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Flucloxacilina
acute generalized exanthematous pustulosis

Quick Read
Fever and generalized rash at the beginning of therapy with flucloxacillin may point to acute generalized exanthematous pustulosis (AGEP). The patient should not be exposed to the antibiotic again.

Flucloxacillin is a broad-spectrum antibiotic from the group of beta-lactamase resistant isoxazolpenicillins, which act on the bacterial wall. It is indicated in infections caused by sensitive microorganisms, especially Streptococci and Staphylococci. AGEP is a generalized pustulous skin eruption. It is usually characterized by fever and leukocytosis together with the sudden appearance of erythematous and edematous features upon which multiple sterile, non-follicular pustules develop. About 90% of cases are drug-induced – more often penicillins and macrolides.

Based on three cases received between November 2011 and June 2015, the Dutch medicines agency raised a safety signal (safety problem suspected) to do with flucloxacillin and the occurrence of acute generalized exanthematous pustulosis (**AGEP**). Taking into account the cases in the European adverse reaction database EudraVigilance, the data from the literature[1-7] and the known association between skin reactions and flucloxacillin, the Pharmacovigilance Risk Assessment Committee (PRAC) agreed that the MA holders of medicines containing flucloxacillin submit the following changes to the Summaries of Product Characteristics (SmPCs):

4.4. Special warnings and precautions for use

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

4.8. Undesirable effects

[…] Frequency not known: AGEP – acute generalized exanthematous pustulosis (see section 4.4)

Márcia Silva

References:

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[2] *Feldmeyer L, et al. Acute Generalized Exanthematous Pustulosis: Pathogenesis, Genetic Background, Clinical Variants and Therapy. Int J Mol Sci 2016; 17(8).*
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Loperamide in high doses:
cardiac reactions from abuse or misuse

Quick Read
Abuse or misuse of loperamide in high doses may be associated with serious cardiac reactions such as *torsades de pointes*.

Loperamide is indicated in the symptomatic treatment of diarrhoea. It binds to opioid receptors in the intestinal wall and inhibits acetylcholine and prostaglandin release, thus reducing peristaltic propulsion and increasing intestinal transit time. Loperamide is a phenylpiperidine derivative with a chemical structure similar to opioid receptor agonists such as diphenoxylate or haloperidol. It presents low oral absorption and minimal potential for central nervous system effects, which is the reason why it had mostly been considered as free from abuse potential (Baker DE, 2007).

The USA FDA (Food and Drug Administration) issued an alert last June concerning the use of loperamide in high doses and its relation with serious heart problems, especially when taken simultaneously with other interacting drugs, thereby increasing its concentration.

Most serious cases reported in the US occurred in individuals who **intentionally** misused or abused this product, by ingesting elevated doses in an attempt to self-treat an opioid withdrawal syndrome or to obtain a state of euphoria.

These events led in November 2016 to changes in the medicinal product's information documents in the US; a warning has been inserted regarding the possibility of torsades de pointes, cardiac arrest and even death, when high doses of the medicine are taken.

In Europe a safety signal has been raised by EMA whose assessment is ongoing:

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2016/09/WC500213110.pdf

Leonor Nogueira, Leandro Ponte

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

Cobicistat
risk of adrenal suppression from interaction with corticosteroids

Quick Read
Cobicistat can interact with corticosteroids resulting in increased risk of adrenal adverse effects.

Cobicistat, through inhibition of liver metabolism, works as a pharmacokinetic "potentiator" of atazanavir, darunavir, elvitegravir, emtricitabine or tenofovir, as part of antirretroviral association therapy in adults with human immunodeficiency virus 1 (HIV-1) infection.

During its routine pharmacovigilance activities, and based on eight cases from the European adverse drug reaction database EudraVigilance, the United Kingdom raised a safety signal (safety problem suspected) regarding a drug-drug interaction between cobicistat and corticosteroids leading to adrenal suppression.

Based on the available data, including the literature,[1-8] the European Medicines Agency has recommended the following changes to the SmPCs:

Cobicistat

4.5. Interaction with other medicinal products and other forms of interaction

Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Interaction not studied with any of the components of <product name>. Plasma concentrations of these medicinal products may be increased when co–administered with <product name>, resulting in reduced serum cortisol concentrations.	Concomitant use of <product name> and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use.

All corticosteroids other than beclomethasone (excluding cutaneous formulations)

Section 4.4 or 4.5, as applicable:

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Beclomethasone containing products (excluding cutaneous formulations)

Section 4.4 or 4.5, as applicable:

Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Márcia Silva

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Metronidazole
serious hepatic and neurologic toxicity in patients with Cockayne syndrome

Quick Read
Cases of serious (including fatal) liver toxicity of very quick onset have been reported in patients with Cockayne syndrome after starting therapy with systemic metronidazole.

Metronidazole has both antibacterial and antiparasitic properties and is indicated in infections caused by a broad variety of agents. It is included in the World Health Organization Model List of Essential Medicines.
Cockayne syndrome is a rare, neurodegenerative condition, with an autosomal recessive inheritance pattern, and whose manifestations include photosensitivity and premature ageing

The publication of a case series in the literature[1] prompted a safety assessment as a result of which the SmPCs (Summaries of Product Characteristics) of metronidazole will be changed to include the following warning:

4.4. Special warnings and precautions for use

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Sílvia Duarte

Reference:
[1] *Wilson BT et al. Metronidazole Toxicity in Cockayne Syndrome: A Case Series. Pediatrics. 2015 Sep;136(3):e706-8.*

Educational Materials published on the Infarmed website

Medicinal product (DCI)	Click on the links (in Portuguese)
Abacavir Sandoz (abacavir)	***Information for healthcare professionals*** Informação de Segurança sobre reações de hipersensibilidade graves associadas à utilização de Abacavir Sandoz® (abacavir) – 1.ª versão aprovada em agosto de 2016 Published on 23-11-2016
Abacavir + Lamivudina Teva (abacavir + lamivudine)	***Information for healthcare professionals*** Material educacional sobre reações de hipersensibilidade graves associadas à utilização de abacavir – 1.ª versão aprovada em novembro de 2016 Published on 23-11-2016
Keytruda (pembrolizumab)	***Information for physicians*** Brochura de informação para os profissionais de saúde – 3.ª versão aprovada em agosto de 2016 ***Information for patients*** Brochura de informação para o doente – 3.ª versão aprovada em agosto de 2016 Cartão de alerta para o doente - 3.ª versão aprovada em agosto de 2016 Published on 23-11-2016
Portrazza (necitumumab)	***Information for healthcare professionals*** Informação de segurança importante sobre os riscos de acontecimentos tromboembólicos e alterações cardiorrespiratórias associados à utilização de Portrazza – 1.ª versão aprovada em novembro de 2016 Published on 29-11-2016
Xalkori (crizotinib)	***Information for healthcare professionals*** Informação de segurança importante sobre a utilização de crizotinib para Profissionais de Saúde – 5.ª versão aprovada em outubro de 2016 ***Information for patients*** Guia para o doente informação de segurança sobre o seu tratamento com Xalkori – 5.ª versão aprovada em outubro de 2016 Published on 23-11-2016

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