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 atomoxetine, the scientific conclusions are as follows:

In view of available data on risk(s) Serotonin syndrome, bruxism and homicidal ideation from literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between atomoxetine and **Serotonin syndrome, bruxism and homicidal ideation** is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing Atomoxetine should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

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

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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

Serotonin syndrome:

- Section 4.4

Serotonin syndrome:

Serotonin syndrome has been reported following concomitant use of atomoxetine with other serotonergic medicinal products (e.g. serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], other SNRIs, triptans, opioids, and tricyclic and tetracyclic antidepressants). If concomitant use of atomoxetine with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

- Section 4.5

Serotoninergic medications

Atomoxetine should be used with caution in combination with serotonergic medicinal products, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), opioids as tramadol, and tetracyclic or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

- Section 4.9

In some cases of overdose involving atomoxetine, seizures, and very rarely QT prolongation **and serotonin syndrome** have been reported.

Aggressive behaviour, hostility or emotional lability:

- Section 4.4

Aggressive behaviour, hostility or emotional lability

Hostility (predominantly aggression, oppositional behaviour and anger) was more frequently observed in clinical trials among children, adolescents and adults treated with atomoxetine compared to those treated with placebo. Emotional lability was more frequently observed in clinical trials among children treated with Atomoxetine compared to those treated with placebo. In general, patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.
Severe cases have been reported concerning paediatric patients, including reports of physical assault, or threatening behaviour and thoughts of harming others. Families and caregivers of paediatric patients treated with atomoxetine should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted, particularly after starting treatment or changing the dose. Physicians should evaluate the need for dose adjustment or treatment discontinuation in patients experiencing behavioural changes.

Bruxism (paediatric patients only):

- Section 4.8

Bruxism should be included for paediatric patients under SOC "Psychiatric disorders" (frequency not known).

Package Leaflet

Serotonin syndrome:

- Section 2. Warnings and precautions

Serotonin syndrome
Serotonin syndrome is a potentially life-threatening condition which may occur when taking [product name] in combination with some other medicines (see section 2 "Other medicines and [product name]"). Signs and symptoms of serotonin syndrome may include a combination of the following: confusion, restlessness, incoordination and rigidity, hallucinations, coma, fast heart beat, increased body temperature, fast changes in blood pressure, sweating, flushing, tremor, overactive reflexes, nausea, vomiting, and diarrhoea. Contact a doctor or go to your nearest emergency department immediately if you think serotonin syndrome is happening to you.

Other medicines:
[Product name] may affect or be affected by other medicines. These include:

- **Some anti-depressants, opioids as tramadol, and medicines used to treat migraine called triptans. These medicines may interact with [product name] and can lead to serotonin syndrome, a potentially life-threatening condition. (See section 2, Warnings and Precautions, Serotonin Syndrome).**

Section 3.
If you take more [product name] than you should contact your doctor or the nearest hospital casualty department.....are gastrointestinal symptoms, sleepiness, dizziness, tremor, and abnormal behaviour. **Very rarely, serotonin syndrome has also been reported, a potentially life-threatening condition. (See section 2, Warnings and precautions, Serotonin Syndrome).**

Aggressive behaviour, hostility or emotional lability:

- Section 2. Warnings and precautions

Treatment with [product name] may make you feel aggressive, hostile or violent; or aggravate these symptoms if they were present before treatment. It may also cause you to have unusual changes in behaviour or mood (including physical assault, threatening behaviour and thoughts of harming others). If you or your family and/or friends notice any of these reactions, talk to your doctor or pharmacist right away.

Bruxism (paediatric patients only):

- Section 4.

- **Involuntary teeth grinding (bruxism)**. (frequency not known).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	8 September 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	7 November 2024