HALMED
Agencija za lijekove i
medicinske proizvode

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NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the Pharmacovigilance Risk Assessment Committee (PRAC) made by Croatian Agency for Medicinal Products and Medical Devices (HALMED):

Product Name in the Referring Member State	Solu-Medrol 40 mg powder and solvent for solution for injection
Procedure name	Medicinal products containing lactose from bovine origin for IV/IM use in acute allergic reactions
Active Substance	To be determined
Pharmaceutical Form	All pharmaceutical forms
Strength	All strengths
Route of Administration	Intravenous/intramuscular
Marketing Authorisation Holder in the Referring Member State	Pfizer Croatia d.o.o.

Solu-Medrol contains methylprednisolone, a corticosteroid, as an active substance. Among other conditions, it is indicated for the treatment of angioedema and anaphylaxis, life-threatening reactions requiring urgent medical treatment. Solu-Medrol 40 mg powder and solvent for solution for injection contains lactose monohydrate derived from 100% bovine milk as an excipient. The lactose contained in Solu-Medol is produced in compliance with European Pharmacopoeia monograph for lactose monohydrate, which does not exclude traces of milk proteins (limit test).

HALMED received an adverse drug reaction report of anaphylactic reaction after administration of Solu-Medrol 40 mg for bronchospasm in a [redacted] child, who previously experienced allergic reaction after administration of Solu-Medrol (positive re-challenge). The anaphylactic reaction was initially considered to be a lack of therapeutic effect and the drug was re-administered. Follow-up information revealed that the child suffered from severe allergy to cow's milk proteins.

HALMED initiated assessment of the safety issue and requested the MAH to perform a review of cases of allergic reactions in patients with a history of multiple food and/or milk allergy reported from all sources. It is noted that the prevalence of cow's milk allergy varies between 0.21% and 4.9%. The following cases were identified and the MAH consequently submitted a variation to include a contraindication for patients with known allergy to cow's milk proteins:

- an additional 26 cases of hypersensitivity reactions were identified in patients treated with methylprednisolone containing lactose, administered intravenously;
- 19 cases (including the case presented above) were life-threatening anaphylactic reactions, out of which 17 cases occurred in paediatric patients (2-15 years old);
- 12 cases reported positive skin prick test only for Solu-Medrol 40 mg product containing lactose and not for other Solu-Medrol products not containing lactose.

Further in October 2016, HALMED received two additional reports of allergic reactions after administration of Solu-Medrol 40 mg in children with allergy to cow's milk proteins, one of which was an anaphylactic reaction.

Both the nature of the allergic condition for which the drug is indicated and the adverse drug reaction itself are life-threatening. In addition, there is a risk that the acute allergic conditions for which Solu-Medrol is indicated may mask anaphylactic reactions caused by the traces of milk proteins in the product. As reported in the above described case, this may be misinterpreted as a lack of therapeutic effect, leading to repeated administrations of the product, further worsening the patient's condition.

In view of the emerging safety issue, its seriousness and considering that it may also apply to other medicinal products for intravenous or intramuscular administration containing lactose derived from bovine milk used in the treatment of acute allergy and anaphylactic shock, HALMED circulated a request for non-urgent information to the network on November 4th 2016. The results showed that:

- there are other medicinal products for IV/IM use containing lactose derived from bovine milk and authorised in the treatment of allergic conditions;
- there are adverse drug reactions reports for other medicinal products for IV/IM use containing lactose derived from bovine milk and authorised in the treatment of allergic conditions;
- the above mentioned variation to add a contraindication has been submitted by the MAH in some other Member States, but does not cover all medicinal products concerned by this issue nor all Member States where they might be authorised.

On the basis of the above, HALMED considers that there is a need for a thorough Union assessment of this safety issue as regards to its impact 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, in particular, the need for risk minimisation measures.

In view of the elements described above and the necessity to take an action at EU level, Croatia considers that it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

[redacted]

Signed

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Date 21. 11. 2016.