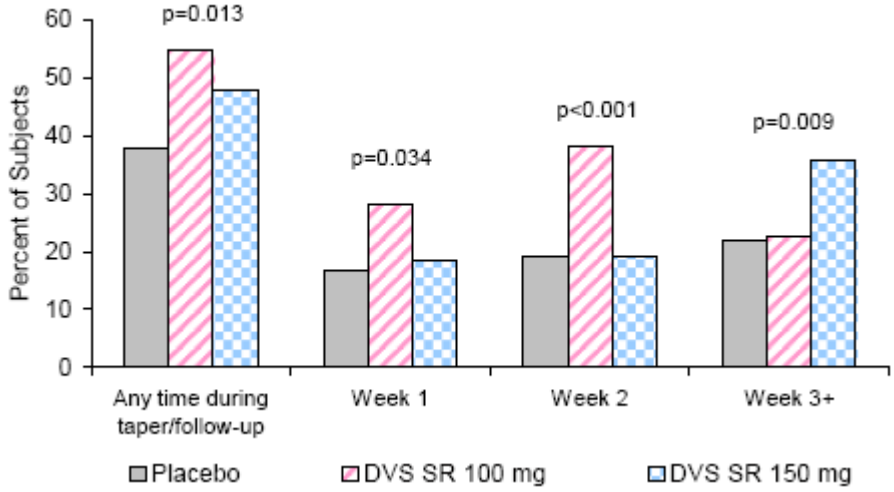
Serious adverse events. No deaths related to the intake of Pristiqs were reported. Six serious cardiovascular adverse events (3 coronary occlusions with revascularization and 3 myocardial

infarctions) were reported in 5 subjects during study 315 (study duration of 12 months). These events were judged by the Applicant as probably or definitely not related to Pristiqs because of the co-existence of relevant risk factors in these subjects e.g smoking, obesity, hyperlipemia. One serious case of hypertension was also reported in study 337 (risk factors: obesity and smoking). No cardiovascular events were reported in the short-term MDD studies. However, in the MDD study with a 10-month open extension 8 cardiovascular or cerebrovascular events were identified, which were not adequately presented in the current as well as the previous submission. Although all 5 patients had pre-existing cardiovascular risk factors, this does not preclude that Pristiqs use may still pose an extra risk on these patients. The use of Pristiqs as well as the parent compound (venlafaxine) is shown to increase blood pressure and heart rate, and serum lipids (total cholesterol, LDL and triglycerides). Although the use of venlafaxine is not contraindicated in patients with cardiovascular risk factors, due to the difference in age of the target populations (post-menopausal vs MDD) and the associated risk factors, these extra cardiovascular burdens would necessitate a more restrictive use in the VMS indication.

No significant ECG changes were observed except an increase in heart rate which is also described with venlafaxine.

Withdrawal symptoms (fixed dose studies 315, 319 and 321). Post-therapy emergent adverse events were significantly more reported in subjects in all DVS SR groups (47.5%) than subjects in the placebo (24.7%) or tibolone groups (23.5%). The most common events were asthenia, headache, vasodilatation, diarrhoea, nausea and vomiting. This high frequency of post-therapy emergent adverse events was probably due to the abrupt cessation of the drug.
Effect of tapering. In study 337, subjects were treated for up to 12 weeks (including 1 week with titration), at the end of which an additional 2 weeks was allowed for tapering the DVS SR dose. Overall, TPEAEs were reported by 57 (38%) subjects in the placebo group and 154 (51%) subjects in the DVS SR groups. The most common reported TPEAEs were dizziness, nausea, hostility, and vertigo.
Despite this gradual tapering of Pristiqs dose by 1-week steps, the incidence of discontinuation symptoms remained significantly higher among subjects receiving DVS SR (51%) than with subjects receiving placebo (38%) (fig 5.3).

Figure 5-3: Incidence of Emergent Discontinuation Symptoms by Week During the Taper/Follow-Up Period in Study 337



However, the difference in incidences of discontinuation symptoms between DVS SR groups and placebo was generally smaller than in previous DVS SR VMS studies with abrupt discontinuation. In contrast with the 100-mg DVS SR group, subjects assigned to the 150-mg DVS SR group, in whom the dose was gradually decreased over 2 weeks experienced significantly more discontinuation symptoms than subjects assigned to placebo only after complete discontinuation of DVS SR. The results do not support that tapering over a longer time is accompanied by a milder withdrawal profile

as suggested by the applicant; more gradual tapering only deferred the symptoms to a later week. The applicant should investigate further strategies to decrease withdrawal symptoms.

Effects on bone
In the newly submitted study 337, measurements of serum bone-specific alkaline phosphatase and CTX were used as bone turnover markers over a period of 3 months. In all treatment groups, there were small significant increases from baseline in adjusted mean bone-specific alkaline phosphatase at the week 12 and final on-therapy evaluations. Adjusted mean serum CTX values showed no significant change from baseline in any treatment group. There were no statistical differences between the DVS SR groups and the placebo group for these measurements. Such limited data are insufficient to conclude that DVS has no effect on bone. The applicant will collect further data in order to exclude a negative effect on bone.

Special populations
Patients with renal and hepatic impairment were excluded from participation. Dose recommendations in these patients are based on the results of the PK studies. Very few patients were recruited in the age group >65 years, which hampers a safety analysis in this population.

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

In general the applicant will perform routine pharmacovigilance activities as surveillance of post-marketing adverse reactions. In addition the application is investigating the feasibility of a pharmacoepidemiological study to proactively investigate drug utilisation patterns and several of the potential risks identified.

For safety concerns the applicant proposes specified action plans:
- Routine pharmacovigilance will be used for QT/QRS interval prolongation, cardiac ischaemia, suicidality including overdose, drug discontinuation, hepatic effects, serum lipid elevations, and risk of fractures.
- Amendments to the product information will be used for cardiac ischaemia, suicidality and overdose, drug discontinuation, and serum lipid elevations.
- Cumulative reviews in the PSURs will be used for lipid effects, hepatic adverse reactions, ischaemic cardiac events/myocardial infarction and fractures.
- Use of a drug utilisation database study will be applied for suicidality and overdose, and dual trade names.

Risk Minimisation Plan

Risk minimisation activities for desvenlafaxine proposed by the applicant include: product labelling, paediatric suicidality medication guide and small (14 day) pack sizes.

Identified safety issues needing risk minimisation activities were increased risk for suicide, possible via overdose. The activities include product labelling, educational materials to inform patients and caregivers of sign and symptoms indicative of suicidality, medication guide regarding paediatric suicidality and providing small pack sizes. Additionally a drug utilisation database study will be performed.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Clinical context

V.2 Benefits

Key Efficacy findings

- Changes in Average Daily Number of Moderate to Severe Hot Flushes
  100 mg Pristiqs: Re-analysis of the primary endpoint based on the population that approached most the ITT population requested (S3 analysis) resulted in a reduction in the already small effect size previously calculated in the original file based on the unaccepted modified ITT population.
  In the 3 US-studies (one dose-response and 2 main studies), the reduction in the mean daily number of hot flushes in post-menopausal women dropped to borderline significance ($p<0.05$). In the fourth active- and placebo-controlled non-US study the effect of Pristiqs remained similar to that of placebo whereas the active comparator tibolone still showed both statistically and clinically significant effects that were not influenced by the new analyses applied.
  Further, in all 3 main studies (319, 321, 337) a decrease in effect size is noted from week 4 to week 12, a trend not observed in the tibolone arm of study 321 (table 1).

  150 mg dose Pristiqs: Using the S3 analysis showed that the difference versus placebo is no longer statistically significant in 2 of the three US-studies, indicating that no additional increase in effect size can be obtained by increasing the dose. Although no argumentation has been given, the 150 mg dose is no longer included in the dose recommendation

- 75% responder rates
  The responder rates (defined as the percentage of subjects with at least a 50% or 75% reduction in the number of moderate to severe hot flushes from baseline) currently submitted were based on the S2 analysis. The responder rates were significantly greater with DVS SR than placebo. However, also for this endpoint, in the actively controlled study 321 the results obtained with DVS SR were not significantly different from placebo and much lower than noted for tibolone.

Strength of evidence

- Methodological deficiencies
  The requested analysis i.e. all randomized patients was not submitted. Three other analyses were submitted (S1, S2, S3). The mixed model of analysis (S1) assumes that the drop-out is at random and does not affect the outcome. This is questioned as the drop-out was differential, i.e. more patients dropped out from the DVS groups than in the placebo groups.
  The last observation carried forward is still the dominant procedure in the other two currently submitted sensitivity analyses. Alternative approaches e.g. assigning the placebo response at time of drop-out were not explored. However, requesting any further sensitivity analyses will not add to the decision of approval/labelling.
  The analysis using an ITT population defined as all randomized and dosed patients with LOCF from baseline (S3) is the nearest to the conventional ITT population that includes all randomised patients and therefore the current assessment is based on the data of this analysis only. However, not all data were presented using this population e.g. responder's rates were presented using the S2 analysis. It is assumed that submitting the data using the conventional definition of ITT (all randomized patients) would further decrease the efficacy.

- Efficacy has not been consistently shown
  In addition, the efficacy of Pristiqs in the VMS indication has not been demonstrated consistently across the studies. Significant results compared to placebo were only shown in two out of three main clinical trials, but in the active-controlled non-US trial the efficacy of Pristiqs was not different from placebo and significantly less than that noted for tibolone. One explanation given by the applicant to account for this discrepancy was the high placebo response which negated the modest efficacy of Pristiqs. However, data show comparable placebo responses across the studies. The other possible explanation pertaining to the difference between the US and the European population was not explored by the applicant.

- The clinical relevance of the obtained results is not clear.
  A minimum difference of 2 flushes per day over placebo is generally accepted as clinically meaningful.
  The applicant indicated in their sample size description that the power calculations of the dose-response study and the 3 main studies were based on the expectation that the differences between active DVS groups and placebo in the daily mean number of hot flushes would be at least 2. This was not reached in any of the studies performed. Instead, there is one negative study, while in the two other main studies although reaching statistical significance, this clinically relevant difference versus placebo was not achieved. Moreover, using the new analysis S3 the absolute difference versus placebo further dropped to 1.11 and 1.09 flush/day in the two main studies.
  The responder rates (defined as the percentage of subjects with at least a 50% or 75% reduction in the number of moderate to severe hot flushes from baseline) currently submitted were based on the S2 analysis. The responder rates were significantly greater with DVS SR than placebo, but the difference was not large. However, also for this endpoint, in the actively controlled study 321 the results obtained with DVS SR were not significantly different from placebo and much lower than noted for tibolone.

In conclusion, the efficacy of Pristiqs in the VMS indication is modest, inconsistent (may be dependent on the population) and of questionable clinical relevance.

V.3 Risks

Among the 2158 subjects who participated in these studies, the overall incidence of the treatment-emergent adverse events (TEAEs) was significantly higher in the Pristiqs treatment groups (91.3%, 87.8%, 91.6%, and 100% for the 50 mg, 100 mg, 150 mg, and 200 mg, respectively) compared to tibolone (65.7%) and placebo (75.4%).

Adverse event pattern

The most common adverse drug reactions reported with Pristiqs 100-mg were nausea (37.4%), dizziness (16.9%), dry mouth (16.0%) insomnia (13.2%) and constipation. These adverse events were reported with tibolone in the following frequencies: 8.4%, 6.6%, 3.0%, 1.8%, 1.8% and 3.0% respectively. The reported AEs are conforming to those reported with other SNRIs, including venlafaxine, and are well reflected in section 4.8 of the proposed SPC.
There was a trend for dose-related increases in the incidence of some TEAEs, mainly in the digestive system (nausea and dry mouth) and the nervous system (dizziness, insomnia and somnolence) with most of the TEAEs of mild to moderate in severity. The number of patients>65 years administered the 100 mg dose are too limited to draw conclusions on the efficacy and safety of this patient group.

Discontinuations (fixed-dose studies 315, 319 and 321). A total of 578 (33.9%) subjects discontinued the test drug in the 3 completed VMS studies, versus 10.8% in the tibolone and 10% in the placebo groups. Most of the subjects withdrew because of adverse events (nausea, dizziness, asthenia and headache). The majority of discontinuations in the Pristiqs treatment groups occurred in the first week of treatment (up to 17%) versus <1% in the tibolone and placebo groups.

Effect of dose titration: In study 337, the incidence of discontinuations due to adverse events did not differ among groups at any time point during the study, including week 1. However, this was not accompanied by a parallel decrease in the incidence of nausea. The results as such probably point to

better patient counselling regarding the incidence of nausea in the beginning of the study 337, rather than an effect of titration per se.

Withdrawal symptoms (fixed-dose studies 315, 319 and 321). (Post-therapy emergent adverse events) were significantly more reported in subjects in all DVS SR groups (47.5%) than subjects in the placebo (24.7%) or tibolone groups (23.5%). The most common events were asthenia, headache, vasodilatation, diarrhoea, nausea and vomiting.
Effect of dose tapering. In study 337, the tapering scheme did not have significant value on the incidence of discontinuation symptoms (dizziness, nausea, hostility, and vertigo) compared to placebo though it was lower than that reported in the earlier studies. The results do not support that tapering over a longer time is accompanied by a milder withdrawal profile as suggested by the applicant; more gradual tapering only deferred the symptoms to a later week.

Cardiovacular safety profile
The use of Pristiqs as well as the parent compound (venlafaxine) is shown to increase blood pressure and heart rate, and serum lipids *(increase in total cholesterol, LDL and triglycerides)*. However, due to the difference in age of the target populations (post-menopausal vs MDD) and the associated risk factors, these extra cardiovascular burdens would necessitate a more restrictive use in the VMS indication.

Bone safety
Current available data on bone safety in this file, i.e. measurement of serum bone-specific alkaline phosphatase and CTX were used as bone turnover markers over a period of 3 months in study 337, are insufficient to conclude that DVS has no effect on bone.

In conclusion, the safety analysis of Pristiqs did not reveal any significant difference from the parent drug venlafaxine used in major depression disorders. Dose titration and tapering did not abate the associated SNRIs adverse events. Although these SNRI-like adverse events and the occurrence of withdrawal symptoms are consistent with the known AE profile of venlafaxine in the treatment of major depression disorders, it is doubtful if these bothersome adverse events could also be acceptable for an indication such as VMS. Regarding cardiovascular safety, the current data show that Pristiqs poses extra burden on CV compromised patients and accordingly these patients should be contraindicated. Similar to venlafaxine, long term cardiovascular safety remains a point of concern. Also bone safety should be assessed.

V.4 Balance

Re-analysis of the efficacy data based on ITT population S3 (analyzed in all randomized and dosed subjects with baseline data carried forward (LOCF) when subjects had no on-therapy data) resulted in a reduction in the effect size previously calculated that was based on the unaccepted m-ITT analysis. The conventional ITT analysis (all randomized patients) was not submitted, but it is expected that when this population is taken, the effect would be further decreased.

In the two main placebo-controlled US-studies, the effect size of the 100 dose versus placebo decreases and drops to borderline significance. Additionally, a decrease in effect size from treatment week 4 to treatment week 12 is noted which seriously questions the maintenance of effect size.
Further, the results remained inconsistent as the efficacy of Pristiqs in the third trial was not different from placebo and significantly less than that noted for tibolone. No appropriate explanation is given for this discrepancy. An exceptional high placebo effect is not supported by the study results, as the reduction in hot flushes noted in the placebo groups is comparable across studies. There are no apparent differences between the studies showing significant results with DVS SR (319/337) versus the study that showed negative results for DVS SR (321) except for the different population studied. Extrapolating the results of US studies to a European population is not addressed but the negative non-US study questions extrapolation of US-studies to a non-US population.

Regarding the results on the 150 mg dose, the difference versus placebo is no longer statistically significant in 2 of the three US-studies, indicating that no additional increase in effect size can be

obtained by increasing the dose. Although no argumentation has been given, these results support the proposal to drop the 150 mg dose from the dose recommendation.

Additionally, the clinical relevance of the results achieved is questioned. A minimum difference of 2 flushes per day over placebo is generally accepted as clinically meaningful. The applicant indicated in their sample size description that the power calculations of the dose-response study and the 3 main studies were based on the expectation that the differences between active DVS groups and placebo in the daily mean number of hot flushes would be at least 2. This was not reached in any of the studies performed. Instead, there is one negative study, while in the two other main studies although reaching statistical significance, this clinically relevant difference versus placebo was not achieved. Moreover, based on the new analyses S3 the absolute difference versus placebo further dropped to 1.11 and 1.09 flush/day.
In the context of clinical relevance responder rates are an acknowledged tool. These responder rates were significantly greater with DVS SR than placebo. However, also for this endpoint, in the actively controlled study 321 the results obtained with DVS SR were not significantly different from placebo and much lower than noted for tibolone. Moreover, the responder rates currently submitted were based on the S2 analysis and not the more appropriate S3 precluding adequate assessment.

The safety analysis of Pristiqs did not reveal any significant difference from the parent drug venlafaxine used in major depression disorders. Dose titration and tapering did not significantly reduce the incidence of SNRI-like adverse effects such as nausea, though dose titration decreased the discontinuation rate noted in the fixed dose studies in the first week. Although comparable to the AE profile of venlafaxine in the treatment of major depression disorders, it is doubtful if the same adverse events could also be acceptable for an indication such as VMS. Regarding cardiovascular safety, the current data show that Pristiqs poses an extra burden on cardiovascular compromised patients by increasing the blood pressure and heart rate, *total cholesterol, LDL and triglycerides* and accordingly these patients should be contraindicated. Similar to venlafaxine, long term cardiovascular safety remains a point of concern. Also bone safety was not assessed according to standard methods (BMD measurements).

Current guidelines consider hormonal replacement therapy (HRT) as the most effective short-term therapy, but because of the unfavourable long-term safety profile, HRT is recommended to be used at the lowest dose and for the shortest duration. Alternative therapies, including clonidine and SSRI/SNRIs, are mentioned, but clear recommendations are lacking and the effect size of these alternatives is unknown.[3] When the benefit/risk balance of Pristiqs is compared with HRT, efficacy is obviously much less, and its relative safety undetermined. While short-term safety of HRT, except for the rare incidence of venous thrombosis is favourable, during Pristiqs treatment especially SNRI-like AEs are prominent and the main reason for discontinuation. Regarding the long-term treatment, HRT is noted to increase the risk of breast cancer and stroke, while for Pristiqs the unknown long-term cardiovascular safety raises concerns. Recently there is a discussion on a possible effect of SSRIs on bone[4], but currently available data on bone safety in this file are too limited to conclude that Pristiqs has no effect on bone. Therefore, it remains unclear whether desvenlafaxine will have an effect, but taking into account the target population, this concern should be further addressed. In addition, discontinuation of SNRIs is accompanied by withdrawal symptoms, which may influence the ability of the patient to stop the use of the drug, especially in long-term treatment. Tapering of the drug before discontinuation did not clearly abate this problem. HRT is not used in patients with breast cancer. Although the applicant is planning a study in breast cancer survivors, in the current file there are no data for the benefit/risk of Pristiqs in this patient population.

In summary, based on the US-studies only, Pristiqs is shown to be slightly better than placebo from a statistical point of view, but based on the non-US study no difference versus placebo was shown, while the active comparator achieved a statistically and clinically relevant effect. In terms of clinical relevance, despite that it would be acceptable that a drug in this indication is less efficacious than

[3] Grady D. Management of menopausal symptoms. NEJM 2006;355:2338-47

[4] Richards et al Ach Int Med 2007;167:188-194

HRT, a minimum difference of 2 flushes per day over placebo that is generally accepted as clinically meaningful should have been reached. Responder rates, which indicate the effect on an individual level, were higher in the test group, but the differences with the placebo group were not large. This together with a less favourable short-term safety due to bothersome SNRI-like AEs, the risk of withdrawal symptoms upon discontinuation and an uncertain long-term cardiovascular safety and a possible effect on bone safety in this population of elderly women questions the benefit/risk of Pristiqs in this indication.

V.5 Conclusions

The overall benefit/risk ratio of Pristiqs in the indication of hot flushes related to the menopause is unfavourable at this stage.