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 dexamethasone (apart from centrally authorised products) the scientific conclusions are as follows:

A cumulative review of adrenal gland disorders and hypothalamus and pituitary gland disorders retrieved 14 medically confirmed cases. Eight of the cases were reported in paediatric patients and ritonavir was reported as a co-suspected medication in two cases. Cushing's syndrome and adrenal suppression were also reported in the literature with prolonged use, in children in many cases, of cutaneous and ocular preparations of glucocorticoids including dexamethasone. Children are known to be at risk of this type of events as drug absorption may be more rapid and half-life may be prolonged. Further, as dexamethasone is metabolised by cytochrome P450 3A4 (CYP3A4), co-administration of ritonavir or other CYP3A4 inhibitors may lead to elevated systemic dexamethasone levels, Cushing's syndrome and adrenal axis suppression even in situations where systemic exposure would normally be low. The PRAC considered that this information should be reflected in the product information of ocular and cutaneous formulations of dexamethasone-containing products. Further, in line with the September PRAC recommendation on a signal for cobicistat, this CYP3A4 inhibitor should also be included as an example in the product information of ocular formulations.

A cumulative review of acute tumour lysis syndrome retrieved seven cases, all from published article and in patients with haematological malignancies, including five cases where dexamethasone was reported as the only medicinal product administered. The PRAC noted that tumour lysis syndrome may occur spontaneously; however, it was considered that this information should be included in the product information of oral and parenteral formulations of dexamethasone-containing products, identifying populations at risk and recommending close monitoring and precautions in those patients.

A cumulative review of central serous chorioretinopathy (CSCR) with glucocorticosteroids retrieved 17 cases with a compatible chronology and no confounding factors, including 13 cases with a positive dechallenge. The prevalence of exogenous administration of glucocorticoid in patients developing CSCR has been reported as being less than 10% in three large retrospective studies, and in two prospective studies as being about 29% and 52%, respectively. In one case-control study it has been observed that CSCR patients have a higher prevalence of corticosteroid use than controls. Glucocorticoids have been reported in the literature as a risk factor for CSCR and cellular mechanisms have been hypothesised. The PRAC considered that this adverse event should be included in the product information of oral and parenteral formulations of dexamethasone-containing products.

Therefore, in view of available data regarding dexamethasone, the PRAC considered that the changes to the product information of medicinal products containing dexamethasone (apart from centrally authorised products), were warranted.

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 dexamethasone (apart from centrally authorised products) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing dexamethasone (apart from centrally authorised products) 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 dexamethasone (apart from centrally authorised products) 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~~)>

[Amendments for all ocular formulations only]

Summary of Product Characteristics

- Section 4.4

[A warning should be added as follows]

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, treatment should be progressively discontinued.

- Section 4.5

[A warning should be amended as follows]

~~Co-treatment with~~ CYP3A**4** inhibitors **(**including **ritonavir and** cobicistat~~-containing products~~**):**~~, is expected to increase the risk of systemic side-effects. Cases of Cushing's syndrome~~ **may decrease dexamethasone clearance resulting in increased effects** and adrenal suppression**/Cushing's syndrome** ~~have been reported~~. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

- Section 4.8

[The following adverse reactions should be added under the SOC Endocrine disorders with a frequency not known]

Cushing's syndrome, adrenal suppression (see section 4.4)

Package Leaflet

- Section 2 What you need to know before you take X

Warnings and precautions:

[A warning should be added as follows]

Talk to your doctor if you experience swelling and weight gain around the trunk and in the face as these are usually the first manifestations of a syndrome called Cushing's syndrome. Suppression of the adrenal gland function may develop after stopping a long-term or intensive treatment with <product>. Talk to your doctor before stopping the treatment by yourself. These risks are especially important in children and patients treated with a drug called ritonavir or cobicistat.

Other medicines and X

[A warning should be added as follows]

Tell your doctor if you are using ritonavir or cobicistat, as this may increase the amount of dexamethasone in the blood

- Section 4 Possible side effects

[The following adverse reactions should be added with a frequency not known]

Hormone problems: growth of extra body hair (particularly in women), muscle weakness and wasting, purple stretch marks on body skin, increased blood pressure, irregular or missing periods, changes in the levels of protein and calcium in your body, stunted growth in children and teenagers and swelling and weight gain of the body and face (called 'Cushing's syndrome') (see section 2, "Warnings and precautions").

[Amendments for all cutaneous formulations only]
Summary of Product Characteristics

- Section 4.4

[A warning should be added as follows]

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of cutaneous dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir). In these cases, treatment should be progressively discontinued.

- Section 4.5

[A warning should be added as follows]

CYP3A4 inhibitors (including ritonavir): may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

- Section 4.8

[The following adverse reactions should be added under the SOC Endocrine disorders with a frequency not known]

Cushing's syndrome, adrenal suppression (see section 4.4)

Package Leaflet

- Section 2 What you need to know before you take X

Warnings and precautions:

[A warning should be added as follows]

Talk to your doctor if you experience swelling and weight gain around the trunk and in the face as these are usually the first manifestations of a syndrome called Cushing's syndrome. Suppression of the adrenal gland function may develop after stopping a long-term or intensive treatment with <product>. Talk to your doctor before stopping the treatment by yourself. These risks are especially important in children and patients treated with a drug called ritonavir.

Other medicines and X

[A warning should be added as follows]

Tell your doctor if you are using ritonavir, as this may increase the amount of dexamethasone in the blood

- Section 4 Possible side effects

[The following adverse reactions should be added with a frequency not known]

Hormone problems: growth of extra body hair (particularly in women), muscle weakness and wasting, purple stretch marks on body skin, increased blood pressure, irregular or missing periods, changes in the levels of protein and calcium in your body, stunted growth in children and teenagers and swelling and weight gain of the body and face (called 'Cushing's syndrome') (see section 2, "Warnings and precautions").

[Amendments for all oral and parenteral formulations only]

Summary of Product Characteristics

- Section 4.4

[A warning should be added as follows]

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

- Section 4.8

[The following adverse reactions should be added under the SOC Eye disorders with a frequency not known]

Chorioretinopathy

Package Leaflet

- Section 2 What you need to know before you take X

Warnings and precautions

You should tell your doctor if you have any of the following:

[A warning should be added as follows]

[…]

Symptoms of tumour lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath, in case you suffer from haematological malignancy.

[…]

- Section 4 Possible side effects

[The following adverse reactions should be added with a frequency not known]

[…]

Visual disturbances, loss of vision

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	20 October 2016 CMDh written procedure
Transmission to National Competent Authorities of the translations of the annexes to the position:	4 December 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 February 2017