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Macrogol
risk of ischaemic colitis

Quick Read
As with other osmotic laxatives, ischaemic colitis can also occur in association with the use of macrogol for diagnostic procedures, namely colonoscopy.

Macrogol (polyethylene glycol), in various molecular weights and presented in isolation or in association with other active ingredients, is characterized by long linear polymers which exert their action through an osmotic mechanism. This results in an increase in the volume of non-absorbed intestinal fluid, a bigger faecal bolus and facilitated defecation. Macrogol is indicated for intestinal cleansing prior to diagnostic procedures.
Ischaemic colitis can supervene following acute blood flow depletion which, in this context, is due to excessive osmotic intestinal fluid loss. This in turn causes blood volume depletion which leads to ulceration of the intestinal mucosa, inflammation and bleeding.

The rare occurrence of ischaemic colitis as an adverse effect of laxative agents such as bisacodyl is well known. Predisposing risk factors include age older than 65 years, abdominal surgery, hypercoagulation states, colonic obstruction and intense physical activity, as well as colonoscopy and medication including other concomitant laxatives, anti-hypertensive agents, oral contraceptives, diuretics, non-steroidal anti-inflammatory agents, pseudoephedrine.

Given the seriousness of the reaction and that patients who are most susceptible may have other risk factors or may be taking bisacodyl or sodium picosulfate simultaneously, a safety assessment review was conducted at European level of products containing macrogol (in various molecular weights and associations) for intestinal prepping in patients submitted to diagnostic procedures including colonoscopy.

EMA reviewed all the cases in the European adverse drug reaction database EudraVigilance (EVDAS), as well as cases in the literature. This review has supported a change to the texts of the SmPCs and Patient Information Leaflets of those medicinal products. The SmPCs will read:

4.4. Special warnings and precautions for use

Ischaemic colitis

Post-marketing cases of ischaemic colitis, including serious, have been reported in patients treated with macrogol for bowel preparation. Macrogol should be used with caution in patients with known risk factors for ischaemic colitis or in case of concomitant use of stimulant laxatives (such as bisacodyl or sodium picosulfate). Patients presenting with sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis should be evaluated promptly.

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ADRs in the literature

Patients with COVID-19 do not seem to be at increased risk of mortality in association with systemic antineoplastic therapy

The possibility of a higher risk of death from COVID-19 in cancer patients has been raised, especially concerning patients undergoing systemic cytotoxic antineoplastic therapy.

Evidence from a prospective observational study in 800 cancer patients in the British network of oncological centres UKCCMP who had a PCR test confirmed diagnosis of COVID-19 did not support the hypothesis above. Mortality in these patients was strongly associated with age and with the presence of comorbidities. The study's authors consider that these results may help to promote confidence in continuation of antineoplastic therapeutic regimes through difficult pandemic times.

- ***Lee LYW et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet. 2020 Jun 20;395(10241):1919-1926.***

In another study, which was also recently published in The Lancet, the authors analysed all-cause mortality in the 30 days following a confirmed diagnosis of COVID-19 in 928 patients. They were all adult individuals from the USA, Canada and Spain, with an active or previous malignant neoplasm and serious forms of COVID-19. These patients with cancer and COVID-19 had a high all-cause 30-day mortality which was associated with general risk factors (e.g., age, smoking, number of comorbidities), as well as with specific oncological risk factors, though not with factors such as race/ethnicity, obesity status, type of neoplasm and of antineoplastic therapy, or recent surgery. Longer term follow-up may help us to better understand the effect of COVID-19 in the outcomes of cancer patients.

- ***Kuderer NM et al. Clinical Impact of COVID-19 on Patients With Cancer (CCC19): A Cohort Study. Lancet. 2020 Jun 20;395(10241):1907-1918.***

Communications to Healthcare Professionals published in the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Capecitabine **5-Fluorouracil** **Tegafur** Capecitabina Aurovitas Capecitabina Accord Capecitabina Farmoz Fluorouracilo Accord Solução injetável ou para perfusão Fluorouracilo Hikma Solução injetável ou para perfusão Fluorouracilo Teva Solução injetável	**Physicians:** oncology **Pharmacists:** hospital	Pre-treatment screening of DPD (dihydropyrimidine dehydrogenase) activity deficiency to detect patients at increased risk of serious toxicity 03-06-2020

Compiled by Patrícia Catalão

Cutaneous amyloidosis and insulin

Quick Read
Cutaneous amyloidosis is a possible class adverse effect of insulin. This risk, in a similar way to lipodystrophy, can probably be reduced by constantly changing the injection site.

Diabetes treatment regimes with insulin include human insulin, insulin analogs (obtained through recombinant DNA technology) and animal origin insulin (with limited availability in some countries for rare cases when patients are not able to get their diabetes under control with a biosynthetic insulin). Current data point to an estimated post-marketing exposure of over 483 million patients-year to human insulin, isophane human insulin and insulin analogs (aspart, degludec, detemir, glargine, glulisine, lispro).
Amyloidosis is a term used for conditions caused by extracellular, systemic or localized deposition of insoluble polymeric fibrillar proteins in tissues and organs.

Insulin-derived amyloidosis is a local reaction that can be more frequent than previously thought. In the 3-year period from 2012 to 2015 the number of cases reported was three times higher than in the thirteen years between 1988 and 2011. The fact that the prevalence of lypo-hypertrophy in diabetic patients increased in parallel with the cases of insulin-derived amyloidosis suggests that the latter may have been underreported on account of being mistaken for lipo-hypertrophy nodules.

A potential safety signal concerning cutaneous amyloidosis and insulin was first detected in 2018 by the FDA (US Food and Drug Administration). In November 2019 this issue was also raised by the Danish medicines agency based on 46 cases for which a causal relation could not be excluded. The **clinicalpicture** of the cases includes one or more hard subcutaneous lumps at injection sites. These are Congo red-positive under polarized microscopy by showing green birefringence. Immunocolouring with insulin antibodies or proteomic analysis shows type A-Ins amyloid deposits.

Taking into account the cases in the European adverse drug reaction report database EudraVigilance and other available evidence, the PRAC at EMA concluded in April 2020 that cutaneous amyloidosis can be a class effect of all types of insulin and recommended **changes to the SmPCs**.

Administering insulin into sites showing amyloid changes potentially risks delaying insulin absorption and worsening of glycaemic control. On the contrary, a sudden change of habitual injection site to a clear area may lead to hypoglycaemia. The changes in the SmPC therefore, are to do mostly with administration instructions: the injection site should be constantly changed. Following these instructions may reduce the risk of lipodystrophy and cutaneous amyloidosis. Nevertheless, it is recommended that blood glucose levels should be monitored following each injection site change; dosing of antidiabetic drugs may have to be adjusted accordingly.

Adriana Gamboa

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

Educational Materials published in the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Deoxycholic acid Belkyra	**Physicians:** plastic surgery	Guide for safe administration 30-06-2020
Ethinylestradiol + Desogestrel or + Etonogestrel Desogestrel + Etinilestradiol Mylan Mystrelle	**Physicians:** gynaecology, general/family medicine (family planning clinics)	Prescriber checklist
	Patients	Information card 15-06-2020
Fentanyl Abstral	**Physicians:** pain units, palliative care units, oncology departments	Prescriber guide
	Patients	Patient guide 16-06-2020
Levonorgestrel Jaydess Kyleena Mirena	**Physicians:** gynaecology, obstetrics, general/family medicine (family planning clinics)	Risk of ectopic pregnancy, and differences between levonorgestrel intrauterine release devices 30-06-2020
Neratinib Nerlynx	**Physicians:** oncology **Nurses**: day care hospitals **Pharmacists**: hospital	Guide for healthcare professionals
	Patients/Caregivers	Treatment guide Treatment diary 16-06-2020
Nivolumab Opdivo	**Patients**	Alert card 15-06-2020
Tafamidis Vyndaqel	**Physicians:** neurology (national paraamyloidosis centres), cardiology; clinical director and cardiology and internal medicine department directors **Pharmacists**: hospital pharmacy services directors	Healthcare professionals guide 26-06-2020
Teriflunomide Aubagio	**Physicians:** neurology	Physician's guide
	Patients	Patient card 26-06-2020

Compiled by Patrícia Catalão