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Co-ordination group for Human Use
EMEA/H/A-31/1449

Position of the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use, pursuant to Article 107k(1) and (2) of Directive 2001/83/EC for

Medicinal products containing lactose of bovine origin for intravenous/intramuscular use in acute allergic conditions

Active substance: methylprednisolone

Medicinal products: see Annex I

Basis for position

Pursuant to Article 31 of Directive 2001/83/EC, Croatia initiated a procedure on 21 November 2016 based on concerns resulting from the evaluation of data from pharmacovigilance activities.

The procedure started on 1 December 2016.

The Pharmacovigilance Risk Assessment Committee (PRAC) recommendation was adopted on 6 July 2017 and is appended to this position.

The steps taken for the assessment and the notification for the procedure are included in the appended PRAC recommendation.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use (CMDh) has considered the recommendation of PRAC in accordance with Article 107k(1) and (2) of Directive 2001/83/EC.

Position

1. The CMDh, having considered the PRAC recommendation, reached the position by consensus that the marketing authorisations for medicinal products containing lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions should be varied.

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The Icelandic and the Norwegian CMDh members agree with the above-mentioned position of the CMDh.

2. The scientific conclusions are set out in Annex II.

3. The amendments to be introduced to the product information of for medicinal products containing lactose of bovine origin for IV/IM use in acute allergic conditions are set out in Annex III.

4. The conditions to the marketing authorisations of for medicinal products containing lactose of bovine origin for IV/IM use in acute allergic conditions are set out in Annex IV.

5. The timetable for the implementation of the CMDh position is set out in Annex V.

To the extent that other medicinal products containing lactose of bovine origin for IV/IM use in acute allergic conditions not included in Annex I are currently authorised in the EU, or are subject to future authorisation procedures by the Member States, the CMDh recommends that the Member States concerned take due consideration of the scientific conclusions set out in Annex II.

This position is forwarded to the Member States, to Iceland and Norway and to the marketing authorisation holders for the above mentioned medicinal products, together with its annexes and appendices.

Annex I

List of medicinal products and presentations

Member State EU/EEA	Marketing authorisation holder	Product name	INN + Strength	Pharmaceutical form	Route of administration
Belgium	Pfizer S.A. (Belgium)	Olu-Medrol S.A.B. (= Sine Alcohol Benzylicus)	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Belgium	Pfizer S.A. (Belgium)	Solu-Medrol S.A.B.	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Belgium	Pfizer S.A. (Belgium)	Solu-Medrol S.A.B. (Sine Alcohol Benzylicus)	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Belgium	Pfizer S.A. (Belgium)	Solu-Medrol	Methylprednisolone 40mg Vial	Solution For Injection	Intramuscular Use | Intravenous Use
Belgium	Teva Pharma Belgium N.V./S.A	Methylprednisolone Teva	Methylprednisolone 40mg Tablet	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
Belgium	Teva Pharma Belgium N.V./S.A	Methylprednisolone Teva	Methylprednisolone 40mg/Ml	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
Bulgaria	Pfizer Enterprises Sarl	солу-медрол	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Bulgaria	Teva Pharmaceuticals Bulgaria Eood	метилпреднизолон тева	Methylprednisolone 40mg/Ml	Powder For Solution For Injection/Infusion	Intravenous Use
Croatia	Pfizer Croatia D.O.O.	Solu-Medrol	Methylprednisolone Sodium Succinate 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Czech Republic	Hikma Farmacêutica (Portugal), S.A.	Methylprednisolone Hikma	Methylprednisolone Sodium Succinate 53mg Vial	Powder For Solution For Injection	Intramuscular Use | Intravenous Use

Member State EU/EEA	Marketing authorisation holder	Product name	INN + Strength	Pharmaceutical form	Route of administration
Czech Republic	Pfizer, Spol. S R.O.	Solu-Medrol	Methylprednisolone Sodium Succinate 53.2mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Denmark	Pfizer Aps	Solu-Medrol	Methylprednisolone 40mg	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Denmark	Teva Denmark A/S	Methylprednisolone Teva	Methylprednisolone 40mg/Ml	Powder For Solution For Injection/Infusion	Intravenous Use
Estonia	Pfizer Enterprises Sarl	Solu-Medrol	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Finland	Pfizer Oy	Solu-Medrol	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
France	Mylan S.A.S	Methylprednisolone Mylan	Methylprednisolone 120mg Bottle	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
France	Mylan S.A.S	Methylprednisolone Mylan	Methylprednisolone Hemisuccinate 25.34mg Bottle	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
France	Mylan S.A.S	Methylprednisolone Mylan	Methylprednisolone Hemisuccinate 50.68mg Bottle	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
France	Pfizer Holding France (S.C.A.)	Solumedrol	Methylprednisolone Hemisuccinate 25.35mg Vial	Lyophilisate And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
France	Pfizer Holding France (S.C.A.)	Solumedrol	Methylprednisolone Hemisuccinate 50.7mg Vial	Lyophilisate And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use

Member State EU/EEA	Marketing authorisation holder	Product name	INN + Strength	Pharmaceutical form	Route of administration
Greece	Pfizer Hellas, A.E.	Solu-Medrol	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Greece	Vianex S.A.	Lyo-Drol	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Hungary	Pfizer Kft.	Solu-Medrol	Methylprednisolone 40mg	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Hungary	Teva Gyógyszergyár Zrt	Metilprednizolon Teva	Methylprednisolone 40mg/Ml	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
Hungary	Teva Gyógyszergyár Zrt	Metilprednizolon Teva	Methylprednisolone 40mg/Ml	Powder For Solution For Injection	Intravenous Use
Hungary	Teva Gyógyszergyár Zrt	Metilprednizolon Teva	Methylprednisolone Sodium Succinate 40mg Vial	Powder For Solution For Injection	Intravenous Use
Iceland	Pfizer Aps	Solu-Medrol	Methylprednisolone 40mg	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Ireland	Pfizer Healthcare Ireland	Solu-Medrone	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection/Infusion	Intramuscular Use | Intravenous Use
Italy	Hikma Farmacêutica (Portugal), S.A.	Metilprednisolone Hikma	Methylprednisolone Sodium Succinate 53mg Vial	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
Italy	Pfizer Italia S.R.L.	Solu-Medrol	Methylprednisolone Sodium Succinate 53.03mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Latvia	Pfizer Europe Ma Eeig	Solu-Medrol	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use

Member State EU/EEA	Marketing authorisation holder	Product name	INN + Strength	Pharmaceutical form	Route of administration
Lithuania	Pfizer Europe Ma Eeig	Solu-Medrol	Methylprednisolone 40mg Bottle	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Luxembourg	Pfizer S.A. (Belgium)	Solu-Medrol S.A.B.	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Luxembourg	Pfizer S.A. (Belgium)	Solu-Medrol	Methylprednisolone 40mg Vial	Solution For Injection	Intramuscular Use | Intravenous Use
Luxembourg	Teva Pharma Belgium N.V./S.A	Methylprednisolone Teva	Methylprednisolone 40mg/Ml	Powder For Solution For Injection	Intravenous Use
Netherlands	Pfizer B.V.	Solu-Medrol	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Norway	Pfizer As	Solu-Medrol	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Poland	Pfizer Europe Ma Eeig	Solu-Medrol	Methylprednisolone 40mg Vial	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Portugal	Laboratórios Pfizer, Lda.	Solu-Medrol	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Portugal	Hikma Farmacêutica (Portugal), S.A.	Metilprednisolona Hikma	Methylprednisolone Sodium Succinate 53mg Vial	Powder For Solution For Injection	Intravenous Use
Romania	Teva Pharmaceuticals S.R.L	Metilprednisolon Teva	Methylprednisolone 40mg/Ml	Powder For Solution For Injection/Infusion	Intramuscular Use | Intravenous Use
Romania	Teva Pharmaceuticals S.R.L	Metilprednisolon Teva	Methylprednisolone Sodium Succinate 53mg Vial	Powder For Solution For Injection/Infusion	Intramuscular Use | Intravenous Use

Member State EU/EEA	Marketing authorisation holder	Product name	INN + Strength	Pharmaceutical form	Route of administration
Romania	Teva Pharmaceuticals S.R.L	Metilprednisolon Teva	Methylprednisolone Sodium Succinate 53mg Vial	Powder For Solution For Injection	Intravenous Use
Slovakia	Hikma Farmacêutica (Portugal), S.A.	Metylprednizolón Hikma	Methylprednisolone 53mg Vial	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
Slovakia	Pfizer Europe Ma Eeig	Solu-Medrol	Methylprednisolone 40mg/Ml	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
Slovenia	Pfizer Luxembourg Sarl	Solu-Medrol	Methylprednisolone Sodium Succinate 53mg/Ml	Powder And Solvent For Solution For Injection/Infusion	Intramuscular Use | Intravenous Use
Spain	Pfizer, S.L.	Solu-Moderín	Methylprednisolone 40mg Vial	Powder For Solution For Injection/Infusion	Intramuscular Use | Intravenous Use
Sweden	Pfizer Ab	Solu-Medrol	Methylprednisolone 40mg	Powder And Solvent For Solution For Injection	Intramuscular Use | Intravenous Use
United Kingdom	Hikma Farmacêutica (Portugal), S.A.	Methylprednisolone Hikma	Methylprednisolone Sodium Succinate 53mg Vial	Powder For Solution For Injection	Intramuscular Use | Intravenous Use
United Kingdom	Pfizer Limited	Methylprednisolone Sodium Succinate Pfizer	Methylprednisolone Sodium Succinate 53mg	Powder For Injection	Intramuscular Use | Intravenous Use
United Kingdom	Pfizer Limited	Solu-Medrone	Methylprednisolone Sodium Succinate 53mg	Powder For Injection	Intramuscular Use | Intravenous Use
United Kingdom	Teva Uk Limited	Methylprednisolone Teva Uk	Methylprednisolone 40mg/Ml	Powder For Solution For Injection/Infusion	Intravenous Use

Annex II

Scientific conclusions

Scientific conclusions

Solu-Medrol 40 mg powder and solvent for solution for injection (hereinafter 'Solu-Medrol') contains methylprednisolone and, as an excipient, lactose monohydrate derived from bovine milk. Serious cases of allergic reactions have been reported in patients allergic to cow's milk administered Solu-Medrol for acute allergic conditions, including cases reporting a positive skin prick test for Solu-Medrol, a skin test for immunoglobulin E mediated allergic response. As Solu-Medrol is administered for an acute allergic condition, any anaphylactic reaction possibly caused by the traces of milk proteins in the product, may be misinterpreted as a lack of therapeutic effect, delaying adequate patient care. In addition, it was noted that patients experiencing an allergic reaction may be more sensitive to exposure to a second allergen.

In view of the above, the Croatian national competent authority (NCA) HALMED considered that the risk of serious allergic reactions in patients allergic to cow's milk treated for acute allergic conditions with intravenous/intramuscular (IV/IM) medicinal products containing as excipient lactose from bovine origin should be reviewed.

On 21 November 2016 the Croatian NCA therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of all medicinal products for intravenous or intramuscular administration containing lactose derived from bovine milk used in the treatment of acute allergy and anaphylactic shock and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure is limited to medicinal products for intravenous or intramuscular administration, containing lactose derived from bovine milk, used in the treatment of acute allergy and anaphylactic shock, thereinafter referred to as acute allergic conditions. It was noted that in the European Union member states (EU MS), Norway and Iceland, at start of the procedure, medicinal products formulated with lactose of bovine origin and authorised for IV/IM use in acute allergic conditions, and therefore concerned by this procedure, were limited to certain strengths of methylprednisolone-containing products.

The PRAC adopted a recommendation on 6 July 2017 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Methylprednisolone-containing products formulated with lactose of bovine origin are authorised for IV/IM use in a range of different indications across EU MSs, including in relation to acute allergic conditions. The benefits of methylprednisolone-containing products, either alone or as adjunctive therapy, in the treatment of acute allergic conditions have been established as reflected in treatment guidelines.

This review was initiated further to reports of serious allergic reactions in patients allergic to cow's milk treated with these products for acute allergic conditions. The PRAC noted that the lactose used in these products is produced in accordance with the European Pharmacopoeia (Ph. Eur.) monograph, which does not exclude traces of milk proteins.

When considering all the data submitted by the marketing authorisation holders (MAHs), in relation to the risk of serious allergic reactions in patients allergic to cow's milk treated for acute allergic conditions with methylprednisolone-containing products formulated with lactose of bovine origin, as well as data available in Eudravigilance and the literature, the PRAC was of the view that medicinal

products containing lactose of bovine origin for IV/IM use in acute allergic conditions are associated with a risk of serious allergic reactions in patients allergic to cow's milk. Further, anaphylactic reactions caused by traces of milk proteins in the product may be misinterpreted as lack of therapeutic effect in acute allergic conditions. The PRAC noted that estimates of prevalence of cow's milk allergy on double blind placebo controlled oral food challenge varies from 0% to 3% and is higher in children than adults. The PRAC further noted that all milk proteins are potential allergens, that the dose of milk proteins sufficient to induce allergic symptoms can vary widely from individual to individual and that trace amounts were detected in analyses of methylprednisolone-containing products that triggered allergic reactions in patients allergic to cow's milk. Thus, data currently available does not allow establishing a safe IV/IM intake threshold for patients allergic to cow's milk and the risk of serious allergic reactions in these patients applies to all products formulated with Ph. Eur. grade lactose for IV/IM use in acute allergic conditions. The PRAC considered that methylprednisolone containing products formulated with lactose of bovine origin must not be used in patients allergic to cow's milk. In addition, healthcare professionals (HCPs) and patients should be informed of the risk and HCPs warned to consider allergy to cow's milk in case the symptoms of patients treated for acute allergy conditions worsen or if new allergic symptoms occur. The summary of products characteristics (SmPC) and patient leaflet (PL) should be amended accordingly. As this risk only applies to certain strengths of methylprednisolone-containing products (i.e. those formulated with lactose of bovine origin) and as these products are mainly used in emergency settings, a warning that the product must not be used in patients allergic to cow's milk should also be implemented on the outer packaging and immediate unit to improve the identification of the products' presentation(s) concerned and further minimise the risk. A letter should also be disseminated to relevant HCPs to inform of the above mentioned risk and measures recommended to minimise it.

The PRAC further considered that in the settings where these products are used, urgency or patients' condition may not always allow patients' medical history to be reviewed in details, hence potentially limiting the effectiveness of routine risk minimisation measures. Taking into account the severity and seriousness of conditions when methylprednisolone-containing products are used, the necessity for rapid management, the absence of a safe threshold of exposure and the population at risk, the PRAC considered that the traces of milk proteins shall be excluded from these methylprednisolone-containing products in order to fully address this risk. To that effect, the PRAC recommends as a condition to the marketing authorisations that the MAHs shall replace the current formulations with formulations free from cow's milk proteins, within an agreed timeframe. MAHs should agree on the modalities of the transition to the lactose-free formulations with their national competent authorities at the time of the application for the new formulations.

The PRAC concluded that the benefit-risk balance of methylprednisolone-containing products formulated with lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions remains favourable, provided the MAHs replace the current formulations with formulations free from cow's milk proteins and submit for assessment the corresponding documentation to the relevant National Competent Authorities by end of June 2019 and provided the agreed changes to the product information are implemented in the interim.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for medicinal products containing lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions (see Annex I).

- The PRAC reviewed the totality of the data provided by the marketing authorisation holders, in relation to the risk of serious allergic reactions in patients allergic to cow's milk treated for acute allergic conditions with methylprednisolone-containing products formulated with lactose of bovine origin, as well as data available in Eudravigilance and the literature.
- The PRAC considers that, in patients allergic to cow's milk, a risk of serious allergic reactions, including anaphylactic reactions, is associated to IV/IM treatment of acute allergic conditions with methylprednisolone-containing products formulated with lactose of bovine origin.
- The PRAC notes that data currently available does not allow establishing a safe threshold for milk proteins in lactose of bovine origin used as excipient in methylprednisolone-containing products for IV/IM use in acute allergic conditions.
- The PRAC concludes that the risk of serious allergic reactions should be minimised through inclusion in the product information of a contraindication in patients allergic to cow's milk and warnings to inform health care professionals and patients of this risk.
- The PRAC also notes that due to the limitations inherent to the emergency settings in which methylprednisolone-containing products are commonly used, these routine measures may not entirely eliminate the risk. In this regard, the PRAC recommends as a condition to the marketing authorisations that the current formulations shall be replaced with formulations free from cow's milk proteins, within the agreed timeframe. In the interim, the above risk minimisation in the form of changes to the summary of product characteristics, labelling and package leaflet shall be implemented.

In view of the above, the Committee considers that the benefit-risk balance of medicinal products containing lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions remains favourable subject to the agreed condition to the marketing authorisations, and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for medicinal products containing lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions.

CMDh position

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

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of medicinal products containing lactose of bovine origin for IV/IM use in acute allergic conditions remains favourable subject to the amendments to the product information and to the condition described above.

Therefore the CMDh recommends the variation to the terms of the marketing authorisations for medicinal products containing lactose of bovine origin for IV/IM use in acute allergic conditions.

Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

Summary of product characteristics

4.3 Contraindications

[The following contraindication should be included]

[…]

<Invented name and strength(s)> is contraindicated in patients with a known or suspected allergy to cow's milk (see section 4.4).

4.4 Special warnings and precautions for use

[The following warning should be included]

Immune System Effects

[…]

Cow's milk allergy [The following clarification in brackets should be included in case of combined SmPC with strength(s) not included in Annex I] (the following paragraphs only apply to <invented name and strength(s)>)

<Invented name and strength(s)> contains lactose <monohydrate> produced from bovine origin as an excipient and may therefore contain trace amounts of cow's milk proteins (the allergens of cow's milk). Serious allergic reactions, including bronchospasm and anaphylaxis, were reported in patients allergic to cow's milk proteins who were treated for acute allergic conditions. Patients with known or suspected allergy to cow's milk must not be administered <invented name and strength(s)> (see section 4.3).

Allergic reactions to cow's milk proteins should be considered in patients receiving <invented name and strength(s)> for the treatment of acute allergic conditions in whom symptoms worsen or who are presenting new allergic symptoms (see section 4.3). Administration of <invented name and strength(s)> should be stopped, and the patient's condition should be treated accordingly.

[…]

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

[…]

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[A warning should be included as follows]

Do not use in cow's milk allergy patients.

[…]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

[…]

6. OTHER

[A warning should be included as follows]

Do not use in cow's milk allergy patients.

[…]

Package leaflet

[…]

2. What you need to know before you are given <invented name>

Do not use <invented name and strength(s)>:

[…]

[A warning should be included as follows. In case of combined package leaflet with strength(s) not included in Annex I, the strength(s) of products in Annex I should be specified in the subheading above]

If you are allergic or suspected to be allergic to cow's milk.

[…]

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine if you have any of the following conditions.

[A warning should be included as follows]

[…]

<invented name and strength(s)> contains cow's milk proteins

If you are allergic or suspected to be allergic to cow's milk, you must not be given this medicine as it may contain trace amounts of cow's milk proteins. Serious allergic reactions have occurred in patients allergic to cow's milk.

Annex IV

Condition to the marketing authorisations

Condition to the marketing authorisations

The marketing authorisation holders shall complete the below condition, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

Condition	**Date**
In order to remove any traces of cow's milk proteins from their finished product, the MAHs should replace the current formulations in their marketing authorisations with formulations free from cow's milk proteins and submit for assessment the corresponding documentation to the relevant National Competent Authorities:	By 30 June 2019

Annex V

Timetable for the implementation of the CMDh position

Timetable for the implementation of the CMDh position

Adoption of CMDh position by consensus:	31 July 2017
Transmission to National Competent Authorities of the translations of the annexes to the position:	30 August 2017
Implementation of the position by the Member States (submission of the Type IB variation by the marketing authorisation holder):	29 September 2017

Appendix 1

PRAC Recommendation

Appendix 2

Direct Healthcare Professional Communication and Communication Plan as agreed by the CMDh