News in brief

Risk of renal failure and proteinuria to be added to the summary of product characteristics of Afinitor® (everolimus), which is used for treatment of advanced renal cell carcinoma

Sections 4.4 and 4.8 of the summary of product characteristics will be updated with information on renal failure and proteinuria due to observed cases of renal failure (including acute renal failure, some with a fatal outcome) and proteinuria in patients treated with Afinitor®. Cases of pulmonary embolism have also been observed, the risk of which will also be included in the summary of product characteristics.

Please see the *CHMP Monthly Report* (p. 3).

New warnings for Vectibix® (panitumumab) for treatment of metastatic colorectal carcinoma

A follow-up on adverse reaction data has called for an update of sections 4.4 and 4.8 of the summary of product characteristics of Vectibix®, adding warnings of keratitis and ulcerative keratitis. These warnings will also be added to the summary of product characteristics of other EGFR inhibitors for which ocular toxicities have already been described. Letters describing the new warnings have been sent to relevant healthcare professionals.

Please see the *CHMP Monthly Report* (p. 3).

New warning for Tasigna® (nilotinib) for treatment of chronic myeloid leukaemia

A safety review has given rise to the inclusion of a warning in the summary of product characteristics of Tasigna® with respect to the risk of Tumour Lysis Syndrome and updated precautions for use prior to initiating treatment with Tasigna®.

Please see the *CHMP Monthly Report* (p. 4).

Tysabri® for treatment of multiple sclerosis and risk of progressive multifocal leukoencephalopathy (PML)

Information about the risk of PML has been added to the summary of product characteristics of Tysabri®.

Please see the *CHMP Monthly Report* (p. 4).

Bricanyl® turbohaler, 200 dose inhaler to be replaced by the 100 dose inhaler due to risk of delivery of excess dose

The European Pharmacovigilance Working Party has supported stopping the sale of Bricanyl® 200 dose inhaler, recommending that the 100 dose inhaler be used instead.

The decision was made due to the risk of delivery of excess medicine if the inhaler has been dropped. If a turbohaler is dropped on the floor or exposed to similar physical impact, the medicine released at the next inhalation could be significantly higher than the normal dose This is because a small amount of medicine is left in the mouthpiece after each inhalation, which could be released by physical impact.

The risk of receiving a too high dose after physical impact to the device is greater the more inhalations have been taken because more medicine could be retained in the mouthpiece.

On average, a seven times higher dose than the normal Bricanyl® dose was released after physical impact to an almost empty 200 dose inhaler. For the 100 dose inhaler, the dose delivered was only three times higher.

Risks of adverse reactions from an excess dose

Individuals who inhale a higher dose after impact to the device, have a greater risk of adverse reactions. The expected adverse reactions from an excessive dose of Bricanyl® (terbutaline), and to a lesser degree Oxis® (formoterol), include tachycardia, hypokalaemia and hyperglycaemia. However, the risk is considered to be insignificant in most patients, because only a single high dose is inhaled. But for more vulnerable patients, Bricanyl® (terbutaline) may involve a potentially higher risk, e.g. patients predisposed to or suffering from a cardiovascular disease, or patients with a metabolic disease – for these patients in particular, rare cases of myocardial infarction, congestive heart failure and cardiac arrest have been reported from overdose from beta2-agonists, such as terbutaline and formoterol.

For combination products, the risk of inhaling a higher dose of medicine after physical impact to the device is smaller because the combination products are supplied in another model than the turbohaler (model M3) than the one that may deliver a higher dose after physical impact to the device (model M2).

Rinse mouth after each inhalation

To minimise systemic uptake of the medicine, it is recommended to rinse the mouth after each inhalation of Bricanyl®, Oxis®, Spirocort® and Pulmicort® turbohaler.

Read more *here*.

Octagam® to be marketed again

The European Medicines Agency (EMA) recommends resuming marketing of both strengths of the medicine Octagam®, 50 mg/ml and 100 mg/ml. Octagam® was recalled in autumn 2010 due to an unexpected increase in adverse reaction reports describing blood clots. The recommendation to resume marketing is based on a number of improvements in the manufacturing process. The recommendation to resume marketing of Octagam® now awaits the adoption by the European Commission.

The Danish Medicines Agency expects Octagam® to be on the market again shortly after the adoption by the European Commission.

Octagam® is a human immunoglobulin, which is injected intravenously. It is used, for example, as replacement therapy in patients with insufficient antibody production and as immunomodulatory therapy for idiopathic thrombocytopenic purpura Guillain-Barré syndrome.

Octagam® has been used only rarely in Denmark, and the Danish Medicines Agency has received no reports of adverse reactions from Octagam® since 2008.

Read more on the Agency's website *here*.

Status on adverse reaction reports regarding contraceptive pills

In this issue, we have chosen to look at reports which describe potential adverse reactions from contraceptive pills or combination products containing oestrogen and progesterone in constant or varying quantities, received from 1 January 2010 to 28 February 2011.

Contraceptive pills are of special interest to us because they are generally used by healthy women.

Overall low risk of blood clots from contraceptive pills

According to the approved product information of combined oral contraceptives (COC), the incidence of venous blood clots in women using a low-strength oestrogen COC (<50 µg ethinylestradiol) is 20 in 100,000 for contraceptives with levonorgestrel (2nd generation COC) whereas the incidence of blood clots for COC with desogestrel/gestodene is 40 in 100,000 (3rd generation COC). The risk of venous thromboembolism from the use of drospirenone-containing contraceptive pills (4th generation pills) is somewhere between the risk of second and third generation pills.

In women not using hormonal contraception, the incidence of blood clots is 5-10 in 100,000 women. In pregnant women, the incidence of blood clots is 60 in 100,000 pregnancies. The risk of having a blood clot is highest in the first 12 months of COC use.

In addition, the risk of developing blood clots increases with age, just as factors such as smoking, positive familial disposition to development of blood clots, hypertension, obesity, prolonged immobilisation as well as certain cardiovascular diseases can increase the risk.

Assessment and examination before starting contraceptive pills

In compliance with the product information, prescribers should:

- take a complete personal and family medical history, and pregnancy must be excluded.
- measure the blood pressure and perform a physical examination if clinically indicated in compliance with contraindications and warnings described in the summary of product characteristics.

Furthermore, the woman should be instructed to carefully read the package leaflet, to ask for advice if she is unsure about something and to adhere to the advice given. The frequency and nature of further examinations should be based on established practical guidelines and adjusted to the individual woman. The woman should be informed that contraceptive pills do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Consumption from 1 January 2010 to 28 February 2011

From 1 January 2010 to 28 February 2011, a total of 419,333 women received treatment with contraceptive pills. 99.6 percent of the women who were treated with contraceptive pills were aged between 13-65 years.

Table 1 shows the number of women treated with contraceptive pills from 1 January 2010 to 28 February 2011 by adolescents (13-18 years) and adults (19-65 years).

Age group	Women treated with contraceptive pills
13-18 years	83,061
19-65 years	334,774

Table 1. Number of women treated with contraceptive pills from 1 January 2010 to 28 February 2011.

Adverse reaction reports related to contraceptive pills, from 1 January 2010 to 28 February 2011

From 1 January 2010 to 28 February 2011, the Danish Medicines Agency received 78 adverse reaction reports concerning the use of contraceptive pills. 50 of the reports are classified as serious.

The most frequently reported adverse reaction is blood clots. 43 of the 50 reports classified as serious concern blood clots in the leg, brain or lungs – four of which had a fatal outcome.

Adverse reactions with a fatal outcome

One report concerned a middle-aged woman who took 2nd generation pills containing ethinylestradiol and levonorgestrel (Malonetta®). The woman died from a blood clot in the lung. The Danish Medicines Agency assesses that there is a potential link between the use of contraceptive pills and the blood clot.

Two other reports concerned women who took 3rd generation pills containing ethinylestradiol and gestoden (Lindynette® and Harmonet®, respectively). Both women died from a blood clot in the lung.

The report concerning the use of Lindynette® described a middle-aged woman of normal weight

with hypertension who had taken contraceptive pills for many years. Her blood pressure was medically well-controlled. The Danish Medicines Agency assesses that there is a potential link between the use of contraceptive pills and the blood clot.

The report concerning the use of Harmonet® described a younger woman with insulin-dependent diabetes who therefore possibly had an unknown increased risk of blood clot formation at the current time. The Danish Medicines Agency assesses that there is a potential link between the use of contraceptive pills and the blood clot.

The last report concerned a younger woman who took 4th generation pills containing drospirenone (Yasmin®). The woman died from a blood clot in the brain. The woman was assessed not to have a predisposition to blood clots. The Danish Medicines Agency assesses that there is a potential link between the use of contraceptive pills and the blood clot.

The Danish Medicines Agency continues to keep a close watch on the pattern of the reported adverse reactions for contraceptive pills.

Conclusion
Considering the high consumption of contraceptive pills, the Danish Medicines Agency receives relatively few reports that concern contraceptive pills. The reports that we do receive are usually categorised as serious, probably because doctors and patients predominantly report serious events. Compared to the quantity consumed, the number and nature of the reported adverse reactions are expected, and there are no reports or other information that have called for further warnings in the summary of product characteristics of contraceptive pills.

Quarterly updates on adverse reactions reported in Denmark

Danish Pharmacovigilance Update will in future bring quarterly updates on the adverse reaction reports we received in Denmark for a selected type of medicine.

New study on the risk of venous thromboembolism from the use of Yasmin®

In April 2011, the British Medical Journal featured two articles describing an increased risk of venous thromboembolism (VTE) from the use of combined oral contraceptives (COC) containing drospirenone, compared to products containing levonorgestrel (so-called 2nd generation COC).

The results strengthen the conclusions from two previous studies prepared by respectively a Dutch and a Danish research team in 2009. The need for possible regulatory measures, e.g. updating the summary of product characteristics, will be discussed at the next meeting of the European Pharmacovigilance Working Party in May 2011.

Yasmin® has been authorised in the EU since 2000, and the risk of VTE has since been monitored continuously, i.a. via the company's comprehensive EURAS study, covering 58,000 women.

The product information for Yasmin® was last updated in April 2010 to reflect the two epidemiological studies from 2009, which concluded that the risk of VTE from the use of Yasmin® was higher than previously expected and is somewhere between 2nd generation COC (levonogestrel) and 3rd generation COC (desogestrel/ gestoden).

Doctors should include this new information when they consider which form of contraception is best for the individual woman.

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