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.