Danish Pharmacovigilance Update

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The following recommendations are a result of an overall review by the European Pharmacovigilance Working Party, involving an evaluation of adverse reaction data from various sources, such as adverse reaction reports, clinical studies and published literature. The recommendations will soon be implemented in relevant summaries of product characteristics and package leaflets.

Avoid concomitant use of valproate and carbapenems

Valproate's effect may be reduced when used together with carbapenem antibiotics because carbapenems decrease valproate plasma concentrations by 60-100 % within two days. The information will be implemented in the summaries of product characteristics and package leaflets for medicines containing valproate and carbapenems.

The interaction between valproate and meropenem (a commonly-used carbapenem) is already described in the Danish Drug Interaction Database. Several references from various publications are also listed here. But this is the first time that concomitant use of valproate and carbapenems is not recommended. The time course and mechanism of the interaction have not been established, and therefore it is not sufficient to compensate for the interaction by adjusting the dose.

You can see the new information in the Danish Drug Interaction Database after the next update on 1 March 2010.

Visit the Danish Drug Interaction Database here:
www.interaktionsdatabasen.dk

New updated product information of hormone replacement therapy (HRT) for post-menopausal women

The product information for hormone replacement therapy (HRT) for post-menopausal women has been updated based on new results from the clinical trials 'Women's Health Initiative' and the 'Million Women Study'.

The following and other information has been added to the product information:

- The risks associated with HRT are likely to outweigh the benefits for the majority of women above the age of 60 years.
- The risks associated with HRT are lower in women with premature menopause.
- The risk profile in women without a uterus using oestrogen-only HRT is more favourable than that associated with combined HRT.

In relation to particular risks, the following conclusions were added to the product information:

Venous thromboembolism

- HRT **is contraindicated** in patients with known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency).
- The risk of venous thromboembolism is lower for oestrogen-only HRT than that associated with combined HRT.

Breast cancer

There is new evidence that the risk of breast cancer is not increased for oestrogen-only HRT than for combined HRT.

Endometrial cancer

The risk of endometrial cancer is not increased for women using combined HRT - neither in users of combined sequential or continuous HRT.

Ovarian cancer

There may be an increased risk of ovarian cancer in women using either combined HRT or oestrogen-only HRT.

Coronary artery disease

There may be an increased risk of coronary artery disease in combined HRT users. The risk increases with age. There is no evidence of a similar risk for oestrogen-only HRT.

Stroke

Evidence shows the same increase in risk of stroke in users of oestrogen-only HRT as in users of combined HRT, which is independent of duration of use.

The updated information will be implemented in all relevant summaries of product characteristics as soon as possible.

Please find a detailed summary of the conclusions and references here:
Monthly report

Bisphosphonates and rare risk of osteonecrosis of the jaw (ONJ)

In the last years, there has been an increase across the EU in the number of ADR reports of osteonecrosis (ONJ) associated with the use of bisphosphonates. From January 2003 to December 2009, a total of 5,000 reports of ONJ were recorded in the EU, while 37 were recorded in Denmark. The chart below shows the annual distribution of reports in Denmark, excluding 2003 which saw no reports of ONJ.

Against this background, the European Pharmacovigilance Working Party initiated a review, which in the long term is to enable the implementation of preventive measures to minimise patients' risk of developing this rare but serious adverse reaction. The review was closed recently.

Possible risk factors

The review showed that the risk of developing ONJ is highest for:

- Treatment with the most potent bisphosphonates (e.g. zoledronate),
- Bisphosphonates in intravenous administration form,
- Treatment for cancer indications,
- Concomitant or prior treatment with corticosteroids, chemotherapy or radiotherapy,
- Local dentoalveolar surgery.

Preventive measures

There is still not much knowledge about which preventive measures are effective. But there is some evidence from retrospective studies that the risk of developing ONJ may be minimised by:

- carrying out dental exam and dental treatment, if required, prior to initiation of bisphosphonate therapy,
- increasing the interval for intravenous administration of bisphosphonates - further investigations are, however, required.

Diagnostic criteria

The review established that the diagnosis ONJ related to bisphosphonates should be based on the following criteria:

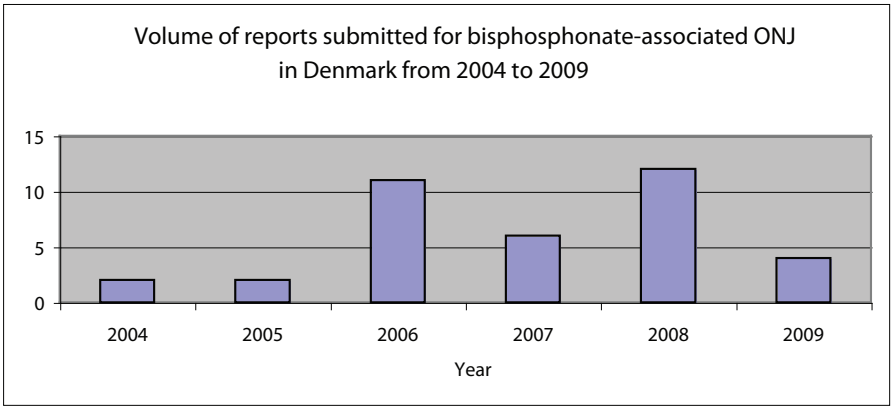
- Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks.
- No history of irradiation of the jaw.
- Current or previous treatment with a bisphosphonate.

Pathophysiological mechanisms

The review also established that a multitude of pathophysiological mechanisms may play a part in the development of ONJ, e.g. bisphosphonate-induced immunomodulation and local jaw vascularisation. Actinomyces infections are also suspected to cause the development of ONJ.

Further experimental studies are, however, necessary to obtain a better understanding of the underlying pathophysiological mechanisms. The development of a suitable animal model to allow examination of bone turnover, immunological mechanisms and vascularisation has first priority.

Find out more about the review here: *CHMP opinion pursuant to Article 5(3) of regulation (EC) No 726/2004, on bisphosphonates and osteonecrosis of the jaw*



Data basis of the review

The review was made on the basis of ADR reports and a review of results from clinical, epidemiological, and experimental studies published in literature. The review took place in close cooperation between experts within odontology, jaw surgery, endocrinology, oncology and pharmacology.

The relevant international scientific societies were briefed about the review and its conclusions in September 2009.

Medicines with special precautions for use

- Isotretinoin-containing medicine
- Aclasta®
- Benefix®
- Cimzia®
- Efient®
- Exjade®
- Gliolan®
- Ilaris®
- Increlex®
- Instanyl®
- Kaletra®
- Lucentis®
- MabCampath®
- Macugen®
- Mircera®
- Mycamine®
- Multaq®
- Nplate®
- Qutenza®
- Renvela®
- Retacrit®
- Revlimid®
- Simponi®
- Soliris®
- Stelara®
- Tasigna®
- Thalidomide Pharmion®
- Thelin®
- Tracleer®
- Tysabri®
- Valdoxan®
- Volibris®
- Zypadhera®

Medicines with special precautions for use

The list to the left contains the names of medicines that doctors must pay special attention to before prescribing them to patients.

For example:
- Prescription may require additional training for doctors.
- Patients must be given important information before use.

Click the name of a medicine to read its special precautions for use and see who is responsible for them.

The list is updated regularly.

The links to the left are to the SPCs in Danish. English versions are available (for centrally authorised products only) at the website of the European Medicines Agency under: *'A-Z Listing of EPARs'*.

Find out more about medicines with special precautions for use: *Medicinal products linked to a risk management plan (in Danish only)*

Medicines with stricter reporting requirements

Prescribers are reminded to report all suspected adverse reactions observed within the first two years following placement on the market.

Click on the list below to see what medicines are subject to stricter reporting requirements.

List of medicines with stricter requirements for doctors, dentists and veterinarians to report side effects (Excel file, only in Danish)

At the Danish website *www.medicin.dk* you can also see if a medicine is subject to stricter reporting requirements. If this is the case, it will be stated under the description of adverse reactions.

Danish Pharmacovigilance Update

The Danish Medicines Agency launches campaign to spur adverse reaction reporting at Danish hospitals

A survey conducted in 2009 by the Danish Medicines Agency and the Danish Medical Association revealed that two in every three hospital doctors encounter serious or unexpected adverse reactions every year. But even so, the Danish Medicines Agency only receives about 600 reports from hospital doctors in a year. In other words, for each reported side effect, another 50 goes unreported. The survey also showed that doctors were unsure about when to report side effects.

Pilot project conducted at selected hospitals

In the summer 2010, the Danish Medicines Agency rolls out a nation-wide campaign at all Danish hospitals to get more hospital doctors to report side effects from medicines. The campaign is presently run as a pilot project at selected hospitals.

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