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**Ihr Zeichen:**

### PHV issue: Venlafaxin

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummern: SE/H/PSUR/0050/001) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Venlafaxin – hältigen Arzneispezialitäten aufzunehmen.

Sollten die Änderungen bereits aufgenommen worden sein, benachrichtigen Sie uns bitte per E-Mail ([pv-implementation@ages.at](mailto:pv-implementation@ages.at)).

**Amendments to the Product Information**

During the assessment of the information in the PSUR the following issue was considered:  
Available data related to CYP3A4 induction and interaction with hormonal contraceptives and post-marketing experiences has resulted in the adding of a precautionary text in SmPC section 4.5 regarding co-administration of venlafaxine and hormonal contraceptives  
It has been agreed that the following amendments to the Product Information are required:

**SmPC wording**

Section 4.4  
Serotonin syndrome

As with other serotonergic agents, the development of a potentially life threatening serotonin-syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, may occur with venlafaxine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs and triptans), with agents that impair metabolism of serotonin such as MAO inhibitors (e.g. methylene blue), or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

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

If concomitant treatment with venlafaxine 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 venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

Section 4.5

Adding:

Effect of venlafaxine on other medicinal products Metabolized by Cytochrome P450 Isoenzymes

In vivo studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) or CYP2C19 (diazepam) in vivo.

and

Oral contraceptives

In post-marketing experience unintended pregnancies have been reported in subjects taking oral contraceptives while on venlafaxine. There is no clear evidence these pregnancies were a result

of drug interaction with venlafaxine. No interaction study with hormonal contraceptives has been performed.

Deleting:

~~Drugs Highly Bound to Plasma Proteins~~

~~Venlafaxine is not highly bound to plasma proteins (27% bound); therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound is not expected to cause increased free concentrations of the other drug.~~

and

~~Drugs Metabolized by Cytochrome P-450 Isoenzymes~~

~~Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4, CYP1A2, and CYP2C9 in vitro. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4), diazepam, (CYP3A4 and CYP2C19), and tolbutamide (CYP2C9).~~

Serotonin syndrome

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

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

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.