News from the EMA

Activities of the CHMP

During its meeting from 14-17 March 2011 the Committee for Medicinal Products for Human Use (CHMP) adopted:
- five positive opinions for the **granting of a marketing authorisation** for:

- **Eliquis** (apixaban), from Bristol-Myers Squibb/Pfizer EEIG, intended for the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery. The review for Eliquis began on 24 March 2010; active review time: 210 days.
- **Yellox** (bromfenac), from Croma-Pharma GmbH, intended for the treatment of postoperative ocular inflammation following cataract extraction in adults. The review for Yellox began on 22 July 2009; active review time: 210 days.
- **Zoely** and **IOA** (nomegestrol acetate/estradiol), from Merck Serono Europe Ltd and N.V. Organon, intended for oral contraception. The review for Zoely began on 19 August 2009 with an active review time of 210 days. The review for IOA began on 23 December 2009; active review time: 210 days.
- **Cinryze** (C1 inhibitor, human), an orphan medicine from ViroPharma SPRL, intended for the treatment and prevention of angioedema attacks in patients with C1 inhibitor deficiency. The review for Cinryze began on 24 March 2010: active review time: 201 days. Yet, since ViroPharma is considered the same applicant as Sanquin, which holds marketing authorisations in some EU Member States for a medicine with the same composition and pharmaceutical form and overlapping indications with Cinryze the granting of a marketing authorisation for Cinryze is not for sure.

- **four positive opinions** for applications for **extensions of indications** for:

- **Herceptin** (trastuzumab), from Roche Registration Ltd, to include treatment of patients with HER2-positive early breast cancer in combination with adjuvant chemotherapy consisting of paclitaxel or docetaxel following adjuvant chemotherapy with doxorubicin and cyclophosphamide, or consisting of docetaxel and carboplatin.
- **Lucentis** (ranibizumab), from Novartis Europharm Ltd, to include treatment of visual impairment due to macular oedema secondary to retinal vein occlusion.
- **Remicade** (infliximab), from Janssen Biologics B.V., to extend the approved indication for severe Crohn's disease to patients with moderately to severely active disease.
- **Revatio** (sildenafil), an orphan medicine from Pfizer Ltd, to include paediatric patients aged one to 17 years with pulmonary arterial hypertension.

- one negative opinion for the extension of the indication for

- **Vectibix** (panitumumab), from Amgen, recommending that the current indication should not be extended to include the use of panitumumab in combination with chemotherapy in patients with wild-type *KRAS* metastatic carcinoma of the colon or rectum.

Possible supply shortage of Thyrogen: Genzyme, the marketing authorisation holder for Thyrogen (thyrotropin alfa), informed the CHMP that due to a manufacturing issue there will be a supply shortage of this medicine until July 2011. Genzyme will only be able to supply Thyrogen to meet approximately 45% of EU demand through to July 2011. Thyrogen is authorised for the diagnosis and treatment of thyroid tissue remnants post thyroidectomy in patients with thyroid cancer. During the shortage, Thyrogen use should be restricted to those patients who are not able to tolerate thyroid hormone withdrawal,

or in whom thyroid hormone withdrawal would not be effective. Where possible, Thyrogen use for other patients should be delayed until supply of Thyrogen improves. If such delay is not acceptable, the treating physician and patient should consider alternative treatment options. These are interim recommendations during the shortage.

Pharmacovigilance:

Arbitration procedure for Canazole concluded: The CHMP completed an arbitration procedure for the generic medicine Canazole (Clotrimazole Cream 1%), from Pinewood, an anti-fungal intended for the treatment of skin infections caused by fungi, such as thrush, ringworm or athlete's foot. This procedure had been initiated because of concerns that therapeutic equivalence of this medicine to the reference product Canesten had not been shown and would need to be proven through a therapeutic equivalence study or other validated model. The C´HMP concluded that the data provided by the company was neither robust nor extensive enough to warrant waiving a clinical study, or other validated model, to show therapeutic equivalence and that it was therefore not possible to establish a positive benefit-risk balance. Therefore a marketing authorisation should not be granted in the concerned Member State, the United Kingdom, and the marketing authorisation in Ireland should be suspended, until further studies have been performed.

Harmonisation procedure for Arimidex concluded: The CHMP recommended the harmonisation of the prescribing information for Arimidex (anastrozole), from AstraZeneca. This medicine is used to treat breast cancer in post-menopausal women.

Review of pioglitazone-containing medicines started: The CHMP has begun looking at the benefit-risk balance of the antidiabetic pioglitazone-containing medicines, from Takeda, to further explore the signal of a possible increased risk of bladder cancer with pioglitazone. The risk of bladder cancer in association with pioglitazone has been under close review by the CHMP since the granting of the first marketing authorisation in 2000. Takeda is conducting a number of post-authorisation studies, including a ten-year epidemiological study aimed at identifying incident malignancies associated with pioglitazone treatment in a cohort of diabetic patients. The three interim study reports have so far not confirmed a clear association between the use of pioglitazone and the occurrence of bladder cancer. However, prompted by an increased number of spontaneous reports of bladder cancer, the CHMP considered that the accumulated evidence provided also by preclinical studies, epidemiological data and the PROactive trial (a placebo controlled clinical trial) taken in its totality, represents a clinically relevant signal which requires further evaluation. Therefore the CHMP will review all available data and will assess their impact on the balance of risks and benefits of these medicines.

Review of Revlimid started: The CHMP has begun looking at the benefit-risk balance of the orphan medicine Revlimid (lenalidomide), from Celgene, following reports indicating that lenalidomide may be associated with an increased risk of second primary malignancies. Revlimid is authorised in the EU for use in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy. This review follows observation of a higher incidence of second primary malignancies in patients treated with lenalidomide in clinical studies conducted outside of the authorised indication. While the review is ongoing, the CHMP is not recommending a delay, modification or restriction in the use of lenalidomide for patients treated according to the authorised indication. Trials currently under way using lenalidomide as an experimental drug are under periodic safety monitoring, and the current review does not affect enrolment/participation of patients in these trials.

Review of Vivaglobin and associated names started: The CHMP has begun a review of Vivaglobin and associated names (human normal immunoglobin for subcutaneous use), from CSL Behring, following reports indicating that Vivaglobin may be associated with thromboembolic events. Vivaglobin is a solution for subcutaneous injection that

contains the active substance human normal immunoglobulin. It is used to treat primary immunodeficiency syndromes and as replacement therapy for patients with secondary hypogammaglobulinaemia and recurrent infections due to myeloma or chronic lymphatic leukaemia. Although thromboembolic events are known to occur with intravenous immunoglobulin medicines, they have not previously been linked with subcutaneous immunoglobulins. The CHMP will now review all available data on the manufacturing process of Vivaglobin thoroughly and will assess their impact on the balance of the risks and benefits of the medicine. The review will include the assessment of the root cause of the thromboembolic potential of the medicine and the possible switch to an alternative manufacturing process with appropriate controls to effectively reduce the thromboembolic contaminants in the product.

Review of Novosis Goserelin, Goserelin cell pharm, Novimp and associated names started: The CHMP has begun looking at the results of a good clinical practice (GCP) inspection indicating that the clinical studies performed as part of the marketing authorisation applications for Novosis Goserelin, Goserelincellpharm, Novimp and associated names (goserelin), have not been GCP compliant. Goserelin is used to treat patients with advanced prostate cancer where an endocrine treatment is indicated. In the light of the GCP results, the marketing authorisations of these medicines have been suspended in the concerned Member States and the medicines have been recalled in Germany and the United Kingdom, the only Members States where these medicines are currently being marketed. The CHMP will now review all available data on the clinical studies performed with these medicines thoroughly and will assess their impact on the quality and reliability of the documentation submitted in support of the marketing authorisation.

Date of the next CHMP meeting: 11-14 April 2011.

Exclusively reported by Dr. Siegfried Throm, German Association of Research-Based Pharmaceutical Companies (e-mail: s.throm@vfa.de)
for:
Guide to Drug Regulatory Affairs www.drugregulatoryaffairs.eu