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 chlorocresol / chlorhexidine / hexamidine, the scientific conclusions are as follows:

In view of available data on hypersensitivity with chlorocresol from the literature including in some cases a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers a causal relationship between chlorocresol / chlorhexidine / hexamidine and hypersensitivity reactions, including dermatitis contact is at least a reasonable possibility. The PRAC concluded that the product information of products containing chlorocresol / chlorhexidine / hexamidine should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for chlorocresol / chlorhexidine / hexamidine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing chlorocresol / chlorhexidine / hexamidine is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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 amended as follows:

[…]

Dermatitis contact (including allergic) were reported with hexamidine, **chlorhexidine and chlorocresol**, and two excipients contained in the cutaneous solution (see section 4.8). In case of severe symptoms, CYTEAL should be interrupted and the patients should seek medical advice before use CYTEAL again.

This medicine can cause serious generalised allergic reaction due to the chlorhexidine content, that could occur within a few minutes after exposure.

[…]

- Section 4.8

The existing footnotes (*) for anaphylactic shock and dermatitis contact should be moved to a new sub-section 'Description of selected adverse reaction' under the table of ADRs in alignment with the QRD template.

A footnote (*) is amended to reflect that anaphylactic shock has been reported with chlorhexidine.

A new wording is added in the dermatitis contact paragraph to reflect that allergic dermatitis contact cases due to chlorocresol or chlorhexidine.

[…]

SOC Immune system disorders

- Anaphylactic shock[1] (frequency not known)
- Hypersensitivity~~[1]~~ (frequency not known)
- Dermatitis contact~~[2]~~ (frequency not known)

SOC Eye disorders

- Eye irritation[3] ~~[2]~~ (frequency not known)
- Corneal erosion, epithelium defect/corneal injury, significant permanent visual impairment[4] ~~[3]~~ (frequency not known)

Skin and subcutaneous tissue disorders

- Application site reaction[5] ~~[4]~~ (frequency not known)

[…]

[1]. Reported with chlorhexidine.

~~[1]. Risk of generalised allergy to chlorhexidine, which may result in anaphylactic shock that could be life-threatening if immediate medical care is not provided. It includes difficulty breathing, swelling of the face, severe skin rash. In case of patient faces an allergic reaction to Chlorhexidine, he should immediately stop the usage of the product and seek appropriate medical care.~~

~~2. Dermatitis contact to hexamidine is associated with specific features of the Arthus reaction, suggesting the involvement of humoral immunological mechanisms.~~

~~Hexamidine may cause sensitisation. Its frequency increases with severity of epidermal abnormalities. Clinically, it is usually different in appearance to classical contact eczema: the rash is usually infiltrated and made up of papular or papulo-vesicular hemispherical lesions, either in isolation or in clusters. These are more numerous and coalesce at the application site of the antiseptic and spread out into isolated lesions. They frequently resolve slowly.~~

~~Contact dermatitis suspected to be caused by cocamidopropyl betaine and diethanolamide of coprah fatty acids, two excipients contained in the cutaneous solution, have been reported during the postmarketing period (see section 4.4).~~

~~Contact eczema (possible local allergy to chlorhexidine, particularly when used on broken skin or mucus membranes and on leg ulcers). This may aggravate a super infected lesion.~~

~~3~~2. Eye irritation: in context of accidental exposure.
~~4~~3. Cases of severe corneal erosion and permanent significant visual impairment due to inadvertent ocular exposure have been reported post-marketing, leading to some patients requiring corneal transplant (see section 4.4)
~~5~~4. Local intolerance reactions: smarting, itching, burning sensation skin, dry skin, redness, particularly following repeated use.

Description of selected adverse reactions

Anaphylactic shock

Risk of generalised allergy to chlorhexidine, which may result in anaphylactic shock that could be life-threatening if immediate medical care is not provided. It includes difficulty breathing, swelling of the face, severe skin rash.

In case of a patient faces an allergic reaction to chlorhexidine, he should immediately stop the usage of the product and seek appropriate medical care.

Dermatitis contact

Allergic dermatitis contact cases due to chlorocresol or chlorhexidine have been reported.

Contact eczema (possible local allergy to chlorhexidine, particularly when used on broken skin or mucus membranes and on leg ulcers). This may aggravate a super infected lesion.

Dermatitis contact to hexamidine is associated with specific features of the Arthus reaction, suggesting the involvement of humoral immunological mechanisms. Hexamidine may cause sensitisation. Its frequency increases with severity of epidermal abnormalities. Clinically, it is usually different in appearance to classical contact eczema: the rash is usually infiltrated and made up of papular or papulovesicular hemispherical lesions, either in isolation or in clusters. These are more numerous and coalesce at the application site of the antiseptic and spread out into isolated lesions. They frequently resolve slowly.

Dermatitis contact suspected to be caused by cocamidopropyl betaine and diethanolamide of coprah fatty acids, two excipients contained in the cutaneous solution, have been reported during the postmarketing period (see section 4.4).

~~Contact eczema (possible local allergy to chlorhexidine, particularly when used on broken skin or mucus membranes and on leg ulcers). This may aggravate a super infected lesion.~~

[…]

Package leaflet

- Section 2

[…]

Dermatitis contact (including allergic) were reported with Cyteal due to the presence of hexamidine or **chlorhexidine or chlorocresol**, or two excipients contained in the cutaneous solution.

This medicine can cause serious generalised allergic reaction due to the chlorhexidine content, that could occur within a few minutes after exposure.

[…]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 May 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 July 2025