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From the Editor

Tiocolchicoside, a commonly used muscle relaxant, has new dosage restrictions and is contraindicated in pregnancy and during breastfeeding on account of a risk of aneuploidy. Also in this issue: safety of infusion solutions containing hydroxyethilamide, risk of hypermagnesaemia with parenteral nutrition, especially in premature new-borns, safety of GLP-1-based therapies for diabetes, prevention of lipodystrophy on the site of administration of insulin, and novel restrictions for the use of ergot derivatives. In the interactions section the pharmacological approach to acne is brought in focus.

How can I report an adverse reaction?

- **ADR Portal (Portal RAM):**
  http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
- **Report Card online printout link:**
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What do they stand for?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorisation
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
SPC	Summary of the Product's Characteristics

Tiocolchicoside

(Coltramyl, Relmus, Tiocolquicosido Arrowblue, Tiocolquicosido Generis ; Adalgur N)

Short term only, not during pregnancy

Tiocolchicoside is a muscle relaxant indicated in the treatment of painful muscle conditions. In Portugal several products containing tiocolchicoside are authorized for both ***oral*** *and* ***intramuscular*** *use (Coltramyl, Relmus, Tiocolquicosido Arrowblue, Tiocolquicosido Generis and Adalgur N (association with paracetamol).*

A safety review was triggered by the Italian medicines agency following new experimental data suggesting that a tiocolchicoside metabolite, called M2 or SL59.0955, may damage cells during cell division causing ***aneuploidy*** *(abnormal number or disposition of chromosomes). According to the available data the levels of M2 after administration of tiocolchicoside in the recommended doses do not seem to be much lower than dose needed to cause aneuploidy. Aneuploidy is a risk factor for foetal damage, spontaneous abortion, reduced male fertility, and can theoretically increase the risk of cancer.*

EMA has concluded that, given the available evidence, the benefit-risk ratio of these products remains however positive, provided appropriate ***risk minimization*** *measures are implemented. To ensure that they are used as safely as possible, recommendations have been issued to restrict the maximum dose and length of treatment, to include contraindications of use during pregnancy and breastfeeding, in women of childbearing age not using any contraceptive method, in children, and in the treatment of chronic conditions.*

EMA and Infarmed recommend:

- *Tiocolchicoside for systemic use is only recommended for adjuvant therapy of acute muscle contracture in spinal conditions, in* ***adults and adolescents aged 16 or more years****.*
- *It is* ***not*** *recommended for* ***prolonged*** *use.*
- *With* ***oral formulations****, the maximum dose is 8 mg every 12 hrs for* ***not longer than 7 consecutive days****.*
- *For* ***intramuscular formulations****, the maximum dose is 4* ***mg every 12 hrs for 5 days****.*
- *It should* ***not*** *be given during* ***pregnancy, breastfeeding****, or to women of* ***childbearing age*** *who are not using a contraceptive method.*
- *Treatment of patients with systemically administered tiocolchicoside should be* ***reviewed*** *in the following medical appointment.*
- **Pharmacists** *should refer patients with repeat prescriptions for tiocolchicoside to the prescribing physician.*

These recommendations do not apply to medicines with tiocolchicoside for topical application since the levels of M2 produced are not enough to affect cellular genetic material. These formulations in any case are not marketed in Portugal.

Medicines containing tiocolchicoside will be tagged with a **black triangle** *(see previous issue of the Boletim).*

INDEX CARD | **Director:** Alexandra Pego **Editor:** Rui Pombal **Assistant Editor:** Leonor Nogueira **Contributors:** Ana Araújo, Catarina Fernandes Costa, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Inês Clérigo, Joana Oliveira, Leonor Nogueira Guerra, Magda Pedro, Margarida Guimarães, Pedro Marques Silva, Teresa Santos Dias **Publishing Assistant:** Inocência Pinto **Advisory Board:** Conselho Directivo do INFARMED, I.P.; Comissão de Avaliação de Medicamentos **Publisher:** 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: 217 987 316 – E-mail: infarmed@infarmed.pt **Design and production:** Letras & Sinais, Comunicação e Imagem, Lda. **ISSN:** 0873-7118

Hydroxyethylamide – containing Solutions (HES)
Contraindications and Precautions

EMA has finalized a safety review of all the solutions containing hydroxyethylamide (HES). These are volume expanders which replace fluid loss. They are used in the **treatment and prevention of** imminent or manifest **hypovolaemia**, as well of **hypovolaemic shock** in critical patients, in particular with sepsis, burns, trauma or those submitted to surgery.

Following the publication of recent studies comparing HES with other volume expanders in critical patients, several safety issues have arisen. In one study the use of HES and of Ringer acetate (another volume expander) was compared in patients with severe sepsis, demonstrating that patients treated with HES had a higher risk of death and a higher need for renal function replacement therapy.[1] The results of this study were similar to those from a previous one in patients with severe sepsis.[2]

Furthermore, in a third study in 7,000 intensive care patients comparing the use of HES with saline solutions, greater need for renal function replacement therapy was demonstrated for patients being treated with HES, albeit without increased risk of death.[3]

EMA and Infarmed recommend the following to health professionals in what concerns HES-containing solutions:

- They can **only be** used in the treatment of hypovolaemia caused by **acute blood loss** and when the use of **chrystalloid** fluids has **not** been **sufficient**.
- They should **not** be used in patients with **sepsis, burns or in critical condition**, due to an increased risk of renal injury and mortality.
- They are **contraindicated** in patients with **renal failure or on dialysis**, and their use should be discontinued at the first signs of kidney injury (greater need for dialysis has been reported within 90 days following administration of HES).
- They are **contraindicated** in patients with **serious coagulopathy**, and their use should be discontinued at the first signs of coagulation disorder.
- They should be used in the **lowest effective dose** and for the **shortest possible period of time** (shorter than 24 hours).
- **Continuous haemodynamic monitoring** should be undertaken so that the infusion may be suspended as soon as adequate levels are reached.
- **Renal function** should be **monitored**.
- In cases of **repeat administration, coagulation** parameters should be carefully monitored.
- There are no robust long-term data concerning the use of HES in patients with **trauma or undergoing surgery**. Therefore, this should be weighed against the benefits from using HES, and other therapeutic alternatives should be considered (additional studies will be undertaken to address this issue).

Margarida Guimarães

[1] Perner, A. et al. Hydroxyethyl Starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367(2):124-134.

[2] Brunkhorst, F.M. et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358(2):125-39.

[3] Myburgh, J.A. et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care; N Engl J Med 2012; 367(20):1901-11.

Numeta G13%E and Numeta G16%E
Risk of Hypermagnesaemia

Numeta G13%E preparations for **parenteral nutrition** have been associated with cases of asymptomatic hypermagnesaemia in **premature babies**, which has prompted EMA to undertake a safety review.

The Marketing Holder of Numeta has identified 14 cases of hypermagnesaemia associated with Numeta G13%E in which the serum levels of magnesium varied between 1.025 mmol/L and 1.5 mmol/L. In no case were any signs or symptoms detected.

The conclusions from the review have led to the **suspension** of the market authorization of **Numeta G13%E**. The MA Holder had already started to voluntarily withdraw this formulation from the market, since initial research had shown that this product contained magnesium levels which were higher than those described in available recommendations for premature new-borns. This suspension will remain in force until the composition of Numeta G13%E is reformulated in order to reduce its magnesium content.

Adequate levels of magnesium for premature new-borns have not been established, though some guidelines point to 0.15 0.25 mmol/kg/day and 0.2 mmol/kg/day for term new-borns and up to one year of age, and 0.15-0.25 mmol/kg/day and 0.1 mmol/kg/day for children between 1 and 2 years.[1-3]

There is no other parenteral nutrition preparation in the market indicated for premature new-born babies, although they may be individually prepared by hospitals as needed.

The **Numeta G16%E** formulation being used in term new-borns and in children up to two years has also been included in this safety review; the attendant **risk/benefit ratio remains positive**. Nevertheless, health professionals should be **aware of the potential risk of hypermagnesaemia**, which is increased in **babies with impaired renal function and in those whose mothers took magnesium supplements before labour**.

Infarmed therefore recommends the following to health professionals:

Regarding Numeta G13%E

- Parenteral nutrition solutions for premature babies should be **prepared individually** as long as the current suspension is in force, i.e. until a new formulation with lower magnesium content is made available.

Regarding Numeta G16%E

- Blood levels of **magnesium** and other **electrolytes** should be **monitored** before each administration and at regular intervals while the product is being used in term new-borns and in children up to two years.

Joana Oliveira

[1] Canada T et al. Parenteral Nutrition Handbook. Silver Spring,Maryland: American Society for Parenteral and Enteral Nutrition. 2009; 167.

[2] Mirtallo et al. Safe Practices for Parenteral Nutrition. JPEN 2004; 28: S 39 – S 70.

[3] Koletzko B et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatric Gastroenterology Nutrition 2005; 41:S1-S87.

GLP-1-based therapies
Safety review

EMA has concluded a safety review of GLP-1-based therapies for the treatment of type 2 diabetes: currently available data do **not** confirm an **increased risk of adverse pancreatic effects**. GLP-1-based therapies (exenatide, liraglutide, lixisenatide, sitagliptin, saxagliptin, linagliptin, vildagliptin) include dipeptidyl peptidase inhibitors (DPP 4) and glucagon-like peptide 1 agonists (GLP-1), known as **incretin mimetics**.

This safety review was initiated after publication of a study whose data suggested a possible increase in pancreatitis and changes into pre-cancerous cells in patients with type 2 diabetes being treated with incretin mimetics.[1] However, following a review of the study and consultation to a group of experts, EMA considered that the it had a series of methodological flaws and potential sources of bias which prevent its results from being reliably interpreted. EMA further concluded that there was no evidence regarding risk of associated adverse pancreatic effects, neither did data from clinical trials indicate an increased risk of pancreatic cancer.

Nevertheless, there remain doubts about pancreatic effects from long-term use on account of these products' mechanism of action – beta cell stimulation or alpha cell suppression.

Since the number of ADR reports is too small for any definitive conclusions to be reached, EMA will keep collecting data on this matter in close collaboration with the MA Holders. Moreover, in the Spring of 2014 the first results are expected from two major independent studies funded by the European Commission and ongoing since 2011 on the risk profile of diabetes therapies, more specifically in what concerns the pancreas.

Catarina Costa

[1] Butler et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013 Jul; 62(7):2595-604.

Lipodystrophy at the Site of Administration of Insulin
Reinforce advice to diabetics

Lipodystrophy at the site of administration of insulin is common in diabetics as an adverse reaction whose occurrence is **not unexpected**, although one which can be **minimized**. According to the information in the SPCs of products containing insulin, lipodystrophy may occur at the site of injection, but **constantly varying the site of administration** can contribute towards attenuating or preventing this type of adverse reaction. Lipodystrophy can interfere with treatment by delaying the absorption of insulin.

Earlier this year cases of lipodystrophy associated with insulin of various brands were reported to the National Pharmacovigilance System. It appeared from those reports that there might have been some of lack of information given to patients on how to avoid it and to urge them to tell a health professional about its occurrence. **Information** on how to give oneself insulin seems to be provided by health professionals at the time of the initial prescription, but as time goes by patients tend to **forget** that they should not inject themselves on the same spot every time. In addition, it seems that the **sites of administration** of insulin are not always regularly **observed** by health professionals for early signs of lipodystrophy.

On the other hand, cases were reported of switched **pen needles** used by patients for insulin administration (e.g., 5-mm instead of 8-mm needles), twisted needles or use of the same needle several times.

Constant endeavour by health professionals in contact with these patients is recommended to inform them on lipodystrophy prevention, both at the time of prescription and of dispensing repeat prescriptions, not only when initiating therapy. It is also important to regularly observe the needles and pens, as well as the administration sites. For instance, routine encounters can be used to ask patients to demonstrate how they self-administer their insulin. These occasions can also be ideal for helping patients to better watch for signs of lipodystrophy.

In order for lipodystrophy at the site of administration of insulin to be prevented as much as possible it is essential that every health professional involved in caring for these patients, the patients themselves and, if applicable, their caregivers, collaborate at the times of prescription, dispensing and administration.

Fátima Pereira de Bragança

From now on you can also access the Alerts and News at the Infarmed website

on LinkedIn

and Twitter

Online reporting
of adverse drug reactions by health professionals and patients

Portal RAM for ADR reporting.
Online forms for both
health professionals and patients.

Ergot derivatives
Restrictions of use

EMA has concluded from a safety review of products containing ergot derivatives (dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline, and dihydroergocryptine) that they should not go on being used for the treatment of circulatory conditions, memory and perception disorders, nor for migraine prevention, given that for those indications risks outweigh benefits. Indeed, it was concluded that there is an **increased risk of fibrosis and ergotism** (manifestations of prolonged excessive doses of ergotamine, such as muscle spasms and vasoconstriction in the extremities) associated with these medicines.

Products containing ergot derivatives which are **authorized only for the treatment of conditions related to blood circulation, memory and perception disorders, or migraine prevention**, are thus now **suspended** within the European Union.

The above recommendations from EMA do not apply however to medicines used for other indications (not encompassed by this review), namely treatment of Alzheimer's disease, acute treatment of migraine (not prevention), and treatment of Parkinson's disease and dementia in the elderly. Authorization and approved indications within this scope stand. In Portugal, the products with the above indications which **remain unaltered** are Striatal (**dihydroergocryptine**) and Sermion 30 (**nicergoline**).

EMA and Infarmed reiterate the following recommendations to health professionals:

- Medicinal products containing dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or dihydroergocryptine **are not to be used** for the following indications:
  - Symptomatic treatment of chronic cognitive conditions or neurosensorial disorders in the elderly (excluding Alzheimer's and other forms of dementia).
  - Adjuvant treatment of intermittent claudication in symptomatic, stage II, peripheral arterial occlusive disease.
  - Adjuvant treatment of Raynaud's disease.
  - Adjuvant treatment of decreased visual acuity and visual field disorders of vascular origin.
  - Acute retinopathy of vascular origin.
  - Migraine prophylaxis.
  - Orthostatic hypotension.
  - Symptomatic treatment of veno-lymphatic insufficiency.
- The treatment plan of patients on these medicines for the above-mentioned indications should be reviewed.

Margarida Guimarães

Interactions to keep in mind!
Patients with Acne

- Medicines which **cause or worsen acneiform eruptions** and which **antagonize antiacne agents**:
  - androgenic agents
    - testosterone
    - danazol
    - DHEA (dehydroepiandrosterone)
    - hormonal contraceptives containing progestins with androgenic effects
      - noretisterone, levonorgestrel, linestrol, dienogest, norgestrel
    - gonadoreline agonists and antagonists
    - ulipristal
    - human menopausal gonadotrophins (e.g., menotrophin)
  - corticoids, including for local dermatological use
  - antineoplastic agents such as cetuximab, methotrexate, etc.
  - immunosuppressants such as tacrolimus, sirolimus, everolimus, micophenolate
  - antiepileptic agents such as barbiturates, phenytoin, valproate
  - isotretinoin at the beginning of treatment
  - lopinavir
  - isoniazide
  - lithium
  - antithyroid agents
  - dilitiazem
  - products containing iodide
  - vitamin B12
  - etc.
- The main drug interactions of **topical antiacne agents** are to do with their **irritating** or **photosensitizing** effects.
- Undesirable effects of **retinoids** potentiated by:
  - **photosensitizing** agents in general
  - vitamin A
  - medicines which cause hyperlipaemia
  - medicines causing depressive or even suicidal ideation
- **Retinoids + "cycline" antibiotics:** risk of intracranial hypertension
- **"Cycline" antibiotics**
  - Absorption of cyclines decreased by:
    - iron, zync, calcium
    - antiacids
    - cholestyramine
    - didanosine (both in tablet and drinking solution forms)
    - strontium
    - …
  - Cyclines may **potentiate** (by increasing their bioavailability):
    - digoxin
    - methotrexate
    - ciclosporin
    - tacrolimus
  - Cyclines may decrease the bioavailability of an antimalarial agent:
    - **atovaquone**

Adapted from:
La revue Prescrire

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