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Pharmacovigilance Working Party (PhVWP)

November 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its November 2011 plenary meeting on 14-16 November 2011.

Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy. The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States. For the publication policy, readers are referred to http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500006181.pdf.

The PhVWP also provides advice to the Committee for Medicinal Products for Human Use (CHMP) on centrally authorised products and products subject to ongoing CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the Meeting highlights from the CHMP published under http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/11/news_detail_001381.jsp&mid=WC0b01ac058004d5c1 .

Atomoxetine – Updated information on effects on blood pressure and heart rate

The PhVWP recommended update of the product information, pre-treatment screening and periodic cardiovascular monitoring during treatment to minimise any risk of cardiovascular disorders in patients treated with Atomoxetine.

A new analysis requested by the PhVWP showed that approximately 6-12% of children and adults with ADHD (attention deficit hyperactivity disorder) treated with atomoxetine experienced clinically relevant changes in heart rate (20 bpm or greater) and/or blood pressure (15-20 mmHg or greater). The absolute number of patients with these types of changes was small but since in approximately 15-32% of them these changes were sustained or persistent, the PhVWP recommended a series of measures to

European Medicines Agency
7 Westferry Circus ● Canary Wharf
London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

HMA Management Group
Kevin O'Malley House ● Earlsfort Centre
Earlsfort Terrace ● Dublin 2 ● Ireland
Telephone +353 1 634 3453 **Facsimile** +353 1 661 4764
E-mail hma-ps@imb.ie **Website** www.hma.eu

minimise any risk of cardiovascular adverse effect. These measures include a recommendation for pre-treatment screening and periodic cardiovascular monitoring during treatment, and a contraindication for the use of atomoxetine in patients with severe cardiovascular or cerebrovascular disorders (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Escitalopram – Risk of QT interval prolongation

Escitalopram may cause QT prolongation and the product information will be updated, including a reduction of the maximum daily dose in the elderly to 10 mg/day.

The PhVWP concluded its review of the antidepressant escitalopram and the risk of QT prolongation with recommendations to update the summaries of product characteristics (SmPCs) and package leaflets (PLs) of escitalopram-containing medicinal products in the EU (see Annex 2 for the Summary Assessment Report). The update should include a reduction of the maximum daily dose to 10 mg/day in the elderly, a contraindication against concomitant use with other medicines known to prolong the QT interval and a number of other contraindications and warnings.

The PhVWP will inform the CMDh accordingly. For the final wording to be included in the in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Rosuvastatin - Risk of gynaecomastia

The PhVWP recommended updating the product information to inform patient and healthcare professionals that, very rarely, gynaecomastia could be observed during treatment with rosuvastatin.

Following the identification of a signal of gynaecomastia with rosuvastatin in European pharmacovigilance databases the PhVWP performed a review of the cases of gynaecomastia reported during treatment with rosuvastatin. Non-clinical data, clinical study data and post-marketing data were reviewed.

The available non-clinical data did not show any effect on mammary glands. However for several cases collected during post-marketing experience a causal relationship between rosuvastatin and gynaecomastia cannot be ruled out and the PhVWP decided to inform patients and healthcare professionals of the occurrence of this very rare adverse reaction (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Tibolone – Risk of venous thromboembolism, myocardial infarction, breast cancer and ovarian cancer

The product information of all tibolone-containing medicines in the EU should be updated to add information from clinical trials and epidemiological studies on the risks of venous thromboembolism, myocardial infarction, breast cancer and ovarian cancer.

The PhVWP reviewed the proposal from the originator MAH for tibolone to update the product information with data from clinical trials and epidemiological studies on the risks of venous thromboembolism, myocardial infarction, stroke, breast cancer and ovarian cancer and with statements from the third revision of the Core SmPC for Hormone Replacement Therapy Products[1].

With a view to facilitating accurate and harmonised product information across the EU, the PhVWP concluded that the product information of all tibolone-containing medicinal products in the EU should be updated in relation to venous thromboembolism, myocardial infarction, breast cancer and ovarian cancer and be updated with the implementation of the Core SmPC. With regard to the risk of stroke, the PhVWP considered that the data did not justify changes in the current product information (see Annex 4 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Topiramate – Updated information on risk of congenital malformations

Section 4.6 (Fertility, Pregnancy and Lactation) of the SmPC of topiramate has been updated with information on the increased risk of congenital malformations.

The PhVWP finalised their review of recent findings from two antiepileptic drug pregnancy registries, namely the North American Antiepileptic Pregnancy Registry (NAAED) and the UK Epilepsy and Pregnancy Register, concluding that the product information should be updated to reflect that infants having been exposed to topiramate during the first trimester of pregnancy have an increased risk of congenital malformations (see Annex 5 for the Summary Assessment Report).

The PhVWP will inform the CMDh accordingly. For the final wording to be included in the in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

[1] Available under: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/Core_SPC_PL/Core_SPCs/CMDh_131_2003_Rev3_Clean_2010_01_Core_SmPC_for_HRT.pdf.

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMDh – Co-ordination Group for Mutual Recognition and Decentralised Procedures for Human Medicines

EU – European Union

HMA – Heads of Medicines Agencies

PASS – post-authorisation safety study

PhVWP – CHMP Pharmacovigilance Working Party

PL – package leaflet

PSUR – periodic safety update report

RMP – risk-management plan

SmPC – summary of product characteristics

Annex 1

Summary Assessment Report of the PhVWP November 2011

Atomoxetine – Updated information on effects on blood pressure and heart rate

Key message

Trial data in children and adults with Attention-Deficit/Hyperactivity Disorder (ADHD) show that atomoxetine can cause clinically important changes in blood pressure and/or heart rate in some patients. Atomoxetine should not be used in those with severe cardiovascular or cerebrovascular disorders. Pre-treatment screening and ongoing monitoring of cardiovascular status should be conducted.

Safety concern and reason for current safety review

A signal from an ECG study in healthy adult male poor metabolisers showed that the mean changes in blood pressure and heart rate were greater than expected relative to the overall clinical trial population. To fully characterise the haemodynamic effects of atomoxetine, the Pharmacovigilance Working Party (PhVWP) recommended that the MAH perform a comprehensive analyses of the whole clinical trial database.

Clinical setting

Within Europe, atomoxetine was first authorised in the UK in May 2004 (Strattera) and then in the rest of Europe for the treatment of ADHD in children over the age of 6 years, adolescents and adults (only continuing use from childhood into adulthood where there is clear evidence of benefit and continuing need for treatment).

Information on the data assessed

The PhVWP preformed a review of clinical trial data for atomoxetine in children and adults with ADHD along with other relevant observational and post-marketing spontaneous data.

Outcome of the assessment

This review suggested that for the vast majority of patients receiving atomoxetine the changes to heart rate and blood pressure are as outlined in the product information (mean increase in pulse of < 10 bpm and in blood pressure of < 5 mmHg). However, the new analyses showed that approximately 6-12% of children and adults experience clinically important changes in heart rate (20 bpm or greater) and/or blood pressure (15-20 mmHg or greater) and that is some of these patients (Approximately 15-32%) the effects were sustained or progressive. The absolute numbers of patients who will experience these clinically important changes is small. Despite the overall lack of evidence (from post-marketing spontaneous and observational data) of a risk of serious clinical cardiovascular and cerebrovascular outcomes, the consequences of progressive or persistent / sustained changes in blood pressure and heart rate of the clinically relevant magnitudes found in the MAH review in some patients could still be very serious in a minority of patients.

Given that it is not possible to identify particular at risk groups based on the data reviewed, it was deemed necessary to ensure that patients who may be particularly susceptible to adverse clinical cardiovascular outcomes if exposed to atomoxetine should undergo pre-treatment screening and ongoing monitoring of cardiovascular status. In particular:

- atomoxetine use should be contraindicated in severe cardiovascular or cerebrovascular disorders
- patients should be subject to pre-treatment screening and ongoing monitoring (and recording) of cardiovascular status during treatment
- specialist cardiac evaluation and advice should be sought if prior to treatment, initial findings suggest cardiac disease or history, or if during treatment symptoms suggestive of cardiac disease are found.

The PhVWP considered it was important that this issue was communicated to prescribers and that checklists and recording tools for actions to take prior to treatment initiation and during ongoing treatment should be developed by the MAHs along with a physician's guide to prescribing.

Annex 2

Summary Assessment Report of the PhVWP November 2011

Escitalopram – Risk of QT interval prolongation

Key message

Escitalopram may cause QT prolongation and the product information will be updated, including a reduction in the maximum daily dose to 10 mg/day in the elderly.

Safety concern and reason for current safety review

The PhVWP assessed data from a randomised, multi-centre, double-blind, placebo-controlled, crossover pharmacokinetic and thorough QT-study undertaken in healthy volunteers given daily doses of 10 and 30 mg escitalopram.

Following its October 2011 meeting, the PhVWP communicated about a review undertaken for the antidepressant citalopram and the risk of QT prolongation. Citalopram is a racemic mixture of two enantiomers, S-citalopram (escitalopram) and R-citalopram. The PhVWP concluded its review with recommendations to update the SmPCs and PLs of citalopram-containing medicinal products in the EU. These updates should include a reduction of the maximum daily dose in adults, in the elderly and in patients with impaired liver function, a contraindication against concomitant use with other medicines known to prolong the QT interval and a number of other contraindications and warnings.

Clinical setting

Esitalopram is indicated for the treatment for major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder.

QT interval prolongation is an indication of abnormal heart rhythm, which can lead to ventricular arrhythmia, including *torsade de pointes*, and sudden cardiac death.

Information on the data assessed

The PhVWP assessed the results of a randomised, multi-centre, double-blind, placebo-controlled, crossover pharmacokinetic and thorough QT-study undertaken in healthy volunteers given daily doses of 10 and 30 mg escitalopram. The PhVWP additionally evaluated data from the MAH provided in response to a list of question from the PhVWP. Finally, spontaneously reported cases of suspected reactions which could be related to QT interval prolongation were reviewed.

Outcome of the assessment

Following review of the thorough QT-study, the PhVWP concluded that a dose-dependent increase in QT interval was shown in this thorough QT study, particularly with doses of 30 mg/day.The change from baseline in QTc (Fridericia-correction) was 4.3 (90% CI: 2.2- 6.4) msec with 10 mg/day and 10.7 msec (90% CI: 8.6 - 12.8) msec with 30 mg day. The study was considered of good quality, although testing of a higher dose would have been desirable (in accordance with the ICH E14 guideline). A positive control was included, i.e. moxifloxacin 400 mg/day, which showed expected results, thus confirming assay sensitivity.

Further, the PhVWP considered that cases of QT interval prolongation and ventricular arrhythmia including *torsade de pointes* were spontaneously reported, predominantly in female patients, with hypokalemia, pre-existing QT interval prolongation or other cardiac diseases. Most of the reported cases of *torsade de pointes* had a temporal relationship with starting of the treatment of escitalopram or with the increase in dosing, and/or at the time of other risk situations, e.g. with hypokalaemia. Recovery from the event was reported when escitalopram was discontinued in most of the reported cases. The data from spontaneous reporting indicated a signal for QT prolongation and the potential for underreporting was recognised.

Overall, the PhVWP considered that the results from the study indicated that escitalopram causes dose-dependent QT interval prolongation. In considering the appropriate risk minimisation strategy, the PhVWP also noted that elderly patients achieve higher systemic exposure than younger patients.

Based on a review of the available data, the PhVWP concluded that the summary of product information for escitalopram-containing medicinal products in the EU should be updated to

- limit the daily dose in the elderly to 10 mg/day;
- contraindicate use of escitalopram with other medicinal products known to prolong the QT interval;
- include relevant contraindications and warnings; and
- include ventricular arrhythmia including *torsade de pointes* as adverse reactions.

The package leaflet should be updated accordingly and include advice to patients to

- contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking escitalopram;
- not to stop taking escitalopram or change or reduce the dose without first consulting their healthcare professional, as withdrawal symptoms may occur when escitalopram treatment is discontinued, particularly if this is abrupt.

Healthcare professionals are advised to review patients on doses that are above the now recommended maximum dose and gradually reduce it accordingly.

Annex 3

Summary Assessment Report of the PhVWP November 2011

Rosuvastatin – Risk of gynaecomastia

Key message

The PhVWP recommends that section 4.8 of the SmPCs of all rosuvastatin-containing products should be updated to list gynaecomastia as an adverse reaction of 'very rare' occurrence.

Safety concern and reason for current safety review

Following the identification of a signal of gynaecomastia with rosuvastatin in European pharmacovigilance databases, the MAH for CRESTOR was requested to submit a cumulative overview of all cases of gynaecomastia. The PhVWP assessed the data submitted by the MAH in order to facilitate the harmonised implementation of any necessary regulatory actions across the EU.

Clinical setting

Rosuvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and a member of the statin class of lipid-lowering agents. It is indicated for the treatment of primary hypercholesterolaemia, mixed dyslipidaemia, and homozygous familial hypercholesterolaemia.

Gynaecomastia has been recognized as an adverse drug reaction for atorvastatin, another member of the statin class of lipid-lowering agents.

Information on the data assessed

The MAH submitted a comprehensive cumulative review of clinical study data, post-marketing data from the MAH's Global Patient Safety database, the scientific/medical literature, and the FDA AERS database.

From the literature, two case reports of gynaecomastia were identified. A review of these reports, taking into account the temporal relationship between discontinuation of rosuvastatin and recovery of the patient and confounding factors, suggested a relationship between rosuvastatin and gynaecomastia.

The available non-clinical data did not show any effect on mammary glands.

From the trials performed to support the original marketing application for CRESTOR, one case of gynaecomastia was reported. In one out of four other long-term placebo controlled trials, gynaecomastia was reported more frequently in rosuvastatin-treated patients than in placebo-treated patients (1.6% vs. 1.1%).

From post-marketing experience, several cases with positive dechallenge were reported, of which a few had a close temporal relationship between discontinuation of rosuvastatin and resolution of the gynaecomastia. One case with positive rechallenge was also reported. Based on these reports, a relationship between rosuvastatin and gynaecomastia could not be ruled out. Rosuvastatin could have a contributory role in patients susceptible to gynaecomastia, i.e. older or obese males.

Outcome of the assessment

Considering the available data, a relationship between rosuvastatin and gynaecomastia could not be ruled out. This relationship was supported by several cases with positive dechallenge, of which several had a close temporal relationship between discontinuation of rosuvastatin and resolution of the gynaecomastia, and one case with positive rechallenge. Rosuvastatin could have a contributory role in patients susceptible to gynaecomastia, i.e. older or obese males.

Therefore, the PhVWP recommended that section 4.8 of the SmPCs of all rosuvastatin-containing products should be updated to list gynaecomastia as an ADR of 'very rare' occurrence.

Annex 4

Summary Assessment Report of the PhVWP November 2011

Tibolone – Risk of venous thromboembolism, myocardial infarction, breast cancer and ovarian cancer

Key message

The product information of all tibolone-containing medicines in the EU should be updated to add information from clinical trials and epidemiological studies on the risks of venous thromboembolism, myocardial infarction, breast cancer and ovarian cancer.

Safety concern and reason for current safety review

The originator MAH for tibolone submitted a proposal to update the product information with adding information from clinical trials and epidemiological studies on the risks of venous thromboembolism, myocardial infarction, stroke, breast cancer and ovarian cancer. By means of the proposal, the MAH also planned implementing, as relevant, the third revision of the Core SmPC for Hormone Replacement Therapy Products[2].

The PhVWP agreed to assess the proposal with a view to facilitating accurate and harmonised product information across the EU.

Clinical setting

Tibolone is a synthetic hormone which has oestrogenic, progestagenic and androgenic properties.

In the Member States of the EU where the originator product LIVIAL is available, it is indicated for the treatment of symptoms due to oestrogen deficiency in women who are at least one year postmenopausal at a dose of 2.5 mg. In some Member States (but not in Belgium, France, Germany, the Netherlands and Spain) it is additionally indicated for the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products authorised for the prevention of osteoporosis.

Information on the data assessed

A population-based case-control study in the UK General Practice Research Database (GPRD) investigating the effect of tibolone and other hormone therapies on the incidence of venous thromboembolism [1], which was part of the risk management plan for tibolone, was assessed, together with data from clinical trials and adverse reaction reports from spontaneous case reporting.

For the risk of myocardial infarction, data from another epidemiological study using GPRD [2] was assessed.

In relation to stroke, a re-analysis of data from the Women Health Initiative study [3] was assessed.

Concerning breast cancer and ovarian cancer, results of the Million Women study (MWS) [4] had been submitted to support the proposed changes to the product information.

[2] Available under: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/Core_SPC_PL/Core_SPCs/CMDh_131_2003_Rev3_Clean_2010_01_Core_SmPC_for_HRT.pdf.

Outcome of the assessment

The PhVWP considered that the results of the GPRD study [1] indicated no increased risk of venous thromboembolism during short-term use of tibolone. However, the data are too limited to conclude that an increased risk during tibolone use compared with non-use can be excluded.

Concerning the risk of myocardial infarction, the number of people taking tibolone in the GPRD study [2] was very small and too low to detect differences with non-users. Whilst the data were insufficient to estimate the exact magnitude of any possible risk, the data were sufficient to suggest that tibolone does not protect against myocardial infarction.

A re-analysis of data from the Women Health Initiative study [3] did not justify changes in the product information with regard to the risk of stroke, which is currently based on data from the LIFT study [5].

The Million Women study [4] provided figures on the risk of breast cancer associated with the use of tibolone, and the reflection of these figures in the proposed product information was considered appropriate.

A proposed statement for the product information on the risk of ovarian cancer, also in accordance with the results of the Million Women study [4], was considered acceptable by the PhVWP.

Considering the above, the PhVWP concluded that the SmPCs of all tibolone-containing medicinal products in the EU should contain:

- the statements of the Core SmPC for Hormone Replacement Therapy Products, Rev 3[3] (where a statement applies equally to hormone replacement therapy (HRT) and tibolone, this should be made clear by replacing "HRT" with "HRT or tibolone" in the SmPCs for tibolone); and in addition
- statements in SmPC section 4.4 on warnings and special precautions for use stating that:
  - in the Million Women Study it was shown that the relative risk for ovarian cancer with use of tibolone was similar to the risk associated with use of other types of HRT;
  - in a UK epidemiological study using GPRD the risk of venous thromboembolism in association with tibolone was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of tibolone and a small increase in risk compared with non-use cannot be excluded;
  - in a UK epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone;
- statements in SmPC section 4.8 on undesirable effects stating that:
  - the risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60, while there is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT;
  - long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer (in the Million Women study 5 years of HRT resulted in 1 extra case per 2500 users) and that the Million Women study showed that the relative risk for ovarian cancer with tibolone was similar to the risk with other types of HRT; and
- including in SmPC section 4.8 on undesirable effects

[3] Available under: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/Core_SPC_PL/Core_SPCs/CMDh_131_2003_Rev3_Clean_2010_01_Core_SmPC_for_HRT.pdf.

- a table detailing the overall risk ratios (RR) for breast cancer resulting from the Million Women study (RR tibolone: 1.3; RR oestrogen-only HRT: 1.2; RR oestrogen+progestagen HRT: 1.7).

The package leaflets should be updated in accordance with the recommended SmPC changes.

References

[1] Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost. 2010; 8: 979–986.

[2] de Vries CS, Bromley SE, Farmer RDT. Myocardial infarction risk and hormone replacement: differences between products. Maturitas. 2006; 53: 343–350.

[3] Rossouw, JE, Prentice RL, Manson JE, Wu LL, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. J Am Med Assoc. 2007; 297: 1465-1477.

[4] Million Women Study Collaborators, eds. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003; 362: 419–427.

[5] Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R; LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. N Engl J Med. 2008; 359: 697-708.

Annex 5

Summary Assessment Report of the PhVWP November 2011

Topiramate – Updated information on risk of congenital malformations

Key message

Section 4.6 (Fertility, Pregnancy and Lactation) of the SmPC of topiramate has been updated with information on the increased risk of congenital malformations as a result of a renewed evaluation.

Safety concern and reason for current safety review

On 4 March 2011, the US Food and Drug Administration (FDA) announced a change in the recommendation for use of topiramate in pregnancy after evaluation of data from registries of adverse reactions reports and published literature. The same data have now been reviewed in the framework of a renewal procedure in Europe for the originator product containing topiramate.

The product information for topiramate already contained information on increased risk for birth defects with use in pregnancy. This information was based on relatively limited data including registry data.

Clinical setting

Topiramate is indicated for:

- monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures
- as adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome
- in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment. Topiramate is contraindicated as migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception.

Information on the data assessed

Data from two antiepileptic drug pregnancy registries, the North American Antiepileptic Pregnancy Registry (NAAED), and the UK Epilepsy and Pregnancy Register, have been assessed. The new registry data provided more extensive information on the use of topiramate in pregnancy and on birth defects in children born by mothers treated during pregnancy.

Outcome of the assessment

In both registries, there were cases of major malformations associated with topiramate treatment, both when used in monotherapy or in combination treatment.

Although the number of cases in the registries is still relatively small, the data continue to show an increased risk of birth defects with topiramate which strengthens the previous findings. Non-clinical data also clearly show a teratogenic potential.

The product information, section 4.6 of the SmPC, should be updated to reflect this most recent knowledge that data from the two registries indicate that infants exposed to topiramate monotherapy in the first trimester have an increased risk of congenital malformations e.g. craniofacial defects, such as cleft lip/palate, hypospadias, and anbomalies involving various body systems.