ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR REVOCATION OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING CLOBUTINOL (see Annex I)

Clobutinol is a synthetic non-opioid cough suppressant. It is used for the short-term treatment of irritable, non-productive cough.

Medicinal products containing clobutinol have been available since 1961 and are authorised in a number of EU Member States (see Annex I for the list of clobutinol containing medicinal products authorised in the EU). They include tablets, oral solutions, syrups and solutions for injection, and are available over-the-counter in many EU Member States. They are available as generic or branded medicines, mostly marketed by Boehringer Ingelheim under the trade name Silomat. All clobutinol containing medicinal products in the EU are authorised according to national procedures.

On 30 August 2007, the German Competent Authority (BfArM) issued a Rapid Alert informing the Members States, the EMEA and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of its decision to suspend the marketing authorisation of all clobutinol containing medicinal products in Germany on 31 August 2007 due to an increased risk of serious arrhythmia associated with clobutinol.

The decision of the German Competent Authority was based on newly available preliminary results from a clinical trial performed by Boehringer Ingelheim that have shown a prolongation of the QTc interval under treatment with clobutinol.
At the same time as the decision of the BfArM to suspend all clobutinol containing medicinal products in Germany, Boehringer Ingelheim decided to withdraw voluntarily its clobutinol containing medicinal products worldwide from the market.

The CHMP discussed the matter at its September 2007 plenary meeting and the procedure in accordance with Article 107(2) of Directive 2001/83/EC, as amended was started at the September 2007 CHMP meeting.

Safety

Further to a publication (Bellocq et al., 2004) of a case of a young boy with a congenital long QT-Syndrome who developed syncopes and Torsades de Pointes after intake of clobutinol, the German Competent Authority requested Boehringer Ingelheim to perform a preclinical investigational program and - at a later date - a clinical study to evaluate the risk of QT prolongation.

Boehringer Ingelheim performed both *in vitro* and *in vivo* electrophysiological studies in order to further characterise the torsadogenic potential of clobutinol. The non-clinical study results indicate that clobutinol has a potential to prolong the QTc interval.

To further investigate the torsadogenic potential of clobutinol a multiple rising dose study in healthy volunteers with doses exceeding the highest recommended therapeutic dose of 80 mg clobutinol t.i.d. (three times a day) was performed by Boehringer Ingelheim. The primary objective of the study was to investigate safety parameters with special emphasis on ECG (electrocaridiogram), tolerability and pharmacokinetics of clobutinol in healthy male and female volunteers following oral administration of a 80 mg single dose and of repeated rising doses of t.i.d. 80 mg (= maximum recommended therapeutic dose), 160 mg, 240 mg and 320 mg over 7 days plus a final dose in the morning of day 8 (= over 8 days). The multiple rising dose trial was randomised, double-blind and placebo controlled within dose groups. 48 healthy volunteers (male and female) were planned to participate according to four sequential groups of twelve volunteers each.

The observed maximum mean increase of QTc interval at one specific time point was 32 ms for the 240 mg daily dose, 43 ms for the 480 mg daily dose and 54 ms for the 720 mg daily dose. The study was prematurely discontinued on day 2 in the third group (720 mg dose group).

These preliminary clinical trial results show a strong QT prolongation potential in healthy volunteers. According to the ICH E14-Guideline ("The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs", 2005) drugs "that prolong the mean QT/QTc interval by > 20 ms have a substantially increase likelihood of being proarrhythmic …". The observed maximum mean increase of QTc interval at one specific time point was 32 ms for the 240 mg daily dose, 43 ms for the 480 mg daily dose and 54 ms for the 720 mg daily dose. The results show that the QT/QTc prolongation is clearly dose dependent. The ICH E 14 limits of 20 ms are clearly exceeded even under therapy with the highest recommended and approved dose (240 mg).

It was concluded that there is a potential risk of life-threatening arrhythmia under treatment with clobutinol.

Benefit/risk

Potentially life-threatening torsades de pointes may be caused by QT prolongation.

The preliminary clinical trial results show a strong QT prolongation potential in healthy volunteers. The results show that the QT/QTc prolongation is clearly dose dependent. The ICH E 14 limits of 20 ms are clearly exceeded even under therapy with the highest recommended and approved dose (240 mg).

Clobutinol is a non-opioid cough suppressant and the expected benefit is symptomatic. Alternative options are available. In addition, clobutinol-containing products are usually used outside structures where an adequate monitoring could be performed to prevent or detect QTc-prolongation related events.

Taking all these elements into account, the CHMP concluded that the benefit/risk ratio for clobutinol is not considered favourable and recommended the revocation of the Marketing Authorisations for the medicinal products referred to in Annex I. The CHMP also recommended that temporary measures are needed in view of the potentially life-threatening risk associated with QT prolongation and therefore recommends to the European Commission that the marketing and the use of clobutinol containing medicinal products be suspended forthwith in all concerned EU Member States awaiting the adoption of final measures.

GROUNDS FOR THE REVOCATION OF THE MARKETING AUTHORISATIONS

Whereas,

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing clobutinol

- The Committee concluded, after having reviewed the available data, that clobutinol has a clear potential for QT prolongation

- The Committee concluded that the QT/QTc prolongation is clearly dose dependent and that the ICH E14 limits of 20 ms are clearly exceeded even under therapy with the highest recommended and approved dose (240 mg)

- The Committee considered that clobutinol is approved for a condition which is not life-threatening and for which alternative treatments are available, and the expected benefit is only symptomatic; furthermore the CHMP took into account that clobutinol could be available over the counter

- The Committee, in light of the above findings, concluded that the benefit/risk balance of clobutinol containing medicinal products is not favourable.

Following the provisions under Article 107(2) of Directive 2001/83/EC, as amended, the Agency's Committee for Medicinal Products for Human Use (CHMP) prepared an opinion on 18 October 2007 recommending the revocation of the Marketing Authorisations for all clobutinol containing medicinal products in Annex I. The CHMP also recommended that temporary measures are needed in view of the potentially life-threatening risk associated with QT prolongation and therefore recommends to the European Commission that the marketing and the use of clobutinol containing medicinal products be suspended forthwith in all concerned EU Member States awaiting the adoption of final measures.