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 budesonide, the scientific conclusions are as follows:

Budesonide is indicated for treatment of disease in three organ systems; the respiratory system, the intestine and the skin.

Having considered the evidence presented in the periodic safety updated report (PSUR), the PRAC concluded the following:

Blurred vision

Blurred vision is a common adverse drug reaction (ADR) in the summary of product characteristics of budesonide capsules (Entocort), but not for other budesonide products. Cumulatively, 126 cases of blurred vision were received for the inhaled and intranasal forms. As the effect is supposed to occur through systemic uptake of budesonide, and other budesonide formulations also are absorbed systemically, the ADR is mechanistically relevant for all formulations. In conclusion, the term “blurred vision” is relevant for all formulations of budesonide.

Based on the number of ADRs reported, the frequency of blurred vision should be with the frequency ‘rare’ for enteral and intranasal formulations, and ‘uncommon’ in inhaled dermatological and formulations.

Central serous chorioretinopathy (CSCR)

Central serous chorioretinopathy (CSCR) is characterised by the accumulation of subretinal fluid at the posterior pole of the fundus, ultimately causing a retinal detachment. This retinal disorder is highly linked to stress and the use of corticosteroid, and has been described after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal and periocular routes. Cumulative evidence suggests a possibility that topical forms of budesonide increase the risk of CSCR. Therefore, it is important in case of eye problems, to draw the attention of patients and physicians towards the possibility that topical glucocorticoid is a possible contributor to disease onset and/or worsening.

In conclusion, a warning should be placed in the summary of product characteristics advising physicians to refer patients to an ophthalmologist if signs of visual disturbance, e.g. caused by CSCR, occur. The package leaflet should be updated 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 budesonide, were warranted.

The CMDh agrees with the scientific conclusions made by the PRAC.

The CMDh also notes the PRAC consideration for the fixed combination products containing budesonide to also implement the changes recommended as these ADRs are considered relevant, and the warning to be inserted in the product information.

In addition as shown in published literature blurred vision and central serous chorioretinopathy are considered as an issue for the whole class of corticosteroids and thei product information should also be amended to reflect this additional warning and adverse drug reactions accordingly.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for budeonside the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing budesonide 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 budesonide 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~~)

Enteral formulations of budesonide

Summary of Product Characteristics

- Section 4.4.

A warning should be added as follows:

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

- Section 4.8

The following adverse reaction should be added under the SOC Eye disorders with a frequency rare: **Vision, blurred (see also section 4.4)**

Package Leaflet

- Section 2

Warnings and precautions:

Contact your doctor if you experience blurred vision or other visual disturbances.

- Section 4

The following possible side effects should be added to section 4, with a frequency rare (may affect up to 1 in 1,000 people): **Blurred vision**

Inhaled formulations of budesonide

Summary of Product Characteristics

- Section 4.4.

A warning should be added as follows:

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous

chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

- Section 4.8

The following adverse reaction should be added under the SOC Eye disorders with a frequency uncommon: **Vision, blurred (see also section 4.4)**

Package Leaflet

- Section 2

Warnings and precautions:

Contact your doctor if you experience blurred vision or other visual disturbances.

- Section 4

The following possible side effects should be added to section 4, with a frequency Uncommon (may affect up to 1 in 100 people): **Blurred vision**

Intranasal formulations of budesonide

Summary of Product Characteristics

- Section 4.4.

A warning should be added as follows:

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

- Section 4.8

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

Vision, blurred (see also section 4.4)

Package Leaflet

- Section 2

Warnings and precautions:

Contact your doctor if you experience blurred vision or other visual disturbances.

- Section 4

The following possible side effects should be added to section 4, with a frequency rare (may affect up to 1 in 1,000 people): **Blurred vision**

Dermatologic formulations of budesonide

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

- Section 4.8

The following adverse reaction should be added under the SOC Eye disorders with a frequency uncommon: **Vision, blurred (see also section 4.4)**

Package Leaflet

- Section 2

Warnings and precautions:

Contact your doctor if you experience blurred vision or other visual disturbances.

- Section 4

The following possible side effect should be added to section 4, with a frequency uncommon (may affect up to 1 in 100 people): **Blurred vision**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holders):	10 May 2017