The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of “drug information officers” and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Quality Assurance and Safety: Medicines, EMP-HSS, World Health Organization, 1211 Geneva 27, Switzerland,
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This Newsletter is also available on our Internet website:
http://www.who.int/medicine

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No. 6, 2012

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document. We thank you for your interest in this publication and wish you a healthy and fulfilling year in 2013.
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## Safety of medicines

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Agomelatine

Risk of dose-related hepatotoxicity and liver failure

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that there have been several serious cases of hepatotoxicity reported with agomelatine (Valdoxan®, Thymanax®). These include six reports worldwide of hepatic failure. The agency advised health-care professionals that the existing recommendations to perform liver function tests in all patients receiving agomelatine at treatment initiation and during treatment have been extended to include testing when the dose is increased. Agomelatine should be immediately discontinued if patients present with symptoms or signs of potential liver injury, or if an increase in serum transaminases in liver function tests exceeds 3 times the upper limit of normal. It is also recommended that patients should be informed of the symptoms of potential liver injury and advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.

Agomelatine is an antidepressant indicated for the treatment of major depressive episodes in adults. Agomelatine is a melatonin MT1 and MT2 receptor agonist, and antagonist at the serotonin 5-HT2c receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

Reference:

Denosumab

Fatal cases of severe symptomatic hypocalcaemia

UK. The MHRA reported that cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120 mg (Xgeva®) or 60 mg (Prolia®). Some of these cases were fatal in those receiving the 120 mg dose.

The MHRA advised health-care professionals that pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving the 120 mg dose unless hypocalcaemia is present. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time.

Hypocalcaemia is a known risk with denosumab use, especially in patients with severe renal impairment (creatinine clearance <30 mL/min; estimated glomerular filtration rate [eGFR] 15 – 29 mL/min/1.73m²) or receiving dialysis. Severe symptomatic hypocalcaemia, including three fatal cases, has been reported in patients receiving denosumab 120 mg. Severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcaemia receiving denosumab 60 mg.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment.

Periodic monitoring of calcium levels (at the discretion of the prescriber) is recommended after use of denosumab in patients predisposed to hypocalcaemia, including those with severe renal impairment. In patients receiving 120 mg denosumab, supplementation of calcium and vitamin D is required unless hypocalcaemia is present; if hypocalcaemia occurs, additional calcium supplementation may be necessary.

Reference:

Denosumab

Association with the risk of atypical femoral fractures

Canada. AMGEN Canada Inc., in consultation with Health Canada, informed health-care providers of new important safety information regarding the risk of atypical femoral fractures associated with denosumab (Prolia®) treatment. According to the manufacturer, there have been no confirmed Canadian cases of atypical femoral fractures associated with denosumab to date. Amgen proactively evaluated the potential for atypical femoral fractures in patients treated with the drug in clinical trials and the post marketing setting.

Cases of atypical femoral fracture have been confirmed in patients receiving denosumab participating in the on-going open label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). Events of atypical femoral fracture have occurred very rarely (<1/10,000) based on 31,266 subject years of exposure to denosumab in bone loss studies.

It is recommended that, during denosumab treatment, health-care professionals should advise the patients to report new or unusual thigh, hip, or groin pain. Patients presenting
with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined.

The Warnings and Precautions section of the Product monograph was updated to reflect this new information on atypical femoral fractures.

Reference:

Intravenous 0.18% saline/4% glucose solution ('hypotonic saline') in children

Contraindicated in children except under expert medical supervision in paediatric specialist settings

UK (1). The MHRA announced that four children have died of cerebral oedema caused by very low levels of serum sodium after receiving intravenous hypotonic saline (0.18% saline/4% glucose solution) in hospital. This solution is now contraindicated in children except under expert medical supervision in paediatric specialist settings – such as renal, cardiac, liver, high dependency and intensive care units.

The MHRA also advised healthcare professionals to remove 0.18% saline/4% glucose intravenous infusions from stock and general use in areas that treat children and ensure that suitable alternatives are available (in line with local guidelines) and to restrict availability of 0.18% saline/4% glucose intravenous infusions to critical care and specialist wards. If hypotonic intravenous fluids do need to be prescribed to children (according to the strict conditions above), the child's individual clinical needs and possibility of increased anti-diuretic hormone secretion should be taken into account – fluid balance, plasma and urinary electrolyte concentrations must be carefully monitored during treatment.

Acute symptomatic hyponatraemic encephalopathy is a medical emergency. Health-care professionals should therefore be aware of and take prompt action if children receiving hypotonic intravenous fluids develop the signs and symptoms of hyponatraemia (headache, nausea, seizures, lethargy, coma, cerebral oedema).

Following the restart of a public inquiry primarily into the deaths of three children in the UK who died of cerebral oedema secondary to hyponatraemia after administration of intravenous hypotonic saline, the Commission on Human Medicines (CHM) has recently reviewed all data on the benefits and risks of this solution when used in children.

There have been over 50 reported permanent neurological injuries or deaths in children worldwide as a result of iatrogenic hyponatraemia associated with the use of hypotonic intravenous fluids, often in previously healthy children undergoing routine elective surgery. In addition, several published studies and reviews have demonstrated hyponatraemia after administration of hypotonic intravenous fluids such as 0.18% saline/4% glucose.

On the basis of the evidence from the review, the CHM concluded that the use of 0.18% saline/4% glucose should be contraindicated in all but a limited group of children treated by experts in paediatric specialist settings, such as renal, cardiac, liver, high dependency, and intensive care units.

Egypt (2). The Pharmacovigilance Committee-Central Administration for Pharmaceutical Affairs (CAPA) decided to contraindicate the use of Intravenous (I.V.) solution containing 0.18% NaCl in children aged 16 years or less, except under expert medical supervision in paediatric specialist settings such as kidney, heart, liver, high-dependency and intensive care units.

In addition, the Pharmacovigilance Committee also requested that all Marketing Authorization Holders of I.V. solution containing 0.18% NaCl in Egypt to distribute "Dear Healthcare Professional Communication (DHPC)" to HealthCare settings to where your product is distributed to inform them with the new safety information.

Reference:
(2) Newsletter of the Egyptian Pharmaceutical Vigilance center, No. 35, Volume 3 December 2012.

Ondansetron

Dose restriction for intravenous use due to dose-dependent QT interval prolongation

Canada. GlaxoSmithKline Inc., in consultation with Health Canada, informed of new information regarding the risk of electrocardiographic QT interval prolongation associated with ondansetron (ZOFRAN®). A recently completed study identified a dose-dependent prolongation of the corrected QT interval (QTc) among healthy subjects treated with ondansetron. QTc interval prolongation can lead to Torsade de Pointes (TdP), a
potentially life-threatening heart rhythm abnormality.

Recommendations based on this new study are as follows:

- The new maximum recommended single intravenous (IV) dose is 16 mg infused over 15 minutes.
- The 32 mg IV dose and the 8 mg IV dose followed by a 1 mg/hour continuous infusion are no longer recommended and should not be used.
- Avoid ondansetron in patients with congenital long QT syndrome. Use caution if administering ondansetron to patients with other risk factors for QT interval prolongation, such as electrolyte abnormalities, congestive heart failure, bradycardia, or use of other medicines that can lead to either QT prolongation or electrolyte abnormalities.
- Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to ondansetron administration.

Physicians are recommended to assess their patients for risk factors for QT interval prolongation or TdP before prescribing ondansetron. For adults treated with intravenous ondansetron prior to chemotherapy, the usual dose is 8 mg infused over 15 minutes at least 30 minutes prior to chemotherapy. It is recommended that the drug should not be administered more rapidly than recommended as more rapid infusion can lead to greater QTc prolongation.

It is also recommended that patients should be advised to contact their health-care professional if they experience signs or symptoms of an abnormal heart rate or rhythm while taking ondansetron (e.g., dizziness, palpitations, syncope).

There are no changes to recommended oral dosing in adults. There are no changes to recommended oral or intravenous dosing in children.

Reference:

Proton Pump Inhibitors and Methotrexate

Interaction of proton pump inhibitors with methotrexate

Canada. Health Canada informed that the labelling for methotrexate and Proton Pump Inhibitors (PPIs) is being updated to include information on a potential interaction between these products. The new information will be in the "Warnings and Precautions" section of the methotrexate and the PPIs labelling. The use of high-dose methotrexate and of PPIs at the same time by patients may increase the amount of methotrexate in the blood leading to side effects. The possible risks to health include kidney failure, low red blood cell count, inflammation of the digestive tract, irregular heartbeat, muscle pain, infections, and diarrhea.

While a definite association between PPI use and an increase in methotrexate has not been confirmed, there have been a number of studies suggesting a possible interaction between PPIs and methotrexate. The potential for an increased risk of methotrexate side effects is very likely, which is why Health Canada informed this change in labelling. Health Canada will continue to evaluate the scientific evidence as it emerges and take appropriate action as needed.

It is recommended that patients should not stop taking their medication unless they have been advised to do so by their health-care professional. Patients using PPIs and methotrexate should consult with their doctor if they have any concerns about their health or these products.

Health-care practitioners are reminded that PPIs, in general, should be prescribed at the lowest dose and for the shortest duration of therapy appropriate to the condition being treated. As noted in the drug labels, a temporary withdrawal of the PPI may be considered by the health-care practitioner in some patients receiving treatments with high-dose methotrexate.

(See WHO Pharmaceuticals Newsletter No. 2, 2010 for updates on warning about interaction between clopidogrel and proton pump inhibitors in Europe and New Zealand and No. 3, 2010 for updated advice on possible interactions in UK).

Reference:
Dabigatran etexilate mesylate

Safety review of post-market reports of serious bleeding events

USA. The U.S. Food and Drug Administration (US FDA) evaluated new information about the risk of serious bleeding associated with use of the anticoagulants dabigatran (Pradaxa®) and warfarin (Coumadin®, Jantoven®, and generics). This assessment was done using insurance claims and administrative data from the US FDA’s Mini-Sentinel pilot of the Sentinel Initiative. The results of this assessment indicate that bleeding rates associated with new use of dabigatran do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa®. The US FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue. The US FDA has not changed its recommendations regarding the drug.

(See WHO Pharmaceuticals Newsletters No. 1, 2012 for safety review of post-market reports of serious bleeding events in the USA, Australia and New Zealand; Risk of serious haemorrhage, need for renal function testing in UK, No.3, 2012 for updated labelling regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves in Canada and Saudi Arabia and No.4, 2012 for modifications to product information for clearer guidance in EU).

Reference:

Human papillomavirus vaccine (Cervarix)

Cervarix: safety review shows balance of risks and benefits remains clearly positive

UK. The MHRA announced that a safety review conducted at the end of its routine use during the on-going human papillomavirus (HPV) immunisation programme found that no new risks have been identified for HPV vaccine Cervarix®, and that the balance of its risks and benefits remains clearly positive. Cervarix® was replaced in the programme by the HPV vaccine Gardasil® from September 2012. Since September 2008 the human papillomavirus (HPV) vaccine Cervarix® has been used extensively in the UK routine HPV immunisation programme to prevent cervical cancer.

The MHRA previously reported on the safety of the vaccine following the first and second year of use and the agency conducted a further safety review of the totality of the UK experience with Cervarix® up to the end of July 2012. No new safety concerns were identified and the number and nature of adverse reaction (ADR) reports received was as expected after administration of at least 6 million doses of the vaccine in the UK.

Before Cervarix® was first used the MHRA anticipated that a range of medical conditions naturally prevalent in the adolescent female population would occur in temporal association with vaccination and might be reported as suspect side effects. Statistical methods were therefore put in place to rapidly assess whether such reports were consistent with chance, or whether they could be new side effects of the vaccine. One such condition was chronic fatigue syndrome (CFS) – the level of reporting for which was found to be well within the expected background incidence rate. An ecological study and a self-controlled case series study using the Clinical Practice Research Datalink (CPRD) also did not find an increased risk of fatigue syndromes with Cervarix®.

Reference:

Non-steroidal anti-inflammatory drugs (NSAIDs)

Pharmacovigilance Risk Assessment Committee to consider need for updated treatment advice for diclofenac in follow-on review

Europe. The European Medicines Agency (EMA) finalised a review of recently published information on the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs). The Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that evidence from newly available published data sources, including meta-analysis of clinical trials and observational studies, and the results of a European Union-funded independent research project, the ‘safety of non-steroidal anti-inflammatory drugs’ (SOS) project, on the cardiovascular safety of this class of medicines confirm findings from previous reviews, conducted in 2005 and 2006.

Most of the data related to the three most widely used NSAIDs – diclofenac, ibuprofen and naproxen. In relation to naproxen and ibuprofen, the CHMP was of the opinion that the current treatment advice adequately reflects the
knowledge regarding the safety and efficacy of these medicines.

For diclofenac, the latest evidence appears to show a consistent but small increase in the risk of cardiovascular side effects for diclofenac compared with other NSAIDs, similar to the risks of COX-2 inhibitors, another class of painkillers. As a follow-on to this review, the Agency’s new Pharmacovigilance Risk Assessment Committee (PRAC) will now assess all available data on diclofenac (both published and unpublished) to consider the need for updated treatment advice.

Reference:

Over-The-Counter Eye Drops and Nasal Sprays

Serious adverse events from accidental ingestion by children

USA. The US FDA warned health-care professionals and the public that accidental ingestion by children of over-the-counter eye drops used to relieve redness and nasal decongestant sprays can result in serious and life-threatening adverse events. The eye drops and nasal sprays that have been involved in the cases of accidental ingestion contain the active ingredients tetrahydrozoline, oxymetazoline, or naphazoline.

The cases of accidental ingestion reviewed by the US FDA occurred in children 5 years of age and younger. No deaths were reported; however, serious events requiring hospitalization such as nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma have occurred. Ingestion of only a small amount (1-2 mL; for reference, there are 5 mL in a teaspoon) of the eye drops or nasal spray can lead to serious adverse events in young children.

Most of these redness-relief eye drops and nasal decongestant sprays currently do not come packaged with child-resistant closures, so children can accidentally ingest the drug if the bottles are within easy reach. These products are sold under various brand names, as generics, and as store brands.

The US FDA recommended that consumers should store these products out of reach of children at all times. It is also recommended to call local poison control center immediately if a child accidentally swallows OTC redness-relief eye drops or nasal decongestant spray.

Reference:

Simvastatin

Evidence supporting recent advice on dose limitations with concomitant amlodipine or diltiazem

UK. In August 2012 the MHRA published advice that simvastatin is contraindicated with concomitant use of certain medicines, such as ciclosporin, danazol, and gemfibrozil. In addition, the recommendations for the maximum dose of simvastatin changed when used with a number of other medicines, including amlodipine and diltiazem. These changes were driven primarily by concerns about an increased risk of myopathy and/or rhabdomyolysis at higher plasma concentrations of simvastatin, which may result from such drug interactions.

Following further consideration by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines, the MHRA published an article summarises the evidence underlying the new advice that the maximum recommended dose for simvastatin in conjunction with amlodipine and diltiazem is now 20 mg/day. The prescribed doses of amlodipine and diltiazem need not be changed.

In summary, the available evidence supports the recommendation that the maximum daily dose of simvastatin should not exceed 20 mg when co-administered with amlodipine or diltiazem:

- concomitant use of either amlodipine or diltiazem increases the exposure to simvastatin through CYP3A4 interactions
- the incidence of myopathy is increased with higher doses of simvastatin when co-administered with amlodipine or diltiazem, compared to the absence of amlodipine or diltiazem, or lower doses of simvastatin
- approximately 75% of the LDL-lowering effect is apparent at lower doses of simvastatin and only an additional 6% effect would be expected by doubling the dose from 20 mg to 40 mg

In the absence of further evidence, the recommendation for a maximum daily dose of simvastatin of 20 mg applies with amlodipine at doses of both 10 mg and 5 mg.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 and No.1, 2012 for new restrictions, contraindications, and dose...
limitations in the USA and No. 5, 2012 for updated advice on drug interactions and contraindications in the UK.)

**Reference:**
Drug Safety Update, October 2012, Volume 6, issue 3, H1 MHRA, ([www.mhra.gov.uk](http://www.mhra.gov.uk)).
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™. The database contains over 7 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC’s current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 15). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: info@who-umc.org.

Ethinylestradiol/Drospirenone and Spinal cord infarction

Response from Bayer Healthcare

It is estimated that spinal cord infarction accounts for 1% of stroke hospitalizations1. Because of the rarity of spinovascular disease compared to cerebrovascular disease, only few large clinical investigations exist, mostly discussing spinal cord ischemia due to aortic surgery. Pathogenesis and natural history of spontaneous or nonsurgical spinal cord infarctions remains largely unknown2.

Spinal cord infarction was not reported in Drospirenone + Ethinylestradiol (EE/DRSP) clinical studies analyzed to date, which included over 9,800 women.

Post authorization safety studies investigating the arterial (ATE) and venous thromboembolism (VTE) risk with EE/DRSP have included over 130,000 treatment years; one case of spinal cord infarction was derived from these populations.

There are no published case reports on spinal cord infarction in association with EE/DRSP.

A cumulative retrieval in Bayer Pharma’s worldwide safety database of all cases applying the MedDRA term (PT): “Spinal cord infarction” in association with all EE/DRSP products irrespective of causality revealed a total of four cases, including all three UMC cases. Cases were all medically confirmed, originated from US (2), Germany (1) and Denmark (1) and were either received as spontaneous reports (1), from a postmarketing-surveillance study (1) or via litigation procedures (2). Treatment duration varied between 3 and 7 years of partly intermittent intake of EE/DRSP. In 3 cases magnetic resonance imaging (MRI) confirmed spinal cord infarction at thoracical and/or cervical level. Patient age varied between 32 and 49 years at the time of the event. Risk factors for ATE (smoking, hypercholesterinaemia, advanced age, migraine, protein S deficiency) were reported in three cases.

The frequency of spinal cord infarction with EE/DRSP reported to Bayer Pharma is 0.06 reports per 1 million treatment years, based on 67.2 million treatment years estimated cumulative total exposure with EE/DRSP.

As of last PSUR, the cumulative reporting frequency for non-cerebral and cerebral ATE with EE/DRSP was 0.1 per 10,000 treatment years. Within that dataset, the proportion of spinal cord infarction was 0.6%. By comparison, a cohort study of COC users reported an ATE incidence rate of 1-2 ATE per 10,000 treatment years3.

Conclusion

As stated in the companies’ Reference Safety Information (RSI) of EE/DRSP containing COCs and implemented in local labelling, “epidemiological studies have suggested an association between the use of COCs and an
increased risk of arterial and venous thrombotic and thromboembolic diseases”. Events occur rarely and may very rarely involve spinal cord arteries resulting in spinal cord infarction and leading to significant morbidity. Accordingly, the company considers them listed events. The seriousness of the condition is reflected in the RSI of EE/DRSP stating that “arterial thromboembolic events may be life-threatening or may have a fatal outcome No new safety finding arises from the analysis of these cases. Reports of ATE including vascular involvement of the spinal cord will continued to be closely monitored.

The company’s assessment of the benefit-risk balance for EE/DRSP remains favourable. This is supported by consistent clinical findings over a 15-year period and up to 10 years of post-marketing study results.

Fesoterodine – GI haemorrhage

Dr Richard Hill, Australia

Summary

VigiBase™ contains seven reports of gastrointestinal haemorrhage following use of the muscarinic receptor antagonist fesoterodine. A number of the reports describe short time to onsets and in most cases recovery occurred on stopping fesoterodine. A plausible mechanism for this adverse reaction involves reduction in gastric motility and consequent increased exposure to gastric irritants, particularly concomitant drugs.

Fesoterodine

Fesoterodine is a muscarinic receptor antagonist used for the treatment of symptoms associated with overactive bladder. The usual dose is 4-8 mg daily. Fesoterodine is rapidly hydrolysed to the active metabolite 5-HMT (the same active metabolite as tolterodine), which is subsequently metabolised by CYP3A4 and CYP2D6. Elevated plasma levels of 5-HMT may occur in the presence of potent inhibitors of CYP3A4 and CYP2D6.

Fesoterodine is said to have relatively increased selectivity for muscarinic M2 and M3 receptors and decreased selectivity for M1 receptors. This may result in less cognitive impairment compared to nonselective antimuscarinic drugs, but is not expected to reduce gastrointestinal adverse effects such as decreased gastrointestinal motility and constipation.

GI haemorrhage

This association was detected for the WHO-ART High Level Term (HLT) GI haemorrhage, which contains the Preferred Terms (PTs) GI haemorrhage, haematemesis, haemorrhage rectum and melaena.

References


Labelling

GI haemorrhage is not labelled in either the US product label or the UK Summary of Product Characteristics (SPC). Labelled gastrointestinal adverse effects include abdominal pain, dyspepsia, constipation and diarrhoea. According to the US product label "fesoterodine should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.”

In the UK SPC, "decreased gastrointestinal motility" is included under special warnings and precautions for use.

Reports in VigiBase

This signal was identified during a pilot study investigating electronic health records (EHRs) as an additional source of reference during signal detection in the WHO Global ICSR database, VigiBase™. The EHRs used in the study came from The Health Improvement Network (THIN), an electronic medical record data resource covering three and a half million active patients in the UK. After elimination of one duplicate, VigiBase contains seven reports of GI haemorrhage following fesoterodine use, received from five countries (Germany and the US two each; Netherlands, Switzerland and UK one each) as shown in Table 1.

Comment

The reports are notable for the short time to onset in four of seven reports and positive dechallenge (recovery after stopping fesoterodine) in five of seven reports. Two of the reports list concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and three other reports list other concomitant medications (oxycodeone, bendrofluethiazide,
tramadol) described as being associated with "gastric irritation" in UK SPCs. No reports mention constipation as an ADR and no reports list concomitant CYP2D6 or CYP3A4 inhibitors.

Discussion
Six reports in VigiBase contain sufficient information regarding time to onset and recovery after dechallenge to support an association between fesoterodine and gastrointestinal bleeding. Gastrointestinal adverse effects, including abdominal pain, diarrhoea, dyspepsia, and constipation, are common with fesoterodine and it is possible to envisage at least two mechanisms which may explain this association.

A recent meta-analysis found that fesoterodine is associated with a doubling of risk of constipation compared to placebo. Chronic constipation is already a significant health problem in the elderly, the same group of patients prescribed fesoterodine, and constipation itself increases the risk of other sequelae such as haemorrhoids, which may result in bleeding.

Secondly, drugs with antimuscarinic activity, such as fesoterodine, can reduce gastric motility, possibly reducing the absorption of concomitantly administered medications. The US product label for fesoterodine specifically mentions this as a possible mechanism for some drug interactions.

In the case of drugs which are gastric irritants, this reduced absorption may result in increased gastric irritation, with consequent GI bleeding. Clearly, this will also apply to non-prescription medicines, such as 'over-the-counter' NSAIDs, which may not be captured in full on spontaneous ADR reports.

VigiBase additionally contains 52 reports with the HLT GI haemorrhage in association with tolterodine, and a published review states that gastrointestinal haemorrhage and decreased GI motility have been reported infrequently in association with tolterodine use.

Conclusion
Reports in VigiBase lend support to an association between fesoterodine and GI bleeding. Key features in the reports include rapid time to onset, recovery on stopping fesoterodine, and co-administration with drugs known to cause gastric irritation, suggesting a possible mechanism for this adverse reaction.

References
Response from Pfizer

Search and analysis/review of the medical literature and the Pfizer clinical and safety databases for gastrointestinal haemorrhage-related terms do not indicate a risk of gastrointestinal haemorrhage associated with fesoterodine and therefore there are no newly identified issues that may impact on the benefit/risk profile for fesoterodine.

Background

The Uppsala Monitoring Centre (UMC) has identified 7 Individual Case Safety Reports (ICSR) related to Gastrointestinal haemorrhage from patients treated with fesoterodine (Toviaz) in the WHO ICSR VigiBase™ database. Six of these cases were reported by the UMC to contain sufficient information regarding time to onset and recovery after de-challenge to support a possible association between fesoterodine and gastrointestinal bleeding. The UMC proposed theoretical mechanisms by which drugs with antimuscarinic activity, such as fesoterodine, may increase gastrointestinal motility by increasing the risk of constipation and may also reduce gastrointestinal motility leading to increased exposure of the gastrointestinal tract to concomitantly-administered gastric irritants such as NSAIDs.

<table>
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<th>Outcome</th>
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<th>Concomitant drugs</th>
<th>GI reactions</th>
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<td>12 mg</td>
<td>aspirin, nitrendipine, atenolol, nifedipine</td>
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<td>NS</td>
<td>diclofenac, acetylcysteine, bisoprolol, ramipril, Zolpidem</td>
<td>GI haemorrhage</td>
</tr>
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<td>2 days</td>
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<td>melaena, haemorrhage rectum</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>2 days</td>
<td>not known</td>
<td>8 mg</td>
<td>sertraline, tramadol, gabapentin</td>
<td>GI haemorrhage abdominal distension</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>NS</td>
<td>not known</td>
<td>NS</td>
<td>NS</td>
<td>GI haemorrhage (reported term: diarrhoea haemorrhagic)</td>
</tr>
</tbody>
</table>

Table 1. VigiBase™ reports of fesoterodine and GI haemorrhage

TTO - time to onset; NS - not stated; Drugs in bold have known association with gastric irritation

Response

Pfizer has conducted a search of the relevant medical literature and the company safety and clinical databases to identify cases of gastrointestinal haemorrhage using the Gastrointestinal haemorrhage Standardized MedDRA Query (SMQ, version 15.0, narrow event terms). A broad search of the medical literature for gastrointestinal haemorrhage-related events reported with urinary antimuscarinic drugs (including fesoterodine, tolterodine, solifenacin, darifenacin and oxybutynin using both generic and trade names) was conducted to assess whether there was evidence for association with the antimuscarinic mechanism of action. This search identified a published review, also identified in the WHO report, where reference is made to the Pfizer Periodic Safety Update Report in which gastrointestinal haemorrhage and decreased GI motility were reported infrequently in association with tolterodine use. There were no other reports in the literature indicative of an association between gastrointestinal haemorrhage events and use of antimuscarinic drugs, including fesoterodine, for treatment of overactive bladder.

The Pfizer safety database contains cases of Adverse Events reported spontaneously, cases reported from Regulatory Authorities, cases published in the medical literature, and cases of Serious Adverse Events reported from clinical trials and other solicited sources. This database was searched for events contained within the
Gastrointestinal haemorrhage SMQ specifically from cumulative fesoterodine data (from the International Birth Date 20th April 2007 through 28th May 2012). Of the 3,446 fesoterodine ICSRs in this database, 17 gastrointestinal haemorrhage-related events (0.5% of all fesoterodine cases in the database) were identified. Nine of these cases were consumer reports without medical confirmation. There were no deaths in this dataset and six of the cases reported hospitalization. Only two of the cases co-reported constipation with the gastrointestinal haemorrhage term indicating that the two outcomes are not necessarily linked. Six of the 7 cases identified by UMC appear to be included in this dataset. The reported events did not indicate a specific pattern and included (n): Diarrhoea haemorrhagic (1), Gastric haemorrhage (1), Gastrointestinal haemorrhage (3), Haematemesis (2), Haematochezia (5), Rectal haemorrhage (2) and Ulcer haemorrhage (3).

The clinical database of all completed double-blind and open label Phase 2-4 fesoterodine trials was searched for terms contained within the Gastrointestinal haemorrhage SMQ. Of 9,762 subjects exposed to fesoterodine, 16 subjects (0.2%) reported relevant events, only one of which was considered to be treatment-related (a case of Gastrointestinal haemorrhage). In double-blind clinical trials, 7 subjects of 6,132 exposed to fesoterodine (0.11%) and 7/3,993 (0.18%) subjects exposed to placebo experienced gastrointestinal haemorrhage-related adverse events. In subjects for whom patient profiles are available, the gastrointestinal event was reported with constipation by 2/15 subjects exposed to fesoterodine and 2/6 subjects exposed to placebo. Treatment emergent events in the fesoterodine exposed clinical dataset included the following (n): Anal haemorrhage (1), Gastrointestinal haemorrhage (1, considered treatment-related), Haematemesis (1), Haematochezia (4), Hemorrhoidal haemorrhage (1), Occult blood positive (1), Rectal haemorrhage (7).

Conclusions
The reporting rate of gastrointestinal haemorrhage-related events in the fesoterodine safety and clinical databases is very low and there is insufficient evidence to link these events to the use of fesoterodine. For those events identified by the UMC that were present in the Pfizer safety database and in which gastrointestinal irritant concomitant medications were present, the case narratives do not clarify whether or not the concomitant medication could be directly responsible for the event. In addition, none of the narratives for these cases state whether the concomitant medications were also discontinued at the same time as fesoterodine, which may have led to the symptom improvement on de-challenge. Only two of the cases in the Pfizer safety database report constipation in addition to the gastrointestinal haemorrhage event whilst none of the cases identified in the UMC search report constipation events. Similarly, in clinical trials, gastrointestinal haemorrhage events were not associated with constipation in subjects exposed to fesoterodine in comparison with subjects exposed to placebo. In double-blind clinical trials, gastrointestinal haemorrhage-related events did not occur more frequently in subjects exposed to fesoterodine compared with those exposed to placebo.

Review of cases of gastrointestinal haemorrhage-related events in the literature for antimuscarinic drugs prescribed for overactive bladder, and in the Pfizer safety and clinical databases for fesoterodine does not indicate a risk of gastrointestinal haemorrhage associated with fesoterodine use. Pfizer will continue to monitor all adverse events reported to its clinical and safety databases and will ensure that product labeling appropriately reflects the benefit / risk profile for fesoterodine.

References
CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

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