IMPORTANT

MEDICINE SAFETY INFORMATION

03 December 2018

Valproate-containing medicines: High risk of congenital abnormalities and developmental disorders

Dear Healthcare Professional

Aspen Pharmacare, Brimpharm SA (Pty) Ltd, Adcock Ingram Limited, Sandoz SA (Pty) Ltd and Takeda (Pty) Ltd in collaboration with the South African Health Products Regulatory Authority (SAHPRA) would like to inform you of the risks related to the use of valproate containing medicines (sodium valproate, valproic acid) during pregnancy and lactation. A similar letter was communicated by Sanofi Aventis (Pty) Ltd dated 9 December 2015.

Background information on the safety concern

Risk of abnormal pregnancy outcomes

Valproate is associated with a risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. A threshold dose below which no risk exists cannot be established based on available data. The following findings have been reported in the children exposed to valproate in utero:

- The risk of congenital malformations at birth (such as neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems)). The risk is estimated to be 10,73 % in children exposed to valproate in utero compared to 2 % to 3% of children in the general population. [1]
- Studies in pre-school children show developmental problems in up to 30 % to 40 % of children exposed to valproate *in utero.* These developmental delays include talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. [1]
- Intelligence quotient (IQ) measured in school aged children (age 6 years old) with a history of valproate exposure *in utero* was on average 7 to 10 points lower than in children exposed to other antiepileptic medicines. The risk of intellectual impairment may be independent from maternal IQ.[2,3]
- Available data show that children exposed to valproate *in utero* are at an increased risk of autism spectrum disorder (approximately 3 times higher than the general population) and childhood autism (approximately 5 times higher than the general population).[1,3]
- Limited data suggests that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).[1,3]

Recommendations

Due to this data, Aspen Pharmacare, Brimpharm SA (Pty) Ltd, Adcock Ingram Limited, Sandoz SA (Pty) Ltd and Takeda (Pty) Ltd recommend the following:

- Valproate should not be used in women of childbearing potential unless other treatments are ineffective or not tolerated. [1]
- Valproate treatment must be initiated and supervised by a doctor experienced in managing epilepsy or bipolar disorder. [1]
- In women of childbearing potential, pregnancy testing should be performed before initiation of valproate.[2]
- Regularly review the need for treatment and re-assess the balance of the benefits and risks for female patients taking valproate and for girls reaching puberty.[1]
- If a woman treated with valproate plans a pregnancy or becomes pregnant, the valproate should be stopped and be replaced with medicines that are less harmful in pregnancy. [1]
- If no alternative treatment can be prescribed, women of childbearing potential must use effective contraception during treatment with valproate. [1]
- If valproate treatment has to be continued during pregnancy:
    - The lowest effective dose should be used and the daily dose should be divided into several smaller doses to be taken throughout the day. [1]
- Female patients should be fully informed of and should understand:
    - The risks associated with valproate during pregnancy;
    - The need to use effective contraception;
    - The need for regular review of treatment;
    - The need to rapidly consult her prescribing doctor if she is planning a pregnancy or becomes pregnant. [1]

Aspen Pharmacare, Brimpharm SA (Pty) Ltd, Adcock Ingram Limited, Sandoz SA (Pty) Ltd and Takeda (Pty) Ltd are in the process of:

- Updating the Professional Information and Patient Information Leaflets of valproate containing medicines to reflect the relevant safety information.
- Developing a Risk Management Plan, risk minimisation measures and educational materials for Health Care Professionals and patients to inform them of the relevant safety issues and how it should be implemented and managed.

Healthcare providers should report all suspected adverse events associated with the use of valproate products to:

Company	**Contact Details**
SAHPRA Pretoria Office	**Tel**: 012 395 9133 **Fax:** 086 620 7253 **E-mail:** adr@health.gov.za
National Adverse Event Monitoring Centre (NADEMC)	**Tel:** 021 447 1618 **Fax:** 021 448 6181

OR

Product	**Company**	**Registration Number**	**Contact Details**
NAVALPRO 400 mg/4 ml	Aspen Pharmacare	A40/2.5/0342	**Tel**: 0800 118 088, **Fax:** 011 239 6306, **E-mail:** drugsafety@aspenpharma.com
NAVALPRO CR 200 **NAVALPRO CR 300** **NAVALPRO CR 500** **EPROLEP CR 200** **EPROLEP CR 300** **EPROLEP CR 500**	Brimpharm SA (Pty) Ltd	45/2.5/0411 45/2.5/0091 45/2.5/0092 45/2.5/0412 45/2.5/0093 45/2.5/0094	**Tel:** 0800 118 088 **Fax:** 011 239 6306 **Email**: drugsafety@aspenpharma.com
Valeptic CR 300 **Valeptic CR 500**	Adcock Ingram Limited	44/2.5/0069 44/2.5/0070	**Tel:** 011 635 0134 **Fax:** 086 553 0128 **Email:** adcock.aereports@adcock.com
SANDOZ SODIUM VALPROATE 300 CR **SANDOZ SODIUM VALPROATE 500 CR** **CEREPIV 300 CR** **CEREPIV 500 CR**	Sandoz SA (Pty) Ltd.	43/2.5/0861 43/2.5/0862 43/2.5/0865 43/2.5/0866	**Tel**: +27 11 347 6600 **Fax**: +27 11 929 2262 **E-mail address:** patientsafety.sacg@novartis.com
CONVULEX® SYRUP **CONVULEX® 150** **CONVULEX® 300** **CONVULEX® 500**	Takeda (Pty) Ltd	W/2.5/390 R/2.5/218 R/2.5/219 W/2.5/20	**Tel:** 011 514 3000 **Fax:** 011 514 3007 **E-mail:** DSO-ZA@takeda.com

Yours sincerely,

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References

1. European Medicines Agency. Valproate used by women and girls – Information about the risks of taking valproate medicines during pregnancy. Last updated 2 August 2018. Available [online] at: https://www.gov.uk/guidance/valproate-use-by-women-and-girls
2. MHRA approved Guide for Healthcare Professionals. Information on the risks of Valproate use in girls (of any age), women of childbearing potential and pregnant women. Published May 2018.
3. DHPL: Important medicine safety information: Medicines containing valproate and valproate derivatives: Epilim range – CR 200; CR 300; CR 500; 100 Crushable; Liquid Sugar-Free; Intravenous; Epilizine range – CR 200; CR 300; CR 500; Intravenous 400 – high risk of congenital abnormities and developmental disorders. Dated 09 December 2015.