# ARMACO boletim de SEPTEMBER 2019 **IGILÂNCIA**

## Valproate and valproic acid: Reinforcement of pregnancy exposure prevention measures

Valproate / valproic acid is indicated for the treatment of epilepsy or bipolar disorder and, in the case of valproate semisodium, for the prophylaxis of migraine attacks.

In May 2018 new measures were adopted to prevent in utero exposure to medicinal products containing valproate or related substances, on account of a risk of foetal malformations and developmental problems in children after birth.

At a national level, those measures were implemented through a set of actions:

- New contraindications and warnings for use during pregnancy in the Summary of the Product's Characteristics and Patient Information Leaflet, namely:
  - contraindication in the prophylaxis of migraine attacks and in bipolar disorder;
  - contraindication in the treatment of epilepsy, unless no therapeutic alternative is available;
- Pregnancy Prevention Programme (PPP): use in women of childbearing age (for any indication) only when conditions are met.

#### Educational materials (as part of the PPP) to ensure that prescribers and patients are fully aware of risks and the need to avoid pregnancies:

- Prescriber's quide
- Patient information guide
- Annual risk acknowledgment form\*
- "Contraception and pregnancy" patient card\* to be handed out on dispensation of the product, allowing pharmacists to reinforce the PPP to patients and to remind them of the programme's key messages.
- Pregnancy risk alert on the product's packaging.

These measures have been communicated through a letter to physicians, namely neurologists, psychiatrists, GPs/ family doctors, paediatricians and obstetricians/gynaecologists. They were also disseminated to pharmacists and other family planning centre healthcare professionals.

In order to prevent additional cases of exposure of pregnant women to valproate it is essential that all healthcare professionals and patients follow the above risk minimisation measures.

#### Ana Isabel Severiano

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\* Not applicable to injectable formulations which are indicated for short-term use only.

Alerts and News at the Infarmed websit **INDEX CARD** Director: Fátima Canedo Editor: Rui Pombal ntributors: Ana Severiano, Ana Sofia Martins, Cristina Mousinho, Elsa de Fátima Costa, Fátima Bragança, Fátima Hergy, Magda Pedro, Márcia Silva, Miguel Antunes, Sílvia Duarte Publishing Assistant: Inocência Pinto Advisory Board: Conselho Diretivo do INFARMED, I.P. 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: farmacovigilancia@infarmed.pt Design and production: Letras & Sinais, Comunicação e Imagem, Lda ISSN: 0873-7118 REPÚBLICA Infarmed PORTUGUESA

### **ADRs in the literature** Risk of medicines in pregnancy: knowledge transfer and ethical consequences\*

The prevalence of **major congenital abnormalities** is estimated to be 1.7 per 100 live births. **Two to five per cent can be ascribed to medicines**, that is 34 to 85 cases for every 100,000 live births.

The use of medicines during pregnancy is essential and beneficial in certain conditions and aims to protect or improve both the mother's and the child's health. Most pregnant women take some kind of medicine that has either been prescribed to them or used as self-medication. Evidence on the safety of medicines in pregnancy is usually scarce since pregnant women are excluded from clinical trials and studies in animals cannot reliably predict risk in humans. Of **new medicines administered to pregnant women, 73% lack data on human gestation** and 2% only have adequate clinical information to determine their safety.

In some countries there are teratological information services (usually by phone) that provide individualised advice on medicines and other risks. Nevertheless, the main source of information for physicians revolves around pregnancy risk classifications of medicines. Several simplified classifications have been developed, for example by the FDA in the USA. However, the need for complex interpretation of data of limited evidence and the push for overly simple categories, can explain why major **classifications**, though similar in appearance, **do not coincide in 29% of categories**. Risk classifications have indeed become too simple and categorical. This has led to imprecise risk perceptions modulating decisions such as therapy or pregnancy discontinuation.

There is a problem in knowledge transfer from research to physicians and to pregnant women. Important baseline messages such as the following are not often conveyed:

- Risk in pregnancy does not automatically mean there will be any teratogenic effects.
- The existence of risk, even when serious, does not imply in and of itself a high probability of occurrence.
- Risk nature and probability usually vary with gestational age.

For all the above reasons, **traditional simplified pregnancy risk classifications are on their way out**. In 2015, for instance, the FDA removed their own A/B/C/D/X classification from the medicinal products' information and replaced it with more specific statements on the effects of the products on pregnancy.

There is therefore renewed interest in pregnancy risk information services for healthcare professionals. For adequate weighing of the safety of use of medicines in pregnancy, the **data provided** by those services **needs to include**:

- Type of harm, its nature, and whether it is acute or chronic, reversible or irreversible.
- The probability of occurring harm and of it being serious.
- The period of pregnancy during which actual risk exists: prior to gestation, in the first, second or third trimester, in the postpartum period.
- The actual evidence supporting risk definition: studies in humans, studies in animals with therapeutic equivalent doses, studies in animals with macrodoses, biological plausibility.

Cristina Mousinho

# Communications to Healthcare Professionals published on the Infarmed <u>website</u>

#### -Click on the links.

INN Medicinal product	Target	Comunication Online publication date
<b>Blinatumomab</b> Blincyto	<b>Physicians:</b> haematologists and paediatricians at centres treating paediatric patients with ALL <b>Nurses:</b> at day care hospitals where this product is administered	Clarification on pre-medication with dexamethasone in paediatric patients 04-09-2019
<b>Fingolimod</b> Gilenya	<b>Physicians:</b> neurologists, gynaecologists, obstetricians and child neurologists <b>Pharmacists:</b> hospital	New contraindication in pregnant women and in childbearing-age women who are not using effective contraception 04-09-2019
<b>Ingenol mebutate</b> Picato	Physicians: dermatology and general/family medicine Pharmacists: community	Precaution of use in patients with a history of skin cancer 25-09-2019
Medicinal products for parenteral nutrition Aminoplasmal Paed Clinoleic 20% Intralipid 10%, 20% Lipofundina MCT/LCT 10%, 20% Lipoplus Numeta G13%E, G16%E, G19%E Pediaven G15, G20, G25, NN1, NN2 Primene 10% Smofilipid Vaminolact	Physicians: paediatricians Nurses Dieticians	Need to protect from light to reduce the risk of serious adverse reactions in premature newborns 02-09-2019

Compiled by Magda Pedro

### Educational Materials published in the <u>Infomed</u> product information webpage <sup>Click on the links.</sup>

INN Medicinal product	Target	Comunication Online publication date
Adalimumab	Patients	Safety card
Amgevita	Paediatric patients	Paediatric patient safety card 05-09-2019
Blinatumomab	<b>Physicians:</b> prescribing haematologists and paediatricians, at centres treating ALL	Educational brochure
Blincyto		04-09-2019
Crizotinib	Patients	Guide: safety information
Xalkori		16-09-2019
Darbepoetin alfa	<b>Physicians:</b> haematology, oncology and nephrology department directors at hospitals and clinics procuring this medicine	Checklist for training in
Aranesp — Surecclick pre-filled pen		autoadministration Reusable demonstration device reactivation instructions
	Patients	Instructions for use poster (for reduced vision patients/caregivers)
		20-09-2019

# **Educational Materials published in the <u>Infomed</u> product information webpage** Click on the links.

Click on the links.		
INN Medicinal product	Target	<b>Comunication</b> Online publication date
Emtricitabine + Tenofovir disoproxil Emtricitabina + Tenofovir disoproxil Mylan Tenofovir disoproxil	<b>Physicians:</b> infectious diseases, internal medicine, gastroenterology and paediatrics	<u>Recommendations for use in treatment</u> of adolescents with chronic hepatitis <u>B</u> and/or HIV-1 infection
Tenofovir disoproxil Mylan		10-09-2019
<b>Etanercept</b> Enbrel – MYCLIC pre-filled pen	<b>Physicians:</b> rheumatologists, internists and dermatologists <b>Nurses:</b> at clinics treating rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis, non-radiographic axial spondyloarthritis, plaque paediatric psoriasis; home training programmes <b>Pharmacists:</b> hospital (directors or pharmacists in charge)	<u>Guide on administration technique</u>
	Patients	Guide: use of pre-filled pen
		Instruction video: use of pre-filled pen 27-09-2019
<b>Infliximab</b> Remsima	<b>Physicians:</b> gastroenterology, rheumatology, dermatology and internal medicine specialists who treat autoimmune diseases	Important safety information Patient screening form
	Nurses: at day care hospitals Pharmacists: at hospitals handling biologicals	19-09-2019
<b>Mecasermin</b> Increlex	<b>Physicians:</b> child endocrinologists and paediatricians undertaking paediatric endocrinology clinics	Safety information
	Patients	Safety information Instructions for use 19-09-2019
<b>Prasugrel</b> Prasugrel Pentafarma	Physicians: cardiology, internal and general/family medicine	Important safety information 20-09-2019
<b>Rituximab</b> Mabthera	Physicians: rheumatology and internal medicine	Important safety information for non- oncological indications
ויימטעורכומ	<b>Patients:</b> with rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis or pemphigus vulgaris	Brochure with safety information for non- oncological indicatons 05-09-2019
Sulfate, magnesium + Sulfate, potassium + Sulfate, sodium Eziclen	Physicians: gastroenterology	Leaflet
	Patients	Instruction and record form 26-09-2019
Testosterone	Physicians: urology and endocrinology	Prescriber's guide (injectables)
Nebido		19-09-2019