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 dextromethorphan, the scientific conclusions are as follows:

Based on the review of the post-marketing data, the PRAC recommends the addition of warnings in section 4.4 of the SmPC on serotonin syndrome, drug dependence and use in children. Furthermore, as the risk of overdose has been further characterised through the evaluation of the post-marketing surveillance, the PRAC considers that information on the symptoms and management of overdose should be included in section 4.9 of the SmPC. The Package leaflet is updated accordingly.

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

Cases of dextromethorphan abuse **and dependence** have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

[...]

Serotonin Syndrome

Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, treatment with <brand name> should be discontinued.

[...]

<Paediatric population >(only for products with pediatric indication below 12 years of age)
Serious adverse events may occur in children in case of overdose including neurological disorders. Caregivers should be advised not to exceed the recommended dose.

Section 4.9:

Symptoms and signs:
Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.
In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.
Management:
-Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

-For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used."

Package Leaflet

This medicine can lead to dependence. Therefore the treatment should be of short duration.

[...]

Talk to your doctor or pharmacist <or nurse> before taking <Brand name>:

- **If you are taking medicines such as certain antidepressants or antipsychotics <Brand name> may interact with these medicines and you may experience mental status changes (e.g. agitation, hallucinations, coma), and other effects such as body temperature above 38°C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g nausea, vomiting, diarrhoea).**

Section 3

<Paediatric population >(only for products with pediatric indication below 12 years of age)
Serious adverse events may occur in children in case of overdose including neurological disorders. Caregivers should not exceed the recommended dose.

[...]

If you take more <brand name> than you should, you may experience the following symptoms: nausea and vomiting, involuntary muscle contractions, agitation, confusion, somnolence, disturbances in consciousness, involuntary and rapid eye movements, cardiac disorders (rapid heart beating), coordination disorders, psychosis with visual hallucinations, and hyperexcitability.

Other symptoms in case of massive overdose may be : coma, severe breathing problems, and convulsions.

Contact your doctor or hospital straight away if you experience any of the above symptoms.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June / 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 August 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09 October 2019