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Patient Health Protection

PhVWP monthly report on safety concerns, guidelines and general matters

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The CHMP Pharmacovigilance Working Party (PhVWP) held its July 2012 plenary meeting on 16-18 July 2012.

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/landing/news_and_events.jsp&mid=.

Allopurinol – Risk of skin reactions associated with HLA-B*5801 allele

Allopurinol-induced serious cutaneous adverse reactions (SCAR), including Steven Johnson’s syndrome (SJS) and toxic epidermal necrolysis (TEN), are associated with a genetic marker, the HLA-B*5801 allele. The sensitivity of prior testing for HLA-B*5801 may be as low as 50% in European populations. This suggests that potentially half of European patients that do develop SCAR will not be identified by prior testing. Although the sensitivity of prior testing is likely to be higher in other populations, particularly the Han Chinese, there is a lack of suitable alternative therapies to allopurinol. Furthermore, the clinical utility of testing for this allele prior to treatment with allopurinol is not proven in any population.

Therefore, the recommendation at present is that:

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- **The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.**
- **Routine testing for HLA-B*5801 is not recommended in any patients. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.**

The PhVWP reviewed pharmacogenetic study findings regarding allopurinol-induced severe cutaneous (i.e. skin) adverse reactions (SCAR) and finalised their conclusions for updating the product information of allopurinol-containing medicinal products authorised in the EU (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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.

Bisphosphonates for oral use – Risk of oesophageal irritation (but insufficient evidence on causal relationship with oesophageal cancer)

A review of four new epidemiological studies supports the outcome of the PhVWP review in October 2010 that there is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer. However, bisphosphonate tablets can cause irritation to the oesophagus and patients should therefore carefully follow the instructions in the package leaflet on how to take the medicine and report to their physician any signs of oesophageal irritation, such as difficulties or pain on swallowing, chest pain or heartburn. In patients with known Barrett’s oesophagus caution should be used and physicians should carefully consider the benefits and potential risks of treatment with alendronic acid, ibandronic acid and risedronic acid.

The PhVWP completed a review of four new epidemiological studies regarding the risk of oesophageal cancer with bisphosphonates for oral use¹. The review of the new studies did not change the conclusion of PhVWP from 2010 that there is insufficient evidence to support a definite causal relationship between oral bisphosphonates and oesophageal cancer.

However, as a possible causal association cannot be excluded, the PhVWP considered that a warning about use in patients with known Barrett’s oesophagus (a condition which, in a small number of people, can lead to oesophageal cancer) should be included in the product information for all nitrogen-containing bisphosphonates for oral use. Such a warning already exists in the product information for alendronic acid and ibandronic acid for oral use. The PhVWP advised that this warning should now also be added to the product information for risedronic acid-containing medicinal products authorised in the EU for oral use (see Annex 2 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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 The active substances included in this review were alendronic acid, clodronic acid, etidronic acid, ibandronic acid, risedronic acid and tiludronic acid.

Carbamazepine – Risk of skin reactions in association with HLA-B*1502 allele in patients from some Asian populations and with HLA-A*3101 allele in patients of European and Japanese descent

Carbamazepine-induced severe cutaneous adverse reactions (SCAR) in European Caucasians and Japanese patients are associated with a newly identified genetic marker, the HLA-A*3101 allele. However, the evidence to date shows that the sensitivity of testing for HLA-A*3101 allele identifies only about 40% of patients that develop carbamazepine-induced SCAR. The clinical utility of testing for this allele in the above population prior to treatment with carbamazepine is not proven.

Carbamazepine-induced SCAR are also associated with the HLA-B*1502 allele, and clinical utility of testing for HLA-B*1502 allele in patients of Han Chinese and Thai origin has been proven. Almost 100% of cases could be avoided by prior genetic testing. The evidence supporting the testing for this allele in other Asian populations at genetic risk is weaker.

Therefore, the recommendation at present is that:

- **Individuals of Han Chinese and Thai origin should, whenever possible, be tested for HLA-B*1502 allele prior to treatment with carbamazepine.**
- **Testing for HLA-B*1502 allele in other Asian populations at genetic risk may be considered.**
- **Routine testing for HLA-A*3101 allele is not recommended. If European Caucasians or patients of Japanese descent are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed the risks.**

The PhVWP reviewed new pharmacogenetic study findings regarding carbamazepine-induced severe cutaneous (i.e. skin) adverse reactions (SCAR) and finalised their conclusions for updating the product information of carbamazepine-containing medicinal products authorised in the EU (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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.

Oxcarbazepine – Risk of skin reactions potentially associated with HLA-A*3101 and HLA-B*1502 alleles

Carbamazepine-induced severe cutaneous adverse reactions (SCAR) in European Caucasians and Japanese patients are associated with a newly identified genetic marker, HLA-A*3101, but routine testing for HLA-A*3101 allele in European Caucasians and Japanese patients is not recommended for carbamazepine or the structurally related oxcarbazepine. If European Caucasians or patients of Japanese descent are known to be positive for HLA-A*3101 allele, the use of oxcarbazepine may be considered if the benefits are thought to exceed the risks.

Carbamazepine-induced SCAR are also associated with the HLA-B*1502 allele, and clinical utility of testing for HLA-B*1502 allele in patients of Han Chinese and Thai origin has been proven. Individuals of Han Chinese and Thai populations should, whenever possible, be tested for the HLA-B*1502 allele before starting treatment with the structurally related

oxcarbazepine. Testing for the HLA-B*1502 allele in other Asian populations may be considered.

Given data on genetic associations with carbamazepine-induced severe cutaneous (i.e. skin) adverse reactions (SCAR), the PhVWP reviewed data for the structurally related oxcarbazepine and finalised their conclusions for updating the product information of oxcarbazepine-containing medicinal products authorised in the EU (see Annex 4 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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.

Donepezil – Risk of neuroleptic malignant syndrome (but insufficient evidence on causal relationship with serotonin syndrome)

Neuroleptic malignant syndrome (NMS) has been reported in patients treated with donepezil with or without concomitant antipsychotic medication, and if a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, donepezil should be discontinued.

The PhVWP reviewed data in relation to concerns over serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) in association with donepezil. The PhVWP concluded that modifications to the summaries of product characteristics and package leaflets of donepezil-containing medicinal products authorised in the EU are necessary to include the risk of NMS, especially in patients who are concomitantly treated with antipsychotics, and recommended implementation of this conclusion to the competent authorities in Member States (see Annex 5 for the Summary Assessment Report).

Levodopa, dopamine agonists and COMT inhibitors – Risk of impulse control disorders

Behavioural symptoms of impulse control disorders (ICDs) may occur in patients taking levodopa and/or dopamine agonists at normal doses, irrespective of the indication. Patients should be regularly monitored for ICD symptoms, which include pathological gambling, hypersexuality, increased libido, compulsive buying or spending and compulsive or binge eating.

Accumulating data on the risk of impulse control disorders (ICDs) in association medicinal products containing levodopa and/or a dopamine agonist have become available. Some of the ICDs described are not currently included in the product information for these products, and also the data suggest that ICDs may occur in indications for these products other than Parkinson's disease. The PhVWP therefore agreed to review these data to ensure that the product information reflects the latest available evidence². The PhVWP concluded to recommend updates to the product information for all medicinal products authorised in the EU containing levodopa (single substance and combination products including those containing COMT inhibitors), a dopamine agonist or a catechol-O-methyltransferase (COMT) inhibitor (as single substances product to be used together with levodopa) (see Annex 6 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well

² The active substances included in this review were levodopa, the dopamine agonists apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, quinagolide, ropinirole and rotigotine and the COMT inhibitors benserazide, carbidopa, entacapone and tolcapone.

as practical information on implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

The CHMP was informed accordingly in relation to the centrally authorised medicinal products STALEVO and LEVODOPA/CARBIDOPA/ENTACAPONE ORION (containing levodopa + carbidopa + entacapone), MIRAPEXIN and SIFROL (pramipexole), NEUPRO and LEGANTO (rotigotine), TASMAR (tolcapone) and COMTESS, COMTAN and ENTACAPONE ORION (entacapone). The product information of the centrally authorised generics OPRYMEA, PRAMIPEXOLE ACCORD and PRAMIPEXOLE TEVA (pramipexole) and ENTACAPONE TEVA (entacapone) will follow their respective originator product. Interested readers are asked to observe the agency's webpage for human medicinal products http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 for updates to the product information as necessary.

Pantoprazole and other proton pump inhibitors – Evidence does not confirm increased risk of pneumonia

The possibility of a causal association of pantoprazole and other proton pump inhibitors (PPIs) with risk of pneumonia has not been confirmed, but remains under close monitoring.

Given that observational studies and meta-analyses had suggested that use of proton pump inhibitors (PPIs) may increase the risk of pneumonia, the PhVWP agreed to review the available data and its potential impact on the product information for PPIs³, in particular of pantoprazole given its wide use and availability in the EU without prescription. The PhVWP concluded that the evidence did not confirm an increased risk of pneumonia and no risk minimisation measures were considered warranted by the current evidence. However, the PhVWP recommended that this issue should remain under review (see Annex 7 for the Summary Assessment Report).

The CHMP was informed accordingly in relation to the centrally authorised pantoprazole-containing medicinal products CONTROLLOC CONTROL, PANTECTA CONTROL, PANTOLOC CONTROL, PANTOZOL CONTROL and SOMAC CONTROL.

Pimecrolimus – Concerns over off-label use

Due to concerns of a potential but yet unconfirmed increased risk of malignant disease, pimecrolimus should not be used for conditions other than corticosteroid-resistant dermatitis and should not be used in patients below 2 years of age.

Following an update of the risk management plan (RMP), the PhVWP reviewed off-label use occurring with pimecrolimus.

Pimecrolimus is a topical calcineurin inhibitor, authorised for the treatment of patients aged 2 years and above with mild to moderate atopic dermatitis where treatment with topical corticosteroids is inadvisable or not possible, e.g. due to intolerance to corticosteroids or lack of effect. The product is applied to the skin, in the face and neck region, over long time periods of treatment.

Due to its immunosuppressive effects, there is concern over the potential for an increased risk of malignant disease, which is addressed by means of a RMP. Updates of the RMP have to be submitted by the marketing authorisation holder yearly. Closely related to this safety concern is the concern over off-label use for skin manifestations other than atopic dermatitis or, more importantly, the off-label use for authorised or unauthorised indications in children below 2 years of age.

³ The active substances included in this review were esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

The PhVWP therefore reviewed the data in the most recently submitted RMP and considered that it appeared that off-label use still occurs to a considerable extent. Prescription data from 2009 to 2010 showed that prescriptions for atopic dermatitis account only for 62.7% of the total number of prescriptions. Overall, the number of off-label prescriptions decreased across the EU by 24% on average, from 378,901 in 2009 to 287,505 in 2010. However in some Member States, an increase in the range of 2 to 19% occurred. The number of off-label prescriptions in patients below 2 years of age was estimated as an average of 4.4% of the total number of prescriptions in the EU in 2010. There were differences across the EU, with significant increases in some and significant decreases in other Member States.

Due to the persistent off-label use in some Member States, the PhVWP concluded that it is necessary to emphasise the authorised indication and discourage off-label use observed for skin manifestations other than atopic dermatitis and in particular off-label use observed in patients below 2 years of age in authorised or unauthorised indications. Because of the particular concern over off-label use in children below 2 years of age, the PhVWP recommended to request the marketing authorisation holder to consider further risk minimisation measures to reduce use of pimecrolimus in this age group.

Prazepam – Not contraindicated in glaucoma

Product information for prazepam should be updated to delete contraindication in glaucoma.

Given inconsistent product information for prazepam across the EU, the PhVWP reviewed data in relation to benzodiazepines and the possible risk of glaucoma. On the basis of this review, the PhVWP considered that there was insufficient evidence to require a contraindication for glaucoma in the summary of product characteristic (SmPC) of any benzodiazepine, and therefore recommended deleting the glaucoma contraindication from the SmPCs for prazepam-containing medicinal products authorised in the EU (see Annex 8 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For practical information on implementation, interested readers are advised to consult the HMA website (<http://www.hma.eu/cmdh.html>) for upcoming information.

Tramadol – Risk of adverse reactions of the central-nervous system and dosing in the elderly and those with renal or liver impairment

Updating the product information for tramadol has been recommended to minimise certain adverse reactions of the central-nervous system and to advise on dosing in the elderly and those with renal or liver impairment.

The PhVWP conducted a review in relation to tramadol and safety concerns including dosing in elderly patients and in patients with renal or hepatic insufficiency as well as risks of seizures, serotonin syndrome and suicidal ideation or behaviour. The PhVWP concluded upon recommendations for updating the product information of tramadol-containing medicinal products authorised in the EU (see Annex 9 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. 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.

Guidelines and general matters

Below is a summary of the main discussions on guidelines and other general matters of an organisational, regulatory or methodological nature.

Good Pharmacovigilance Practices (GVP) for the EU – Modules IV and XV for public consultation

The PhVWP noted that two further modules of good pharmacovigilance practices (GVP) (see PhVWP Monthly Report 1206) are in the process of finalisation for release for public consultation in the following week, namely GVP Module IV on pharmacovigilance audits and GVP Module XV on safety communication. The public consultation will be open for eight weeks. Interested readers and those wanting to participate in the public consultation are referred to the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac05804fcdb1).

The meeting in July 2012 was the last meeting of the PhVWP. The PhVWP held regular meetings between March 1995 and July 2012. New EU legislation, taking effect in July 2012, introduces a new scientific committee at the agency, the Pharmacovigilance Risk Assessment Committee (PRAC), which had its inaugural meeting on 19-20 July 2012. Therefore, this is the last issue of the PhVWP Monthly Report.

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

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

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 July 2012

Allopurinol – Risk of skin reactions associated with HLA-B*5801 allele

Key message

Allopurinol-induced serious cutaneous adverse reactions (SCAR) including Steven Johnson's syndrome (SJS) and toxic epidermal necrolysis (TEN) are associated with a genetic marker, the HLA-B*5801 allele. The sensitivity of prior testing for HLA-B*5801 may be as low as 50% in European populations. This suggests that potentially half of European patients that do develop SCAR will not be identified by prior testing. Although the sensitivity of prior testing is likely to be higher in other populations, particularly the Han Chinese, there is a lack of suitable alternative therapies to allopurinol. Furthermore, the clinical utility of testing for this allele prior to treatment with allopurinol is not proven in any population.

Therefore, the recommendation at present is that:

- The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.
- Routine testing for HLA-B*5801 is not recommended in any patients. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

Safety concern and reason for current safety review

The PhVWP noted a publication in the medical literature on a pooled analysis of case-control studies, conducted by the US Food and Drug Administration (FDA) and concluding that allopurinol may need to be avoided in patients who are known carriers of the HLA-B*5801 allele because of their risk of developing severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [8]. The PhVWP also noted that the product information for the innovator product in the EU contains pharmacogenetic information in section 4.8 of the summary of product characteristics (SmPC) in some Member States but was not harmonised across all allopurinol-containing medicinal products authorised in the EU.

The PhVWP therefore agreed to conduct a review of the recent medical literature to determine whether it has implications for the product information.

Clinical setting

Allopurinol is indicated for reducing uric acid formation in conditions where uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy). It is also indicated for management of 2,8-dihydroxyadenine renal stones related to deficient activity of adenine phosphoribosyltransferase and for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid and dietary measures have failed.

Information on the data assessed

The PhVWP considered the recently published articles on the association of allopurinol-induced SCAR and the HLA-B*5801 allele [1-8], together with information collected from Member States.

Input was received from the Pharmacogenetic Working Party (PGWP) and external experts.

Outcome of the assessment

The PhVWP considered the following:

Six key case-control pharmacogenetic studies [1-6] and two pooled analyses of individual case-control studies [7-8] identified an association between carriage of the HLA-B*5801 allele and SCAR including SJS and TEN in allopurinol-treated patients.

The study in Han Chinese [1] included a total of 51 cases that developed SCAR following allopurinol treatment, of which 21 cases were SJS/TEN (SJS: 13 cases, TEN: 3 cases, SJS/TEN: 5 cases). The authors reported a carriage frequency of the HLA-B*5801 allele of 100% in the case group, 15% in the tolerant control group and 20% in the population control group (OR = 393; 95% CI: 23-6665). The incidence of SCAR in the Han Chinese population is uncertain and estimated to be approximately 0.4%. The sensitivity and specificity of the HLA-B*5801 allele for predictions of allopurinol-induced SJS/TEN was reported as 100% and 89.5%, respectively. However, the number needed to test in order to avoid one case of SJS/TEN is likely to be large in view of the low incidence of SCAR and the high frequency of the HLA-B*5801 allele in this population.

In the study of Thai patients [4], all 27 cases (100%) of SJS/TEN (SJS: 2 cases, TEN: 1, SJS/TEN: 1) were HLA-B*5801-positive. Of the tolerant controls, 7 (13%) subjects carried the HLA-B*5801 allele (OR = 348.3; 95% CI: 19-6337). The sensitivity and specificity of the HLA-B*5801 allele for predictions of allopurinol-induced SJS/TEN was 100 and 87%, respectively. As the incidence of SJS/TEN was not available in a Thai population, the authors assumed a 0.2% incidence rate. The benefit of screening in this population is likely to be limited given that the incidence of SJS/TEN is not known.

In the other studies [2, 3, 5] in Japanese, European and Korean populations respectively, not all cases of SJS/TEN following allopurinol treatment were identified to be carriers of the HLA-B*5801 allele. The carriage frequency in the cases ranged from 56% to 92%. The evidence for an association with HLA-B*5801 allele and the risk of SJS/TEN is weaker in the Japanese, Korean and European populations. These studies may indicate that this allele is not the sole factor in determining the risk of SJS/TEN in patients and that development of these adverse reactions is likely to be multifactorial, with other genes and the environment also playing a role.

Another study in Korean patients was conducted to determine the incidence of allopurinol-induced hypersensitivity in patients with chronic renal insufficiency [6]. In this study a cohort of 448 patients with chronic renal insufficiency underwent serologic HLA typing for future kidney transplantation. 16 subjects (16/448 or 3.6%) experienced allopurinol hypersensitivity. Among these 16 subjects, 9 cases were further defined as SCAR (9/448 or 2%) with 22 SJS and 7 allopurinol hypersensitivity syndrome (AHS) cases. The remaining 7 subjects had simple rashes. All 9 SCAR cases were HLA-B*5801-positive (100%). HLA-B*5801 was present in 9.5% of allopurinol-tolerant subjects. The incidence of allopurinol-associated SCAR (SJS and AHS) was 18% among HLA-B*5801-positive patients in the cohort compared to 0% among HLA-B*5801-negative patients. The allopurinol hypersensitivity "simple rash" cases were excluded from the case population when calculating the performance characteristics of HLA-B*5801.

The two pooled analyses revealed a significant association of the HLA-B*5801 allele and the increased risk of allopurinol-induced SJS/TEN [7-8]. However [8] commented that the clinical performance characteristics of HLA-B*5801 genotyping cannot be determined using the existing case-control data and lack of clearly defined incidence rates for SJS/TEN in patients receiving allopurinol.

Considering the evidence regarding the association between allopurinol-induced SCAR, including SJS and TEN, and the HLA-B*5801 allele, the PhVWP concluded that the evidence to date suggests that there is uncertainty in the incidence of these reactions and that the false positive results rate for HLA-B*5801 testing is likely to be high. Also, the sensitivity of prior testing for HLA-B*5801 may be as low as 50% in European populations. This suggests that potentially half of European patients that do develop SCAR will not be identified by prior testing. Although the sensitivity of prior testing is likely to be higher in other populations, particularly the Han Chinese, there is a lack of suitable alternative therapies to allopurinol. Furthermore, the clinical utility of testing for this allele prior to treatment with allopurinol is not proven in any population.

Therefore, the PhVWP agreed that the product information for allopurinol-containing products should be updated in order to include the following information:

- The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.
- Routine testing for HLA-B*5801 is not recommended in any patients. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

Although there is growing evidence that chronic renal impairment is a risk factor for allopurinol-associated SCAR, further research was considered required on the association of the HLA-B*5801 allele and SCAR in patients with chronic renal insufficiency before a recommendation on HLA testing in these patients could be made.

The PhVWP recommended that the summaries of product characteristics (SmPCs) of allopurinol-containing products authorised in the EU should be updated to include:

in SmPC section 4.4, that:

- allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN; these reactions are clinical diagnoses, and their clinical presentations remain the basis for decision-making; and if such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN; corticosteroids may be beneficial in overcoming hypersensitivity skin reactions;

- the HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol-related hypersensitivity syndrome and SJS/TEN; the frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin; the use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established; if the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks; extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms;

in SmPC section 4.8 (under Immune system disorders), that:

- delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occur in various combinations; other organs may also be

affected (e.g. liver, lungs, kidneys, pancreas, myocardium and colon); if such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn immediately and permanently; when generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

The PhVWP recommended that the package leaflets (PLs) of allopurinol-containing products authorised in the EU should be updated to include:

in PL section 2, that:

- serious skin rashes (hypersensitivity syndrome, SJS, TEN) have been reported with the use of allopurinol; frequently, the rash can involve ulcers of the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes); these serious skin rashes are often preceded by influenza-like symptoms fever, headache, body ache (flu-like symptoms); the rash may progress to widespread blistering and peeling of the skin; these serious skin reactions can be more common in people of Han Chinese or Thai origin;

- if a rash or these skin symptoms develop, allopurinol should be stopped and the physician be contacted immediately.

in PL section 4 (under Rare (affects less than 1 in 1000 people)):

- fever and chills, headache, aching muscles (flu-like symptoms) and generally feeling unwell;

- any changes to the skin, for example ulcers of the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes), widespread blisters or peeling;

- serious hypersensitivity reactions involving fever, skin rash, joint pain, and abnormalities in blood and liver function tests (these may be signs of a multi-organ sensitivity disorder).

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Annex 2

Summary Assessment Report of the PhVWP July 2012

Bisphosphonates for oral use – Risk of oesophageal irritation (but insufficient evidence on causal relationship with oesophageal cancer)

Key message

A review of four new epidemiological studies supports the outcome of the PhVWP review in October 2010 that there is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer. However, bisphosphonate tablets can cause irritation to the oesophagus and patients should therefore carefully follow the instructions in the package leaflet on how to take the medicine and report to their physician any signs of oesophageal irritation, such as difficulties or pain on swallowing, chest pain or heartburn. In patients with known Barrett's oesophagus caution should be used and physicians should carefully consider the benefits and potential risks of treatment with alendronic acid, ibandronic acid and risedronic acid.

Safety concern and reason for current safety review

In October 2010, the PhVWP concluded a review of the risk of oesophageal cancer with bisphosphonates for oral use. This review followed the publication of a study conducted in the UK General Practice Research Database (GPRD) which found an increased risk of oesophageal cancer in patients receiving oral bisphosphonates [1]. Given the limitations of this study and a lack of supporting evidence from other studies, including an additional study in GPRD [2-4], the 2010 review concluded that there was insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer, but that any new data emerging from the ongoing monitoring of this potential risk should continue to be evaluated.

Since 2010, further data on oesophageal cancer and oral bisphosphonates have become available from four new epidemiological studies [5-7; one not published], which the PhVWP reviewed.

Clinical setting

Bisphosphonates are medicines that are used for the treatment and prevention of bone disorders including hypercalcaemia (high levels of calcium in the blood), for the prevention of bone problems in patients with cancer, and for the treatment of osteoporosis (a disease that makes bones fragile) and Paget's disease (a disease involving bone destruction and re-growth that causes deformity).

The active substances belonging to the class of bisphosphonates for oral use are alendronic acid, clodronic acid, etidronic acid, ibandronic acid, risedronic acid and tiludronic acid.

Oesophageal cancer is cancer of the oesophagus or lower part of the gullet, i.e. the tube that leads from the mouth to the stomach.

Information on the data assessed

The PhVWP reviewed data from a study in the UK General Practice Research Database (GPRD) submitted by the originator marketing authorisation holder for alendronic acid (not published), two studies from Denmark [5, 6] and one from Taiwan [7].

Outcome of the assessment

The PhVWP considered the following:

The study in the UK GPRD database found a small increase in the risk of developing oesophageal cancer two or more years after starting an oral bisphosphonate; however, no increased risk was observed after four or more years after starting treatment. The increased risk with oral bisphosphonates after two or more years appeared to be higher for adenocarcinoma than squamous cell carcinoma, particularly for risedronic acid; however, the findings regarding cell type are uncertain due to the small numbers of cases with histological information.

The two studies from Denmark used data from national registries. One study found an increased risk of oesophageal cancer with alendronic acid and etidronic acid; however, they were lacking dose- and duration-response effect [5]. The second study did not show any increase in the incidence of oesophageal cancer or deaths due to oesophageal cancer in alendronic acid users [6].

The study in the Taiwanese population suggested that oral bisphosphonates do not increase the risk of oesophageal cancer [7]. However the relevance of these findings to the European population is limited, as there are differences in the prevalence and type of oesophageal cancers between European and Asian countries, which are likely to be related to differences in the prevalence of risk factors for oesophageal cancer in the respective populations.

Overall, the PhVWP considered that the new studies are inconsistent in showing an increase in the risk of oesophageal cancer with oral bisphosphonates and have a number of limitations including a possible increased detection rate of oesophageal cancer in patients receiving bisphosphonates, incomplete information about bisphosphonate exposure in long-term analyses and a lack of information about known risk factors for oesophageal cancer, particularly smoking and alcohol exposure, which are difficult to capture accurately in studies.

The PhVWP therefore concluded that, overall, the new data do not alter the previous PhVWP conclusion that there is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer.

However, the PhVWP considered that a possible causal association could not be excluded and a warning about use in patients with known Barrett's oesophagus should be included in the product information for all nitrogen-containing bisphosphonates for oral use. Barrett's oesophagus is an uncommon disease where the cells that line the lower oesophagus become damaged and change due to reflux of acid from the stomach. Barrett's oesophagus can lead to oesophageal cancer in a small number of people.

Such a warning already exists in the product information for alendronic acid and ibandronic acid for oral use and should now be added for risedronic acid, the other nitrogen-containing bisphosphonate for oral use. The summaries of product characteristics of risedronic acid-containing medicinal products authorised in the EU for oral use should advise physicians to use caution if risedronic acid is given to patients known to have Barrett's oesophagus. In the package leaflet, patients should be asked to tell their physician if they have been told to have Barrett's oesophagus.

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Annex 3

Summary Assessment Report of the PhVWP July 2012

Carbamazepine – Risk of skin reactions in association with HLA-B*1502 allele in patients from some Asian populations and with HLA-A*3101 allele in patients of European and Japanese descent

Key message

Carbamazepine-induced severe cutaneous adverse reactions (SCAR) in European Caucasians and Japanese patients are associated with a newly identified genetic marker, the HLA-A*3101 allele. However, the evidence to date shows that the sensitivity of testing for HLA-A*3101 allele identifies only about 40% of patients that develop carbamazepine-induced SCAR. The clinical utility of testing for this allele in the above population prior to treatment with carbamazepine is not proven.

Carbamazepine-induced SCAR are also associated with the HLA-B*1502 allele, and clinical utility of testing for HLA-B*1502 allele in patients of Han Chinese and Thai origin has been proven. Almost 100% of cases could be avoided by prior genetic testing. The evidence supporting the testing for this allele in other Asian populations at genetic risk is weaker.

Therefore, the recommendation at present is that:

- Individuals of Han Chinese and Thai origin should, whenever possible, be tested for HLA-B*1502 allele prior to treatment with carbamazepine.
- Testing for HLA-B*1502 allele in other Asian populations at genetic risk may be considered.
- Routine testing for HLA-A*3101 allele is not recommended. If European Caucasians or patients of Japanese descent are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed the risks.

Safety concern and reason for current safety review

In July 2008, the PhVWP recommended updating the product information for carbamazepine-containing medicinal products authorised in the EU in relation to the risk of Stevens-Johnson syndrome (SJS) for patients carrying the HLA-B*1502 allele with advice to test, whenever possible, patients of Han Chinese and Thai origin for HLA-B*1502 prior to treatment, as this allele strongly predicts the risk of serious carbamazepine-associated SJS [1].

Since this review, new study findings have become available regarding this allele in other Asian populations, such as Malaysian and Indian (Hindu) [2, 3]. In addition, clinical utility of HLA-B*1502 screening before starting carbamazepine treatment has recently been demonstrated in the Han Chinese in Taiwan [4].

Further, in 2011, a new genetic marker HLA-A*3101 was identified in Japanese and European Caucasian patients for carbamazepine-induced adverse cutaneous reactions such as SJS, toxic epidermal necrolysis (TEN), drug rash with eosinophilia (DRESS) and less severe acute generalised exanthematous pustulosis (AGEP) and maculopapular rash [5, 6].

Following these recent publications, the PhVWP agreed to review the available data.

Clinical setting

Carbamazepine is used to control tonic-clonic (grand mal) and partial seizures in epilepsy, and for the treatment of trigeminal neuralgia as well as alcohol withdrawal syndrome.

Cutaneous adverse reactions are adverse reactions affecting the skin.

Information on the data assessed

The PhVWP performed a review of the recently published articles on the association between carbamazepine-induced cutaneous reactions and the HLA-B*1502 [2-4] and HLA-A*3101 alleles [5-6]. A variation application submitted by the originator marketing authorisation holder to update the product information with pharmacogenomic information on carbamazepine-induced cutaneous reactions was also assessed. This variation application included the studies [2-6].

The PhVWP consulted the Pharmacogenomic Working Party (PGWP) and additional experts.

Outcome of the assessment

HLA-B*1502 allele

Clinical utility of HLA-B*1502 screening

In a recent HLA-B*1502 screening study in the Han Chinese in Taiwan on prospectively identifying subjects at genetic risk of carbamazepine-induced SJS/TEN, carbamazepine was only given to patients who were HLA-B*1502-negative [4]. No cases of SJS were reported in the study and, by comparing the outcome with the estimated historical incidence of carbamazepine-induced SJS/TEN (0.23%), it was estimated that about 11 cases among 4877 subjects had been prevented. Assuming that all these prevented cases could have occurred among HLA-B*1502-positive patients (n=372), this study indicated that the presence of the HLA-B*1502 allele may increase the risk of SJS/TEN to 3%, whereas the screening and avoidance of carbamazepine in the HLA-B*1502-positive may reduce the risk to 0% (no case was reported in 4483 HLA-B*1502-negative patients).

On the basis of this study, it can be considered that clinical utility of HLA-B*1502 screening in this population has been shown. The positive and negative predictive values of this allele would be estimated to be 3% and 100%, respectively, and about 440 patients would need to be screened to prevent one case of hypersensitivity.

Association of the HLA-B*1502 allele and carbamazepine-induced SJS in Asian populations other than Han Chinese and Thai

A study in Indian subjects included 8 patients with carbamazepine-induced SJS and 10 randomly selected unrelated healthy controls from the same population [2]. 6 out of the 8 patients had the HLA-B*1502 allele, while none of the 10 controls were found to be positive (odds ratio: 71.40; 95% CI: 3.0-1698; P = 0.0014). Since the association is not as strong as that being observed in the Han Chinese community, other genes or combinations of genes might play a role in carbamazepine-associated cutaneous reactions.

The allele frequency of HLA-B*1502 in India ranges from 0 to 6% (with an average of 2.5%) in the different communities. The 8 studied patients belonged to the Hindu community, the biggest community of India comprising one billion Indians. Studies extended to different ethnic sub-groups from different regions in India will be needed to obtain a clear picture of the generalisability of this finding within India.

Chang et al [3] studied 21 unrelated Malaysians with carbamazepine-induced SJS/TEN and 300 race-matched healthy controls. The HLA-B*1502 allele was present in 75.0% (12/16) of Malay patients with carbamazepine-induced SJS/TEN and in only 15.7% (47/300) of the healthy controls (odds ratio: 16.15; 95% CI: 4.57-62.4; corrected P-value: 7.87×10^{-6}), which suggests a strong association between HLA-B*1502 and carbamazepine-induced SJS/TEN, although the odds ratio seems to be lower in the Malay in Malaysia than in the Han Chinese.

Conclusion

It was concluded previously that the HLA-B*1502 allele in individuals of Han Chinese and Thai origin is strongly associated with the risk of SJS in carbamazepine treatment. These individuals should, whenever possible, be tested for this allele before starting treatment with carbamazepine, as already recommended by the PhVWP since 2008. The PhVWP has now considered the new studies and concluded that there were some data which suggested an increased risk of serious carbamazepine-associated SJS/TEN in some Asian populations other than those identified in 2008. Because of the prevalence of the HLA-B*1502 allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), the PhVWP recommended that genetic testing in these at-risk populations prior to treatment with carbamazepine is not essential but may be considered.

HLA-A*3101 allele

Association of the HLA-A*3101 allele and carbamazepine-induced SJS in the Japanese population

Following a genome-wide association study (GWAS) in 53 Japanese subjects with carbamazepine-induced cutaneous adverse reactions, including SJS, TEN and drug-induced hypersensitivity syndrome, and in 882 subjects of a general Japanese population with no history of treatment with carbamazepine, Ozeki et al [5] genotyped the individual HLA-A alleles for 61 cases and 376 carbamazepine-tolerant controls.

The prevalence of carriers of HLA-A*3101 was significantly higher in patients with carbamazepine-induced cutaneous adverse reactions (60.7%) than in carbamazepine-tolerant controls (12.5%) (odds ratio: 10.8; 95% CI: 5.9-19.6). The authors calculated that, assuming a 2.9% prevalence of carbamazepine-induced cutaneous adverse reactions, the positive and negative predictive values of this allele would be estimated to be 12.7% and 98.7%, respectively. This association was validated by a replication study using an independent sample of 16 cases and 44 carbamazepine-tolerant controls (odds ratio: 5.3; 95% CI: 1.5-24.5). In the combined cohort of 77 cases, there were 6 cases of SJS/TEN, of whom 5 were positive for HLA-A*3101 and 1 tested negative (odds ratio: 33.9; 95% CI: 3.9-295.6).

A previous study in the Han Chinese population reported an association between HLA-A*3101 and maculopapular eruptions with carbamazepine, but not for SJS/TEN [7]. The discrepancy between the Japanese and Chinese studies may be due to ethnic differences in the allele frequencies.

Association of the HLA-A*3101 allele and carbamazepine-induced SJS in European populations

McCormack et al [6] performed a genome-wide association study (GWAS) in 22 subjects with carbamazepine-induced hypersensitivity syndrome, 43 subjects with carbamazepine-induced maculopapular exanthema and 3987 healthy population controls, all of European Caucasian descent. An independent set of 80 subjects with carbamazepine-induced hypersensitivity reactions and 257 carbamazepine-tolerant controls were then used to replicate the associations.

By pooling all patients with hypersensitivity reactions and comparing them to the carbamazepine-treated controls, the HLA-A*3101 allele was identified as a risk factor for hypersensitivity syndrome (10/27 in cases and 10/257 in controls; odds ratio: 12.41; 95% CI: 1.27-121.03), maculopapular exanthema (23/106 in cases; odds ratio: 8.33; 95% CI: 3.59-19.36) and SJS/TEN (5/12 in cases;

odds ratio: 25.93; 95% CI: 4.93-116.18). Assuming a 5.0% prevalence of carbamazepine-induced hypersensitivity, the positive and negative predictive values of this allele would be estimated to be 26.0% and 96.2%, respectively, and 83 patients would need to be screened to prevent one case of hypersensitivity.

Conclusion

A new genetic marker, the HLA-A*3101 allele, has been identified in Japanese and European Caucasian patients for carbamazepine-induced severe cutaneous adverse reactions such as SJS, TEN, DRESS and less severe AGEP and maculopapular rash.

The PhVWP noted that the sensitivity of HLA-A*3101 testing for SJS in European Caucasian and Japanese patients is relatively low (42%, 5 of 12 cases in European Caucasians; 83%, 5 of 6 cases in Japanese, compared with that for the HLA-B*1502 test in Han Chinese, i.e. almost 100%). The number of SJS cases studied with regard to the HLA-A*3101 allele was relatively low. So far there is no prospective study on the clinical utility of HLA-A*3101 testing in any population.

In this context, the PhVWP considered that the increased odds ratio for cutaneous reactions in HLA-A*3101 allele carriers in European Caucasians warrants updating of product information and recommended that the product information of carbamazepine-containing products authorised in the EU should be updated to include the new information on genetic risk factors. However, at present, the lack of proven clinical utility of prior testing for the genetic marker, together with the low sensitivity of the test precludes the mandating of testing for this allele prior to carbamazepine treatment. If patients of European Caucasian or Japanese descent are known to be positive for the HLA-A*3101 allele, the use of carbamazepine may be considered as long as the benefits are considered to outweigh the risks on the basis of clinical judgment.

Recommendations for the product information

Given the conclusions above, the PhVWP recommended that the summaries of product characteristics (SmPCs) (and accordingly the package leaflets (PLs)) of carbamazepine-containing products authorised in the EU should be updated to include,

in SmPC section 4.2, that:

- before deciding to initiate treatment with carbamazepine, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated SJS;

in SmPC section 4.4, that:

- serious and sometimes fatal cutaneous reactions including TEN and SJS have been reported during treatment with carbamazepine, and that these reactions are estimated to occur in 1-6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher;

- there is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions;

- the HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing severe cutaneous reactions known as SJS when treated with carbamazepine; the prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations; and whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine, and if these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option;

- tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still rarely occur;

- there are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations, and because of the prevalence of the HLA-B*1502 allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), genetic testing of at risk populations for the presence of HLA-B*1502 may be considered;
- the prevalence of the HLA-B*1502 allele is negligible in e.g. persons from European descent, African populations, Hispanic populations sampled and in Japanese and Koreans (< 1%);
- there are some data that suggest that the HLA-A*3101 allele is associated with an increased risk of carbamazepine-induced cutaneous adverse reactions including SJS, TEN, DRESS, or less severe acute AGEP and maculopapular rash in people of European descent and the Japanese;
- the frequency of the HLA-A*3101 allele varies widely between ethnic populations and its prevalence is 2-5% in European populations and about 10% in the Japanese population;
- the presence of the HLA-A*3101 allele may increase the risk for carbamazepine-induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%;
- there are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment;
- if patients of European descent or Japanese origin are known to be positive for the HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks;

in SmPC section 4.8, that:

- there is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous adverse reaction such as SJS, TEN, DRESS, AGEP and maculopapular rash; in Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele; another marker, the HLA-B*1502 allele, has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry.

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Annex 4

Summary Assessment Report of the PhVWP July 2012

Oxcarbazepine – Risk of skin reactions potentially associated with HLA-A*3101 and HLA-B*1502 alleles

Key message

Carbamazepine-induced severe cutaneous adverse reactions (SCAR) in European Caucasians and Japanese patients are associated with a newly identified genetic marker, HLA-A*3101, but routine testing for HLA-A*3101 allele in European Caucasians and Japanese patients is not recommended for carbamazepine or the structurally related oxcarbazepine. If European Caucasians or patients of Japanese descent are known to be positive for HLA-A*3101 allele, the use of oxcarbazepine may be considered if the benefits are thought to exceed the risks.

Carbamazepine-induced SCAR are also associated with the HLA-B*1502 allele, and clinical utility of testing for HLA-B*1502 allele in patients of Han Chinese and Thai origin has been proven. Individuals of Han Chinese and Thai populations should, whenever possible, be tested for the HLA-B*1502 allele before starting treatment with the structurally related oxcarbazepine. Testing for the HLA-B*1502 allele in other Asian populations may be considered.

Safety concern and reason for current safety review

Oxcarbazepine is structurally related to carbamazepine, and during the review of severe cutaneous adverse reactions induced by carbamazepine in association with the HLA-B*1502 and HLA-A*3101 alleles (see Summary Assessment Report 3), the concern arose that oxcarbazepine could have a similar risk or that there could be a risk of cross-reactivity with carbamazepine.

Clinical setting

Oxcarbazepine is a derivative of carbamazepine and belongs to the class of second generation antiepileptics. It is effective as a short-term combination treatment for patients with drug-resistant partial epilepsy.

Cutaneous adverse reactions are adverse reactions affecting the skin.

Information on the data assessed

The data assessed derived from ongoing or completed clinical trials and from case reports published in the medical literature [1-5]. Further, data collected through spontaneous reporting schemes in Member States were reviewed.

Outcome of the assessment

With regard to data from spontaneous reporting schemes in Member States, the reporting rates of cutaneous adverse reactions for oxcarbazepine range from rare to very rare between Member States.

Based on the cumulative analysis of the safety data from the marketing authorisation holder's clinical trial programme, cutaneous hypersensitivity and other hypersensitivity reactions with delayed onset were reported in only a minority of patients (reporting rates: 0.9% for oxcarbazepine-treated patients and 1.1% for placebo/control patients).

There is a limited number of case reports and studies in the medical literature linking oxcarbazepine-induced cutaneous adverse reactions to the HLA-B*1502 allele: 4 patients in study [2], 3 patients in study [3] and 2 individual case reports [4, 5].

There are no publications to date linking oxcarbazepine-induced adverse reactions to the HLA-A*3101 allele.

Based on results from a case-control study showing a statistically significant association between the HLA-B*1502 allele and oxcarbazepine-induced cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [3], as well as cross-reactivity in carbamazepine-sensitised individuals receiving oxcarbazepine, the PhVWP concluded that the demonstrated strong association between the HLA-B*1502 allele and SJS/TEN cannot be excluded for carbamazepine-related substances (imino stilbene antiepileptics). Therefore, despite that data are limited, the PhVWP recommended that the product information for oxcarbamazepine should include advice similar to that for carbamazepine-containing products.

The PhVWP recommended that the summaries of product characteristics (SmPCs) (and accordingly the package leaflets (PLs)) of oxcarbamazepine-containing medicinal products authorised in the EU should be updated to include,

in SmPC section 4.4, that:

- the HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as SJS when treated with carbamazepine; the chemical structure of oxcarbazepine is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with oxcarbazepine; and there are some data that suggest that such an association exists also for oxcarbazepine;
- the prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations; whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or a chemically-related active substance; if patients of these origins have tested positive for the HLA-B*1502 allele, the use of oxcarbazepine may be considered if the benefits are thought to exceed risks;
- because of the prevalence of the HLA-B*1502 allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), genetic testing of at risk populations for the presence of HLA-B*1502 may be considered;
- the prevalence of the HLA-B*1502 allele is negligible in e.g. persons of European descent, African populations, Hispanic populations sampled and in Japanese and Koreans (< 1%);
- there are some data that suggest that the HLA-A*3101 allele is associated with an increased risk of carbamazepine-induced cutaneous adverse reactions including SJS, TEN, drug rash with eosinophilia (DRESS), or less severe acute generalised exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese;
- the frequency of the HLA-A*3101 allele varies widely between ethnic populations; the HLA-A*3101 allele has a prevalence of 2-5% in European populations and about 10% in Japanese population;
- the presence of HLA-A*3101 allele may increase the risk for carbamazepine-induced cutaneous reactions (mostly less severe) from 5.0% in the general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%;
- there are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compound treatment;
- if patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

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Annex 5

Summary Assessment Report of the PhVWP July 2012

Donepezil – Risk of neuroleptic malignant syndrome (but insufficient evidence on causal relationship with serotonin syndrome)

Key message

Neuroleptic malignant syndrome (NMS) has been reported in patients treated with donepezil with or without concomitant antipsychotic medication, and if a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, donepezil should be discontinued.

Safety concern and reason for current safety review

The PhVWP became aware of serotonin syndrome (SS) in association with donepezil as a possible safety concern and agreed to assess this signal. The PhVWP expanded their review to include neuroleptic malignant syndrome (NMS), since the diagnosis of NMS may include symptoms of SS in addition to other symptoms such as muscle stiffness and very high temperature.

Clinical setting

Donepezil is authorised for the treatment of Alzheimer's disease. It is a specific and reversible inhibitor of acetyl-cholinesterase and its efficacy is believed to be attained through the augmentation of acetylcholine-mediated synaptic transmission.

The overall exposure worldwide is estimated as approximately 18 million patient-years since 1997.

Information on the data assessed

Pre-clinical, clinical trial and spontaneous reporting data (from the originator marketing authorisation holder and the EudraVigilance adverse reaction database maintained by the agency) were assessed in addition to information from the medical literature [1-4]. Data held in the adverse reaction database of the UK competent authority were also reviewed.

Outcome of the assessment

Having reviewed all evidence from pre-clinical studies, clinical trials and spontaneous reporting, the evidence to support an association between donepezil and SS was not considered strong. There were no case reports of SS from clinical trials and very few spontaneous case reports of SS. In all of the 4 cases reported by the marketing authorisation holder co-suspect medication (paroxetine, sertraline or trazodone) occurred.

There were 3 cases of NMS from the marketing authorisation holder's clinical trial database and considerably more cases of NMS (67) than of SS (4) from the marketing authorisation holder's spontaneous report database. The PhVWP considered that there was reasonably good evidence that NMS occurs in causal relation with donepezil, both when used alone and together with other medication, usually antipsychotics. Factors that suggested causality included positive dechallenge in 42 cases and positive rechallenge in 1 case. In addition there were several cases where the clinical event

occurred in a plausible time relationship to administration and there were at least 5 cases where NMS developed after a dose increase. Review of data held in the adverse reaction database of the UK competent authority and EudraVigilance data and of cases published in the medical literature [1-4] supported the PhVWP's view.

Further, it was considered that there are plausible biological mechanisms. The neuropathophysiology of NMS is thought to relate to dysregulation of cortical-subcortical circuits between motor cortex and basal ganglia. Blockage of the striatal D2-receptors relative to regulatory cholinergic pathways was considered to be the most likely neurochemical cause. Thus an NMS-like syndrome may be precipitated by increasing cholinergic functioning in the presence of a compromised dopaminergic system.

Based on all information assessed, the PhVWP concluded that modifications to the summaries of product characteristics (SmPCs) and package leaflets (PLs) of all donepezil-containing medicinal products authorised in the EU are necessary to include:

in SmPC section 4.8) (under Nervous system disorders):

- NMS as an adverse reaction;

in SmPC section 4.4:

- that NMS is a potentially life-threatening condition and characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels; additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure;

- that NMS has been reported to occur very rarely in association with donepezil, particularly in patients also receiving concomitant antipsychotics;

- that if a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued;

in PL (under Serious side effects):

- advice to tell a physician immediately if as a patient one notices fever with muscle stiffness, sweating or a lowered level of consciousness (a disorder called "Neuroleptic Malignant Syndrome"), as urgent medical treatment may be needed.

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Annex 6

Summary Assessment Report of the PhVWP July 2012

Levodopa, dopamine agonists and COMT inhibitors – Risk of impulse control disorders

Key message

Behavioural symptoms of impulse control disorders (ICDs) may occur in patients taking levodopa and/or dopamine agonists at normal doses, irrespective of the indication. Patients should be regularly monitored for ICD symptoms, which include pathological gambling, hypersexuality, increased libido, compulsive buying or spending and compulsive or binge eating.

Safety concern and reason for current safety review

Accumulating data on the risk of impulse control disorders (ICDs) in association with levodopa- and/or dopamine agonist-containing medicinal products have become available. Some of the ICDs described are not currently included in the product information for these products, and also the data suggest that ICDs may occur in indications for these products other than Parkinson's disease. The PhVWP therefore agreed to review these data to ensure the product information reflects the latest available evidence.

Clinical setting

Levodopa and dopamine agonists have been available since the 1970s as forms of dopamine replacement therapy in Parkinson's disease (PD), a disease which is caused by loss of nerve cells in certain part of the brain leading to a reduction in the amount of the neurotransmitter dopamine in the brain. Some medicinal products containing levodopa or a dopamine agonist are authorised for indications other than PD.

Levodopa is used alone or in combination with various metabolic inhibitors, including catechol-O-methyltransferase (COMT) inhibitors. COMT is an enzyme degrading dopamine in the body.

The active substances included in the review were levodopa, the dopamine agonists apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, quinagolide, ropinirole and rotigotine and the COMT inhibitors benserazide, carbidopa, entacapone and tolcapone.

Information on the data assessed

Data from spontaneous reporting schemes, published case reports and studies on the risk of ICDs with levodopa and dopamine agonists, especially data on ICDs currently not included in the product information and on the risk of ICDs in non-PD indications, were assessed [1-41].

Outcome of the assessment

The PhVWP considered that the updated review of the more recent spontaneous reporting data, published case reports and studies [1-41] showed that a range of behavioural symptoms of ICDs may occur in patients taking levodopa and/or dopamine agonists, at normal doses, irrespective of the indication. Reported symptoms included pathological gambling, hypersexuality and increased libido, which are already included in the product information for most products containing levodopa or a

dopamine agonist. The symptoms also included compulsive buying or spending and compulsive or binge eating, which are currently not included in the product information for most products.

The PhVWP concluded to recommend that the summaries of product characteristics (SmPCs) and package leaflets (PLs) should be updated as follows:

for levodopa-containing medicinal products authorised in the EU (single substance and combination products including those containing COMT inhibitors) to include:

in SmPC section 4.4, that:

- patients should be regularly monitored for the development of impulse control disorders; patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa; review of treatment is recommended if such symptoms develop;

in SmPC section 4.8:

- impulse control disorders: pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa (see SmPC section 4.4);

in PL section 2, that:

- one should tell the physician if the patient, family member or the carer notices that the patient is developing urges or cravings to behave in ways that are unusual for the patient or the patient cannot resist the impulse, drive or temptation to carry out certain activities that could harm the person or others; these behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or an increase in sexual thoughts or feelings; the physician may need to review the treatments;

in PL section 4, that:

- the patient may experience the following side effects: inability to resist the impulse to perform an action that could be harmful, which may include: strong impulse to gamble excessively despite serious personal or family consequences, altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive, uncontrollable excessive shopping or spending, binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger), and to tell the physician if any of these behaviors are experienced; the physician will discuss ways of managing or reducing the symptoms;

for apomorphine, bromocriptine, cabergoline, lisuride, pergolide, priribedil, pramipexole, quinagolide, ropinirole or rotigotine-containing medicinal products authorised in the EU to include:

in SmPC section 4.4, that:

- patients should be regularly monitored for the development of impulse control disorders; patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists; dose reduction/tapered discontinuation should be considered if such symptoms develop;

in SmPC section 4.8:

- impulse control disorders: pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists (see SmPC section 4.4);

in PL section 2, that:

- one should tell the physician if the patient, family member or the carer notices that the patient is developing urges or cravings to behave in ways that are unusual for the patient or the patient cannot resist the impulse, drive or temptation to carry out certain activities that could harm the person or others; these behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a an increase in sexual thoughts or feelings; the physician may need to adjust or stop the dose;

in PL section 4, that:

- the patient may experience the following side effects: inability to resist the impulse to perform an action that could be harmful, which may include: strong impulse to gamble excessively despite serious personal or family consequences, altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive, uncontrollable excessive shopping or spending, binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger), and to tell the physician if any of these behaviors are experienced; the physician will discuss ways of managing or reducing the symptoms;

for entacapone or tolcapone-containing medicinal products authorised in the EU (COMT inhibitor single substance products, but use only recommended together with levodopa) to include:

in SmPC section 4.4, that:

- patients should be regularly monitored for the development of impulse control disorders; patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments in association with levodopa; review of treatment is recommended if such symptoms develop;

in SmPC section 4.8:

- impulse control disorders: pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments in association with levodopa (see SmPC section 4.4);

in PL section 2, that:

- one should tell the physician if the patient, family member or the carer notices that the patient is developing urges or cravings to behave in ways that are unusual for the patient or the patient cannot resist the impulse, drive or temptation to carry out certain activities that could harm the person or others; these behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a an increase in sexual thoughts or feelings; the physician may need to review the treatments;

in PL section 4, that:

- the patient may experience the following side effects: inability to resist the impulse to perform an action that could be harmful, which may include: strong impulse to gamble excessively despite serious personal or family consequences, altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive, uncontrollable excessive shopping or spending, binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger), and to tell the physician if any of these behaviors are experienced; the physician will discuss ways of managing or reducing the symptoms.

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Annex 7

Summary Assessment Report of the PhVWP July 2012

Pantoprazole and other proton pump inhibitors – Evidence does not confirm increased risk of pneumonia

Key message

The possibility of a causal association of pantoprazole and other proton pump inhibitors (PPIs) with risk of pneumonia has not been confirmed, but remains under close monitoring.

Safety concern and reason for current safety review

A meta-analysis of observational studies on the risk of pneumonia with proton pump inhibitors (PPIs) [4] found a modest increased risk of community-acquired pneumonia with current use of PPIs (adjusted OR 1.34, 95% CI: 1.14-1.57). Other observational studies investigated the association of pneumonia acquired in the community and in hospital with use of proton pump inhibitors (PPIs). The evidence from the studies and meta-analyses of these studies suggested that use of PPIs (including pantoprazole) may increase the risk of pneumonia but these findings were not supported by evidence from clinical trials for pantoprazole. The PhVWP agreed to review the available data and its potential impact on the product information for PPIs, in particular of pantoprazole, given its wide use and availability in the EU without prescription.

Clinical setting

Proton pump inhibitors (PPIs) are indicated for treatment of duodenal and gastric ulcers and are used in combination with antibacterials for the eradication of *Helicobacter pylori*. They are used to treat gastro-oesophageal reflux disease (GORD), dyspepsia and Zollinger-Ellison syndrome. Proton pump inhibitors are also used for prevention and treatment of ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs). PPIs work by reducing gastric acid in the stomach.

The PPIs included in this review were esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

Information on the data assessed

The data considered comprised a review of 25 published studies (including observational studies, meta-analyses, systematic reviews and a review of clinical trial data for esomeprazole [1-25] and case reports for pantoprazole. In addition, responses to a list of questions to the marketing authorisation holder for the centrally authorised pantoprazole-containing products CONTROL, PANTECTA CONTROL, PANTOLOC CONTROL, PANTOZOL CONTROL and SOMAC CONTROL were assessed.

Outcome of the assessment

The PhVWP considered the following:

Possible mechanism

Gastric acid is an important barrier against pathogen invasion through the gastrointestinal tract. Potential pathophysiological mechanisms for the association of pneumonia with PPI use include

possible increased bacterial growth and colonisation of the upper gastrointestinal tract with subsequent translocation to the respiratory tract. Similarly, PPIs may cause alterations in the pH value of the respiratory tract which may allow growth of respiratory pathogens. PPIs have also been found to negatively affect the immune system. Leukopenia is known as a very rare adverse reaction with pantoprazole and included in the product information for PPIs.

Two observational studies included data on microbial aetiology: A study published in abstract form [14] found that PPI users were more susceptible to present with community-acquired pneumonia caused by *Streptococcus pneumoniae*. After adjustment for baseline differences, the risk of PPI users being infected with *S. pneumoniae* was 2.18 times greater (95% CI: 1.2-3.6) compared to those not on acid suppressive therapy with the risk increasing for those on higher doses. However, insufficient information was available in the abstract [14] to establish whether PPI users may have risk factors for *S. pneumoniae* infection. [17] found that among patients with community-acquired pneumonia, *S. pneumoniae* was identified in 30% of the cases, in 36% of the cases a causative organism could not be identified and in only 2% of current PPI users, community-acquired pneumonia was caused by gastrointestinal bacteria. These findings would not seem to support the hypothesis that community-acquired pneumonia associated with PPI use is predominantly caused by aspiration of gastrointestinal bacteria.

Observational studies for proton pump inhibitors as a class

The majority of studies were case-control studies. Studies examined community-acquired pneumonia (n=13 primary studies) and nosocomial pneumonia (n=7 primary studies). Overall the increased risk of community-acquired pneumonia with current use of PPIs was found to be modest. Two meta-analyses published in 2010 found current PPI use conferred increased odds of community-acquired pneumonia with overall risk estimates of OR 1.27 (95% CI: 1.11-1.46) [4] and OR 1.36 (95% CI: 1.12-1.65) [11], though heterogeneity in meta-analysis of observational studies must be acknowledged.

The studies identified did not provide robust evidence of a causal association of PPIs with hospital-acquired pneumonia. A meta-analysis of three studies did not find a statistically significant association [1, 10, 22]. Two studies published subsequently are consistent with this finding [12, 21].

It is acknowledged that observational studies have limitations of incomplete information on potential confounding factors, extent of exposure and the validity of database coding. A risk factor for pneumonia which is likely to be underreported in medical records is smoking status. In the case-control studies, the pneumonia cases typically concerned people with more comorbidities and poorer health status than the comparator group without pneumonia. The reduction of the risk estimate following covariate adjustment demonstrates that important confounders are included in the covariates. It is to be expected that the better analyses are controlled for potential confounding, the more the observed risk diminishes.

Some of the studies found that the risk estimate was greater for patients newly starting a PPI. The issue of protopathic bias was considered and the PhVWP commented that two of the observational studies had attempted to address this issue in their analysis [13, 17]. The PhVWP commented that it was possible that biases accounted for the short-term effect seen in some studies but that the Canadian study [6] benefited from detailed baseline information on potential confounders and had shown an association of recurrent pneumonia in high-risk elderly patients newly starting acid-suppressants.

The PhVWP noted the publication in May 2012 [8], a meta-analysis of nine of the studies included in previous meta-analyses and already considered as part of this issue. [8] provides a stronger analysis of these studies and concludes that patients receiving PPIs, particularly for more than 30 days or at

high dose, showed an association with community-acquired pneumonia. Nevertheless, limitations of the observational studies, particularly with respect to the completeness of recording alcohol and nicotine consumption and indication for treatment with a PPI, remain with regard to the potential for residual confounding given the difficulty in obtaining complete information on potential confounders and disease severity.

Case reports for pantoprazole

The marketing authorisation holder for the centrally authorised pantoprazole-containing products identified 101 cases of pneumonia in its pharmacovigilance database up to 24 May 2011. Of these, 49 had more likely alternative explanations. In 6 of the spontaneously reported cases (including 4 non-medically-confirmed cases), there was insufficient evidence to exclude a possible causal association.

Clinical trial data

One of the published studies identified by the marketing authorisation holder for centrally authorised pantoprazole-containing products in its literature review was an analysis of another marketing authorisation holder's clinical trial with esomeprazole and the incidence of respiratory tract infections [5]. The pooled data did not reveal an imbalance in the incidence of pneumonia between esomeprazole-treated subjects and those receiving placebo or comparator gastric acid suppressants.

The marketing authorisation holder also provided a review of 87 short- and long-term phase II-IV clinical trials of pantoprazole versus either placebo, other PPI, H2-receptor antagonists (H2RA) and/or other comparator. The studies were conducted in outpatients in the therapeutic indications of acute or prophylactic treatment of GORD, gastric ulcer, duodenal ulcer, functional dyspepsia, acid-related dyspepsia, NSAID-induced dyspepsia and NSAID-induced gastrointestinal lesions. There were a total of 40,135 patients in the trials, of which 27,056 patients were treated with pantoprazole and 13,079 patients were treated with comparators. Among the comparator groups, 7,210 patients were treated with PPIs, 4,013 patients were treated with H2RA, 1,598 patients were treated with placebo and 258 patients were treated with other comparators.

A total of 50 adverse events of pneumonia were reported during the trials. There was a greater frequency of pneumonia amongst pantoprazole-treated subjects (41/27,056; 0.15%) compared to the pooled comparator group (9/13,079; 0.07%). An analysis restricted to placebo-controlled clinical trials only did not identify a statistically significant difference in pneumonia between pantoprazole and placebo treated groups but, as indicated by the marketing authorisation holder, the sample size (approximately 4,000 subjects) may not be adequate to allow detection of small differences in the incidence of pneumonia. No clear dose response was observed.

The incidence of pneumonia per 100 patient-years was greater in the pantoprazole group relative to the placebo group, however analysis of time to onset as Kaplan-Meier survival plots did not show a significant difference between the pantoprazole group and the placebo or comparator groups.

Case level assessment of clinical trial cases showed that 6/50 cases have a confounding medical history of respiratory disorder, and that 23/50 cases lack a case narrative and information on medical history and test results.

Stratification of the clinical trial data by age found an increasing frequency of pneumonia with age, which is to be expected as older age is a risk factor for pneumonia. The differences were not found to be statistically significant for the pantoprazole group relative to the comparator groups when stratified by age.

Conclusion

The PhVWP considered that evidence from pharmacoepidemiological studies of an association between PPIs as a class and pneumonia was inconsistent and might be subject to residual confounding, including incomplete information on potential confounding factors, extent of exposure and the validity of database coding. Furthermore, the analysis of clinical trial data for pantoprazole which was retrospective and therefore lacked diagnostic information on cases of pneumonia, did not allow a definitive conclusion to be made regarding the risk of pneumonia, particularly in view of the fact that the majority of the data came from studies in patients with GORD. Therefore, the PhVWP agreed that the evidence at present did not support the need for risk minimisation measures for pantoprazole or any other PPI.

Nevertheless, a body of pharmacoepidemiological evidence exists to support an association between PPI use and risk of pneumonia which, if causal, was considered likely to be a class effect. The PhVWP agreed that the issue should remain under review with respect to the class of PPIs and possibly increased risk of pneumonia.

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Annex 8

Summary Assessment Report of the PhVWP July 2012

Prazepam – Not contraindicated in glaucoma

Key message

Product information for prazepam should be updated to delete contraindication in glaucoma.

Safety concern and reason for current safety review

The PhVWP was informed by its member from the French competent authority about inconsistent information in the product information of prazepam-containing medicinal products across Member States regarding the contraindication of glaucoma, which was included in the product information in some, but not all Member States. The PhVWP therefore agreed to review the risk of glaucoma with benzodiazepines and prazepam in particular.

Clinical setting

Prazepam is a benzodiazepine, indicated in the treatment of anxiety. Benzodiazepines act by stimulating the gamma-aminobutyric acid (GABA) receptor complex.

Glaucoma is a disease in which damage to the optic nerve leads to progressive and irreversible vision loss. It is normally associated with increased fluid pressure in the eye called intraocular hypertension. Glaucoma can be divided into two main categories, open angle and closed angle glaucoma.

Intraocular hypertension is a known adverse reaction reported for medicines with anticholinergic effects such as antipsychotic medicines. This could lead to serious consequences in patients with underlying glaucoma. Furthermore, glaucoma is also a known adverse reaction of some selective serotonin reuptake inhibitors (SSRIs). The mechanism is related to the presence of serotonin receptors on the ciliary corpus of the eye.

Information on the data assessed

The PhVWP reviewed data from the medical literature related to the risk of glaucoma with benzodiazepines [1-7]. Additionally, spontaneously reported cases of glaucoma with a benzodiazepine as a suspected medicine collected in the agency's adverse reaction database EudraVigilance and in the French adverse reaction database were reviewed.

Outcome of the assessment

The PhVWP considered that three publications were case reports showing an association between benzodiazepines and glaucoma [1-3] and four publication articles did not show a link [4-7].

In the French adverse reaction database and in EudraVigilance, very few cases of glaucoma were reported in association with the use of benzodiazepines. Furthermore, in most of these few cases patients had received concomitantly other medicines with known risk of glaucoma, such as antipsychotics or SSRIs. These risk factors being present in the reported cases, together with the absence of evidence suggesting a biologically plausible role for prazepam or any benzodiazepine in the development of glaucoma lead the PhVWP to the conclusion that a causal relationship between benzodiazepines and glaucoma is unlikely.

On this basis, the PhVWP considered that there was insufficient evidence to require a contraindication for glaucoma in the summary of product characteristic (SmPC) of any benzodiazepine, and therefore the PhVWP recommended deleting the glaucoma contraindication from the SmPC for prazepam-containing medicinal products authorised in the EU.

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Annex 9

Summary Assessment Report of the PhVWP July 2012

Tramadol – Risk of adverse reactions of the central-nervous system and dosing in the elderly and those with renal or liver impairment

Key message

Updating the product information for tramadol has been recommended to minimise certain adverse reactions of the central-nervous system and to advise on dosing in the elderly and those with renal or liver impairment.

Safety concern and reason for current safety review

Following a safety review relating to tramadol conducted by the Italian competent authorities, the PhVWP agreed to review tramadol in relation to safety concerns, including dosing in elderly patients and in patients with renal or hepatic insufficiency as well as risks of seizures, serotonin syndrome and suicidal ideation and behaviour.

Clinical setting

Tramadol is a prescription-only medicine indicated for the treatment of moderate to severe pain. It is a centrally acting opioid analgesic, and other mechanisms contributing to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Information on the data assessed

The data assessed included clinical and pharmacokinetic trial data, periodic safety update reports (PSURs) as well as spontaneous adverse reaction reports provided by the originator marketing authorisation holder. Two lists of questions were sent to the originator marketing authorisation holder, and their responses (including a review of the medical literature) were assessed as well.

Outcome of the assessment

The PhVWP considered the following:

Dosing for patients older than 75 years of age

The data from clinical trials that included elderly patients did not indicate that the frequency of adverse events observed in this age group was substantially higher than that for other age groups. Further, these data suggested that the daily dose needed for optimal pain relief with minimal adverse reactions is similar for the different age groups.

No relevant effect of age on the pharmacokinetics of tramadol in patients younger than 75 years of age was shown. However, in patients older than 75 years the elimination half-life of tramadol was prolonged by approximately 15% and the area under the curve (AUC; i.e. the overall amount of a medicine in the blood plasma) was increased by approximately 50% with high inter-subject variability. The mean maximum plasma concentration was 30% higher in patients older than 75 years which might represent an overdose in some patients.

On the basis of these data, the PhVWP concluded that a recommendation for general dose reduction in patients older than 75 years was not justified. In particular it was considered that there was no scientific basis for reducing the maximum daily dose to 300 mg as recommended in the US prescribing information of tramadol.

The PhVWP took the view that the fact that elimination half-life might be prolonged in patients above 75 years of age is addressed in the current originator summary of product characteristics (SmPC) for tramadol-containing medicinal products authorised in the EU through the following advice: "If necessary the dosage interval is to be extended according to the patient's requirements". The available data did not allow more precise recommendations regarding extension of the dosing interval.

Overall, the PhVWP considered that lowering the maximum daily dose or specific dosing intervals could lead to under-dosing in some patients above 75 years of age.

Dosing for patients with renal or hepatic impairment

No specific risks were observed in clinical trials nor described in PSURs for patients with renal or hepatic impairment.

In patients with renal impairment, mean maximum plasma concentrations were approximately 20% higher, the AUC was considerably increased and terminal half-lives were prolonged. However, inter-subject variability was high and no relationship between the degree of renal impairment and AUC or terminal half-life was noted.

In patients with hepatic impairment of any degree, maximum plasma concentrations were up to 50% higher, which might represent an overdose in some patients. Smaller increases were observed in patients with mild to moderate impairment only. Mean AUC and terminal half-life were also considerably increased by up to 200%. There seems to be a relationship between the degree of hepatic impairment (Child Pugh A or B) on one side and mean AUC and terminal half-life on the other. However, inter-subject variability of pharmacokinetic parameters was high in patients with hepatic impairment. No clear relationship between all degrees of hepatic impairment and increase in mean AUC and terminal half-life were observed.

Given these data, the PhVWP concluded that a general dose reduction, lower maximum daily dose or increased dosing interval in patients with renal or hepatic impairment was not justified. In particular there seemed to be no scientific basis for specific recommendations in patients with a glomerular filtration rate (GFR) less than 30 ml/min or patients with cirrhosis or severe hepatic impairment.

The fact that elimination half-life might be prolonged in patients with renal or hepatic impairment was considered addressed in the current originator SmPC, which includes the advice that "In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements". Available data did not allow more precise recommendations regarding extension of the dosing interval.

Overall, the PhVWP considered that lowering the maximum daily dose or specific dosing intervals could lead to under-dosing in some patients with renal or hepatic impairment.

General dosing recommendations

The PhVWP noted that the current originator SmPC already contains an introductory statement in section 4.2 of the SmPC that "The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient." and further a statement in a 4.2 sub-section on adults and adolescents above the age of 12 years that "The lowest analgesically effective dose should generally be selected". The PhVWP concluded that the latter advice should be included after the sentence in the introductory statement.

Role of pharmaceutical formulations for dosing in general and for those with renal or hepatic impairment

Tramadol-containing medicinal products are available as immediate or extended release formulations. As the above conclusions regarding dosing are of general nature, they apply to both immediate and extended release formulations.

In the case of extended release formulations, a prolongation of the dosing interval might mean that tramadol is administered only once daily instead of twice daily.

With regard to patients with renal or hepatic impairment, the PhVWP noted that the current originator SmPC of the extended release formulation contains the statement "In cases of severe renal and/or hepatic insufficiency, tramadol prolonged-release tablets are not recommended".

Risk of convulsion

In addition to the patient groups described as being at higher risk of convulsion in the current originator SmPC, the PhVWP identified patients on certain concomitant medication as being at risk due to interactions. The following active substances, which are currently not explicitly mentioned in the SmPC section 4.5, were associated with interactions leading to convulsion in more than two spontaneous adverse reaction case reports: bupropion, mirtazapine, tetrahydrocannabinol and venlafaxine.

The PhVWP concluded that bupropion, mirtazapine and tetrahydrocannabinol should be added to section 4.5 of the SmPC, as well as the class of serotonin norepinephrine reuptake inhibitors (SNRIs), which includes venlafaxine and duloxetine, which has also been reported as an interacting substance leading to convulsion.

An analysis of substances with known potential to lower the seizure threshold for which two or less case reports of convulsion were received did not identify further classes of medicines or single substances warranting inclusion in SmPC section 4.5 at this time. However, the PhVWP concluded that all cases of interaction involving convulsion should be closely monitored on an ongoing basis and further classes or substances should be added to SmPC section 4.5 as necessary in the future.

Risk of serotonin syndrome

The literature review suggested that, apart from the concomitant administration of serotonergic medicines, there were no patient groups that have an increased risk of serotonin syndrome.

The following concomitant active substances or classes of substances with serotonergic potential were identified in more than two case reports of serotonin syndrome with tramadol: selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, tricyclic antidepressants (TCAs) and monoamine oxidase (MAO)-inhibitors.

The PhVWP noted that SSRIs and MAO-inhibitors are already included as serotonergic medicines in SmPC section 4.5, and concluded that SNRIs, mirtazapine and TCAs should be added to SmPC section 4.5, given the substantial number of case reports on interactions with the concerned active substances.

Analysis of serotonergic substances for which two or less case reports of serotonin syndrome were received did not identify further groups of drugs or single substances warranting inclusion in SmPC section 4.5 at this time.

Further, the PhVWP concluded that all interactions linked to serotonin syndrome should continue to be closely monitored and further substances or classes should be added to SmPC section 4.5 as necessary in the future.

The PhVWP endorsed the originator marketing authorisation holder's suggestion to replace the symptoms of serotonin syndrome in SmPC section 4.5 with the Hunter Serotonin Toxicity Criteria [1]. However a simpler presentation of the Hunter criteria was proposed.

Risk of suicidal ideation and behaviour

The PhVWP agreed that the present data did not support a causal relationship between tramadol and suicidal ideation or behaviour.

The PhVWP considered that this signal arose most likely due to the higher risk of suicidal behaviour of patients with (chronic) pain. In addition, in a large proportion of case reports of suicidal ideation or behaviour, patients were also using antidepressants (indicative of a history of depression) and/or had a history of psychiatric disorders. Psychiatric disorders, in particular depression, are associated with an increased risk of suicidal behaviour.

Moreover, a part of the case reports might be due to the possibility that tramadol is used alone or in combination with other substances as a means to commit suicide. This is supported by the large proportion of cases where tramadol was reported to have been used only once and by the finding that there is disproportional reporting for medical events closely related to suicidal acts but not to suicidal or self-injurious ideation or suicidal depression.

Likewise, the low affinity of tramadol for binding to or inhibiting the serotonin transporter does not support the concept that tramadol exerts similar effect as observed for SSRIs and therefore cannot be considered to have a similar risk of suicide.

The PhVWP therefore concluded that a warning regarding the use of tramadol in patients who are suicidal, suffering from emotional disturbances or depression, as introduced in the US prescribing information in 2010, was disproportionate at this time, also considering that other medicines with potential for suicide do not carry a similar warning and that there was no evidence that tramadol is used more frequently in suicidal acts.

Recommendations for the product information

Given the conclusions above, the PhVWP recommended that the product information of all tramadol-containing products authorised in the EU should be updated to include,

in SmPC section 4.2, that:

- the dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient and the lowest effective dose for analgesia should generally be selected;
- a dose adjustment is not usually necessary in patients up to 75 years of age without clinically manifest hepatic or renal insufficiency; in elderly patients over 75 years elimination may be prolonged; therefore, if necessary, the dosing interval is to be extended according to the patient's requirements;
- in patients with renal and/or hepatic insufficiency the elimination is delayed and prolongation of the dosing interval should be carefully considered according to the patient's requirements.

in SmPC section 4.5, that:

- tramadol can induce convulsions and increase the potential for SSRIs, SNRIs, TCAs, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions;

- concomitant therapeutic use of tramadol and serotonergic medicines, such as SSRIs, SNRIs, MAO inhibitors (see SmPC section 4.3), TCAs and mirtazapine may cause serotonin toxicity; serotonin syndrome is likely when one of the following is observed: spontaneous clonus, inducible or ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, hypertonia and body temperature >38°C and inducible or ocular clonus; withdrawal of the serotonergic medicines usually brings about a rapid improvement; treatment depends on the type and severity of the symptoms;

in the package leaflets (PLs), that:

- the dosing should be adjusted to the intensity of the pain and individual pain sensitivity; in general the lowest pain-relieving dose should be taken;

- in elderly patients (above 75 years of age) the excretion of tramadol may be delayed; and if this applies, the physician may recommend prolonging the dosing interval;

- patients with severe liver and/or kidney insufficiency should not take tramadol; if the insufficiency is mild or moderate, the physician may recommend prolonging the dosing interval;

- the risk of adverse reactions increases, if one is taking medicines which may cause convulsions, such as certain antidepressants or antipsychotics; the risk of convulsion may increase if one takes tramadol and one of these medicines at the same time; the physician will tell the patient whether tramadol is suitable, if one is taking certain antidepressants; tramadol interacts with these medicines and one may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C.

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