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Esmya® (ulipristal acetate)
Minimization of the risk of serious liver injury

Quick Read

New measures to minimize the risk of serious hepatic adverse reactions with Esmya® have been implemented (more safety discussions concerning ulipristal in the following past issues of the Boletim: Jul-2018; Feb-2018; Oct-2017; Oct-2016; 3rdquarter-2014; 4thquarter-2013).

Ulipristal acetate is an orally active, selective synthetic modulator of the progesterone receptor, which exerts partial antagonistic effect on tissue-specific progesterone. It acts directly on myomata by reducing their size through inhibition of cell proliferation and induction of apoptosis.

The PRAC at EMA has concluded a safety review of Esmya® to assess the risk of liver toxicity following the report of three cases of serious hepatic injury culminating in transplantation.

A causal association between ulipristal and serious liver injury was considered plausible, taking into account all the available data and the opinion of various ad-hoc experts. Given the seriousness of those reactions and the fact that ulipristal's benefits vary depending on the clinical condition, PRAC concluded that the use of Esmya® should be restricted and its therapeutic indications changed as follows:

- **Contraindication** in patients with underlying **liver disorders**.
- Esmya should only be used in women who are **not eligible for surgical** treatment.
- Esmya continues to be **indicated for one course (lasting up to 3 months)** of pre-operative treatment for moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Liver function tests to be performed **before starting each treatment course**, monthly during the first 2 treatment courses, and thereafter as clinically indicated.
- Liver testing also to be performed again **2-4 weeks after stopping** treatment.
- Esmya should not be started if levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) are **more than 2 times** the upper limit of normal (ULN).
- Treatment should be stopped in patients with ALT or AST levels **more than 3 times** ULN.
- Patients should be made aware of the need to **look out for signs and symptoms** of liver injury and to stop treatment and consult with their doctor should they appear.

These measures have been disseminated through Dear Healthcare Professional Communications which are available on INFARMED"s website:

http://app7.infarmed.pt/infomed/downloadMatEduc.php?filename=Esmya/DHPC_Esmya_versao_final_26-07-2018.pdf

and

http://app7.infarmed.pt/infomed/downloadMatEduc.php?filename=Esmya/Esmya 5mg Art. 20_DHPC_PT.PDF

Sílvia Duarte

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Lenalidomide
Risk of Progressive Multifocal Leucoencephalopathy (PML)

Quick Read

Cases have been reported of progressive multifocal leucoencephalopathy (PML) in patients receiving lenalidomide, which occurred from several months to several years after treatment had been started, or with previous treatment with other immunosuppressive chemotherapeutic agents (more safety discussions concerning lenalidomide in the following past issues of the Boletim: Nov-2016; 4th quarter-2011).

Lenalidomide is an immunomodulator with the following therapeutic indications:

- *Multiple myeloma – As monotherapy, for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. As combination therapy – for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. In combination with dexamethasone – for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.*
- *Myelodysplastic syndromes – As monotherapy, for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.*
- *Mantle cell lymphoma – As monotherapy, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.*

PML is a rare and serious brain condition caused by JC (John Cunningham) virus reactivation. This virus is frequently found in the general population and causes PML only when the immune system is weakened.

In November 2017, during routine pharmacovigilance activities, EMA detected various cases of lenalidomide-associated PML.

Taking into account the cases in the European adverse drug reaction report database Eudravigilance and in the literature[1-6]*, the PRAC agreed in May 2018 that the Marketing Authorisation Holder of Revlimid® submit the following change to the* **SPC** *texts (section 4.4):*

4.4. Special warnings and precautions for use

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued.

Márcia Silva

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Prevention of Medication Errors
Tall Man Lettering

The most effective method to reduce look-alike medication errors consists of the insertion of capital letters (TML – Tall Man Lettering). A global implementation strategy is needed.

Medication errors relating to packaging or labelling are a significant issue in healthcare provision. Whenever associated with an ADR those errors should be reported as an additional way to improve the safety of medicinal products. Errors associated with **look-alike sound-alike medicines (LASA)**, whose spelling and/or phonetics and/or visual aspect is similar to other product(s), are among the most widely recognized and frequent medication errors. LASA medicines could be associated with around 15-25% of all medication errors.[1]

Several methods to minimize the risk of wrongly switching products have been used, such as writing their names partly with capital letters (Tall Man Lettering – TML).

Examples of Tall Man Lettering

hydrALAzine versus hydrOXIzine
aDRENALine versus aTROPine

Colour coding is another method, which ascribes a different and exclusive colour to each therapeutic class.

In Portugal, the General Health Directorate has issued a norm (nr. 020/2014, updated on 14-12-2015) with national recommendations for the prevention of medication errors associated with LASA products in healthcare organizations, including a detailed list of LASA medicines existing in this country and TML method rules.[2]

Recently Lamerné-Beld et al[3] reviewed the literature for look-alike product related medication error prevention methods, including TML and colour coding. Of the 16 studies that were evaluated, eleven assessed the efficacy of TML while two looked at colour coding.

Although those studies were undertaken in a context of social experimentation rather than in a real life environment, thus excluding well-known medication error triggering phenomena such as stress or high workload, considerable evidence was obtained that confirmed **TML as consistently effective** in reducing medication errors.

Colour coding showed **inconsistent effectiveness**, which could however, also be due to sampling limitations. In any case, this method has been put into question, both on account of its being restricted to colours recommended by international norms (such as ISO 26825:2008) which do not allow for two LA medicines of the same therapeutic class to be told apart, and on account of high world prevalence of colour blindness (estimated to be around 8% for males and 0.4% for females)[4]. It is nevertheless the most commonly used method in anaesthesiology in the United Kingdom, Australia and New Zealand.[3]

All things considered and perhaps even more relevant, the Lamerné-Beld *et al*[3] study also highlighted the lack of an integrated strategy for the implementation of TML in the whole of the health organization chain. LA medicines to be included need to be clearly indicated and every stakeholder involved should be adequately informed about the objectives in mind. One other study underscores significant differences in the results depending on whether the participants knew that the study was aiming to improve medication error prevention.[5]

As in many other health system issues, identifying the problem and the way to solve it is not the stumbling block, rather how to implement a medication error reduction strategy that is well structured and consistent.

Miguel Antunes

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Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Mycophenolic acid or Mycophenolate Mofetil Ácido Micofenólico Accord Ácido Micofenólico Teva CellCept Micofenolato de Mofetil Accord Micofenolato de Mofetil Aristo Mycophenolate Mofetil Teva Myfenax Myfortic	**Physicians:** directors of every hospital nephrology, urology, gastroenterology, cardiology, surgery, cardiothoracic surgery, general surgery, haematology, rheumatology, internal medicine, pneumology, neurology, and gynaecology and obstetrics departments; clinical directors of all hospitals. **Pharmacists:** directors of pharmaceutical services of all hospitals.	Guide for healthcare professionals on risk of teratogenicity Questionnaire for pregnancy follow-up
	Patients: to be handed out by doctors	Information on risks for the unborn baby 06/09/2018

Compiled by Fernanda Marques

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