Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for venlafaxine, the scientific conclusions are as follows:

The well-established risks for serious outcomes due to suicide attempts, misuse, overdoses and serious poisoning involving venlafaxine are confirmed by the overall pattern of reported data within this PSUSA. This includes that a proportion of cases, including with fatal outcomes, is reported as combined poisoning and/or in patients having morbidity associated with the risk for a suicide event, including the underlying disease (e.g. major depression) which in itself is one important risk factor for suicidal events.

Thus, the overall pattern of reported events confirms a clinically well-known high complexity in cases of suicidal /suicide event, also involving severe intoxication with venlafaxine and often combined poisoning involving alcohol, and/or other medicines or other substances.

Clinical experience and recent literature show that such overdose cases can be extraordinary challenging to manage, with symptoms involving e.g. serotonin syndrome, severe seizures and serious cardiac risks. From literature, there is information describing the quantities that can result in severe toxicity; including that intake of approximately 3 g or more can lead to severe poisoning symptoms in adults. This information is considered of value for the prescriber. Due to the complexity in rescue treatment, prompt contact with e.g. [*wording to be adapted nationally*] national Poison information center or poisoning specialist is recommended.

In view of available data on risk(s) from the literature and spontaneous reports, the PRAC concluded that the product information should be amended accordingly

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for venlafaxine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing venlafaxine is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing venlafaxine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)>

Summary of Product Characteristics

- Section 4.4

Addition of the following, prior to the section Suicide/Suicidal Thoughts or Clinical Worsening:

Overdose
Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects (section 4.5). Overdose with venlafaxine has been reported predominantly in combination with alcohol and/or other medicinal products, including cases with fatal outcome (section 4.9).

Prescriptions for venlafaxine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose (see 4.9)

- Section 4.5

Ethanol

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

To be replaced with:
Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects.

- Section 4.9

In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products, ***including cases with fatal outcome.*** The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other reported events include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation [see section 5.1]), ventricular tachycardia, bradycardia, hypotension, vertigo, and deaths**. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.**

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear.

~~Prescriptions for venlafaxine should be written for the smallest quantity of the medicinal product consistent with good patient management in order to reduce the risk of overdose~~**.** [move to section 4.4]

Recommended treatment

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving venlafaxine, prompt contact with [*e.g. national poison information center, poisoning specialist, to be adapted nationally*] is recommended.

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

Package Leaflet

Section 2. Warnings and precautions

Addition of the following, prior to the section Thoughts of suicide and worsening of your depression or anxiety disorder:

Do not drink alcohol while being treated with [product name] as it can lead to extreme tiredness and unconsciousness. Concomitant use with alcohol and/or certain medicines can make your symptoms of depression and other conditions, such as anxiety disorders worse.

[product name] with food, drink and alcohol

~~You should avoid alcohol while you are taking [product name]~~**. Do not drink alcohol while being treated with [product name]. Concomitant use with alcohol can lead to extreme tiredness and unconsciousness and can make your symptoms of depression and other conditions, such as anxiety disorders worse.**

Section 3. How to take [product name]

If you take more [product name] than you should

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

Overdose can be life-threatening, especially with concomitant use of alcohol and/or certain medicines (see "Other medicines and [product name]").

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

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 March 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 May 2023