# **NEW RISK MINIMIZATION MEASURES FOR VALPROATE**

Manuel Toledo, MD PhD

Epilepsy Unit. Vall d'Hebron University Hospital

### Introduction

Valproate (VPA) is used for treating epilepsy and depending on the countries, is also indicated in bipolar disorder.

The first approval for valproate and related substances was obtained in France on 23 January 1967. Valproate and related substances are approved and marketed in more than 120 countries. In the European Union, Valproate and related substances are registered via national procedures in 28 countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden & United Kingdom).

In October 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA), concluded a review of all available data on the safety and efficacy of Valproate and related substances in women of childbearing potential (WCBP) and pregnant women, due to the risk of major congenital malformations and neurodevelopmental disorders in babies and/or children exposed to Valproate in utero. Restrictions on the use of Valproate containing substances were applied to the label, and risk minimization measures such as educational materials for physicians and patients were implemented.

In March 2017, due to the observed insufficient effectiveness of these risk minimization measures (RMMs), the PRAC initiated a new review. As a result in May 2018, the European Commission endorsed the new measures recommended by the PRAC strengthening previous restrictions on use of valproate along with the set-up of a pregnancy prevention program (PPP).

The strengthened measures include contra-indications of Valproate in the following situations:

#### Treatment of epilepsy

#### **Treatment of bipolar disorder**

- in pregnancy unless there is no suitable alternative treatment.
- in pregnancy.
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled.
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled.

Amongst the new prescribing conditions, it is also highlighted that WOCBP should have a negative pregnancy test at treatment initiation and during treatment as needed and must have an effective contraception during their treatment with Valproate.

### **Key Points / PRAC recommendation**

The purpose of the revised measures is to avoid any unnecessary exposure to Valproate during pregnancy and to further increase :

- The effectiveness of the communication to Health Care Professionals (HCPs) on the prescribing conditions.
- The understanding of the patients and their awareness on the educational materials.

#### Revision of the labeling

Contra-indication section reviewed to clarify the conditions of Valproate prescription in WCBP.

#### Outer box warnings / pictogram

**QR code** on patient leaflet to link with educational materials according to national health authorities decision.

### This medicine can seriously harm an unborn baby.

Always use effective contraception during treatment with "Invented name". If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently. Do not stop "invented name" unless your doctor tells you to.

WARNING FOR WOMEN AND GIRLS

#### Implementation of a Pregnancy Prevention Program (PPP),

which includes measures:

- To ensure HCPs are aware of the risks and recommendations on the use of Valproate during pregnancy.
- To ensure patients are informed by their HCPs and understand the information on the risks.
- And counselling on the need for effective contraception, pregnancy planning, annual visit with a specialist.

Creation of a web-based platform where educational materials are posted, is considered to be the most useful communication tool to further contribute to the effectiveness of the PPP.

## The Pregnancy Prevention Program (PPP)

**Educational Materials** 

What is A PPP is a set of interventions aimed at minimizing pregnancy exposure during treatment a PPP ? with a medicinal product with known or potential teratogenic effects

- Educational tools to HCPs and patients with information and recommendations on the teratogenic risk and actions to minimize these risks.
- Controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the HCP before initiating and/or dispensing the prescription.

#### **Objectives**

- To ensure HCPs are aware of the recommendations and / or contra-indication on use of the medicinal product during pregnancy.
- To ensure patients are informed and understand the information on the risks from their HCPs.

#### The Pregnancy Prevention Program in patients treated with Valproate

- The educational materials have been updated in line with the revised labeling to reinforce the right use of Valproate in WCBP and avoid any unnecessary exposure to Valproate during pregnancy.
- The educational materials are the following:
  - $\rightarrow$  A HCP Guide  $\rightarrow$  A Patient Card
- → A Patient Guide
- → An Annual Risk Acknowledgement Form

**Counselling** in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

The educational tools are complementary to the routine Risk Minimization Measures (SPC, package leaflet, packaging visual warnings, pictogram).

In line with the educational materials, a Direct Healthcare Professional Communication (DHPC) have been distributed to raise awareness of the new recommendations, with the key elements of the product information and the Pregnancy Prevention Program.

		ks of Valproate in f nancy prevention			what you show	uld know communic	ate - Contraception a	IMPROVE the RM	
INCREASE PATIENTS' AWARENESS & UNDERSTANDING THE RISKS OF USING VALPROATE						ON THE PREGNANCY PREVENTION PROGRAMME REDUCE THE NUMBER OF EXPOSED PROGRAMME INCREASE PATIENTS' AWARENESS & UNDERSTANDING THE RISKS OF US			
EXECUTIVE SUMMARY	ROLE OF THE HCPS	PRESCRIBING VALPROATE	TREATMENT OF FEMALE PATIENTS	SWITCH AND DISCONTINUATION	Monteside addre provinside di respectatione and a descera Expected de Malacemente y Produces Teachers (partice Expected) GUÍA DE LA PACIENTE	KEY INFORMATION	CONTRACEPTION	RING PREGNANCY RISKS	WHAT DOES IT MEAN FOR ME
MAKE SURE PATIEN		ERSTAND THE RISK AND A			VALPROATO ( * DEPAKINE*/ * DEPAKINE CRONO*): MEDIDAS QUE DEBE ADOPTAR PARA EVITAR EL EMBARAZO DURANTE EL TRATAMIENTO		PATIENT ARE AWARE AND UND TO REDUCE THE NUMBER		
One page shortened information	Reinforce the role of each stakeholer to clarify expectations	Clarify the prescribing conditions in line with new label & PPP	Different situations, different recommendations	Recommendations specific to the medical condition	Sur Motion Interactive resources associated and that conservations in the second associated and the second associated associate	One page short summary of key information	Importance of effective counselling and compliance	Awareness and understanding	Recommendation specific to their situation
ummary of instructions, ecommendations and uidances	Specialist General Practioner Gynecologist / Obstetrician / Midwife Pharmacist	Contraindication: Different wording for pregnancy and WOCBP - Bipolar disorder - Epilepsy	Female patient: First prescription WOCBP: not planning pregnancy WOCBP: planning pregnancy	Bipolar disorder Epilepsy	In the sense of the selection of the sense of the selection of the selection. See Selection Sele	Key safety messa to keep in mind	ages Why do I need to use contraception What type of contraception should I use	Birth effects Neurodevelopmental disorders	Starting treatment with Valproate Taking Valproate: not planning a family Taking Valproate: planning a family
		Conditions of the Pregnancy Prevention Program (PPP)	WOCBP: unplanned pregnancy					Tarieta de inform	Taking Valproate: becoming pregnant
Spe <ul> <li>Annual treatm</li> </ul>		Pregnancy Prevention	WOCBP: unplanned pregnancy	Pa	ENT CARD - Key mo	te:	eep in mind	Depakine/     Depakine/     Depakine/     Anticoncepción y el     Valproato es un medicamer     Valproato puede causar gra     Utilice siempre un método     todo el tiempo que esté en     Recuerde visitar a su especie	becoming pregnant nación para la paciente so Depakine Crono (valproat nbarazo - Lo que debe saber ito eficaz para la epilepsia y el trastorno bipoli ves daños al feto si se toma durante el embara a naticonceptivo eficaz sin interrumpirlo dur tratamiento con valproato. alista al menos una vez al año.
Spe Annual treatm Risk information Contraception prevention cond Switching and	ecialist n n and pregnancy	Pregnancy Prevention Program (PPP) Gynecologist & mid • Risk information • Contraception counselling, prevention	WOCBP: unplanned pregnancy / obstetrician lwife n GUIA PARA ( GUIA PARA ( Riesgos (▼Depaki) durante al	Provension de meger autorisats per la Astrona Especies mentres y producers anotario (AEMPO) prios per la PROFESIONALES SANITARIOS e del uso de valproato ne/ v Depakine Cropo)	atient Card for Valproat ontraception & Pregnat <b>/hat you must KNOV</b> Valproate is an effectiv	te: ncy <b>N</b> * ve medicine	Patient Card for Valproa Contraception & Pregna What you must DO *	Depakine/     Depakine/     Depakine/     Depakine/     Depakine/     Depakine/     Subject of the second of	becoming pregnant becoming preg
Spe Annual treatm Risk information Contraception prevention con Switching and Patient Guide	ecialist nent n and pregnancy unselling	Pregnancy Prevention Program (PPP) Gynecologist & mid • Risk information • Contraception counselling, p	WOCBP: unplanned pregnancy / obstetrician lwife n GUIA PARA ( GUIA PARA ( Riesgos (▼Depaki) durante al	Provense an recept a definition of the Advected Execution Provense of the Advected Execution PROFESIONALES SANITARIOS a del uso de valproato ne/ ▼ Depakine Crono) embarazo y Programa nción de Embarazos	atient Card for Valproat ontraception & Pregnat <b>/hat you must KNOV</b> Valproate is an effective for epilepsy and bipola Valproate can serious unborn child when tak	te: ncy <b>N</b> * ve medicine ar disorder. ly harm an	Patient Card for Valproa Contraception & Pregna What you must DO * • Read the package lea • Never stop taking val to as your condition n	Anticoncepción y en Valproato es un medicamen Valproato puede causa gra Valproato puede causa gra Valproato puede causa gra Valproato puede causa gra Recuerde visitar a su especi Recuerde visitar a su especi Valterega esta tarjeta en un kagar segurite pudera uside tener. Puede consultar la forma Valterega esta tarjeta en un kagar segurite pudera uside tener. Puede consultar la forma Nationación sobre prevención Medicamentos y Pro Afflet carefully before proate unless your do nay become worse.	becoming pregnant becoming pregnant becoming pregnant becoming pregnant becoming pregnant become a la paciente so bepakine Crono (valproat become a la paciente so become a la paciente a la paciente so become a la paciente
Spe Annual treatm Risk information Contraception prevention con Switching and Patient Guide Annual Risk A Form General Risk information	ecialist nent n and pregnancy unselling I discontinuation Accknowledgment Practitioner	Pregnancy Prevention Program (PPP) Gynecologist & mid • Risk information • Contraception counselling, p prevention • Refer to specia in case	WOCBP: unplanned pregnancy / obstetrician wife n regnancy alist nacist	Reveaued and magnetized and and and and and and and and and an	atient Card for Valproat ontraception & Pregnat /hat you must KNOV Valproate is an effectiv for epilepsy and bipola Valproate can serious	te: ncy N* ve medicine ar disorder. ly harm an ten during contraception uring entire ate.	Patient Card for Valproa Contraception & Pregna What you must DO * • Read the package lea • Never stop taking val	<ul> <li>✓ Depakine/ ✓</li> <li>Anticoncepción y el <ul> <li>Valproato es un medicamen <li>Valproato puede causar gra <li>Utilice siempre un método do el tiempo que esté en <li>Recuerde visitar a su especi restrictamente está sujita y mujere Mantenga esta talgita en un lugar segur vister nédicamente está sujita y segur vister nédicamente está sujita y segur vister nédicamente está sujeta a seguina vister nédicamente setá sujeta a seguina vister nédicamentos y Prot Afflet carefully before proate unless your de nay become worse. out having a baby, de ception before you tal regnant: schedule ar un doctor.         </li> </li></li></li></ul></li></ul>	becoming pregnant hación para la paciente so Depakine Crono (valproat mbarazo - Lo que debe sabel to eficaz para la epilepsia y el trastorno bipo ves daños al feto si se toma durante el emba o anticonceptivo eficaz sin interrumpirlo du tratamiento con valproato. alista al menos una vez al año. se ue usen valproato y que podrían que darse emba para que siem grimportante comunicar los efectos ad dehacerlo en el prospecto del medicamento. de riesgos autorizada por la Agencia Espa paductos Sanitarios (AEMPS) junio 2018 USE. O cotor tells you o not stop using alked to your docta n urgent

Part B: To be completed and signed \*\* by the patient/ caregiver / legal representative

**Objective** Ensure discussion and understanding of the risks related to the use of Valproate during pregnancy.

#### Key topics addressed in the form

- Risk information.
- Use during pregnancy, conditions of the pregnancy prevention program.
- Regular (at least annually) treatment review.
- Negative pregnancy test at treatment initiation.
- Effective contraception.
- Consultation when planning pregnancy.
- Urgent consultation in case of pregnancy.

#### Instructions

- To complete both Parts A and B, tick all boxes, and sign: "signing subject to national implementation".
- To be kept by patient / recorded by the specialist (electronic version).

\* Pending National Competent Authority approval - May be adapted upon national healthcare organization - \*\* Sign off depends on national decision



### **KEY MESSAGES of the EDUCATIONAL MATERIALS - Contraception and pregnancy prevention program**

- Contraindication in epilepsy and bipolar disorder
  - $\rightarrow$  with wording in bipolar disorder and epilepsy in pregnancy
  - → In WOCa specific BP unless the conditions of the PPP are met
- Pregnancy test before initiation of treatment and as needed thereafter.
- Counselling on need for effective contraception.
- Counselling on pregnancy, Planning pregnancy.
- Switch and discontinuation.
- Inform and ensure the understanding of the Patient through a Patient Guide, a Patient Card, an Annual Risk Acknowledgement Form.