



**FINAL OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
PURSUANT TO ARTICLE 12 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED FOR**

Medicinal products

International non-proprietary name:	Chlormezanone
Names:	see Annex A
Pharmaceutical forms:	see Annex A
Strengths:	see Annex A
Routes of administration:	see Annex A

Background

A CPMP opinion for chlormezanone, pursuant to Article 12 of Council Directive 75/319/EEC as amended, was adopted on 22 January 1997 (Annex B) recommending that the EU Marketing Authorisations of all chlormezanone-containing medicinal products should be withdrawn. The scientific conclusions and the grounds for withdrawal of the Marketing Authorisations were set out in Annex to the opinion (Annex C).

Valid intents of appeal against the opinion were submitted by two of the Marketing Authorisation Holders of chlormezanone-containing medicinal products, Azupharma GmbH and Merckle GmbH, on 7 February and 10 February 1997 respectively. All Marketing Authorisation Holders were notified of the appeal on 20 February 1997.

Joint grounds for appeal were submitted by the trade associations of the German pharmaceutical industry "Bundesverband der Pharmazeutischen Industrie e.V.", "Bundesfachverband der Arzneimittelhersteller e.V.", "Verband aktiver Pharmaunternehmen e.V." and "Verband Forschender Arzneimittelhersteller e.V.", on behalf of Azupharma GmbH and Merckle GmbH, on 21 March 1997.

Grounds for appeal

The grounds for appeal lodged by Marketing Authorisation Holders can be summarised as follows:

1. objection to the view that there is a lack of efficacy data.
2. discrepancy raised by the difference in incidence rates of serious skin reactions in France and Germany.
3. objection to the conclusions of the ELYS-SCAR study (Roujeau, 1995, NEJM, 333; 1600-1607).
4. a model of the fatal adverse effects of substitute therapies.
5. a proposal that amendment of the Summary of Product Characteristics (SPC) and patient information should lead to the desired risk minimisation.

Final Opinion

Regarding the grounds for appeal lodged by Marketing Authorisation Holders, the CPMP considers that:

1. The evidence of efficacy for chlormezanone is limited and demonstrates similar efficacy to the simple analgesic, paracetamol. Comparative studies with agents used for the recommended indications of chlormezanone are not available.
2. Although the incidence of all serious cutaneous reactions (Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and Erythema multiforme majus) occurred at different rates in Sweden and France versus Germany, TEN occurred at a similar rate in France, Germany and Sweden. Positive rechallenges and epidemiological data confirm that chlormezanone causes serious skin reactions.

3. Since its publication, further results from the ELYS-SCAR study show that the use of chlormezanone alone is significantly linked with a risk of Stevens-Johnson Syndrome and TEN.
4. No conclusions can be drawn from the modelling exercise as the presentation of the results did not include a sensitivity analysis to the assumptions.
5. It is considered that amendment of the product information would not lead to a satisfactory level of risk minimisation.
6. In conclusion, in view of the established risk of serious skin reactions and the evidence of efficacy the risks are considered to outweigh the benefits.

In summary, taking into account the limited evidence of efficacy and the risk of serious skin reactions, the risk/benefit balance remains negative.

The CPMP, having considered the grounds for appeal submitted on 21 March 1997, has concluded that its opinion of 22 January 1997 should not be revised and that the Marketing Authorisations for all medicinal products referred to in Annex A should be withdrawn.

This opinion is forwarded to the European Commission, to Member States and to Marketing Authorisation Holders, together with its annexes and appendices.

London, 14 May 1997

On behalf of the CPMP
Prof. J.-M. Alexandre, Chairman

ANNEX C
SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA FOLLOWING THE
OPINION OF THE CPMP GIVEN ON 22 JANUARY 1997 FORMULATED UNDER
ARTICLE 12 OF COUNCIL DIRECTIVE 75/319/EEC

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CHLORMEZANONE

On 25 September 1996 Germany, related to the concerns about the risk of patients using chlormezanone developing serious skin adverse reactions, requested that the CPMP, under Article 12 of Council Directive 75/319/EEC as amended, provide an opinion on whether there is an unfavourable benefit/risk relation for chlormezanone in the indication where it is most widely used in the EU, that is lower back pain with muscle contracture.

The CPMP at their meeting of 20-22 January 1997 considered the matter and reached the following conclusions, based on the evaluation of the CPMP's Pharmacovigilance Working Party and the assessment reports distributed by the Rapporteur and Co-Rapporteur:

Overview of the Efficacy:

Evidence of efficacy with chlormezanone is limited and of poor quality.

With regard to efficacy of chlormezanone and other centrally-acting muscle relaxants in low back pain, the main indication for which chlormezanone is used in the EU, there are no valid studies which were designed according to current standards and which have proven an effect exceeding that of analgesics. No study comparing the efficacy of chlormezanone with other muscle relaxants has been performed.

Overview of the Safety:

In considering the overall safety profile of chlormezanone the most relevant risk was concluded to be life-threatening cases of toxic epidermal necrolysis and other bullous reactions. Evidence from two French Pharmacovigilance Surveys, a multi-national case control study, and spontaneous reporting have suggested a causal association between chlormezanone and serious skin reactions.

Serious skin reactions may also occur with other muscle relaxants, however, the available data suggest that the relative frequency of serious skin reactions is greater with chlormezanone.

Overall risk/benefit assessment:

The CPMP considered the risk/benefit balance of chlormezanone-containing compounds to be unfavourable.

GROUNDINGS FOR WITHDRAWAL OF THE MARKETING AUTHORISATIONS

Whereas,

- the Committee considered the referral made under Article 12 of Council Directive 75/319/EEC for chlormezanone.
- the Committee agreed that there was particular concern related to the safety of chlormezanone-containing medicinal products, in particular the risk of toxic epidermal necrolysis and other serious skin reactions, following an evaluation of the risks of the product.
- the Committee agreed that evidence of efficacy with chlormezanone is limited and of poor quality, there are no valid studies available which were designed according to current standards and which have proven an effect exceeding that of analgesics.
- the Committee considered the risk/benefit balance of chlormezanone. It concluded that it should not be maintained on the market because in view of the limited evidence of benefit and the risk of serious life-threatening adverse reactions, even at low incidence, the risk/benefit balance of chlormezanone-containing compounds was considered to be unfavourable.

the European Agency for the Evaluation of Medicinal Products has recommended the withdrawal of the Marketing Authorisations of all chlormezanone-containing medicinal products.