ANNEX II

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

SCIENTIFIC CONCLUSIONS

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

Carisoprodol is a centrally acting drug mainly indicated for short-term treatment of acute lower back pain.

Medicinal products containing carisoprodol have been available in Europe since 1959 and are authorised in a number of EU Member States (see Annex I for the list of carisoprodol containing medicinal products authorised in the EU). They include tablets and supositories available under prescription in 12 EU Member States. All carisoprodol containing medicinal products in the EU are authorised according to national procedures.

On 20 April 2007, the Norwegian Competent Authority (NoMA) issued a Rapid Alert informing the Member States, the EMEA and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of the decision by the Marketing Authorisation Holder Actavis to voluntarily withdraw as of 1 May 2008 the Marketing Authorisations for carisoprodol containing medicinal products in its Member State. The Marketing Authorisation Holder decided on the voluntary withdrawal on the basis of the assessment performed by the Norwegian Competent Authority. In its assessment NoMA concluded that carisoprodol was associated with an increased risk of abuse or addiction, intoxication and events related to psychomotor impairment.

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

There is available evidence that carisoprodol is associated with a risk of abuse, psychomotor impairment and intoxication. There are several scientific publications analysing the adverse effects of intoxication and psychomotor impairment. In addition there is information on spontaneous reports as well as reports from poison centers in Europe and in the US that there are problems related to intoxications. The three observational studies published in Norway in 2007 gave evidence for the signals of abuse and impairment identified by the spontaneous reporting system in Norway. In one of these studies it was concluded that patients receiving carisoprodol seemed to have an increased risk of being involved in traffic accidents involving person injury. The study gave support to earlier work published on the impairing effects of carisoprodol.

As pharmacological studies with carisoprodol have been limited to single dose studies, there have been some uncertainties to the mechanism for the observed effects of carisoprodol and whether they are associated with carisoprodol itself or with its metabolites. In the results from the study which was submitted during this procedure sedation, psychomotor impairment and other impairments were observed about 1.5 hour after ingestion, indicating these are effects associated with carisoprodol itself and not its metabolites.

The pharmacokinetic part of the above mentioned study showed that the blood concentration curve of carisoprodol increases and falls rapidly. This means that adverse drug reactions related to high carisoprodol concentrations are easier to identify. The serum concentrations for carisoprodol together with the pharmacodynamic results on somnolence found in this study clearly confirmed the Norwegian observational study results that there should be strong warnings against the use of motor vehicle due to somnolence when using carisoprodol medication.

The lack of recent safety studies comparing carisoprodol to other analgesic products with a better studied safety profile available for the same indication emphasizes the need for further systematic investigation.

Several risk minimisation activities (such as restriction of the indication, recommendation of only short term treatment, supply of only small package and change of the prescription category to a more restrictive) have been proposed by the MAHs. In Norway most of these activities were implemented already in 1995 without any effect on the way the product was prescribed and used. In the recent observational studies the prescribing patterns continued to be distorted. In this perspective it is considered that unless the risk minimisation measures can be monitored and their impact can be evaluated accurately they could not be a valuable point in the evaluation of the use of carisoprodol.

Benefit/risk

Carisoprodol is associated with a risk of abuse, psychomotor impairment and intoxication.

Acute lower back pain is the only indication that has been documented by three randomised, controlled clinical studies using carisoprodol 350mg performed in the 60's and 70's and which do not fulfill current stardard for the Phase III clinical trials. For other indications authorised in some countries it must be concluded that the efficacy is not documented, but it is based on anecdotal reports on clinical effect. Alternative options are available in the EU for the concerned indications.

Taking all these elements into account, the CHMP concluded that the benefit/risk ratio for carisoprodol is not considered favourable and recommended the suspension of the Marketing Authorisations for the medicinal products referred to in Annex I.

GROUNDS FOR THE SUSPENSION OF THE MARKETING AUTHORISATIONS

Whereas

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

The Committee concluded that there is increasing evidence for carisoprodol-associated risk of abuse, psychomotor impairment and intoxications. These symptoms are attributable to the low therapeutic index of carisoprodol. A number of articles describing its abuse potential, toxicity and dependence have been published. In addition there is data from poison information centres confirming these concerns.

The Committee considered that carisoprodol is indicated primarily for acute low back pain, however, because of the nature of low back pain this has resulted in a tendency for more chronic use of the drug, increasing the risk of dependence. Therefore, in practice a safe pattern of use of carisoprodol containing products is difficult to achieve in many patients.

The Committee considered that the efficacy of carisoprodol containing products is poorly documented; only three relatively old studies are available to demonstrate efficacy in acute low back pain. The proof of efficacy for different dosing of carisoprodol and for combination products is missing completely. The MAHs of carisoprodol containing products have not provided any sound clinical data, which would demonstrate the efficacy of carisoprodol. Furthermore the CHMP took note that there are other effective medications with a more favourable safety profile for the treatment of acute low back pain.

The Committee in light of the above findings concluded that the benefit/risk balance of carisoprodol containing medicinal products is no longer positive.

Thus the CHMP recommended the suspension of the Marketing Authorisations for all carisoprodol containing medicinal products listed in Annex I. For the suspension to be lifted the Marketing Authorisation Holders would need to provide:

- Data demonstrating that the products can be used safely taking into account information on intoxications from poison centres in Europe.
- Data demonstrating convincing efficacy and safety derived from appropriately designed clinical trials (including an active comparator) and data justifying the proposed dose.
- Detailed risk minimisation measures and ways to ensure that the impact of such measures could be adequately evaluated once in place.