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 ropinirole, the scientific conclusions are as follows:

- Dopamine agonist withdrawal syndrome (DAWS)

The occurrence of DAWS is described with other dopamine agonists (rotigotine, pramipexole): such syndrome seems to be a pharmacological class effect for non-ergoline D2/D3 dopamine agonists, and it is largely described in literature. This syndrome is associated with clinical manifestations that can be psychiatric, autonomic, gastrointestinal and sensory. As the MedDRA Preferred Term (PT) DAWS does not exist, it is difficult to find cases on it. A search can be done with PTs such as “drug withdrawal syndrome”, “withdrawal syndrome” and “drug dependence”. According to the data provided by the Marketing Authorisation Holder during the reporting period, at least 23 serious cases of drug “withdrawal syndrome” or “withdrawal syndrome” or “drug dependence” have been reported with ropinirole. In the view of the above, DAWS is considered to be an identified risk for ropinirole. Sections 4.4 and 4.8 of the SmPC of ropinirole should be therefore amended, in order to reflect such risk. Furthermore, in section 4.2 a cross-reference to section 4.4 should be added. The package leaflet should be updated accordingly.

- Hallucinations

Hallucination is listed as an adverse reaction in section 4.8 of the SmPC (frequency: ‘common’). During the reporting period, a total of 227 cases where reported to the MAHs, including literature cases. Moreover, hallucinations are a pharmacological class effect for dopamine agonists and are well documented in literature. Therefore, as it is done for other dopaminergic agonists, the PRAC recommends that a warning should be added in section 4.4 of the SmPC to alert prescribers to inform patients on this risk; the Package Leaflet should be updated accordingly, with a recommendation to not drive or use machines, if affected by hallucinations.

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

Dopamine agonist withdrawal syndrome

To discontinue treatment in patients with Parkinson's disease, ropinirole should be tapered off (see section 4.2). Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including ropinirole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain which may be severe. Patients should be informed about this before tapering the dopamine agonist, and monitored regularly thereafter. In case of persistent symptoms, it may be necessary to increase the ropinirole dose temporarily (see section 4.8).

(…)

Hallucinations:

Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that hallucinations can occur.

- Section 4.8

The following adverse reaction should be added in both ADR tables under the SOC General Disorders and administration site conditions with a frequency not known:

Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain.

(…)

Section 4.8 (below the ADR tables)

Dopamine agonist withdrawal syndrome

Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including ropinirole (see section 4.4).

Furthermore in section 4.2 a cross reference to section 4.4 should be added:

"As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week (**see section 4.4)**."

Package Leaflet

Section 2, What you need to know before you take [TRADENAME]

Warnings and precautions

Tell your doctor if you experience symptoms such as depression, apathy, anxiety, fatigue, sweating or pain after stopping or reducing your Ropinirole treatment. If the

problems persist more than a few weeks, your doctor may need to adjust your treatment.

(...)

Driving and using machines
Ropinirole can cause hallucinations (seeing, hearing or feeling things that are not there). If affected, do not drive or use machines.

Section 4, Possible side effects

(...)

Not known:

After stopping or reducing your [TRADENAME] treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (called dopamine agonist withdrawal syndrome or DAWS).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	6 May 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	5 July 2017