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 Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency 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 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).3

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 rise 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.4 However the study by Cardwell et al. is also limited by the same weaknesses as the study by 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.