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 tapentadol the scientific conclusions are as follows:

Seizures/epilepsy/convulsion

Considering the risk of seizures it is noted that out of 156 spontaneous reports received cumulatively, 72 reported co-administration of at least one medication known to lower the seizure threshold including serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants. Moreover, in 25 cases, the patients had a history of convulsions, seizures or epilepsy. The PRAC considers that the information regarding the risk of patients taking other medicinal products that lower the seizure threshold and patients with epilepsy should be included in the sections 4.4 and 4.5 of the SmPC of tapentadol in line with the product information of tramadol.

Serotonin syndrome

The PRAC acknowledged that the risk of serotonin syndrome is already mentioned in section 4.5 of the SmPC as a statement that there have been reports of serotonin syndrome in isolated cases and that it has a temporal connection with the use of tapentadol in combination with other drugs. However, the cumulative number of cases is high (191), while in the majority of cases concomitant medication known to cause serotonin syndrome was reported (148/191). Taking into consideration the high cumulative number of cases, the PRAC considers that the existing stament is misleading and should be amended.

Additionally the PRAC considered that the MAH should replace the symptoms of serotonin syndrome currently included in the product information by a statement regarding the Hunter criteria similarly with the SmPC of tramadol. The Hunter criteria are internationally accepted for the assessment of possible cases of serotonin syndrome wheras the symptoms currently mentioned in the SmPC are less specific. Moreover, more serotonergic drugs other than SSRIs that have been observed as concomitant drugs in the spontaneous reports, should be added to section 4.5 of the SmPC including SNRIs and tricyclic antidepressants.

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 tapentadol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tapentadol 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 tapentadol 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

Seizures

<TRADEMARK> has not been systematically evaluated in patients with a seizure disorder and such patients were excluded from clinical studies. However, like other analgesics with mu-opioid receptor agonist activity <TRADEMARK> should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures. **In addition, tapentadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold (see section 4.5).**

- Section 4.5

<TRADEMARK> can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other medicinal products that lower the seizure threshold to cause convulsions.

~~In isolated cases there~~ **There** have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tapentadol in combination with serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs**), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants**. ~~Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.~~ **Serotonin syndrome is likely when one of the following is observed:**

• Spontaneous clonus

• Inducible or ocular clonus with agitation or diaphoresis

• Tremor and hyperreflexia

• Hypertonia and body temperature > 38°C and inducible ocular clonus.

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Package Leaflet

Section 2

Warnings and precautions

<Talk to your doctor or pharmacist before taking <TRADEMARK> if you:>

- **if you have a tendency towards epilepsy or fits or if you are taking other medicines known to increase the risk of seizures because the risk of a fit may increase.**

Other medicines and X

<Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.>

The risk of side effects increases if you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk of having a fit may increase if you take <TRADEMARK> at the same time. Your doctor will tell you whether <TRADEMARK> is suitable for you.

If you are taking a type of medicine that affects serotonin levels (e.g. certain medicines to treat depression), speak to your doctor before taking <TRADEMARK> as there have been cases of "serotonin syndrome". Serotonin syndrome is a rare, but life threatening condition. The signs include ~~confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles, myoclonus and diarrhoea~~ **involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension and body temperature above 38ºC.** Your doctor may advise you on this.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	8 September 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	7 November 2018