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 montelukast, the scientific conclusions are as follows:

Based on the gathered cumulative data, the issue of neuropsychiatric ADRs deserves specific attention. Cases have been reported in which various neuropsychiatric events have caused significant hindrance and suffering to patients before the symptoms have been recognized as likely ADRs. Therefore, the possibility that neuropsychiatric events, even rare, may occur, should be distinctly communicated to the healthcare professionals and patients. Even though neuropsychiatric adverse events seem to be infrequent and are already widely described in the SmPC 4.8, the MAH is requested to add a warning in section 4.4 in order to further increase the understanding and awareness that neuropsychiatric events possibly occurring during montelukast use may be associated to the medicinal product and further actions may be necessary.

A certain number of cases of dysphemia was reported. The majority of these cases involved the paediatric population (aged 17 years and under), especially young children less than five years of age. The time to onset was relatively short (median 8 days for PT Dysphemia; 13 days for PT Speech disorder). Over half of the Dysphemia cases described positive dechallenges (symptoms disappeared when the medication was discontinued), including 4 positive rechallenged (symtoms reoccurred when the medication was readministered), all in children. Based on the review of these data, Dysphemia and other closely related Speech disorders may be associated with montelukast. Whilst the Summary of Product Characteristics (SmPC) for montelukast currently lists several psychiatric and nervous system reactions, Dysphemia is not listed as an adverse drug reaction (ADR). In light of the cumulative review analysis, the MAHs are requested to update the SmPC (section 4.8) and package leaflet 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 montelukast the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing montelukast 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 montelukast 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

A warning should be added as follows:

Neuropsychiatric events have been reported in adults, adolescents, and children taking [Product name] (see section 4.8). Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with [Product name] if such events occur.

- Section 4.8

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency very rare:

Dysphemia

Package Leaflet

Section 2

Warnings and precautions

Patients should be aware that various neuropsychiatric events (for example behaviour and mood-related changes) have been reported in adults, adolescents and children with [Product name] (see section 4). If <you> <or> <your child> develop(s) such symptoms while taking [Product name], you should consult your <child's> doctor.

Section 4

Very rare: may affect up to 1 in 10,000 people

- **Stuttering**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 May 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 July 2019