PFIZER
PRISTIQ®
Desvenlafaxine succinate

1. NAME OF THE MEDICINAL PRODUCT

PRISTIQ®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

50 mg

Each extended-release tablets contains 75.87 mg of desvenlafaxine succinate equivalent to 50 mg desvenlafaxine.

100 mg

Each extended-release tablets contains 151.77 mg of desvenlafaxine succinate equivalent to 100 mg desvenlafaxine.

3. PHARMACEUTICAL FORM

50 mg extended-release tablets

Light pink, square (pyramid, one sided), film coated tablets debossed “W” over '50' on the flat side.

100 mg extended-release tablets

Reddish orange, square (pyramid, one sided), film coated tablets debossed “W” over '100' on the flat side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRISTIQ, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD). The efficacy of PRISTIQ has been established in four 8-week, placebo controlled studies of outpatients who met DSM-IV criteria for major depressive disorder.

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The efficacy of PRISTIQ in maintaining a response in major depressive disorder for up to 24 weeks following 12 weeks of acute treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use PRISTIQ for extended periods, i.e., beyond 9 months, should continue to periodically re-evaluate the long-term usefulness of the drug for the individual patients.

4.2 Posology and method of administration

Major depressive disorder

The recommended dose for PRISTIQ is 50 mg once daily, with or without food. In clinical trials, doses of 50 to 400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day. Based on clinical judgement, if dose increases are indicated for individual patient, they should occur gradually and at intervals of not less than 7 days. The maximum dose should not exceed 200 mg/day.

When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms ***(see section 4.4: SPECIAL WARNINGS AND PRECAUTIONS FOR USE).***

PRISTIQ should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

Use in patients with renal impairment

The recommended starting dose in patients with severe renal impairment (24-hr CrCl <30 mL/min) or end-stage renal disease (ESRD) is 50 mg every other day. Because of individual variability in clearance in these patients, individualization of dosage may be desirable. Supplemental doses should not be given to patients after dialysis ***(see section 5.2: PHARMACOKINETIC PROPERTIES).***

Use in patients with hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment ***(see section 5.2: PHARMACOKINETIC PROPERTIES).***

Pediatric use

Safety and effectiveness in patients less than 18 years of age have not been established.

Efficacy was not demonstrated in two adequate and well controlled, 8-week, randomized, double-blind, placebo-controlled, parallel group studies conducted in 587 patients (7 to 17 years of age) for the treatment of MDD.

Use in elderly patients

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose ***(see section 5.2: PHARMACOKINETIC PROPERTIES).***

Greater sensitivity to desvenlafaxine in some older patients cannot be ruled out.

Discontinuing desvenlafaxine

Symptoms associated with discontinuation of desvenlafaxine, other SNRIs and SSRIs have been reported. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate ***(see section 4.8: UNDESIRABLE EFFECTS).*** In some patients, discontinuation may need to occur over periods of months or longer.

Switching patients from other antidepressants to desvenlafaxine

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to desvenlafaxine. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

Use of desvenlafaxine with reversible MAOIs such as linezolid or methylene blue

Do not start PRISTIQ in a patient who is being treated with a reversible MAOI such as linezolid or in whom intravenous methylene blue has been administered because there is increased risk of serotonin syndrome ***(see section 4.3: CONTRAINDICATIONS)***. In a patient who requires more urgent treatment of a psychiatric condition, non-pharmacological interventions, including hospitalization, should be considered.

In some cases, a patient already receiving PRISTIQ therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, PRISTIQ should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for two weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first ***(see section 4.4: SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***. Therapy with PRISTIQ may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with PRISTIQ is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use ***(see section 4.4: SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***.

4.3 Contraindications

Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the desvenlafaxine formulation.

Desvenlafaxine is an inhibitor of both norepinephrine and serotonin reuptake. Desvenlafaxine succinate must not be used in combination with a monoamine oxidase inhibitor (MAOI), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of desvenlafaxine succinate, at least 7 days should be allowed after stopping desvenlafaxine succinate before starting an MAOI. Starting desvenlafaxine succinate in a patient who is being treated with a reversible MAOI such as linezolid or in whom intravenous methylene blue has been administered is also contraindicated because of an increased risk of serotonin syndrome ***(see sections 4.2 and 4.4: POSOLOGY AND METHOD OF ADMINISTRATION; SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***.

4.4 Special warnings and precautions for use

Special Warnings

<u>Clinical worsening of depressive symptoms, unusual changes in behavior, and suicidality</u>

Desvenlafaxine succinate is an SNRI, a class of medicines that may be used to treat depression. All patients treated with desvenlafaxine should be monitored appropriately and observed closely for clinical worsening, suicidality or unusual change in behaviour. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal

ideation, especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in depressed patients, and the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18 to 24 years) with major depressive disorder (MDD) and other psychiatric disorders. Short-term trials did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 years and older.

Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.

Discontinuation effects

During marketing of serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), there have been post-marketing reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, seizures, visual impairment, and hypertension. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms, and sometimes these effects can be protracted and severe. In addition, suicide/suicidal thoughts, and aggression have been observed in patients during changes in desvenlafaxine dosing regimen, including during discontinuation.

Patients should be monitored when discontinuing treatment with desvenlafaxine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered (***see sections 4.2 and 4.8: POSOLOGY AND METHOD OF ADMINISTRATION; UNDESIRABLE EFFECTS***). In some patients, discontinuation may need to occur over periods of months or longer.

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (***see section 4.8: UNDESIRABLE EFFECTS***). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Mania/Hypomania

In clinical trials, mania was reported for 0.03% of patients treated with desvenlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, desvenlafaxine should be used cautiously in patients with a history or family history of mania or hypomania ***(see section 4.8: UNDESIRABLE EFFECTS).***

Serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions

As with other serotonergic agents, the development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions may occur with desvenlafaxine treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs ,

amphetamines and triptans), with opioids, with drugs that impair metabolism of serotonin (e.g., MAOIs**,** including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists ***(see sections 4.2 and 4.3: POSOLOGY AND METHOD OF ADMINISTRATION; CONTRAINDICATIONS)***. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea). Serotonin syndrome, in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes ***(see section 4.5: INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).***

If concomitant treatment with desvenlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of desvenlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma

Mydriasis has been reported in association with desvenlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored ***(see section 4.8: UNDESIRABLE EFFECTS).***

Other information - Residual inert matrix tablet

Patients receiving desvenlafaxine succinate may notice an inert matrix tablet passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

Precautions

Co-administration of drugs containing venlafaxine and/or desvenlafaxine

Desvenlafaxine is the major active metabolite of venlafaxine, a medication used to treat major depressive, generalized anxiety, social anxiety and panic disorders. Products containing desvenlafaxine succinate should not be used concomitantly with products containing venlafaxine hydrochloride or other products containing desvenlafaxine succinate.

Effects on blood pressure

Increases in blood pressure were observed in some patients in clinical trials, particularly with higher doses. Pre-existing hypertension should be controlled before treatment with desvenlafaxine. Patients receiving desvenlafaxine should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with desvenlafaxine. Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving desvenlafaxine, either dose reduction or discontinuation should be considered. Caution should be exercised in treating patients with underlying conditions that might be compromised by increases in blood pressure ***(see section 4.8: UNDESIRABLE EFFECTS).***

Cardiovascular/cerebrovascular disorders

Caution is advised in administering desvenlafaxine to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and heart rate were

observed in clinical trials with desvenlafaxine. Desvenlafaxine has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical trials ***(see section 4.8: UNDESIRABLE EFFECTS).***

Serum lipids

Dose-related elevations in fasting serum total cholesterol, LDL (Low Density Lipoprotein) cholesterol, and triglycerides were observed in clinical trials. Measurement of serum lipids should be considered during treatment with desvenlafaxine ***(see section 4.8: UNDESIRABLE EFFECTS).***

Seizures

Cases of seizure were reported in clinical trials with desvenlafaxine. Desvenlafaxine has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical trials. Desvenlafaxine should be prescribed with caution in patients with a seizure disorder ***(see section 4.8: UNDESIRABLE EFFECTS).***

Abnormal bleeding

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including desvenlafaxine, may increase risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening haemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of desvenlafaxine and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

Hyponatremia

Cases of hyponatremia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion have been described with SNRIs (including desvenlafaxine succinate) and SSRIs, usually in volume-depleted or dehydrated patients, including elderly patients and patients taking diuretics ***(see section 4.8: UNDESIRABLE EFFECTS)***.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOI)

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (including reversible MAOIs such as linezolid and intravenous methylene blue) and started on antidepressants with pharmacological properties similar to desvenlafaxine (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI ***(see sections 4.2 and 4.4: POSOLOGY AND METHOD OF ADMINISTRATION; SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***. Concomitant use of desvenlafaxine in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated ***(see section 4.3: CONTRAINDICATIONS)***.

Central nervous system (CNS)-active agents

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

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with desvenlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, amphetamines, lithium, sibutramine opioids (e.g., fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, meperidine, methadone, pentazocine) or St. John's Wort (*Hypericum perforatum*), with drugs that impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI] and methylene blue), or with serotonin precursors (such as tryptophan supplements) ***(see sections 4.2, 4.3 and 4.4: POSOLOGY AND METHOD OF ADMINISTRATION; CONTRAINDICATIONS; SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***.

If concomitant treatment with desvenlafaxine and an SSRI, an SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of desvenlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended ***(see section 4.4: SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***.

Ethanol

A clinical trial has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking desvenlafaxine.

Potential for other drugs to affect desvenlafaxine

- Inhibitors of CYP3A4

CYP3A4 is minimally involved in desvenlafaxine elimination. In a clinical trial, ketoconazole (200 mg BID) increased the area under the concentration vs. time curve (AUC) of desvenlafaxine (400 mg single dose) by approximately 43%, a weak interaction, and C_{max} by about 8%. Concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 may result in higher exposure to desvenlafaxine.

- Inhibitors of other CYP enzymes

Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine.

Potential for desvenlafaxine to affect other drugs

- Drugs metabolized by CYP2D6

Clinical trials have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at a dose of 100 mg daily. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased approximately 17%. When 400 mg was administered, the AUC of desipramine increased approximately 90%. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 60 mg dose of codeine, a CYP2D6 substrate metabolized to morphine, the AUC of codeine was unchanged, the AUC of morphine decreased approximately 8%. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in increased concentrations of that drug and decreased concentrations of its CYP2D6 metabolites.

- Drugs metabolized by CYP3A4

In vitro, desvenlafaxine does not inhibit, or induce the CYP3A4 isozymes. In a clinical trial, desvenlafaxine (400 mg daily) decreased the AUC of midazolam (single 4 mg dose), a CYP3A4 substrate, by approximately 31%. In a second study, PRISTIQ 50 mg daily was co-administered

with a single 4 mg dose of midazolam. The AUC and C_{max} of midazolam decreased by approximately 29% and 14%, respectively. Concomitant use of desvenlafaxine with a drug metabolized by CYP3A4 may result in lower exposures to that drug.

- Drugs metabolized by a combination of both CYP2D6 and CYP3A4 (tamoxifen and aripiprazole)

Clinical studies have shown that desvenlafaxine (100 mg daily) does not have a clinically relevant effect on drugs metabolized by a combination of both CYP2D6 and CYP3A4 enzymes.

A single 40 mg dose of tamoxifen, which is metabolized to active metabolites 4-hydroxy-tamoxifen and endoxifen primarily by CYP2D6 with minor contributions to metabolism by CYP3A4, was administered in conjunction with desvenlafaxine succinate (100 mg daily). The AUC increased by 3% with concomitant administration of desvenlafaxine succinate. The AUC of 4-hydroxy-tamoxifen increased by 9%. Endoxifen AUC was decreased by 12%.

Desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 5 mg dose of aripiprazole, a CYP2D6 and CYP3A4 substrate metabolized to the active metabolite dehydro-aripiprazole. The AUC of aripiprazole increased by 6%, with concomitant administration of desvenlafaxine succinate. The AUC of dehydro-aripiprazole increased by 3%, with concomitant administration.

- Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19

In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes.

P-glycoprotein transporter

In vitro, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter.

Drug-laboratory test interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of desvenlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine.

Electroconvulsive therapy

There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with desvenlafaxine treatment for MDD.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of desvenlafaxine in human pregnancy has not been established. Studies have demonstrated that desvenlafaxine crosses the human placenta. Desvenlafaxine must only be administered to pregnant women if the expected benefits outweigh the possible risks. If desvenlafaxine is used until, or shortly before birth, discontinuation effects in the newborn should be considered.

Complications, including the need for respiratory support, tube feeding or prolonged hospitalization, have been reported in neonates exposed to SNRIs or SSRIs late in the third trimester. Such complications can arise immediately upon delivery.

Data from the Quebec Pregnancy Cohort reported that, following exposure to SNRIs (including desvenlafaxine) during the second half of pregnancy, persistent pulmonary hypertension of the newborn (PPHN) was identified in 0.2% of all neonates; no statistical significance in the increased risk of PPHN in response to second/third trimester exposure could be established.

In a prospective, observational study, the median (interquartile range [IQR]) gestational age was higher in infants born to control mothers than those born to mothers treated with antidepressants (40 [39-40 weeks] vs. 39 [38-40 weeks]; $p<0.05$). Neonates born to control mothers also had a longer median (IQR) length at birth (51 [49-51.6] cm vs. 49 [47-51] cm; $p<0.05$) than infants born to mothers in the cases group. The infants also displayed mild behavioral anomalies, categorized as less optimal functioning for habituation and motor and autonomic clusters (using the Brazelton Neonatal Behavioral Assessment Scale [BNBAS]); however these events were self-limiting and usually resolved in 1 to 2 weeks.

In another study, 6 of the 7 neonates with *in utero* exposure to venlafaxine at near term had acceptable Apgar scores at birth; however an improvement in Apgar scores at 5 minutes was observed in all 7 neonates. No cases of intrauterine growth retardation were recorded. The adverse events observed in 5 neonates at birth, included respiratory distress, tachypnea, irritability, tremors, excessive suckling, rigidity, increased tonus, vomiting, hyper-reflexia, disorganized movements of limbs, initial decreased reactivity, agitation, poor sleep and liquid/abundant stool. In 4 of the 5 neonates, the events resolved spontaneously without the need for any pharmacological treatment, while one neonate required resuscitation and continuous positive airway pressure (C-PAP) for 48 hours. Although respiratory distress was attributed to the plasma concentration of venlafaxine or desvenlafaxine at birth, the occurrence of the other adverse events correlated with the declining levels of venlafaxine, suggests that these events could potentially signal withdrawal symptoms in the neonate following a decline in levels of venlafaxine after exposure to significantly high levels of the drug *in utero.*

A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia, and exposure to SNRIs near delivery may increase the risk for postpartum haemorrhage. Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

Lactation

Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. No adverse events occurred in either the lactating mothers or the nursing infants, however, the effect in infants have not been established. Desvenlafaxine should only be taken by lactating women if the expected benefits outweigh the possible risks.

4.7 Effects on ability to drive and use machines

Interference with cognitive and motor performance

The results of a clinical trial that assessed the effects of desvenlafaxine on behavioral performance of healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any CNS-active drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that desvenlafaxine therapy does not adversely affect their ability to engage in such activities.

4.8 Undesirable effects

Clinical trials experience

The safety of desvenlafaxine was established in a total of 11,444 patients who were exposed to at least one dose of desvenlafaxine ranging from 10 to 400 mg/day in MDD and VMS clinical trials (8,453 in MDD trials; 2,991 in VMS trials) or from post-marketing experience. Long-term safety was evaluated in 3,502 patients (2,140 in MDD and 1,362 in VMS) who were exposed to desvenlafaxine for at least 6 months and with 1,372 (421 in MDD and 951 in VMS) patients exposed for 1 year. In general, the adverse reactions were most frequent in the first week of treatment.

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

Adverse Events Table - Combined MDD and VMS Studies						
System Organ Class	**Very Common ⩾1/10**	**Common ⩾1/100 to <1/10**	**Uncommon ⩾1/1,000 to <1/100**	**Rare ⩾1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Frequency Not Known (cannot be estimated from available data)**
Immune System Disorders			Hypersensitivity			
Metabolism and Nutrition Disorders		Decreased appetite		Hyponatremia		
Psychiatric Disorders	Insomnia	Withdrawal syndrome, anxiety, nervousness, abnormal dreams, irritability, libido decreased, anorgasmia	Depersonalisation, orgasm abnormal	Mania, hypomania, hallucination		
Nervous System Disorders	Headache, dizziness, somnolence	Tremor, paraesthesia, disturbance in attention, dysgeusia	Syncope, extrapyramidal disorder	Serotonin syndrome*†, convulsion		
Eye Disorders		Vision blurred, mydriasis				
Ear and Labyrinth Disorders		Vertigo, tinnitus				
Cardiac Disorders		Tachycardia, palpitations		Stress cardiomyopathy (takotsubo cardiomyopathy)*†		
Vascular Disorders		Blood pressure increased, hot flush	Orthostatic hypotension, peripheral coldness			
Respiratory, Thoracic, and Mediastinal		Yawning	Epistaxis			

Disorders						
Gastrointestinal Disorders	Nausea, dry mouth, constipation	Diarrhoea, vomiting		Pancreatitis acute		
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, rash	Alopecia	Stevens-Johnson syndrome*†, angioedema, photosensitivity reaction		
Musculoskeletal and Connective Tissue and Disorders		Musculoskeletal stiffness				
Renal and Urinary Disorders			Urinary retention, urinary hesitation, proteinuria			
Reproductive System and Breast Disorders		Erectile dysfunction‡, ejaculation delayed‡	Ejaculation disorder*‡, Ejaculation failure‡, sexual dysfunction			
General Disorders and Administration Site Conditions		Fatigue, asthenia, chills, feeling jittery				
Investigations		Liver function test abnormal, weight increased, weight decreased	Blood cholesterol increased, blood triglycerides increased, blood prolactin increased			

* ADR identified post-marketing
‡ ADR Frequency estimated using "The Rule of 3"
‡ Frequency is calculated based on men only
ADR = Adverse drug reaction; MDD = Major depressive disorder; VMS = Vasomotor symptoms.

Ischemic cardiac adverse events

In clinical trials, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine treatment as compared to placebo ***(see section 4.4: SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***.

Discontinuation symptoms

Adverse drug reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical trials at a rate of ≥2% include: dizziness, withdrawal syndrome, nausea and headache. In general, discontinuation symptoms occurred more frequently with higher doses and with longer duration of therapy ***(see sections 4.2 and 4.4: POSOLOGY AND METHOD OF ADMINISTRATION; SPECIAL WARNINGS AND PRECAUTIONS FOR USE)***.

Adverse reactions leading to discontinuation of therapy

The most common adverse reactions leading to discontinuation in at least 2% of the desvenlafaxine-treated patients in the short-term trials, up to 12 weeks, was: nausea (2%); in the long-term studies, up to 11 months, no events lead to discontinuation in at least 2% of the patients and at a rate greater than placebo in the double-blind phase.

Pediatric patients

In general, the adverse reaction profile of PRISTIQ (in placebo-controlled clinical studies) in children and adolescents (aged 7 to 17) was similar to that seen for adults.

The most frequently reported events from the placebo-controlled studies were: Headache (17.3%), Nausea (8.6%), Abdominal pain upper (8.5%), Nasopharyngitis (5.3%), Dizziness (4.6%), Upper respiratory tract infection (4.2%), Decreased appetite (4.2%), Vomiting (3.9%), Fatigue (3.2%), and Insomnia (3.2%). Of these, events with an incidence in the PRISTIQ groups >2 times that of the placebo group were: Fatigue (4.2% vs. 1.7%), and Insomnia (4.2% vs. 1.7%).

When compared to adverse event rates in adults, the following events occurred more frequently in pediatric patients *(incidence of ≥3% in pediatric patients and <3% in adults)*: Abdominal pain upper, Weight increased, Gastroenteritis viral, Dysmenorrhoea, Accidental overdose, Cough, Irritability, Oropharyngeal pain, and Sinusitis.

As with adults, increased blood pressure, abnormal bleeding, mania/hypomania, discontinuation syndrome, seizure, suicide attempt, suicidal behavior, self-injurious behavior and suicidal ideation were observed in pediatric clinical studies (see section 4.4).

Geriatric use

Of the 7,785 patients in MDD clinical trials treated with desvenlafaxine, 5% of patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term placebo-controlled trials, there was a higher incidence of systolic orthostatic hypotension and in both short-term and long-term placebo-controlled trials, there were increases in systolic blood pressure in patients ≥65 years of age compared to patients <65 years of age treated with desvenlafaxine.

Adverse reactions reported with other SNRIs

Although gastrointestinal bleeding is not considered an adverse reaction for desvenlafaxine succinate, it is an adverse reaction for other SNRIs and may also occur with desvenlafaxine succinate.

4.9 Overdose

There is limited clinical experience with desvenlafaxine succinate overdosage in humans.

Among the patients included in the major depressive disorder clinical trials of desvenlafaxine succinate, there were four adults who ingested doses greater than 800 mg of desvenlafaxine succinate (4,000 mg [desvenlafaxine alone], 900, 1,800 and 5,200 mg [in combination with other drugs]); all patients recovered. In addition, one patient's 11-month-old child accidentally ingested 600 mg of desvenlafaxine succinate, was treated, and recovered.

In post-marketing experience, overdose cases (including cases with fatal outcome) have been reported with desvenlafaxine in combination with alcohol and/or other medicinal products.

No specific antidotes for desvenlafaxine are known. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered.

4.10 Abuse and dependence

Physical and psychological dependence

Although desvenlafaxine has not been systematically studied in preclinical or clinical trials for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical trials.

5. PHARMACOLOGICAL PROPERTIES

Mode of Action

Non-clinical trials have shown that desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The clinical efficacy of desvenlafaxine is thought to be related to the potentiation of these neurotransmitters in the central nervous system.

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors has been hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In the same comprehensive binding profile assay, desvenlafaxine also lacked 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.

In preclinical rodent models, desvenlafaxine demonstrated activity predictive of antidepressant, anxiolytic and thermoregulatory actions, and pain inhibitory properties.

5.1 Pharmacodynamic properties

Clinical Efficacy

The efficacy of desvenlafaxine as a treatment for depression was established in four, 8-week, randomized, double-blind, placebo-controlled, fixed-dose trials and two relapse prevention trials in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder. In the first trial, patients received 100 mg (n = 114), 200 mg (n = 116), or 400 mg (n = 113) of desvenlafaxine once daily, or placebo (n = 118). In a second trial, patients received either 200 mg (n = 121) or 400 mg (n = 124) of desvenlafaxine once daily, or placebo (n = 124). In two additional trials, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of desvenlafaxine once daily, or placebo (n = 150 and n = 161).

Desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}) total score in four trials and, as measured by the Clinical Global Impressions Scale-Improvement (CGI-I), in three of the four trials. There was no clear evidence that doses greater than 50 mg/day conferred any additional benefit.

In a long-term trial, adult outpatients meeting DSM-IV criteria for major depressive disorder, who responded to 8 weeks of open-label acute treatment with 50 mg/day desvenlafaxine and subsequently remained stable for 12 weeks on desvenlafaxine, were assigned randomly in a double-blind manner to remain on active treatment or switch to placebo for up to 26 weeks of

observation for relapse. Response during the open phase was defined as a HAM-D_{17} total score of ≤11 and CGI-I ≤2 at the day 56 evaluation; stability was defined as not having a HAM-D_{17} total score of ≥16 at any office visit. Relapse during the double-blind phase was defined as follows: (1) a HAM-D_{17} total score of ≥16 at any office visit, (2) discontinuation for unsatisfactory efficacy response, (3) hospitalized for depression, (4) suicide attempt, or (5) suicide. Patients receiving continued desvenlafaxine treatment experienced statistically significantly longer time to relapse compared with placebo. At 26 weeks, the Kaplan-Meier estimated probability of relapse was 14% with desvenlafaxine treatment versus 30% with placebo.

In a second long-term trial, adult outpatients meeting DSM-IV criteria for MDD and who responded to 12 weeks of acute treatment with desvenlafaxine were assigned randomly to the same dose (200 or 400 mg/day) they had received during acute treatment or to placebo for up to 26 weeks of observation for relapse. Response during the open phase was defined as a HAM-D_{17} total score of ≤11 at the day 84 evaluation. Relapse during the double-blind phase was defined as follows: (1) a HAM-D_{17} total score of ≥16 at any office visit, (2) a CGI-I score of ≥6 (versus day 84) at any office visit, or (3) discontinuation from the trial due to unsatisfactory response. Patients receiving continued desvenlafaxine treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics. There was insufficient information to determine the effect of race on outcome in these trials.

Pediatric

The PRISTIQ pediatric development program investigated the acute treatment of MDD in pediatric patients (ages 7 to 17) and consisted of 6 studies: 2 Phase 2 studies (Study 3151A6-2000-US hereafter referred to as B2061012, and its 26-week open label extension (OLE) Study 3151A6-2001-US here-after referred to as B2061013), and 4 Phase 3 studies (8 week Studies B2061014 and B2061032 hereafter referred to as the placebo-controlled studies, and their respective 26 week OLE Studies B2061031 and B2061030). A total of 761 subjects were evaluated across the clinical development program, of which 684 unique patients received DVS SR in at least one of the 6 studies.

The results of the two placebo-controlled studies showed no statistically significant difference between placebo and PRISTIQ for the pre-defined primary endpoint [change from baseline to Week 8 in the Children's Depression Rating Scale – Revised (CDRS-R)]. There was no relationship between desvenlafaxine exposure and change from baseline to Week 8 CDRS-R total score.

5.2 Pharmacokinetic properties

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 50 to 600 mg/day. The mean terminal half-life ($t_{1/2}$) is approximately 11 hours. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 to 5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

The pharmacokinetics of desvenlafaxine have been thoroughly evaluated in women and men. There are minimal differences based on gender; data from all subjects are presented below.

Absorption and distribution

Desvenlafaxine succinate is well absorbed, with an absolute oral bioavailability of 80%. Mean time to peak plasma concentrations (T_{max}) is about 7.5 hours after oral administration. AUC and C_{max} of 6,747 ng·hr/mL and 376 ng/mL, respectively, are observed after multiple doses of 100 mg.

Effects of food

A food-effect trial involving administration of desvenlafaxine to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the C_{max} was increased about 16% in the fed state, while the AUCs were similar. This difference is not clinically significant; therefore, desvenlafaxine can be taken without regard to meals.

The plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. Desvenlafaxine's volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.

Metabolism and elimination

Approximately 45% of desvenlafaxine is excreted unchanged in urine. Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

Geriatric

In a trial of healthy subjects administered doses up to 300 mg, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32% increase in C_{max} and a 55% increase in AUC values in subjects greater than 75 years of age, as compared with subjects 18 to 45 years of age. No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose ***(see section 4.2: POSOLOGY AND METHOD OF ADMINISTRATION)***.

Patients with renal impairment

The pharmacokinetics of desvenlafaxine succinate 100 mg were studied in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) requiring dialysis (n = 9) and in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. Total body clearance was reduced by 29% in mild, 39% in moderate, 51% in severe renal impairment and 58% in ESRD compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42% in mild (24-hr CrCl = 50-80 mL/min), 56% in moderate (24-hr CrCl = 30-50 mL/min), 108% in severe (24-hr CrCl < 30 mL/min), and 116% in ESRD subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11.1 hours in the healthy subjects to 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively.

Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure. Therefore, supplemental doses should not be given to patients after dialysis. Dosage adjustment is recommended in patients with significant impairment of renal function *(**see section 4.2: POSOLOGY AND METHOD OF ADMINISTRATION)**.*

Patients with hepatic impairment

The pharmacokinetics of desvenlafaxine succinate 100 mg were studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and in healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe

hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were comparable in subjects with mild hepatic impairment and healthy subjects (<5% difference).

Systemic clearance (CL/F) was decreased by approximately 20% and 36% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (<5% difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively ***(see section 4.2: POSOLOGY AND METHOD OF ADMINISTRATION).***

Thorough QTc trial

In a thorough QTc trial with prospectively determined criteria, in healthy women, desvenlafaxine did not cause QT prolongation. Additionally, no effect on QRS interval was observed.

5.3 Preclinical safety data

Carcinogenicity

Desvenlafaxine succinate administered by oral gavage to mice and rats for 2 years did not increase the incidence of tumors in either trial.

Mice received desvenlafaxine at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The 300 mg/kg/day dose is 90 times, on a mg/kg basis, the maximum recommended human dose (MRHD) of 200 mg/day, and 7 times the MRHD, on a mg/m^2 basis.

Rats received desvenlafaxine at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose was 90 (males) or 150 (females) times, on a mg/kg basis, the MRHD of 200 mg/day, and 15 (males) or 24 (females) times the MRHD of 200 mg/day, on a mg/m^2 basis.

Mutagenicity

Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine was not genotoxic in the *in vitro* CHO mammalian cell forward mutation assay and was negative in the *in vitro* BALB/c-3T3 mouse embryo cell transformation assay.

Impairment of fertility

Reduced fertility was observed in a preclinical trial in which both male and female rats received desvenlafaxine succinate.

This effect was noted at oral doses approximately 30 times, on a mg/kg basis, and 5 times the maximum human dose (MRHD) of 200 mg/day on a mg/m^2 basis. There was no effect on fertility at oral doses approximately 9 times the MRHD on a mg/kg basis, and 1.5 times the MRHD on a mg/m^2 basis. The human relevance of this finding is unknown.

Teratogenicity

When desvenlafaxine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity in rats at any doses tested, up to 30 times on a mg/kg basis and up to 5 times the maximum recommended human dose (MRHD) of 200 mg/day (on a mg/m^2 basis) in rats, In rabbits, there was no evidence of teratogenicity at doses up to 23 times (on a mg/kg basis) the MRHD of 200 mg/day, or 7 times the MRHD (on a mg/m^2 basis).

However, fetal weights were decreased in rats with a no-effect dose 30 times the MRHD (on a mg/kg basis) 5 times the MRHD (on a mg/m^2 basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and increase in pup deaths during the first four days of lactation. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 30 times on a mg/kg basis and 5 times the MRHD of 200 mg/day (on a mg/m^2 basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine at a dose 90 times the MRHD (on a mg/kg basis) and 15 times the MRHD (on a mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not applicable

6.2 Shelf-life

Please refer to details on outer carton.

6.3 Special precautions for storage

Store below 30°C. Keep the blister in the outer carton.

6.4 Nature and contents of container

2 blister strips containing 14 tablets each.

6.5 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

Pfizer Ireland Pharmaceuticals Unlimited Company,
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Date of Revision: 07 NOV 2024