Lægemiddelstyrelsen
Danish Medicines Agency

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DANISH PHARMACOVIGILANCE UPDATE

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Short news

New warning regarding cardiac failure caused by Xalkori (crizotinib) use

A new warning has been added to the summary of product characteristics of Xalkori (crizotinib) regarding cardiac failure after a review of data from clinical trials and clinical practice has shown that there is a risk of cardiac failure.

Xalkori is used for the treatment of ALK-positive advanced non-small cell lung cancer (NSCLC).

Across clinical studies in patients with ALK-positive NSCLC (n=1669), a total of 19 (1.1%) patients treated with crizotinib had any grade cardiac failure, 8 (0.5%) patients had grade 3 or 4, and 3 (0.2%) patients had cardiac failure with a fatal outcome.

In post-marketing experience, it is estimated that more than 14,700 patients have been treated with crizotinib (as of 25 February 2015). Cardiac failure has been reported in 40 patients (0.27%), the majority of incidents occurring during the first month. 15 of the cases had a fatal outcome.

No Danish ADR reports of cardiac failure associated with crizotinib

At the Danish Medicines Agency, we have received no ADR reports of cardiac failure caused by crizotinib. One ADR report describes a case of crizotinib-induced atrial fibrillation. Atrial fibrillation is a known causative factor for cardiac failure.

Doctors are advised to be aware of the following:

- We have received reports of severe, sometimes fatal, cases of cardiac failure in patients with ALK-positive NSCLC treated with crizotinib.
- Cardiac failure has been seen in patients with or without pre-existing heart disease.
- Patients should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain).
- If any of these symptoms are observed, it should be considered carefully to interrupt treatment, reduce the dose or discontinue the treatment.

Indication for crizotinib
Crizotinib is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed at the PRAC meeting in September 2015 concern the following products:

- **Bisphosphonates** – osteonecrosis of the external auditory canal
- **Leflunomide** – pulmonary hypertension
- **Alfa lipoic acid/Thioctic acid** (products on the Danish market have been classed as food supplements, not medicinal products) – insulin autoimmune syndrome
- **Trabectedin** – capillary leak syndrome

See EU's list of recommendations on safety signals: *PRAC recommendations on signals, September* as well as the *Danish translations for the product information*.

Interaction between miconazole and warfarin

In the preceding 5-year period, the Danish Medicines Agency (formerly the Danish Health and Medicines Authority) received several ADR reports of pharmacokinetic interactions between warfarin (e.g. Marevan) and miconazole (e.g. Brentan) causing increased INR. In one of these cases, increased INR was associated with life-threatening gastrointestinal tract bleeding. Doctors and dentists therefore need to increase awareness on interactions between warfarin and miconazole.

Reports of adverse reactions and adverse events involving interactions between warfarin and miconazole

While the Danish Medicines Agency has received nine ADR reports[1] describing the interaction, the Danish Patient Safety Database (DPSD) has received seven adverse event reports[2].

Overall, the reports concern patients on continuous anticoagulant treatment who have been prescribed Brentan oral cavity gel for treatment of fungal infection of the oral cavity[3]. Several of the ADR/adverse event reports describe cases of persistent bleeding after three to seven days treatment with Brentan or increases in INR observed at routine checkups. Also described are conditions such as gingival bleeding, bleeding from mucosal membranes or the skin, haematuria or bleeding with defecation. One patient had double vision as the only symptom of increased INR. In several cases, INR was above 8, and in one single case, it took several weeks before the INR was controlled.

Known interaction

Warfarin is known to interact with many types of medicines. The three antimycotics fluconazole, voriconazole and miconazole interact with warfarin by inhibiting the CYP2C9 enzyme, which clinically is the most important enzyme involved in the metabolism of warfarin. Warfarin plasma concentration thus increases.

Based on these case reports and prospective studies described in the literature, it is recommended to monitor INR frequently when warfarin is used concomitantly with either of these antimycotics.

The interaction between miconazole and warfarin is described in the authorised Danish summary of product characteristics of Brentan oral cavity gel. It is also mentioned in the package leaflet and on Pro.medicin.dk.

It may seem surprising that the interaction produced by warfarin and a topically applied antifungal medication can be so severe and occur so quickly. However, Brentan oral cavity

[1] The nine ADR reports referred to in this article originate from the Danish Medicines Agency's (DKMA) database of adverse drug reactions. The ADR reports have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases to DKMA.
[2] Five of the ADR reports/adverse event reports share so many factual details that we consider them to be duplicates. Consequently, our review is based on 11 of the reports.
[3] In one single case, Brentan 2% antifungal cream had been used for fungal groin infection. Unlike oral cavity gel, the cream is available over the counter.

gel is absorbed systemically, and the plasma half-life is 20-25 hours, so interactions should be expected. The situation is otherwise with Brentan 2% miconazole nitrate for application on the skin, which does not result in measurable plasma concentrations (bioavailability <1%).

Advice for doctors and dentists

If Brentan oral cavity gel and warfarin are used concomitantly, the anticoagulant effect should be carefully monitored and titrated. An alternative could be to use another antifungal medication not interacting with warfarin and having therapeutic activity against the relevant microorganisms.

Estimated number of persons in concomitant treatment with warfarin and miconazole oral cavity gel

In collaboration with the Data Delivery and Medicinal Products Statistics Department at Statens Serum Institut (SSI), we have estimated how many people in 2014 received concomitant treatment with warfarin and miconazole oral cavity gel. Warfarin doses are determined individually for each patient and adjusted according to INR tests. It has therefore been necessary to base our estimate on some assumptions[4].

Under these assumptions, a total of 92,152 persons redeemed prescriptions for warfarin-containing products from October 2013 to December 2014. Of these 92,152 persons, 697 redeemed a prescription for miconazole oral cavity gel in 2014 within three months after redeeming a prescription for warfarin.

[4] The maintenance dose of warfarin is 1-3 2.5 mg tablets once a day. A warfarin package contains 100 tablets. The analysis assumes that the person takes 1 tablet daily, and that the patient redeems a prescription for one warfarin package at a time, in which case the patient will redeem a prescription for warfarin every three months. A person using warfarin as at 1 January 2014 will thus have redeemed the lastest prescription around 1 October 2013 at the earliest. Consequently, data for warfarin-containing products have been extracted for the period covering 1 October 2013 to 31 December 2014. The data extract for miconazole oral cavity gel redeemed on prescription covers all of 2014. Since the dose is determined individually and several packages can be redeemed at a time, the estimated number of people in concomitant treatment with the two medicines is very rough and should be interpreted carefully.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Zelboraf (vemurafenib)** – Potential radiation toxicity associated with Zelboraf. Severe radiation injuries, some of which fatal, have been reported after treatment with Zelboraf.
- **Xalkori (crizotinib)** – Severe, life-threatening or fatal adverse reactions of cardiac failure reported in clinical trials with crizotinib and during post-marketing surveillance. Sections 4.4 and 4.8 of the summary of product characteristics will be updated.

The DHPCs are available in Danish at the DHMA website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*.

Danish Medicines Agency and Danish Health Authority at Medical Days in November

This year's Medical Days are held at the Bella Center from 9 to 13 November. We will be welcoming visitors in our booth together with the Danish Health Authority (including the Institute for Rational Pharmacotherapy). We are looking forward to many good and constructive discussions with physicians. This year, we would like to put focus on the topics below:

Danish Medicines Agency:

- How to make it easier and more practicable for doctors to report suspected adverse reactions to the Danish Medicines Agency to continually ensure optimum safety for patients.
- Reassessment of reimbursement for mild painkillers entering into force in February 2016. Automatic reimbursement for chronically ill patients from the beginning of 2016. For further information in Danish see: *Sundhedsstyrelsen ændrer medicintilskuddet til visse svage smertestillende lægemidler (DHMA changes medicine reimbursement for certain mild painkillers)* and *Automatisk kronikertilskud til berettigede borgere fra 1. januar 2016 (Automatic reimbursement for eligible chronically ill patients from 1 January 2016)*

Danish Health Authority:

- At Medical Days, the Institute for Rational Pharmacotherapy, IRF, will present the updated red-yellow-green list of medicines that may be successfully discontinued in elderly people or where the indication should be reviewed regularly. The IRF will also bring along the substitution list of medicines offering economic gain when switches are made from one medication to another as well as a summary of the conclusions of the must recently published product recommendations. Please also see *www.irf.dk*.
- The Danish Health Authority has developed a series of instructional material on disease prevention in general practice and in hospitals. The material was launched in October 2015. Copies of the material will be available at Medical Days. Further information is provided in Danish on our website: *Sygdomsforebyggelse i almen praksis og på sygehuse (Disease prevention in general practice and in hospitals).*

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