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 granisetron (other formulations except for transdermal patch), the scientific conclusions are as follows:

A cumulative search of the EudraVigilance identified nine cases of serotonin syndrome of which two were literature cases, and seven spontaneous reports including three fatal cases.

During the reporting interval seven cases of serotonin syndrome were retrieved from a MAH database including five serious and two non-serious events.

The Committee also reviewed a case described in the literature where the patient developed serotonin syndrome and posterior reversible encephalopathy syndrome (PRES) which were fatal. A causal relationship between granisetron and described serotonin syndrome were considered possible.

Taking into account that there have been reports of serotonin syndrome with the use of 5-HT3 antagonists either alone, but mostly in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs) the PRAC recommended that a warning be included in the product information accordingly.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing granisetron were warranted.

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 granisetron (other formulations except for transdermal patch) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing granisetron (other formulations except for transdermal patch) 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 granisetron (other formulations except for transdermal patch) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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**

A warning should be added as follows:

Serotonin syndrome
There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone, but mostly in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

- **Section 4.5**

Following information should be added:

Serotonergic medicinal products (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT3 antagonists and other serotonergic medicinal products (including SSRIs and SNRIs) (see section 4.4).

- **Section 4.8**

The following adverse reaction should be added under the SOC Nervous system disorders with a frequency uncommon:

Serotonin syndrome

Package Leaflet

- **Section 2**

Warnings and precautions

Serotonin syndrome is an uncommon but potentially life-threatening reaction that can occur with granisetron (see section 4). The reaction can occur if you take granisetron alone but it is more likely to occur if you take granisetron with certain other medicines (in particular fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, venlafaxine, duloxetine).

Other medicines and granisetron

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

- SSRIs (selective serotonin reuptake inhibitors) used to treat depression and/or anxiety. Examples are fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram.

- SNRIs (serotonin noradrenaline reuptake inhibitors) used to treat depression and/or anxiety. Examples are venlafaxine, duloxetine.

- **Section 4**

The following should be added under the frequency uncommon:

Serotonin Syndrome. The signs may include diarrhoea, nausea, vomiting, high temperature and blood pressure, excessive sweating and rapid heartbeat, agitation, confusion, hallucination, shivering, muscles shakes, jerks or stiffness, loss of coordination and restlessness.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	22 December 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	22 February 2017