boletim de FARMACOVIGILÂNCIA

VOLUME 21
NÚMERO 9
SEPTEMBER 2017

Methylprednisolone injectable formulations containing lactose of bovine origin
risk of hypersensitivity

Quick Read

In patients who are allergic to cow's milk proteins, injectable formulations of methylprednisolone containing lactose of bovine origin as an excipient may cause allergic symptoms. These can be mistaken for worsening of the hypersensitivity condition for which the corticosteroid is being used.

Methylprednisolone is a potent non-steroidal anti-inflammatory agent, which can be part of therapeutic regimens used for allergic conditions, namely in a medical emergency.

EMA has recently concluded a safety review of injectable medicinal products (for IV and/or IM administration) containing methylprednisolone as active ingredient and lactose as an excipient, following reports of serious hypersensitivity reactions in patients treated with those products and who were simultaneously allergic to cow's milk proteins. The available data showed that bovine milk derived lactose can introduce in the product traces of cow's milk proteins which may trigger hypersensitivity reactions in patients who are allergic to those proteins.

This is of special relevance in patients receiving methylprednisolone for the treatment of an allergic reaction, in which case it may be difficult to determine whether the patient's symptoms are due to the superposition of an allergic reaction to the medicine or to worsening of the baseline condition. This in turn may lead to additional doses of the product being given, thus paradoxically worsening the clinical condition it was supposed to treat.

EMA recommends that injectable products containing methylprednisolone as active ingredient and lactose as an excipient **should not be used** in patients who are known or suspected to be allergic to cow's milk proteins, and that the treatment **should be discontinued in case of worsening** of the symptoms or of appearance of new symptoms.

Since methylprednisolone is used in the treatment of serious allergic reactions in an emergency and it is not always possible to know the patient's allergies, EMA recommends that all excipients that may contain cow's milk proteins be withdrawn. MA holders have been requested to take measures **until June 2019** to replace the current formulations with **new lactose-free formulations**.

The injectable products containing methylprednisolone which are authorised in Portugal are the following:

Medicinal product	Dosage	Bovine-origin lactose
Depo-Medrol	40 mg/1 ml	No
Depo-Medrol	80 mg/2 ml	No
Depo-Medrol Com Lidocaína	40 mg/ml + 10 mg/ml	No
Metilprednisolona Hikma	1000 mg	No
Metilprednisolona Hikma	40 mg	Yes
Metilprednisolona Hikma	500 mg	No
Metilprednisolona Hikma*	125 mg	No
Solu-Medrol	500 mg/7.8 ml	No
Solu-Medrol	125 mg/2 ml	No
Solu-Medrol	1000 mg/15.6 ml	No
Solu-Medrol	40 mg/1 ml	Yes

INDEX CARD

Director: Fátima Canedo
Editor: Rui Pombal
Contributors: Ana Sofia Martins, António Leandro Ponte, Cristina Mousinho, Elsa de Fátima Costa, Fátima Bragança, Fátima Hergy, Leonor Nogueira Guerra, Magda Pedro, Márcia Silva, Sílvia Duarte, Vanda Araújo
Publishing Assistant: Inocência Pinto
Advisory Board: Conselho Diretivo do INFARMED, I.P. – Comissão de Avaliação de Medicamentos
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Phone: +351 217 987 100
E-mail: infarmed@infarmed.pt
Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

Methylprednisolone injectable formulations containing lactose of bovine origin
risk of hypersensitivity

Summary of product characteristics

4.3 Contraindications

[…] 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

Immune System Effects […]

Cow's milk allergy

[..]contains lactose 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 (see section 4.3).

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

These measures have been further disseminated to healthcare professionals in Portugal through a Communication available on the INFARMED website (see link in table below).

Sílvia Duarte

Communications to Healthcare Professionals published on the Infarmed website

Click on the links

DCI Medicinal product	Target	Which communication? Date published online
Decitabine Dacogen	**Pharmacists:** hospital **Physicians:** haematologists and oncologists **Nurses:** in haematology and oncology departments	Change in recommendations for dilution of reconstituted solution 08-09-2017
Human Epoetins: **Darbepoetin alfa** Aranesp **Epoetin alfa** Binocrit Eprex **Methoxy polyethylenoglicol epoetin beta** Mircera **Epoetin beta** NeoRecormon **Epoetin zeta** Retacrit	**Physicians:** oncologists, haematologists, nephrologists, dermatologists, haemodialysis clinic directors	Clarification of March 2017 Communication on indications for suspending treatment in case of FEVE reduction 27-09-2017
Trastuzumab Herceptin	**Physicians:** oncologists, radiotherapists, general surgeons, gynaecologists, internists (in charge of senology and with experience in the use of anti-HER2 therapies) and department directors in hospitals procuring Herceptin	New safety information on Serious Cutaneous Adverse Reactions including SJS and TEN 29-09-2017
Methylprednisolone Solu-Medrol 40 mg/1 ml Metilprednisolona Hikma 40 mg	**Physicians:** GP/family doctors, allergy specialists, paediatricians, pneumologists **Intensive care units** **Emergency / A&E Departments** **National Medical Emergency Institute and Red Cross ambulances**	New contraindication in the use of injectables contain lactose as excipientin patients with cow's milk protein allergy, when used to treat allergic reactions 04-09-2017

Compiled by Magda Pedro and Rita Dias

Educational Materials published in the Infomed product information webpage

Click on the links

DCI Medicinal product	Target	Which materials? Date published online
Bosentan Bosentano Accord Bosentano Aurobindo Bosentano Mylan Bosentano Normon Bosentano Sandoz Bosentano Teva	**Physicians:** cardiology, pneumology, Internal medicine, rheumatology and vascular surgery	**Information and guidance for prescribers** 04-09-2017
	Patients and general public	**Guidance for patients** 04-09-2017
Valproic acid Depakine Depakine Chrono 300 Depakine Chrono 500 Depakine Chronosphere	**Patients** and general public	**Patient card – Valproate and Pregnancy (to be handed out by the pharmacist** 27-09-2017
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Disoproxil Mylan **Tenofovir** Tenofovir Disoproxil Mylan	**Physicians:** GP/family medicine, infectious diseases	**Recommendations on renal monitoring and dose adjustment in adult patients** 04-09-2017
Pirfenidone Esbriet	**Physicians:** pneumologia	**Safety checklist** 01-09-2017
Fingolimod Gilenya	**Physicians:** neurology	**Prescriber's safety checklist** 21-09-2017
Eltrombopag Revolade	**Physicians:** haematology **Pharmacists:** pharmaceutical department directors at hospitals in which patients with chronic idiopathic thrombocytopenic purpura are likely to receive treatment	**Safety guide** 27-09-2017
Emtricitabine + Tenofovir Truvada **Tenofovir** Viread	**Physicians:** : infectious diseases, internal medicine (following HIV patients), paediatrics (following HIV patients), hospital paediatrics department directors	**Educational brochure for the treatment of HIV-1 infected children and adolescents** 18-09-2017
Voriconazole Voriconazol Mylan 200 mg pó para solução para perfusão	**Physicians:** haematology, infectious diseases, dermatology, oncology	**Questions and Answers Brochure on safety information for prescribers** 21-09-2017 **Prescriber's checklist** 21-09-2017
	Patients and general public	**Patient alert card** 21-09-2017

Compiled by Magda Pedro and Rita Dias

ADRs in the Literature

Caution is needed whenever dose adjustments based solely on serum creatinine levels are made for patients with renal impairment.

In this article published in the European Journal of Clinical Pharmacology, the authors discuss the use of estimated glomerular filtration rate (eGFR) against the background of the limitations of serum creatinine based formulae. They propose that when trying to determine an adequate posology for patients with kidney function impairment, formulae based on serum creatinine levels should never be used at face value but rather combined with a clinical and pharmacological assessment of each individual patient.

In fact, therapeutic approaches based solely on eGFR have limitations, in addition to complications arising from multiple concomitant conditions and drug interactions. The narrower a drug's therapeutic window, the more relevant the relative weight of the patient's individual characteristics and the less satisfactory dosage recommendations become if given out of context. The authors argue that in patients with renal dysfunction, the following steps should be considered:

1 → Is the drug excreted through the kidneys?

If so: is there a safer alternative available?

2 → Should there be no alternative, could the eGFR be substantially different from the actual GFR?*

If so: consider requesting a 24-hour urine creatinine clearance test.

3 → Is the patient's body surface area substantially different from 1.73 m^2?

If so: calculate the patient's body surface area and adjust the eGFR to millilitres per minute.

4 → Combine **2.** and **3.** to achieve the best possible approximation to actual GFR.

5 → Adjust dose to renal function gradually.

6 → Be especially cautious with medicines with a narrow therapeutic window and consider a different starting dose, depending on the indication.

7 → Consider monitoring effectiveness and/or the occurrence of adverse reactions in some measurable form.

* E.g., Conditions in which GFR is rapidly changing, malnutrition, relatively low or high muscle mass, critically acute conditions.

Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. Willemijn L et al. Eur J Clin Pharmacol (2016) 72:1433–1439

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics