

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 carbidopa / levodopa (except for centrally authorised product), the scientific conclusions are as follows:

Dopamine dysregulation syndrome

Dopamine dysregulation syndrome (DDS) is described as a compulsive pattern of dopaminergic misuse above doses adequate to control motor symptoms.

The DDS associated with levodopa/carbidopa use has been well recognised in the scientific literature with over 30 literature reports published. For the levodopa/carbidopa intestinal gel formulation (LCIG) 36 cases have been reported, 6 of which with a positive dechallenge and additional 4 were related to conversion from oral to LCIG formulation. For oral formulations 5 spontaneous non-literature cases have been reported, 3 of which with a positive dechallenge; additionally in the 13 presented literature articles 31 patients with DDS have been identified, 8 of which reported a positive dechallenge. DDS is already mentioned in product information of other dopaminergic medication used in Parkinson's disease such as apomorphine, levodopa/benserazide, rotigotine, ropinirole, and centrally authorised carbidopa/ levodopa containing medicinal products.

The addition of dopamine dysregulation syndrome term is proposed for section 4.8 of carbidopa/levodopa SmPCs with the frequency "not known".

Moreover, it is proposed that further explanation with regards to DDS is added to section 4.8 to increase awareness and understanding on the pathology, and that wording is added to section 4.4 to recommend relevant precautions.

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 carbidopa / levodopa (except for centrally authorised product), the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing carbidopa / levodopa (except for centrally authorised product), 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 carbidopa / levodopa (except for centrally authorised product), 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: Special warnings and precautions for use

A warning should be added as follows:

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/ levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

- Section 4.8: Undesirable effects

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency “not known”:

Dopamine dysregulation syndrome

The following explanatory text should be added below the ADR table under the subheading:
Description of selected adverse reactions

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

Package Leaflet

Section 2: Warnings and precautions

Tell your doctor if you or your family/carer notices you are developing addiction-like symptoms leading to craving for large doses of <product name> and other medicines used to treat Parkinson's disease.

Section 4: Possible side effects

The following adverse reactions should be added under the frequency “not known (cannot be estimated from the available data)”:

Craving for large doses of <product name> in excess of that required to control motor symptoms, known as dopamine dysregulation syndrome. Some patients experience severe abnormal involuntary movements (dyskinesias), mood swings or other side effects after taking large doses of <product name>.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 August 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 October 2017