IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

39th EDITION

Gardasil – update on national monitoring experience

The HSE human papillomavirus (HPV) schools immunisation programme commenced in May 2010 and it is estimated that since that time, up to 38,000 doses of Gardasil have been administered until the end of October 2010

The Irish Medicines Board has received a total of 64 reports of adverse events associated with use of Gardasil up to the end of October 2010, 55 of which were received since the beginning of the schools immunisation programme.

As a single patient may experience several reactions that will be included in a single report, the total number of reactions may not be equal to the total number of reports. In addition, as some patients have received two or three doses of the vaccines, the total number of doses administered is not necessarily equal to the total number of patients vaccinated.

The vast majority of reports received by the IMB to date have been consistent with the expected pattern of adverse effects for the vaccine, as described in the product information, and include injection site reactions, malaise, headache, myalgia, gastrointestinal symptoms and skin reactions (including urticaria). Reports of hypersensitivity reactions have also been received including reports of anaphylactic-type reactions in two patients, both of whom recovered without sequelae after receiving appropriate treatment.

Anaphylaxis is a very rare side effect of most vaccines. Appropriate medical treatment and supervision should always be readily available in case of a serious allergic reaction and possibly a rare anaphylactic event following the administration of the vaccine.

Vaccination related events such as dizziness and syncope are among the most commonly reported effects and healthcare professionals are reminded that patients should be carefully observed for an appropriate period of time after administration of Gardasil (see Summary of Product Characteristics for further information).

As for all medicines, the IMB and the European Medicines Agency are continuously monitoring the safety profile of HPV vaccines through review of global safety data, in addition to national experience and the balance of benefits and risks for the vaccine remains positive.

Adverse reactions may be reported using the online Adverse Reaction Report form. A downloadable version of the Adverse Reaction Report form is also available, which can be filled in manually and sent to the IMB by freepost.

In this edition

Tamoxifen is a selective oestrogen receptor modulator indicated for palliative and adjuvant treatment of oestrogen receptor positive breast cancer in pre- and post-menopausal women. Tamoxifen undergoes extensive metabolism to form metabolites, which have similar or enhanced pharmacological activity compared with tamoxifen and contributes to the therapeutic effect. The formation of active metabolites e.g. endoxifen is predominantly mediated by the cytochrome P450 CYP2D6 enzyme.

Recently, a number of studies have examined the potential effect of CYP2D6 genetic variants on clinical response to tamoxifen treatment. The studies gave rise to the concern that patients with inherited non-functional alleles of the gene coding for CYP2D6 or patients who are concomitantly treated with medicines inhibiting CYP2D6, might not be suitable for adjuvant tamoxifen therapy, due to reduced concentrations of those metabolites of tamoxifen that bind most strongly with the oestrogen receptor expressed by the breast cancer.

The Pharmacovigilance Working Party of the European Medicines Agency conducted a review of the available evidence in this respect. The review included all currently available data and the limitations and interpretation of the published studies. Further information on the review and details of the references are included in the PhVWP report available from http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097444.pdf.

Overview of Evidence Evaluated:

Effect of tamoxifen in poor CYP2D6 metabolisers

A study [1] including 1325 patients from US and German cohorts (95.4% post-menopausal) with hormone receptor-positive non-metastatic breast cancer at diagnosis and treated with tamoxifen and no chemotherapy afterwards showed a significantly increased risk of breast cancer recurrence for poor CYP2D6 metabolisers (several alleles were analysed in the study: CYP2D6*3, *4 and *5 (HR 1.90, 95% CI 1.10-3.28) and heterozygous metabolisers (HR 1.40, 95% CI 1.04-1.90) compared to extensive metabolisers).

Additional studies including those providing contradictory results were assessed. Several of the studies indicated that poor CYP2D6 metaboliser status may be associated with a reduced response.[2-6] The few studies[7-9] in Caucasian populations showing contradictory results (n=3 from 2005 or 2007) may have been confounded by a number of factors, for example, the higher tamoxifen dose used, small number of poor CYP2D6 metabolisers or limited number of CYP2D6 mutations analysed, all of which may reduce the ability to demonstrate a reduced response of tamoxifen in patients with poor CYP2D6 metaboliser status.

In the most recently published large study,[10] which included patients with invasive breast cancer from SEARCH (Studies of Epidemiology and Risk Factors in Cancer Heredity; 3155 patients were treated with tamoxifen and 3485 patients did not receive tamoxifen), there was some evidence that the poor metaboliser variant CYP2D6*6 (a more uncommon variant with a mean allele frequency (MAF) = 0.01) was associated with decreased breast cancer-specific survival. However, CYP2D6*4 (the most common poor metaboliser variant with MAF = 0.20) was not shown to be associated with poorer clinical outcomes, in contrast to the previous findings.[1] Methodological issues were discussed on the genotyping quality.

Effect of tamoxifen in patients treated with potent CYP2D6 inhibitors

Another study[11] referred to data from a population-based cohort study on selective serotonin reuptake inhibitors (SSRIs) and breast cancer mortality in women receiving tamoxifen. In this study, data from a healthcare record database in Ontario, Canada, were used to evaluate the clinical consequences for women with breast cancer who were treated with both tamoxifen and an SSRI. It was found that the risk of death from breast cancer increased with the length of concomitant treatment with paroxetine, a potent inhibitor of CYP2D6, but not with other SSRIs. For example, if women used paroxetine for 41% of the time that they took tamoxifen, one additional death from breast cancer occurred within five years after stopping tamoxifen for every 19.7 (95% CI 12.5-46.3) women treated. The proportion of time on tamoxifen with overlapping use of paroxetine of 25%, 50%, and 75% was associated with 24%, 54%, and 91% increases in the risk of death from breast cancer.

In a more recent study,[12] no evidence was found for a decrease in efficacy with the co-administration of CYP2D6 inhibitors and tamoxifen. However, the authors, considering the results from the available studies and the strong mechanistic model, concluded that their results should be interpreted with caution.

Overall Conclusions

Based on the totality of evidence, the PhVWP considered that the available published data, mainly on post-menopausal women treated for breast cancer with tamoxifen, suggest that CYP2D6 polymorphism status may be associated with different therapeutic response of patients to tamoxifen. Poor CYP2D6 metaboliser status may be associated with reduced response.

The consequences of the findings for the treatment of poor CYP2D6 metabolisers have not been fully understood. The available data at present have not clearly shown the clinical utility of CYP2D6 testing to predict tamoxifen efficacy and clinical outcome. There is insufficient evidence at present to recommend genotyping patients before starting tamoxifen treatment.

Additionally, the PhVWP noted that pharmacokinetic interactions with CYP2D6 inhibitors were described in the medical literature, showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen.[13] Reduced efficacy of tamoxifen was reported with concomitant use of some SSRI antidepressants (e.g. paroxetine).[11] However, in other studies, a decrease in efficacy of tamoxifen with co-administration of CYP2D6 inhibitors was not evident.[12] As a reduced effect of tamoxifen cannot be excluded, particularly in the context of the pharmacokinetic data and mechanistic plausibility, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should be avoided whenever possible.[14]

Therefore, the summaries of product characteristics and package leaflets for medicinal products containing tamoxifen will be updated to highlight the possible reduction in therapeutic response to tamoxifen in poor CYP2D6 metabolisers and to warn against using potent CYP2D6 inhibitors during tamoxifen treatment whenever possible.

Key message:

- **Avoid use of potent CYP2D6 inhibitors during tamoxifen treatment whenever possible and be aware that poor CYP2D6 metabolisers may respond less well to tamoxifen treatment.**

Oral Bisphosphonates and Risk of Oesophageal Cancer

Oral bisphosphonates are primarily indicated for the prevention and/or treatment of osteoporosis and products currently authorised for use in Ireland include alendronate, ibandronate and risedronate. Some oral bisphosphonates are indicated only for Paget's disease (tiludronate) or for treatment in malignancy indications (clodronate).

The PhVWP of the EMA recently reviewed new publications concerning an association between oral bisphosphonate use for the treatment of bone disorders and oesophageal cancer. Further information on the review and details of the references are included in the PhVWP report available from **www.ema.europa.eu**.

Based on review of the available data, it was concluded that insufficient evidence remains to suggest a definite causal association. However this issue and all emerging data will remain under close review. In the meantime, the IMB wishes to reinforce existing warnings on how best to minimise the risk of oesophageal adverse reactions associated with oral bisphosphonates.

Oesophageal Adverse Reactions
Oesophageal injury is a recognised adverse reaction with bisphosphonates which are thought to cause oesophageal irritation through local effects on the oesophagus. These effects may be exacerbated by frequent bisphosphonate exposure, acidic conditions and/or pre-existing oesophageal irritation.[1] Bisphosphonates may cause oesophageal adverse effects both by the toxicity of the bisphosphonate itself and by contact between the tablet and oesophageal mucosa causing non-specific oesophageal irritation or direct topical damage to the oesophageal mucosa.[2]

Warnings about severe oesophageal reactions (including oesophagitis, gastritis, oesophageal ulcerations and gastro-duodenal ulcerations) in association with bisphosphonates are included in the product information for the three oral bisphosphonates: alendronate, ibandronate and risedronate. The warnings emphasise the importance of the patient adhering to the dosage instructions and advise that the patient should stop taking the drug if they develop any oesophageal symptoms.

Risk of oesophageal cancer
An increased risk of oesophageal cancer has previously been identified as a potential safety concern with oral bisphosphonates and warnings about use in patients with Barrett's oesophagus were added to the product information for some products containing alendronate and ibandronate, authorised through EU assessment procedures.

In light of this, and given the recognised adverse gastrointestinal effects of alendronate, a General Practice Research Database (GPRD) study was initiated in the UK in collaboration with the Cancer Epidemiology Unit at Oxford University to investigate whether there is an increased risk of cancers of the oesophagus, stomach and colorectum associated with bisphosphonate use. The results of this study were published in the British Medical Journal on 3 September 2010 (Green et al, 2010).

The results of the recent GPRD study by Green et al suggest an increased risk of oesophageal cancer associated with prior oral bisphosphonate use that seems to increase with increasing duration of therapy, whether measured by number of prescriptions or actual duration. The study found that the risk of oesophageal cancer approximately doubled after 5 years of oral bisphosphonate use. Although this study had a large sample size and long follow up, it had some limitations including the absence of information on risk factors for oesophageal cancer such as smoking, consumption of alcohol, BMI and previous oesophageal reactions. A possible source of bias in the Green study could be increased detection of non-symptomatic in-situ oesophageal cancers in patients taking bisphosphonates due a greater number of endoscopic investigations as a result of known oesophageal reactions associated with bisphosphonates.

A further limitation of the study was the limited information available on the histology of the

cases. Given that the risk factors differ for the two main histological types of oesophageal cancer, it is possible that the risk with bisphosphonate use may differ for oesophageal squamous cell carcinoma and oesophageal adenocarcinoma. However, this could not be adequately determined in the study by Green et al as the histological type of cancer was only known in one fifth of cases.

In contrast to the findings of Green et al, the additional GPRD study by Cardwell et al did not find any association between oral bisphosphonate use and the risk of oesophageal cancer. However the study by Cardwell et al is also limited by the same weaknesses of the study Green et al regarding incomplete information in the GPRD database and possible increased detection of oesophageal cancer in patients receiving bisphosphonates.

The PhVWP concluded that based on the currently available evidence, the need for a careful benefit-risk evaluation in patients with known Barrett's oesophagus should be reflected in the product information for all medicinal products containing alendronate or ibandronate available in the EU. Therefore, this information will now be implemented for all nationally authorised alendronate-containing medicinal products for oral use, ensuring consistency across the product information. In addition, the PhVWP concluded that, as part of the ongoing monitoring of this risk, particularly for oral bisphosphonates used in the treatment of bone disorders, any emerging data on risedronate will continue to be evaluated.

Conclusions and Recommendations

- Given the limitations in the study by Green et al and a lack of supporting evidence from other studies there is insufficient evidence to suggest a definite causal relationship between oral bisphosphonate use and oesophageal cancer.
- In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of treatment with alendronate or ibandronate on an individual patient basis. The available evidence on risedronate will continue to be monitored.
- Patients should be made aware of the importance of adhering to the dosage instructions included in the package leaflet and how to take the tablets correctly in order to minimise the risk of oesophageal irritation.
- Patients should be advised to stop taking the medicine and to contact their doctor if they develop any oesophageal symptoms.

Calcium Gluconate – risk of aluminium exposure with glass ampoules

At present, there are no authorised injectable calcium gluconate products in Ireland, however the IMB understands such products are used in the management of some acute conditions where the pharmacological action of a high calcium ion concentration is required and understands that there is some use in the preparation of total parenteral nutrition (TPN) solutions.

Consequently, the IMB wishes to remind Healthcare Professionals of the risk associated with calcium gluconate packed in small volume glass containers and of circumstances where it should not be used.

It is recognized that aluminium can be leached from the glass after contact with the calcium gluconate solution, leading to a risk of exposure to aluminium which might have adverse effects on bone mineralisation and neurological development in vulnerable patients such as children and those with renal impairment.

Key messages:

- **In order to avoid the risk of aluminium exposure in vulnerable patient groups, calcium gluconate injection in small volume glass containers should not be used in the following circumstances:**
  - **For repeated or prolonged treatment, including as an intravenous infusion, in children aged younger than 18 years, or in patients with renal impairment**
  - **In the preparation of TPN solutions**

Use of calcium gluconate injection packed in plastic containers provides for a reduction in aluminium exposure in vulnerable patients.

Adverse Reaction Reporting Experience during 2009

The IMB places great emphasis on encouraging and promoting reports from a range of stakeholders in relation to suspected adverse reactions to medicines. These reports are important to signal potential safety issues from medicines in use and ultimately assist the IMB in monitoring the safety of medicines on the Irish market.

During 2009, the IMB received a total of 3,276 suspected adverse reaction reports occurring in Ireland from healthcare professionals and pharmaceutical companies. This unprecedented number included 900 reports associated with use of the pandemic A (H1N1) vaccines, as part of an enhanced surveillance system introduced to monitor experience with their use, at both national and EU level. The reports provided were particularly helpful in confirming the expected safety profiles of these new vaccines and the active participation of healthcare professionals and the public in notifying their experience was extremely useful to the monitoring process.

The IMB greatly appreciates the contribution of busy healthcare professionals in reporting suspected adverse reactions, facilitating the continued surveillance of the safety of medicines. While the time-consuming nature of form-filling and the provision of follow-up information to the IMB is recognised, the collection and evaluation of comprehensive reports is essential to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines. Such reports are essential for the IMB to ensure that regulatory action/proposals take account of all available data.

The on-line reporting system, available to healthcare professionals and patients/consumers was increasingly used during 2009, with 600 reports submitted by year end via this method. Access to the on-line reporting system is available through the IMB website at **www.imb.ie**.

Readers are reminded of the option of registering with the IMB to enable direct and immediate notification of safety and regulatory alerts/updates by email or text message. To facilitate prompt access to these updates, users are encouraged to avail of this option by registering at **www.imb.ie**.

Breakdown of Reports by Source

Marketing Authorisation Holders	1495
General Practitioners	452
Community Nurses	328
Community Care Doctors	281
Hospital Doctors	155
Hospital Nurses	150
Hospital Pharmacists	134
Patient/Consumers	108
Community Pharmacists	81
Clinical Trials	52
Health Care Professionals (other)	40
Total	**3,276**

Relevant, anonymised reports (i.e. serious, suspected cases) notified directly to the IMB by healthcare professionals were forwarded to the appropriate marketing authorisation holders (MAHs) and the European Medicines Agency (EMA) for inclusion on the European database (Eudravigilance). The IMB also provided details of reports received to the WHO for inclusion on its international database.

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