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 aldesleukin, the scientific conclusions are as follows:

For Influenza like illness, cumulatively, three cases were reported with a plausible temporal association and positive rechallenge, and in 55 cases a causal relationship could not be excluded. Development of influenza like illness seems probable considering the immune-modulatory action of aldesleukin. In pooled clinical trial data available for oncology indications, influenza-like illness was reported in 2.2% of patients. Influenza-like illness should be included in the summary of product characteristics (SmPC) with a frequency 'common'.

For hyponatraemia, cumulatively, in 27 cases a causal relation could not be excluded and in 32 cases the event of hyponataemia was considered related to aldesleukin in the context of other reported IL-2 toxicities pointing towards a common pathophysiological mechanism. In pooled clinical trial data available for oncology indications, hyponatraemia was reported in 3.7% of patients. Hyponatraemia should be included in the SmPC with a frequency 'common'.

For hypophosphatemia, cumulatively, in 13 cases a causal relation could not be excluded, and concurrent events were reported that point towards a common pathophysiological mechanism. In pooled clinical trial data available for oncology indications, hypophosphatemia was reported in 2.8% of patients. Hypophosphatemia should be included in the SmPC with a frequency 'common'.

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 aldesleukin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing aldesleukin 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 aldesleukin are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 4.8

The following adverse reaction should be added under the SOC General disorders and administration site conditions with a frequency 'common':

influenza like illness

The following adverse reactions should be added under the SOC Metabolism and nutrition disorders, both with a frequency 'common':

hyponatraemia

hypophosphatemia

Package Leaflet

- Section 4 'Possible side effects'

Common: **Fever and cough with onset following the use of Proleukin (influenza like illness**

Common: **Low sodium levels (hyponatraemia) which may present with tiredness, confusion, muscle twitching**

Common: **Low phosphate levels (hypophosphatemia) which may present with muscle weakness.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 November 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2019