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In this Edition

Valproate-containing medicines:
Recommendation to further restrict the use of valproate in women and girls

A recent Europe-wide review of valproate-containing medicines* has recommended strengthening of restrictions for their use and further characterising the risk of birth defects and developmental disorders in the product information. It is now recommended that valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. There are already detailed warnings contained in product information for patients and prescribers on the potential for birth defects and developmental disorders in children born to women taking valproate during pregnancy, which will now be strengthened further.

Healthcare Professionals should be aware that:

- **Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).**
- **Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.**
- **Prescribers should carefully weigh the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.**
- **Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.**
- **All female patients should be informed of and understand:**
  - **the risks associated with valproate during pregnancy;**
  - **the need to use effective contraception;**
  - **the need for regular review and treatment;**
  - **the need to rapidly consult if a woman is planning a pregnancy or becomes pregnant.**

The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed all the available data from pre-clinical studies, pharmacoepidemiological studies, published literature, and spontaneous reports and sought the views of Healthcare Professionals and patient experts on the awareness, understanding and communication of the risks associated with valproate in-utero exposure. These contributions fed directly into the review process.

Further details of the EU review are available from the HPRA website.

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Advice to Healthcare Professionals

Risk of abnormal pregnancy outcomes

- The risk of congenital malformations is approximately 10% while studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems[1,2,3,4,5].
- Intelligence quotient (IQ) measured in a study of 6 year old children with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics[6].
- Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population[7].
- Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[8].
- Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of childbearing potential unless where other treatments are not tolerated or are ineffective.
- The balance of the benefits of treatment with valproate should be weighed against the risks when prescribing valproate-containing medicines for the first time, at routine reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.
- Women of child bearing potential who are treated with valproate must be advised to use effective contraception during treatment and should be fully informed of the potential risks for the unborn child if they become pregnant during treatment.

Treatment during pregnancy

- If a woman who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to switching to alternative treatments.
- If valproate treatment is continued during the pregnancy then the following advice should be followed:
  - Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder in female patients;
  - The lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day. Prolonged release formulations may be preferable to normal release formulations;
  - Specialised prenatal monitoring should be initiated in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformations;
  - Folate supplementation before the pregnancy may decrease the risk of neural tube defects however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure;
  - All female patients must be fully informed of the risks associated with valproate during pregnancy, the need to use effective contraception, the need for regular review of treatment and the need to urgently discuss with their doctor if she is planning a pregnancy or becomes pregnant.

* *Further details on valproate-containing medicines are available at* ***www.hpra.ie***

References are available on request from the HPRA.

The product information (Summary of Product Characteristics (SmPC) and package leaflet (PL)) for valproate containing products will be updated to include the revised restrictions for use, the strengthened warnings and the additional information on the risks related to exposure during pregnancy to better inform healthcare professionals and patients. Furthermore, educational materials (including materials particularly developed for patients) will be provided to all healthcare professionals in the EU and to women prescribed valproate to inform them of these risks.

Key Message

- Valproate should not be prescribed to female children, female adolescents, women of child bearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).
- Valproate treatment should only be commenced and supervised by a doctor experienced in managing epilepsy and bipolar disorder.
- Before initiating treatment, the balance of the benefits of treatment with valproate must be weighed against the risks. This should be considered at routine treatment reviews, when a female reaches puberty and when a woman plans a pregnancy or becomes pregnant.
- All female patients must be informed of and understand the risks associated with valproate during pregnancy and the steps to take if pregnancy occurs or is planned.
- The product information for valproate-containing medicines will be updated shortly and educational materials will be provided to all healthcare professionals and female patients in the EU.

Ivabradine (Procoralan): New contraindication and recommendations to minimise the risk of cardiovascular events and severe bradycardia

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of ivabradine (Procoralan) and has made recommendations aimed at reducing the risk of adverse cardiac effects, including myocardial infarction and bradycardia in patients being treated for symptomatic chronic stable angina in coronary artery disease. This review was initiated in May 2014 following preliminary results of the SIGNIFY[1] study and these preliminary results were communicated at that time via a Direct Healthcare Professional Communication (DHPC) and also in the 62nd edition of the HPRA Drug Safety Newsletter.

The preliminary results showed a small but statistically significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction with ivabradine compared with placebo in a pre-specified subgroup of patients with symptomatic angina of CCS class II or more. Initial data indicated that the adverse cardiovascular outcomes may be mostly associated with a target heart rate below 60 beats per minute (bpm) however, further evaluation of the data from the SIGNIFY[1] study was needed to fully understand its implications for the clinical use of ivabradine.

The final data from the SIGNIFY study[2] showed that in a subgroup of patients who had symptomatic angina, there was a small but significant increase in the combined risk of cardiovascular death or non-fatal myocardial infarction with ivabradine compared with placebo (3.4% vs. 2.9% yearly incidence rates). The data also indicated a higher risk of bradycardia with ivabradine compared with placebo (17.9% vs. 2.1%). Additional data assessed by the PRAC also showed that the risk of atrial fibrillation (AF) is increased in patients treated with ivabradine compared with controls (4.86% vs. 4.08%).

The benefit risk balance of ivabradine remains positive following review of the final data from the SIGNIFY study for its authorised indications* however a small but significant increase of the combined risk of cardiovascular death, myocardial infarction and cardiac failure was seen in patients with symptomatic angina.

Advice to Healthcare Professionals

- The benefit-risk balance of ivabradine remains positive for its authorised indications.
- In the symptomatic treatment of patients with chronic stable angina, ivabradine is indicated in adults unable to tolerate, or with a contra-indication to the use of beta-blockers, or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.
- Ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) in patients with symptomatic angina.
- Ivabradine is also indicated for treatment of chronic heart failure on the basis of results from the previous SHIFT study. The results of the SIGNIFY study do not impact on the heart failure indication.
- Concomitant use of ivabradine with verapamil or diltiazem, which are moderate CYP3A4 inhibitors, is now contraindicated.
- Treatment with ivabradine should only be initiated in patients whose resting heart rate is at least 70 bpm.
- Prior to starting treatment with ivabradine or prior to dose titration, patients should be carefully monitored (serial heart rate measurements, E.C.G. or ambulatory 24-hour monitoring) for the occurrence of too low resting heart rates or symptoms of bradycardia.
- The risk of developing AF is increased in patients treated with ivabradine. Regular clinical monitoring for the signs and symptoms of AF is recommended and if AF develops, the balance of benefits and risks of continued treatment should be carefully considered.
- Treatment with ivabradine should be discontinued if the symptoms of angina do not improve within 3 months, or the improvement is limited and there is no clinically relevant reduction in resting heart rate within 3 months.
- The usual recommended starting dose of ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.
- If the resting heart rate decreases persistently below 50 beats per minute or the patient experiences symptoms related to bradycardia, the ivabradine dose must be down-titrated, including the possible dose of 2.5 mg twice daily. The dose should only be increased to 7.5 mg twice daily after three to four weeks of treatment if the therapeutic response with 5 mg twice daily is insufficient and if the 5 mg dose is well tolerated. The effect of a dose increase on the heart rate should be carefully monitored.
- A Direct Healthcare Professional Communication (DHPC) outlining these recommendations will be circulated shortly. The approved product information* (Summary of Product Characteristics (SmPC) and package leaflet (PL)) will be updated accordingly.

* *Products currently authorised in Ireland include Procoralan. Further details of indications are available at* ***www.hpra.ie*** *and* ***www.ema.europa.eu***

Key Message

- Ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) in patients with symptomatic angina.
- Serial heart rate measurements are required prior to initiation of therapy or prior to dose titration.
- Concomitant use of ivabradine with verapamil or diltiazem, which are moderate CYP3A4 inhibitors, is now contraindicated.
- Treatment with Ivabradine should only be initiated in patients whose resting heart rate is at least 70 bpm.
- Healthcare professionals should take note of the recommendations and relevant precautions in the product information for ivabradine, particularly in relation to dosing recommendations (not exceed the recommended daily dose of 7.5mg bd), maintenance of therapy, risk of developing AF, monitoring of and the potential impact of concomitant heart rate reducing effects of other medicines.

REFERENCES

1 Study assessInG the morbi-mortality beNefits of the If inhibitor ivabradine in patients with coronary arterY disease

2 Fox K. Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014; 371: 1091-9. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1406430

Agomelatine (Valdoxan): Reminder of the importance of liver function monitoring to reduce the risk of serious hepatic adverse reactions

Agomelatine* is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist, indicated in the treatment of major depressive episodes in adults. It was first authorised for use across the EU in 2009 on the basis of studies showing that the medicine has comparable effects to other antidepressants.

Since agomelatine has a different mode of action and a different safety profile to existing antidepressants, it was concluded that, as long as their liver function is tested regularly, agomelatine could be a valuable treatment for some patients. In the post marketing setting, hepatic adverse reactions have continued to be reported and an EU level review has recently been finalised which concluded that the benefit risk balance for agomelatine remains positive. However there is a need to reiterate the importance of liver monitoring, which is the cornerstone for the safe use of this product.

A risk of hepatic adverse effects has been known to be associated with agomelatine since it was first authorised and the product information has included warnings about these risks and the requirement for regular monitoring of liver function tests during treatment with agomelatine. In December 2012 and December 2013, the HPRA highlighted the risk of hepatotoxicity in its Drug Safety Newsletter (51st and 57th editions) and emphasised the importance of liver function monitoring.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recently concluded its regular benefit-risk assessment (known as a periodic safety update report or PSUR) of agomelatine. As part of this assessment, the PRAC considered cumulative data on severe hepatic adverse effects associated with agomelatine and recommended further reinforcement of measures to minimise the risk of hepatotoxicity.

Reports of hepatic failure included a small number of cases which resulted in a fatal outcome or liver transplantation in patients with hepatic risk factors. Elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have also been reported in patients treated with agomelatine in the post-marketing setting. The majority of these abnormalities occurred during the first months of treatment. The pattern of liver damage appears mainly hepatocellular.

Extra vigilance is advised for patients with risk factors for hepatic injury. The balance of benefits and risks should be carefully considered before initiating treatment in a patient with risk factors for hepatic injury e.g. obesity/overweight, substantial alcohol intake, non-alcoholic fatty liver disease, diabetes, and in patients receiving concomitant medicinal products associated with hepatic injury. Caution should be exercised when agomelatine is administered to patients with pretreatment elevated transaminases.

Efficacy has not been demonstrated in patients' ≥75 years and use of agomelatine is not recommended for patients in this age group. Prescribers are reminded that agomelatine is contraindicated in patients with hepatic impairment i.e. cirrhosis or active liver disease and in patients with transaminases exceeding 3 times the upper limit of normal. Elevations of transaminases (>3 times the upper limit of the normal range) occur more frequently in patients treated with 50mg compared to 25mg. For some patients treated in clinical practice, hepatic reactions occurred following an increase in the dose.

* *Product information for agomelatine is available at* ***www.hpra.ie***

Advice to Healthcare Professionals

- Baseline liver function tests should be performed in every patient and treatment should not be started in patients with transaminases exceeding 3 times the upper limit of normal.
- Liver function must be monitored regularly during treatment, at 3, 6, 12 and 24 weeks and regularly thereafter when clinically indicated.
- Treatment must be discontinued immediately if the increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.
- Patients should be informed of the symptoms of potential liver injury and the importance of liver function monitoring, and should be advised to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.

Key Message

- Cases of liver injury, including hepatic failure, where a small number of cases have resulted in a fatal outcome or liver transplantation, in patients with hepatic risk factors have been reported in association with post-marketing use agomelatine.
- Liver function tests (LFTs) should be monitored in all patients **before and during treatment**, in line with the recommendations described in the approved product information.

PRAC review does not confirm increased risk of cardiovascular events with testosterone medicines: Committee recommends medicines can continue to be prescribed for their authorised indications

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed an evaluation of the available evidence on the risk of stroke, myocardial infarction, and death in men treated with authorised testosterone containing products. This review was initiated following the publication of studies that suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy. The PRAC review of testosterone-containing medicines did not find consistent evidence that their use increases the risk of cardiovascular events.

The PRAC reviewed the available evidence on the risks of serious cardiovascular adverse effects of these medicines and found the evidence to be inconsistent. While some studies did suggest an increased risk of cardiovascular events (myocardial infarction, stroke etc.) in men using testosterone[1,2,3] compared with men not using testosterone, these studies had some limitations and other studies did not identify any risk of cardiovascular disorders[4,5]. The PRAC also noted that a lack of testosterone itself could cause cardiovascular problems. Therefore the PRAC recommended the following:

* *Further details on testosterone-containing medicines are available at* ***www.hpra.ie*** *and* ***www.ema.europa.eu/ema***

Advice to Healthcare Professionals

- Testosterone-containing medicines should only be used if the lack of testosterone has been confirmed by clinical features and biochemical tests. Testosterone levels should be monitored regularly during treatment as well as haemoglobin and haematocrit levels, liver function and blood lipid profile.
- For patients suffering from severe cardiac, hepatic or renal insufficiency, or ischaemic heart disease, treatment with testosterone can cause serious complications characterised by oedema with/without congestive cardiac failure. In these instances, treatment should be stopped immediately.
- Caution should be exercised in patients treated with testosterone with pre-existing hypertension since testosterone increases may cause a worsening of hypertension.
- There is limited data on safety and effectiveness in patients over 65 years of age. The fact that testosterone levels decrease with age and that age-specific testosterone reference values do not exist should be considered.
- The product information for all testosterone products will be updated with these recommendations.

Key Message

- The PRAC review of testosterone-containing medicines did not find consistent evidence that their use increases the risk of cardiovascular problems.
- The benefits of testosterone continue to outweigh its risks but should only be used where lack of testosterone has been confirmed by signs and symptoms as well as laboratory tests.
- Testosterone should not be used in men suffering from severe cardiac, hepatic or renal problems. There is limited safety and efficacy data on use in patients over 65 years of age.
- The product information (SmPC and PL) for these products will be updated accordingly.

REFERENCES

1 Xu et al. 2013. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomised trials. BMC medicine 2013; 11:108.

2 Vigen et al. "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels" JAMA. 2013 Nov 6;310 (17):1829-1836.

3 Finkle et al. "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men." PLoS One. 2014 Jan 29;9(1):e85805.

4 Baillargeon J, Urban RJ, Kuo Y-F, Ottenbacher KJ, Raji MA, Du F, Lin Y-l, Goodwin JS. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014; 48(9):1138-1144.

5 Corona G, Maseroli E, Rastrelli G, Isidori A, Mannucci E, Maggi M. Cardiovascular risk associated with testosterone boosting medications: a systematic review and metaanalysis. Exp Opin Drug Safety 2014 (Posted online on August 19, 2014. (doi:10.1517/14740338.2014.950653)

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Tecfidera (dimethyl fumarate)	Report of a case of Progressive Multifocal Leuoencephalopathy (PML).
Eligard (leuprorelin acetate depot injection)	Risk of lack of efficacy due to incorrect reconstitution and administration process.
Sodium Valproate (Epilim)	Risk of abnormal pregnancy outcomes.
Stelara (ustekinumab)	Risk of exfoliative dermatitis and skin exfoliation.

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