

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

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

Treatment of bipolar disorder

- in pregnancy.
- 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.



WARNING FOR WOMEN AND GIRLS

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.

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)

What is a PPP ?

A PPP is a set of interventions aimed at minimizing pregnancy exposure during treatment 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.
- Counselling** in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

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

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:
 - A HCP Guide
 - A Patient Card
 - A Patient Guide
 - An Annual Risk Acknowledgement Form

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.

Educational Materials

HCP GUIDE - Information on risks of Valproate in female patients and pregnant women - Contraception and pregnancy prevention

INCREASE PATIENTS' AWARENESS & UNDERSTANDING THE RISKS OF USING VALPROATE DURING PREGNANCY				
EXECUTIVE SUMMARY	ROLE OF THE HCPS	PRESCRIBING VALPROATE	TREATMENT OF FEMALE PATIENTS	SWITCH AND DISCONTINUATION
MAKE SURE PATIENT ARE AWARE AND UNDERSTAND THE RISK AND ADVICES IN ORDER TO REDUCE THE NUMBER OF EXPOSED PREGNANCIES				
One page shortened information	Reinforce the role of each stakeholder to clarify expectations	Clarify the prescribing conditions in line with new label & PPP	Different situations, different recommendations	Recommendations specific to the medical condition
Summary of instructions, recommendations and guidances	Specialist General Practitioner Gynecologist / Obstetrician / Midwife Pharmacist	Contraindication: Different wording for pregnancy and WOCBP - Bipolar disorder - Epilepsy Conditions of the Pregnancy Prevention Program (PPP)	Female patient: First prescription WOCBP: not planning pregnancy WOCBP: planning pregnancy WOCBP: unplanned pregnancy	Bipolar disorder Epilepsy

PATIENTS GUIDE - Valproate - Contraception and pregnancy: what you should know

COMMUNICATE - INFORM - EDUCATE ON THE PREGNANCY PREVENTION PROGRAMME		IMPROVE THE RMMs EFFECTIVENESS REDUCE THE NUMBER OF EXPOSED PREGNANCIES	
INCREASE PATIENTS' AWARENESS & UNDERSTANDING THE RISKS OF USING VALPROATE DURING PREGNANCY			
KEY INFORMATION	CONTRACEPTION	RISKS	WHAT DOES IT MEAN FOR ME
MAKE SURE PATIENT ARE AWARE AND UNDERSTAND THE RISK AND ADVICES IN ORDER TO REDUCE THE NUMBER OF EXPOSED PREGNANCIES			
One page short summary of key information	Importance of effective counselling and compliance	Awareness and understanding	Recommendations specific to their situation
Key safety messages to keep in mind	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 Taking Valproate: becoming pregnant

ROLES OF DIFFERENT HCPS

Specialist	Gynecologist / obstetrician & midwife
<ul style="list-style-type: none">Annual treatmentRisk informationContraception and pregnancy prevention counsellingSwitching and discontinuationPatient GuideAnnual Risk Acknowledgment Form	<ul style="list-style-type: none">Risk informationContraception counselling, pregnancy preventionRefer to specialist in case of pregnancy
General Practitioner	Pharmacist
<ul style="list-style-type: none">Risk informationTreatment renewalRefer patient to specialist for switching and discontinuationContraception counsellingPatient Guide	<ul style="list-style-type: none">Patient CardReinforce the safety messagesCounselling on contraception, pregnancyUnpacking

PATIENT CARD - Key messages to keep in mind

Patient Card for Valproate: Contraception & Pregnancy

What you must KNOW*

- Valproate is an effective medicine for epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn child when taken during pregnancy.
- Always use effective contraception without interruption during entire treatment with Valproate.
- Remember to visit your specialist at least annually.

Patient Card for Valproate: Contraception & Pregnancy

What you must DO *

- Read the package leaflet carefully before use.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.
- If you are thinking about having a baby, do not stop using Valproate and contraception before you talked to your doctor.
- If you think you are pregnant: schedule an urgent appointment with your doctor.
- Ask your doctor to give you the patient guide.

* This applies to all girls and women using Valproate and who could become pregnant. Keep this card safe so you always know what to do.

ANNUAL RISK ACKNOWLEDGMENT FORM *

Part A: To be completed and signed ** by the specialist
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
 - 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.