6 July 2017
EMA/459263/2017
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

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

Active substance: methylprednisolone

Procedure number: EMEA/H/A-31/1449

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

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.

2. Scientific discussion

2.1. Introduction

Solu-Medrol 40 mg powder and solvent for solution for IV/IM use contains methylprednisolone and, as an excipient, lactose monohydrate derived from bovine milk. Among other conditions, it is indicated for the treatment of angioedema and anaphylaxis, life-threatening reactions requiring urgent medical treatment.

Methylprednisolone belongs to the corticosteroids class. Corticosteroids have multiple mechanisms of action, including anti-inflammatory, immunosuppressive and antiproliferative effects and are used to treat a variety of clinical conditions, including adrenal insufficiency, asthma, various allergy and autoimmune disorders. Anti-inflammatory effects result from decreased formation, release and activity of the mediators of inflammation hence reducing the initial manifestations of the inflammatory process. The immunosuppressive effect decreases the response to immediate and delayed hypersensitivity reactions while the anti-proliferative effect reduces hyperplastic tissue characteristic of psoriasis.

The lactose used in the manufacture of Solu-Medrol 40 mg powder and solvent for solution is produced in compliance with European Pharmacopoeia (Ph. Eur.) monograph for lactose monohydrate, which does not exclude traces of milk proteins (limit test).

Serious cases of allergic reactions have been reported in patients allergic to cow's milk administered Solu-Medrol 40 mg powder and solvent for solution for injection. Some of the cases reported a positive skin prick test for Solu-Medrol 40 mg powder and solvent for solution for injection but not for lactose-free formulations of Solu-Medrol. In such case as Solu-Medrol is administered for an acute allergic condition any anaphylactic reactions possibly caused by the traces of milk proteins in the product may be misinterpreted as a lack of therapeutic effect. This was reported in one case described in the notification, where it led to repeated administration of Solu-Medrol, and further worsening of the patient's condition was observed. In addition, patients with acute allergic conditions have a lower threshold to allergens and hence may be more prone to experience a second allergic reaction and more severe reactions (Pumphrey, 2007 [1]; Gonzales Perez, 2010 [2]; Boyce, 2010 [3]; Calvani, 2011 [4]; Muraro, 2014 [5]; Smith, 2015 [6]; Turner, 2016 [7]). In view of the above, the Croatian NCA HALMED considered that the risk of serious allergic reactions in patients allergic to cow's milk treated for acute allergic conditions with IV/IM medicinal products containing as excipient lactose from bovine origin should be reviewed.

In the EU MS, Norway and Iceland, at start of the procedure, a limited number of strengths of methylprednisolone-containing products were formulated with lactose of bovine origin and authorised for IV/IM use in acute allergic condition (49 products contain 40 mg, 2 products contain 20 mg and 1 product contains 120 mg of methylprednisolone). While IV/IM medicinal products containing lactose from bovine origin as excipient may be authorised in other indications, it was noted that the information regarding lactose in the guideline on "excipients in the label and package leaflet of medicinal products for human use" (EMA/CHMP/186428/2016) is undergoing a revision by the CHMP excipient drafting group (ExcpDG).

Usually, lactose is added as an excipient (bulking agent) to products of lower strength due to small amount of active substance present. Lower strength of methylprednisolone-containing products (≤40 mg) without lactose are authorised in a limited number of EU MS. Lower doses of methylprednisolone IV/IM formulation are indicated for use in the paediatric population, while higher doses are intended for use both in the adult and the paediatric populations, however if used for paediatric patients dose needs to be adjusted.

In its assessment, the PRAC considered the totality of the data submitted by the marketing authorisation holders (MAHs), available in Eudravigilance (with a data lock point on 31 January 2017) and from the literature. A summary of the most relevant data is included below.

[1] Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. J Allergy Clin Immunol 2007;119:1018–1019.
[2] Gonzalez-Perez A et al. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. J Allergy Clin Immunol 2010;125:1098–104.
[3] Boyce JA et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel. J Allergy Clin Immunol. 2010; 126(6 0): S1–58.
[4] Calvani M et al. Risk factors for severe pediatric food anaphylaxis in Italy. Pediatr Allergy Immunol 2011;22:813–9.
[5] Muraro A et al. Anaphylaxis: guidelines from the European academy of allergy and clinical immunology. Allergy 2014;69:1026–45.
[6] Smith PK et al. Risk multipliers for severe food anaphylaxis. World Allergy Organ J. 2015; 8(1): 30.
[7] Turner PJ et al. Can we identify patients at risk of life-threatening allergic reactions to food? Allergy. 2016 Sep;71(9):1241-55.

2.2. Cow's milk allergy

Cow's milk allergy (CMA), one of the most common food allergies in children, may be defined as a reproducible adverse reaction of an immunological nature induced by cow's milk proteins (Luyt, 2014 [8]). Most children outgrow their CMA in early childhood and only a smaller proportion of patients remain allergic in their adulthood. It should not be confused with lactose intolerance, which is a non-immunologically mediated adverse reaction to food or food intolerance, due to the lack of the enzyme lactase in the small intestines that breaks down lactose into glucose and galactose.

CMA may be immunoglobulin E (IgE) or non-IgE-mediated, occasionally both mechanisms may be involved. The signs and symptoms of CMA may range from mild to severe and may include itching, hives, swelling of the tongue, difficult breathing, vomiting, diarrhoea or drop in blood pressure. In most children with CMA, the condition can be IgE-mediated and is thought to manifest as a phenotypical expression of atopy, together with (or in the absence of) atopic dermatitis, allergic rhinitis and/or asthma. IgE-mediated hypersensitivity leads to immediate symptoms, such as urticaria, angioedema and/or other anaphylactic reaction. Patients with IgE-mediated CMA and asthma are at risk of potentially severe allergic reactions (e.g. anaphylaxis). The diagnosis of IgE-mediated CMA relies primarily on clinical evaluation supported by skin-prick testing (SPT) and *in vitro* measurement of specific IgE, but double blind placebo controlled oral food challenge (DBPCFC) remains the gold standard (Luyt, 2014 [8]).

A subset of patients, however, have non-IgE mediated (probably cell-mediated) allergy and present mainly with gastrointestinal symptoms in reaction to the ingestion of cow's milk. In general, non-IgE-mediated allergy resolves more rapidly that IgE-mediated allergy (Fiocchi, 2010 [9]; Martorell-Aragonés, 2015 [10]).

Based on data available from two meta-analyses, estimates of prevalence of CMA on DBPCFC varies from 0% to 3% (Rona, 2007 [11], Nwaru, 2014 [12]). In addition, a EuroPrevall birth cohort study estimated the incidence of IgE-associated CMA at 0.59% (95% CI 0.43–0.80) (Schoemaker, 2015 [13])

An European Food Safety Authority (EFSA) panel on dietetic products, nutrition and allergies concluded in 2014 that data available from case reports or DBPCFC do not allow the derivation of a level of exposure that could be safe for most milk-allergic consumers, since the amount of cow's milk protiens that may trigger allergic reactions in sensitive individuals varies widely (EFSA, 2014 [14]). The lowest reported minimum observed eliciting dose (MOED) in milk-allergic patients undergoing DBPCFC was 200 µg of milk protein. Since this was the first dose tested, allergic reactions to lower doses cannot be excluded.

[8] Luyt D et al. BSACI guideline for the diagnosis and management of cow's milk allergy. Clin Exp Allergy. 2014;44(5):642-72.
[9] Fiocchi A et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. Pediatr Allergy Immunol 2010: 21: 1–125.
[10] Martorell-Aragonés A et al. Position document: IgE-mediated cow's milk allergy. Allergol Immunopathol (Madr). 2015;43(5):507-26.
[11] Rona RJ et al. The prevalence of food allergy: a metaanalysis. J Allergy Clin Immunol. 2007: 120: 638–46.
[12] Nwaru BI et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014 Aug;69(8):992-1007.
[13] Schoemaker AA et al. Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. Allergy. 2015 Aug;70(8):963-72.
[14] European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. EFSA Journal 2014;12(11):3894.

2.3. Data on safety

Searches in the database of the MAH of the originator and EudraVigilance identified 35 cases, including 32 serious cases, of allergic reactions to parenterally administered methylprednisolone products in patients allergic to cow's milk proteins. Eighteen cases were literature reports. Indications for use of methylprednisolone were: asthma and respiratory symptoms (19 cases), food allergy (5 cases), urticaria (4 cases) and unknown (7 cases).

Outcome of the reactions was reported as recovered/resolved in 25 cases, recovered with sequelae in 2 cases, recovering/resolving in 3 cases and unknown in 5 cases. Outcome was not specified in 7 cases which originated from the literature reports (Levy, 2014 [15]; Nahum 2009 [16]), however, it was reported that all 7 patients undertook further skin tests after the event onset which may suggest that all patients recovered from the allergic reactions. Therefore, the outcome in these 7 cases was considered to be recovered/resolved.

Out of 35 cases, 24 cases involved male patients, 10 cases involved female patients and gender was unknown in 1 case. Age ranged from 5 months to 30 years, with an average (arithmetical mean) age of 7.25 years and median age of 5.5 years. In most cases (82.9%, N=29), the patients were younger than 12 years.

In more than half of the cases (57.1%, N=20), the adverse drug reaction occurred immediately after or within one hour after the administration of drug. It is not precisely specified when the reaction occurred in 2 cases, however, it is stated that the reaction occurred after the administration (1st case) and by the end of that day and during the night (2nd case). While in the remaining cases (N=13), time to onset is unknown.

In 14.3% of all cases reporting medical history of milk allergy, because hypersensitivity reactions were initially considered to be a lack of therapeutic effect, the drug was administered more than once (in 2 cases single re-administration, in 3 cases re-administration occurred twice), leading, in most cases, to even further worsening of the condition for which drug was initially administered.

Skin prick tests were conducted with a panel of corticosteroids in 14 cases. In 9 cases, skin prick test was positive for methylprednisolone-containing product with lactose and negative for methylprednisolone-containing products (or in one case an alternative steroid) without lactose. In 4 further cases, skin prick test was positive for methylprednisolone succinate but no information is provided on skin prick test in non-lactose containing steroid. While in 1 case, skin prick test was negative both for methylprednisolone-containing product with lactose and non-lactose containing steroid and oral food challenge tests confirmed that lactose could be taken at 3 g. In total, there are 13 cases (37.1%) with positive skin prick test to methylprednisolone sodium succinate. Provocation tests were conducted in 3 cases; the results were negative for a full therapeutic dose (125 mg) of methylprednisolone-containing product without lactose in 2 cases and negative for intravenous dexamethasone in 1 case. Additionally, no relapse was observed after switching to non-lactose containing steroid in 2 cases.

Risk factors

All cases were assessed for the following risk factors: asthma, severity of asthma, history of prior anaphylaxis, severity of prior anaphylaxis, underlying cardiovascular disease, mast cell disorders, allergic rhinitis, infective illness, persistent milk/food allergy, late or absent adrenaline, alcohol,

[15] Levy Y, Segal N, Nahum A, et al. Hypersensitivity to methylprednisolone sodium succinate in children with milk allergy. J Allergy Clin Immunol Pract 2014;2(4):471-4.
[16] Nahum A, Garty BZ, Marcus N, et al. Severe hypersensitivity reactions to corticosteroids in children. Pediatr Emerg Care May 2009;25(5):339-41.

concomitant medications, exercise, menstruation, ethnicity (country of origin), severity of CMA, atopic dermatitis and other risk factors. Asthma was reported in 27 cases (77.1%); history of prior anaphylaxis was reported in 9 cases (25.7%), allergic rhinitis was reported in 5 cases (14.3%), infective illness was reported in 7 cases (20%), persistent milk/food allergy was reported in 20 cases (57.1%), severe CMA was reported in 5 cases (14.3%), atopic dermatitis was reported in 6 cases (17.1%), allergy to various food and allergens was reported in 20 cases (57.1%). There were no cases in which use of nonsteroidal anti-inflammatory drug was reported, however, paracetamol use was reported in one out of 5 cases where body temperature was increased and associated with infective illness.

In 8 cases epinephrine was administered as treatment of anaphylactic reaction developed after administration of methylprednisolone; none of these cases reported late treatment with adrenaline as risk factor which could contribute to the severity of the reaction.

Underlying cardiovascular disease, mast cell disorders, alcohol, concomitant medications, exercise and menstruation were not reported as risk factors, as expected given the young age of the treated population (82.9% patients younger than 12 years).

Discussion

The mechanism of action of methylprednisolone-containing products is mediated through their anti-inflammatory and immunosuppressive effects, hence it is not expected that they would cause an allergic reaction or worsening of one, although the possibility remains. In addition, while diagnosing an allergic reaction to corticosteroids is challenging, the steroids themselves, or specific esterified derivative are known to cause allergic reactions (Burgdorff, 2002 [17]; Nucera, 2011 [18]). The safety information submitted by the MAHs, from Eudravigilance and from the literature, comprise 35 cases, including 32 serious cases, of allergic reactions to parenterally administered methylprednisolone products in patients allergic to cow's milk proteins. Positive skin prick tests to methylprednisolone-containing products formulated with lactose and negative for methylprednisolone-containing products formulated without lactose were reported in the cases where the test was conducted. The PRAC considered that the totality of the evidence available demonstrated a causal relationship between the administration of the methylprednisolone product containing traces of bovine milk proteins and the serious allergic reactions, including bronchospasm and anaphylaxis, reported in these patients.

The majority of cases were reported for the originator's medicinal product, which is correlated with exposure data. Quality of lactose used as excipient in pharmaceuticals in the EU must be in accordance with European Pharmacopoeia (Ph. Eur.) or equivalent. Quality of lactose regarding impurities is harmonised between Ph. Eur., United States Pharmacopeia (USP) and Japanese Pharmacopoeia (JP). Ph. Eur. monograph for lactose includes absorbance testing from 210 - 400 nm as non-specific purity test, a limit test for organic impurities as well as residual proteins. Thus, Ph. Eur. grade lactose does not exclude traces of proteins originated from milk. Cow's milk contains over 25 different proteins (total 3 g of protein/100 ml): caseins (alpha(s1)-casein, alpha(s2)-casein, beta-casein and kappa-caseins) and serum (whey) proteins (alpha-lactalbumin, beta-lactoglobulin, bovine lactoferrin, bovine serum albumin and bovine immunoglobulins), in proportions of 80% and 20%, respectively. Any of these proteins may act as an allergen and most patients with IgE-mediated cow's milk proteins allergy present polysensitisation (Martorell-Aragonés, 2015 [19]). The MAH of the originator presented the

[17] Burgdorff T et al. IgE-mediated anaphylactic reaction induced by succinate ester of methylprednisolone. Ann Allergy Asthma Immunol 2002; 89:425.
[18] Nucera E et al. 'Empty sella syndrome': a case of a patient with sodium succinate hydrocortisone allergy. Eur J Endocrinol 2011; 164:139.
[19] Martorell-Aragonés A et al. Position document: IgE-mediated cow's milk allergy. Allergol Immunopathol (Madr). 2015;43(5):507-26.

results of four publications, including 12 individual case reports on allergic reactions associated with methylprednisolone use, in which the authors reported the detection of milk proteins including caseins and β-lactoglobulin at trace amounts (within the range of the 1.7-3.5 parts per million to 112.5 nanograms per vial) from the lactose containing methylprednisolone products (Mina, 2015 [20]; Levy, 2104 [21]; Savvatianos, 2011 [22]; Eda, 2009 [23]). Therefore taking into account the pathophysiology of CMA, the PRAC considered the risk of serious allergic reactions in patients allergic to cow's milk common to all methylprednisolone products containing lactose of bovine origin. Therefore these products should be contraindicated in patients allergic or suspected to be allergic to cow's milk. In addition healthcare professionals (HCP) and patients should be warned that cases of serious allergic reactions have occurred in these patients and that allergic reactions to cow's milk proteins should be considered in patients treated for acute allergic conditions in whom symptoms worsen or who are presenting new allergic symptoms. In such cases, administration of the methylprednisolone product containing lactose of bovine origin should be interrupted and the patient condition should be treated accordingly. Although methylprednisolone products containing lactose of bovine origin were first marketed in the EU around 50 years ago, the first case of allergic reaction in a patient allergic to cow's milk identified in the literature was in 2002, possibly indicative of a low awareness of the risk among HCPs (Morishita, 2002 [24]). This is further supported by the percentage of cases (14.3%) reporting medical history of milk allergy where hypersensitivity reactions were initially misinterpreted as a lack of therapeutic effect and repeated administration which occurred in some cases leading to further worsening of the patient's condition. Therefore the PRAC considered that a direct healthcare professional communication (DHPC) should also be disseminated to relevant HCPs to increase awareness of the above mentioned risk and prevent any misinterpretation of hypersensitivity reaction as the lack of therapeutic effect.

Notwithstanding the above, PRAC noted that methylprednisolone-containing products used for treatment of acute allergic conditions are usually administered in emergency settings, in which context the product information may not always be readily available for HCPs to consult it, therefore the inscription "do not use in cow's milk allergy patients" should also appear on the outer packaging and small immediate packaging units. It remains however, that treatment urgency or patients' condition may not always allow HCPs to take patients' detailed medical history, hence potentially limiting the effectiveness of routine risk minimisation measures. Taking into account severity and seriousness of conditions when methylprednisolone products are used, the population at risk and the necessity for rapid management and the absence of an established safe threshold of exposure, the PRAC considered that the only means to fully address this risk is for the traces of milk proteins to be excluded from these methylprednisolone-containing products. To that effect, the MAHs shall replace the current formulations in their marketing authorisations with formulations free from cow's milk proteins and submit the corresponding documentation for assessment at national level by end of June 2019. Within the corresponding regulatory application for the new formulation, MAHs should discuss with the relevant national competent authorities in order to agree on the modalities of introduction of the new formulation in order to avoid disruption of supply. In the meantime the above mentioned risk minimisation measures should be implemented in the product information and the DHPC should be

[20] Mina I, Teixeira FA, De Andrade Medeiros KB, De Freitas Castello B, Souza P, Santis CL, et al. Allergy to cow's milk protein and reaction to methylprednisolone-case study. World Allergy Organ J. 2015 Apr 08;8 Suppl1.
[21] Levy Y, Segal N, Nahum A, et al. Hypersensitivity to methylprednisolone sodium succinate in children with milk allergy. J Allergy Clin Immunol Pract 2014;2(4):471-4.
[22] Savvatianos S, Giavi S, Stefanaki E, et al. Cow's milk allergy as a cause of anaphylaxis to systemic corticosteroids. Allergy 2011;66(7):983-5.
[23] Eda A, Sugai K, Shioya H, et al. Acute allergic reaction due to milk proteins contaminating lactose added to corticosteroid for injection. Allergol Int 2009;58(1):137-9.
[24] Morishita M, Yamaguchi H, Ito H, Sakamoto T, Torii S. [Anaphylaxis due to lactose contained in steroid for intravenously injection] [abstract]. Arerugi 2002;51:303.

disseminated to healthcare professionals. In addition, the MAH should follow this safety concern via their routine pharmacovigilance activities.

2.4. Data on efficacy

Methylprednisolone-containing products are authorised in a range of different indications in EU MS including in indications related to acute allergic conditions (e.g. anaphylaxis, acute laryngeal oedema, bronchial asthma (exacerbations) and (severe exacerbations of) atopic dermatitis).

The benefit of systemic glucocorticoids such as methylprednisolone in the treatment of acute allergic conditions including bronchial asthma and angioedema is well established, and current treatment guidelines are reflective of this fact (Akdis, 2014 [25], Global Strategy for Asthma Management and Prevention, 2016 [26]). According to the European guideline on the treatment of atopic dermatitis, short term treatment with systemic corticosteroids may be an option to treat an acute flare in exceptional cases of atopic dermatitis. With regards to anaphylaxis, systemic glucocorticoids are in principle used to treat the late-phase allergic reaction as adjunctive therapy to epinephrine or other therapies in anaphylaxis (Boyce, 2010 [3]) Simons, 2011 [27], Choo, 2012 [28]). No significant elements have been submitted within this procedure that would question the efficacy.

3. Benefit-risk balance

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 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

[25] Akdis CA, Agache I (Eds) (2014) Global Atlas of Allergy. European Academy of Allergy and Clinical Immunology.
[26] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Accessed 23 January 2017 at: http://ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf
[27] Simons FE et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011 Feb;4(2):13-37.
[28] Choo KJ et al. Glucocorticoids for the treatment of anaphylaxis. Cochrane Database Syst Rev. 2012 Apr 18;(4):CD007596.

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, 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.

4. Risk management

4.1. Risk minimisation activities

4.1.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk(s) associated with the use of IV/IM methylprednisolone-containing products formulated with lactose of bovine origin indicated in the treatment of acute allergic conditions while these are being reformulated. These changes include amendments to sections 4.3 and 4.4 of the SmPC and to sections 7 and 6, respectively of the outer packaging and small immediate packaging unit.

The PRAC considered that IV/IM methylprednisolone-containing products formulated with lactose of bovine origin should be contraindicated in patients with a known or suspected allergy to cow's milk. Warnings and precautions for use relating to the risk of serious allergic reactions associated with the use of IV/IM methylprednisolone-containing products formulated with lactose of bovine origin in patients allergic to cow's milk were also included. Further a warning that the product is not to be used in cow's milk allergy patients was included on the labelling.

The Package Leaflet was amended accordingly.

4.1.2. Direct healthcare professionals communication and communication plan

The PRAC adopted the wording of a direct healthcare professional communication (DHPC) to inform healthcare professionals of the new contraindication and warning related to the risk of allergic reactions in patients allergic to cow's milk treated with IV/IM methylprednisolone-containing products formulated with lactose of bovine origin. The PRAC also agreed on a communication plan.

5. Condition to the marketing authorisations

The marketing authorisation holder(s) shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

In order to remove any traces of cow's milk proteins from their finished product, the MAH(s) should replace the current formulation(s) in their marketing authorisation(s) with formulation(s) free from cow's milk proteins and submit for assessment the corresponding documentation to the relevant National Competent Authorities:	By 30 June 2019

6. Grounds for 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.