COMMISSION OF THE EUROPEAN COMMUNITIES

SEC(93) 771 Brussels, 12 May 1993

REPORT

ON THE OPERATION OF THE
COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
IN 1991 AND 1992

(Commission Staff Working Paper)

CHAPTER I

INTRODUCTION

1. LEGISLATIVE DEVELOPMENTS

1.1 On 17 December '92, the Council unanimously reached a decision of principle on the Proposal for a Council Regulation laying down Community procedures for the authorization of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products[1], consisting of the Committee for Proprietary Medicinal Products (human medicines) and the Committee for Veterinary Medicinal Products (veterinary medicines). Council also decided to consult the European Parliament on the change of the legal basis for this proposal which will establish a new 'centralized' Community authorization procedure for innovatory medicinal products, from Article 100A of the Treaty to Article 235.

In addition, the Council adopted common positions on three proposals to amend existing Community pharmaceutical legislation to create a new 'decentralized' procedure for the authorization of other categories of human and veterinary medicinal products based upon the principle of mutual recognition of national authorizations, but with binding Community arbitration in the event of disagreement between Member States. These new procedures, decentralized and centralized, have been elaborated from the experience gained with the current Community procedures, namely the 'multi-state' and 'concertation' procedures. This report provides an opportunity to review the operation and outcome of these procedures, especially as this experience will contribute substantially to the preparation of the procedures for the future system.

1.2 The analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products were first set out in the annex to Directive

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1 COM(90)283 of 14.11.1990

75/318/EEC[2]. Adaptation to technical progress is achieved through the Committee on the Adaptation to Technical Progress.

Given the scientific developments since 1975, it was appropriate to up date these requirements. Further, arising from the adoption of Directives 89/341/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, the so-called "extension directives", it was also necessary to establish the requirements for the testing of immunological medicinal products consisting of vaccines, toxins or serums and allergens; radiopharmaceuticals; medicinal products derived from human blood or human plasma.

Following a complete review of the different tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products by the CPMP and its working parties, and a favourable opinion of the Commitee on the Adaptation to Technical Progress, the Commission adopted new testing requirements. These requirements are set out in Directive 91/507/EEC which entered into force on the 1.1.92, to coincide with the entry into force of the "extension directives".

2. CONTENT OF THE REPORT

2.1 This report covers, in accordance with the first paragraph of Article 15 of Council Directive 75/319/EEC, the operation of the procedure laid down in chapter III of that Directive (i.e. the multi-state procedure) and its effects on the development of intra-Community trade, thus updating earlier reports[3].

In performing its role as set out in Directive 75/319/EEC, the Committee for Proprietary Medicinal Products (CPMP) gives an opinion as to whether a particular medicinal product complies with the requirements set out in Directive 65/65/EEC.

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2 In order to facilitate reading this report, references to Community pharmaceutical legislation cited are summarized in chronological order in Annex 1.

3 Reports from the Commission to the Council on the operation of the Committee for Proprietary Medicinal Products: COM(79)59 of 22.2.1979; COM(80)149 of 31.3.1980; COM(81)363 of 13.7.1981; COM(82)787 of 3.12.1982; COM(84)437 of 3.12.1984, (explanatory memorandum); COM(88)143 of 22.3.1988; COM(91)39 of 15.2.91

Its activities are therefore not restricted to applications for new marketing authorizations, but also include consideration of the appropriate scientific and administrative requirements for the submission of applications for marketing authorizations. The work of the CPMP does not end with the decision to grant or refuse a marketing authorization. The Committee maintains a watchful eye on all medicinal products on the market and is constantly active in monitoring the safety and efficacy of these.

2.2 On the basis of its expertise, the CPMP has also supported the Commission in international discussions on technical requirements for the authorization of medicinal products, the exchange of scientific knowledge and efforts towards international harmonisation of testing requirement for pharmaceutical products (International Conference on Harmonisation (ICH)). Much of this work is accomplished by the CPMP through its working parties and expert groups, which provide an invaluable support to the Committee and to the Commission.

2.3 The present working document from the services of the Commission relates to the period between 1.1.1991 and 31.12.1992. It covers the global activities of the Committee for Proprietary Medicinal Products and its working parties, and includes a brief statistical analysis of the operation of the two Community procedures (multi-state and concertation) for the co-ordination of national authorizations to place medicines for human use on the market, as well as developments in the area of pharmacovigilance and international harmonization/activities.

In order to reflect the wide scope of activity of the Committee, all of these aspects are considered.

CHAPTER II

STRUCTURE AND COMPOSITION

1. COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

1.1 The Committee for Proprietary Medicinal Products (CPMP) was established by Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, and is charged with the responsibility of giving an opinion as to whether a particular medicinal product complies with the requirements set out in Directive 65/65/EEC.

Further, Directive 87/22/EEC requires that applications for marketing authorization relating to medicinal products for human use referred to in the annex of that directive i.e. biotechnology/high technology medicinal products, be brought before the CPMP for opinion.

2. MEMBERSHIP OF THE COMMITTEE

2.1 The Committee for Proprietary Medicinal Products, in accordance with its Rules of Procedure (III/492/77), consists of one representative for each Member State and one representative of the Commission. One alternate is appointed for each of the representatives. Each member of the CPMP may be accompanied by up to three experts. The secretariat of the Committee is provided by the services of the Commission.

2.2 The Committee elects its chairman from amongst its members by absolute majority and secret ballot. The term of office of the chairman is three years, renewable once only. In September '88, Professor D. POGGIOLINI was elected for a first term and in September '91 was re-elected for a further term.

Professor POGGIOLINI had been preceded as chairman by Dr. C. TEIJGELER (1983 - 1988) and Dr. L. ROBERT (1977 - 1983).

2.3 The rules of procedure provide for two deputy chairmen;

- one deputy chairman is elected by the Committee in accordance with the same procedure as the chairman, and replaces the chairman in case of absence. In September '91, Professor J.M. ALEXANDRE was re-elected deputy chairman.
- the second deputy chairman is appointed by the Commission in order to conduct routine business on behalf of the Committee between meetings. Mr. F. SAUER continued to serve as deputy chairman during the period under review.

2.4 A list of the membership of the CPMP (as of 31.12.92) is given in annex 2.

2.5 During the period under review, the Committee met on 17 occasions, which was the equivalent of 36 full days of meetings. The working parties and expert groups met 65 times which was the equivalent of 101 full days of meetings. Between CPMP and working party meetings, 137 days of meetings were organised (including travel, interpretation and documentation). It is clear that the resource requirement for the activities of the CPMP, both by the competent authorities of the Member States and by the Commission, is substantial. With the work load of the CPMP and its working parties increasing (see chapters III and IV), the urgent need for the European Agency can be readily appreciated.

3. COMMUNICATION AND INFORMATION

3.1 Given the wide range of activities of the CPMP, it is important that the opinions of the Committee on pharmacovigilance, guidelines on the testing and development of medicinal products and positions on a number of issues of public health interest are available to the pharmaceutical industry, health care professionals and patients, and other interested parties. A series of measures have been introduced to publicise the existence of documents and to ensure their availability.

3.2 The CPMP issues a Press Release after each of its meetings. In the release, the numbers of opinions given for multi-state and concertation procedures are indicated, along with the full text of any pharmacovigilance opinion which has been adopted. All guidelines which are finalized are listed, as well as any draft guideline which is released for consultation. International liaisons and meetings are reported. As relevant, items of special interest are included and in some cases a clarification of requirements may be indicated, such as:

GCP: In March '92, the CPMP issued a clarification regarding the applicability of Good Clinical Practice (GCP) to clinical trials. "Commission Directive 91/507/EEC requiring all phases of clinical investigation to be designed, implemented and reported in accordance with good clinical practice came into force on 1.1.92. The CPMP guideline on Good Clinical Practice recommended that all studies commencing after the 1.7.91 should be undertaken in accordance with GCP. The clinical expert as defined in the Notice to Applicants (Jan. '89) is therefore asked to ensure that all studies commencing after this date have been undertaken in accordance with GCP and to clearly state this in the introduction the Clinical Expert report in an additional section headed 'Compliance with GCP'. The expert should comment on any studies not complying with GCP and give a clear statement as to why the guidelines have not been applied. In this section the expert should also comment on studies commencing before the 1.7.91, noting whether these were undertaken according to GCP. The expert should comment on any deficiencies in these studies."

Hepatitis C: In December '92, "the Committee reaffirmed its position of 17.3.92 regarding the need to screen, for hepatitis C (HepCV), plasma used in the manufacture of medicinal products. Only products which have been screened for the absence of antibodies to HepCV should be used in the production of medicinal products derived from

plasma, as of 1.1.93. For the purpose of clarification, the CPMP confirmed that the date of 1.1.93 applies to the release of the finished product by the manufacturer; in the case of human blood derived products used as an excipient the date of 1.1.93 applies for their incorporation into a medicinal product. Companies were further reminded that the screening test used must be validated and state of the art to avoid false negatives."

3.3 The series 'The Rules governing Medicinal Products in the European Community in which there are 7 volumes, is prepared by the Commission and brings together the legislative texts relating to pharmaceuticals as well as the publications of the CPMP, particularly in regard to guidelines for the testing of medicinal products and the submission of applications for marketing authorizations.

These volumes are regularly updated, as follows:

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY

Volume I	The rules governing medicinal products for human use in the European Community; Catalogue no.CO-71-91 631-EN-C
Volume II	Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community (Second edition); Catalogue no.CB-55-89-293-EN-C
Volume III	Guidelines on the quality, safety and efficacy of medicinal products for human use; Catalogue number CB-55-89-843-EN-C: Addendum (July 1990) CB-59-90-936-EN-C Addendum no. 2 (May 1992) ISBN 92-826-4550-9

Volume IV	Good Manufacturing Practice for medicinal products Catalogue number CO-71-91-760-EN-C

These texts, as well as Volumes V, VI and VII on Veterinary Medicinal Products, are on sale at the:-

Office for Official Publications of the European Communities
2 rue Mercier
L-2985 LUXEMBOURG
tel. (352) 49 92 81 / fax (352) 49 00 03

3.4 In operating the Community procedures for multi-state and concertation applications, the CPMP has developed a number of Operating Procedures. Whilst these texts have always been generally available, it was considered that reference to the texts would be simplified by preparing a compilation into a Procedures Manual. The first edition will be finalized in May '93.

3.5 In a further effort to increase transparency, the Committee has agreed, in March '91, that the assessment report prepared in the concertation procedure would be made available to the applicant. For other issues of general interest, such as in the case of the report on Hypnotics, the Committee has agreed to prepare a summary document which would be made available.

4. WORKING PARTIES AND AD HOC GROUPS

4.1 The CPMP supports its scientific activities with expertise from the competent authorities of the Member States. Given this large pool of resource, a number of structures have been set up.

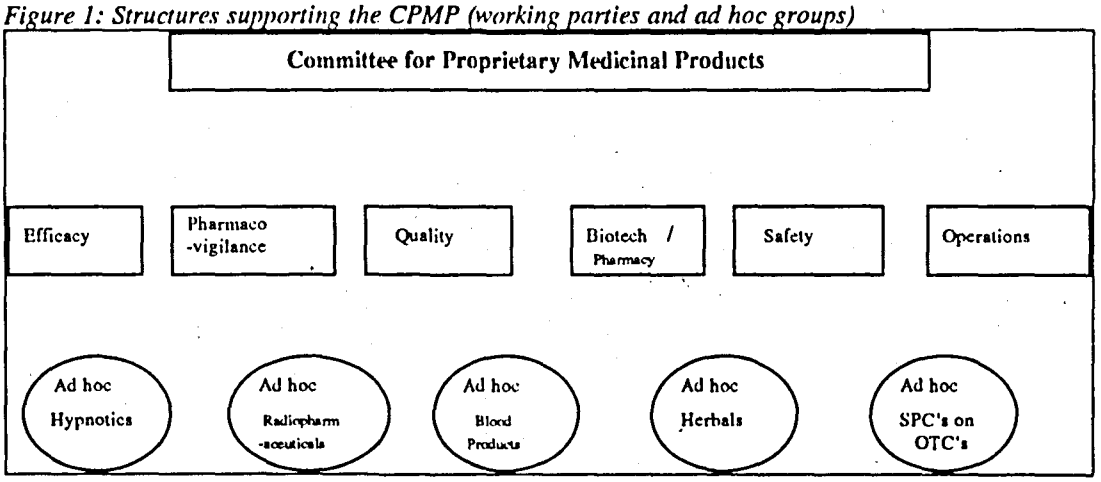
- **Working parties**: a working party gathers experts from all 12 Member States, and generally treats questions relating to the manufacture, demonstration of safety and efficacy of medicinal products and/or administrative procedures. Although

there is a tendency for the same expert to follow developments within the working party, the attendance at any given meeting will be determined by the content of the agenda. Working parties generally meet twice a year, although additional drafting group meetings, for specific topics, may also be called.

- **Ad hoc groups**: Experience has shown that flexible structures which can respond to specific needs and which can regroup expertise either of differing disciplines or specialist interests, are required. Thus ad hoc groups are formed in order to deal with clearly identified tasks/questions. The number of meetings of an ad hoc group will depend on the time scale given for the resolution of the problem and the complexity of the issue.

4.2 The supporting structures of the CPMP are illustrated in Figure 1. Connecting lines have not been drawn, so as to emphasize the fluidity between the main Committee, the working parties and expert groups.

Figure 1: Structures supporting the CPMP (working parties and ad hoc groups)



4.3 The chairman of the CPMP nominates an expert as chairperson of a working party/ad hoc group, which is endorsed by the CPMP. In December '91, the following were appointed as chairpersons, for a term of three years:

- Biotechnology/Pharmacy working party: Professor G. Vicari
- Efficacy working party: Professor Dr. U. Gundert-Remy
- Operations working party: Dr. D. Jefferys
- Pharmacovigilance working party: Professor J. Schou
- Quality working party: Dr. A. Artiges
- Safety working party: Dr. M. Burns

The following accepted to act as chairperson/co-ordinator for the specific topic:

- Ad hoc Blood Products: Dr. D. Sandoval
- Ad hoc Radiopharmaceuticals: Dr. K. Kristensen
- Ad hoc Hypnotics: Professor J.M. Alexandre
- Ad hoc Herbal Remedies: Professor A. Hildebrandt
- Ad hoc Over The Counter (OTC's): Dr. S. Mela

4.4. The activities undertaken in the working parties/ad how groups during the last two years, the numbers of meetings held and guidelines developed are summarised hereunder:

4.4.1. **Biotechnology/Pharmacy:** The biotechnology/pharmacy working party assists the CPMP in reviewing the biotechnology quality aspects of applications received in accordance with List A of the concertation procedure (see chapter IV). In addition, the working party developed guidelines on 'Validation of virus removal and inactivation procedures'; 'Harmonization of requirements for influenza vaccines'; 'Medicinal products derived from human blood and plasma'; 'Guidelines for minimizing the risk of transmission of agents causing spongiform encephalopathies via medicinal products'; 'Allergen products'; and 'Biotech headings for the Notice to Applicants'. With the inclusion of quality aspects of biotechnology products on the programme for ICH 2 (see page 51), the working party is also collaborating in this international activity. The working party met 11 times, which was the equivalent of 22 meeting days.

4.4.2. **Efficacy:** This working party considers the scientific requirements for the demonstration of efficacy of medicinal products. The working party has prepared a number of general clinical guidelines as well as clinical guidelines on specific therapeutic classes of medicines. During 1991-1992, a number of guidelines were finalized, including 'Clinical investigation of hypnotic medicinal products'; 'Investigation of bioavailability and bioequivalence'; 'Summary of Product Characteristics (SPC) of Benzodiazepines used as hypnotics'; 'SPC of ß-adrenergic blocking agents'. The working party also participated, along with other working parties, in the preparation of the topics for the International Conference on Harmonization (ICH). The working party met on 5 occasions, for the equivalent of 9 days.

4.4.3. **Operations:** This working party elaborates administrative requirements and procedures for submissions through the multi-state and concertation procedures. It met on 12 occasions, equivalent to 18 days, and developed a large volume of documents both for internal use by the CPMP and for use by the pharmaceutical industry. Guidelines include 'Summary of Product Characteristics (SPC)'; 'Abridged applications'; 'EC application format'; 'CPMP list of allowed terms'; as well as internal operating procedures for the multi-state and concertation procedures, a 'check-in' procedure for dossiers and a guideline on 'Assessment reports'. The working party is currently preparing a revision to the administrative part of the Notice to Applicants (to be known as Notice to Applicants '93, Volume IIA), a draft of which was released for consultation in December '92. The revisions of Volume IIB will commence in 1993, for finalization during 1994.

4.4.4. **Pharmacovigilance:** This working party continued its work on the harmonisation of approaches towards the monitoring and collection of information on adverse drug reactions (ADR's). A number of guidelines were prepared and adopted: 'Pharmacovigilance exchange of information within the working party'; 'Procedure for causality classification in pharmacovigilance in the EC'; updating the 'Rapid alert system. The working party met on 11 occasions, for a total of 12 days.

4.4.5. **Quality:** This working party reviews analytical testing and development requirements for demonstration of the quality of medicinal products. A number of new guidelines were prepared, 'Ionizing irradiation in the manufacture of medicinal products'; 'Specifications and control tests on the finished product'; 'Quality of prolonged release oral solid dosage forms'. The working party liaises with other bodies including the European Pharmacopoeia. It collaborated actively in the preparations for the ICH conference in November '91 and subsequent ICH meetings. The working party met on 8 occasions, which equated to 14 days.

4.4.6. **Safety:** This working party considers preclinical toxicological and pharmacological issues, both in regard to specific substances and general principles. The possible association of Noscapine, an alkaloid of opium, with polyploidy was reviewed by the group and subsequently led to the CPMP opinion of 4.12.92 (see annex 3). The application of Good Laboratory Practice to safety tests was also examined by the group and the CPMP issued a statement on this in February '93. In addition to the preparation of the guideline on 'Non-clinical local tolerance testing of medicinal products'; the working party participated actively in the ICH discussions. The working party met on 4 occasions, equivalent to 7 meeting days.

4.4.7. Ad hoc groups: the ad hoc groups of the CPMP, particularly those concerned with the co-ordination of the review of the 'extension' products met during this period also:

Radiopharmaceuticals: this ad hoc group met 7 times (10 meeting days) and agreed a programme for the review of radiopharmaceuticals, as well as preparing summaries of product characteristics for many of these products. Two guidelines were prepared, on Radiopharmaceuticals and on radiopharmaceuticals based on monoclonal antibodies, and also specific elements for the Notice to Applicants and for the Pharmaceutical Expert Report

Blood products: the ad hoc group co-ordinating the review of medicinal products derived from human blood or human plasma met on two occasions, and with the co-operation of experts working in the Member States, twenty core SPC's have been finalized.

Herbal Remedies: In response to submissions from the European Scientific Co-operative for Phytopharmaceuticals (ESCOP) , an ad hoc group met for two days and prepared assessment reports on six monographs. This was transmitted from the CPMP to ESCOP in October '92.

Hypnotics: Following the referral in accordance with Article 11 of Directive 75/319/EEC (see page 45) the CPMP established an ad hoc group of rapporteurs to assess the relative benefit/risk of all short acting hypnotics. The ad hoc group met on 4 occasions, for the equivalent of 6 meeting days, and presented a preliminary report to the CPMP in December '92. This report will be finalised during the early part of 1993.

OTC's: In response to submissions from AESGP, and arising from the combined efforts of the experts in the Member States, a number of draft SPC's for OTC products (i.e. medicinal products available without a prescription: over-the-counter) have been released for consultation.

4.5 An important ingredient in the success of the supporting structures of the CPMP is the flexibility, co-operation and hard work shown by the experts who participate in discussions. Thus working parties have worked jointly with other working parties and/or with ad hoc groups, collaborating as full groups or smaller drafting groups; rapporteurs have worked together on applications, assessment reports and guidelines; experts and co-ordinators have liaised with international partners involved in the ICH process.

With the heavy work load of the Committee, the working parties and the ad hoc groups, the need to ensure excellent communication between experts, constant flow of documents and sufficient resources to allow experts to meet, has been clearly identified as a priority. Thus the favourable position of Council regarding the establishment of the European Agency for the evaluation of Medicinal Products points the direction for the future and serves to encourage those involved to continue their excellent efforts.

CHAPTER III

MULTI-STATE PROCEDURE

1. PRINCIPLES OF THE MULTI-STATE PROCEDURE

1.1 The legal rules governing the "multi-state" procedure are set out in Chapter III of Directive 75/319/EEC, as amended by Directive 83/570/EEC. A 'Notice to Applicants' explaining the multi-state procedure was published in 1989 (Rules governing medicinal products in the European Community, Volume II) and is currently being revised. The revised document which will be referred to as Volume IIA is expected to be available in September '93.

1.2 The objective of this Community procedure is to make it easier for a person who has already obtained a marketing authorization in one Member State (the rapporteur country) to get further marketing authorizations for the product concerned in other Member States. On the basis of the same documentation, and taking the marketing authorization granted by the first Member State into due consideration, the authorities of the Member States to which the application is addressed have 120 days to grant authorization to market the product in their country or in exceptional circumstances to formulate reasoned objections.

2. SCOPE OF THE PROCEDURE

2.1 The multi-state procedure may be used for full or abridged applications and certain limited amendments (variations). A full application is one for which the results of physico-chemical, biological, microbiological tests; pharmacological and toxicological tests; and clinical trials are presented (an innovative product). An abridged application is one for which the results of pharmacological and toxicological tests or the results of clinical trials are not required provided that the conditions of Article 4.8.(a) of Directive 65/65/EEC have been met.

2.2 For amendments (variations), the multi-state procedure may be used for medicinal products which have already used the procedure in cases where the amendment (variation) would change the summary of product characteristics (SPC), and for which the same composition, specification, method of manufacture etc. for the finished product is agreed in all Member States, and for which a unanimously favourable opinion was given with an agreed harmonised summary of product characteristics (known as 'the' SPC), . The continued harmonization of 'the' SPC can thus be maintained using the multi-state procedure.

2.3 Directives 89/342/EEC, 89/343/EEC and 89/381/EEC came into effect from the 1.1.92, and extended the scope of Directives 65/65/EEC and 75/319/EEC to immunological medicinal products consisting of vaccines, toxins or serums and allergens; radiopharmaceuticals; medicinal products derived from human blood or human plasma. Therefore, from the 1.1.92, medicinal products of these classes which have been approved in accordance with the criteria laid down by the Community directives may also use the "multi-state" procedure.

3. USAGE OF THE PROCEDURE

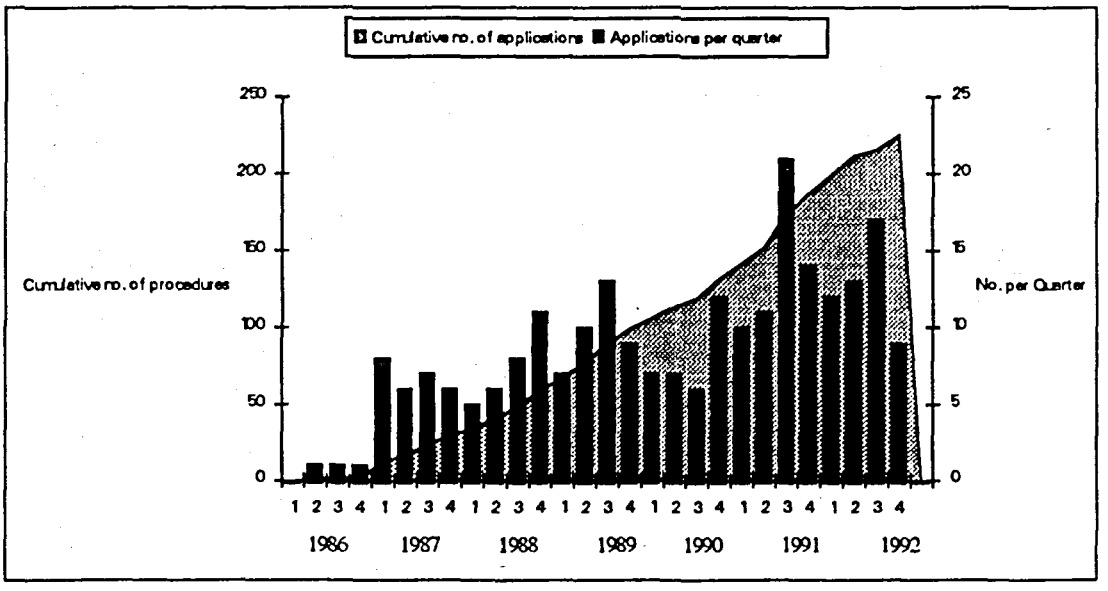
3.1 A multi-state procedure is started by the submission of an application for a marketing authorization in two or more Member States. The application is submitted by the applicant in each of the concerned Member States referring to the procedure laid down in Chapter III of Directive 75/319/EEC, as amended by Directive 83/570/EEC. The secretariat of the CPMP is notified by letter of the intention to start a multi-state procedure.

The application is 'checked in' i.e. validated as containing all the necessary documents, by the concerned Member States within 10 working days of receipt using a commonly agreed procedure. After all concerned Member States have confirmed receipt of the application, the CPMP secretariat notifies all the Member States and the applicant of the start of the 120 day period referred to in Article 9 (3) of Directive 75/319/EEC.

3.2 During the period under review, 126 new procedures were notified to the prodedure. By 31.12.92, 119 of these had been 'checked in' and the period of 120 days had commenced.

Thus the rate of increase of usage of the multi-state procedure, already signalled in the report of 1991, has been maintained and even increased.

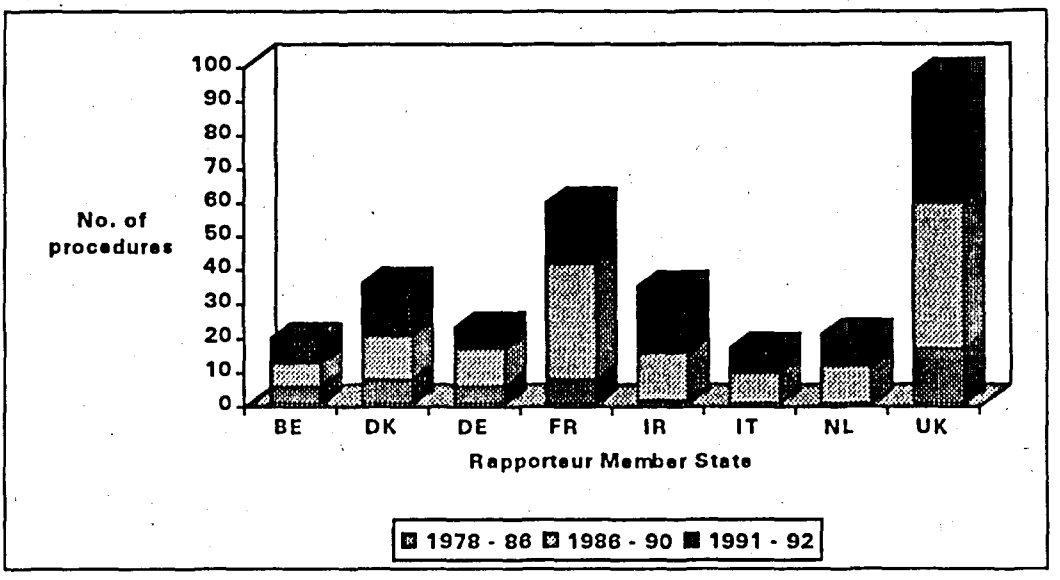
Figure 2: Usage of the multi-state procedure



3.3 As a multi-state procedure co-ordinates a number of simultaneous national applications in the Member States, it is interesting to note that these 119 procedures correspond to the equivalent of 752 national applications i.e. an average of 6.32 national applications per procedure. This average figure illustrates a movement by companies towards the involvement of a greater number of Member States in multi-state procedures. By contrast, during the period, 1988-1990 the average coverage of a multi-state procedure was 5.20. Indeed the average coverage of a multi-state procedure has consistently exceeded 5 countries, despite the reduction of the required number of concerned countries from five to two as a result of Directive 83/570/EEC.

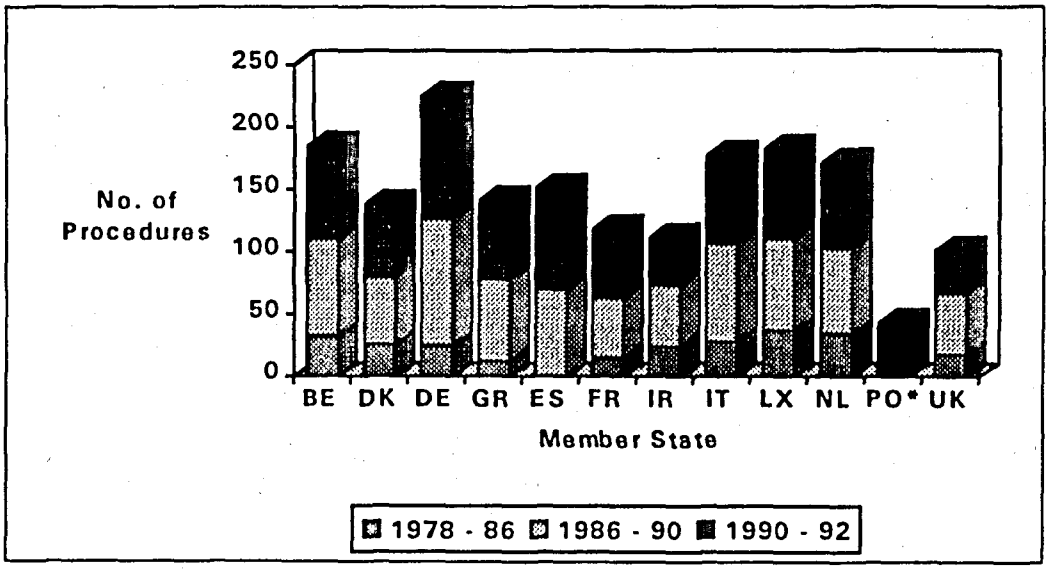
3.4 The role of rapporteur in the multi-state procedure continues to be unevenly distributed amongst the Member States, in that applicant companies appear to have marked preferences for some Member States to act as rapporteur.

Figure 3: rapporteurs in the multi-state procedure



Conversely, the concerned Member States receiving applications through the multi-state procedure continues to reflect the same relative pattern as in previous years.

Figure 4: Recipient Member States in the multi-state procedure



* In accordance with the terms of the Act of Accession, Portugal implemented Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 78/25/EEC, 83/570/EEC on the 1 January 1991 and accepted multi-state applications only from that date.

4. OUTCOME OF THE PROCEDURE

4.1 As in previous reports it must be reported that the multi-state procedure has not lived up to the spirit of the directive which introduced it, since the safeguard clause has been used on every occasion i.e. objections had been raised in every procedure, and every single multi-state application has been referred for a CPMP opinion, with the exception of a new effervescent presentation of an already authorized medicinal product for which no objections were raised within the 120 day period..

Despite the fact that the safeguard clause is used so frequently, it is evident that the procedure is attractive to some of industry, in that the level of usage is still increasing. From companies which have used the procedure, it would appear that the multi-state procedure (in its current form) offers advantages and disadvantages:

Advantages:

a) for selected Member States, faster approval times, especially for innovative or semi-innovative medicinal products;

b) for small companies, which do not have subsidiaries in all Member States, the procedure offers simultaneous handling and co-ordination of applications in concerned countries, allowing for efficient and intensive utilization of limited resources;

c) a single dossier, for which Member State flexibility regarding language requirements is perceived as positive;

d) the strict adherence to the limit of 120 days for receipt of objections serves to save time.

Disadvantages:

a) the lack of acceptance of the first authorization, typified by the systematic referral to the CPMP

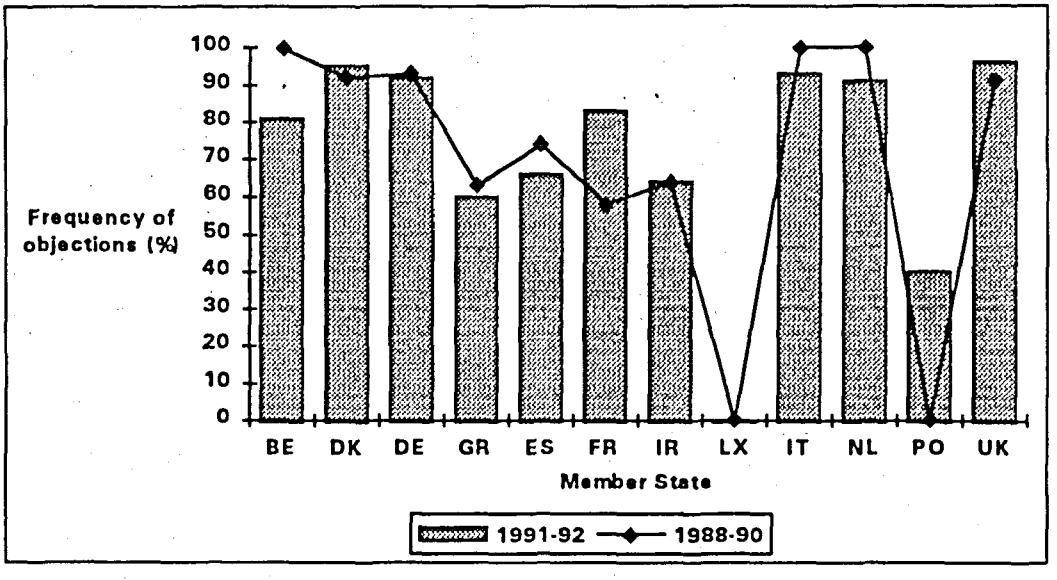
b) varying interpretation amongst the Member States of identical data;

c) the delay in issuing the marketing authorization document by the Member State following the CPMP opinion;

d) the difficulty of achieving a harmonized SPC due to 'precedent' in concerned Member States.

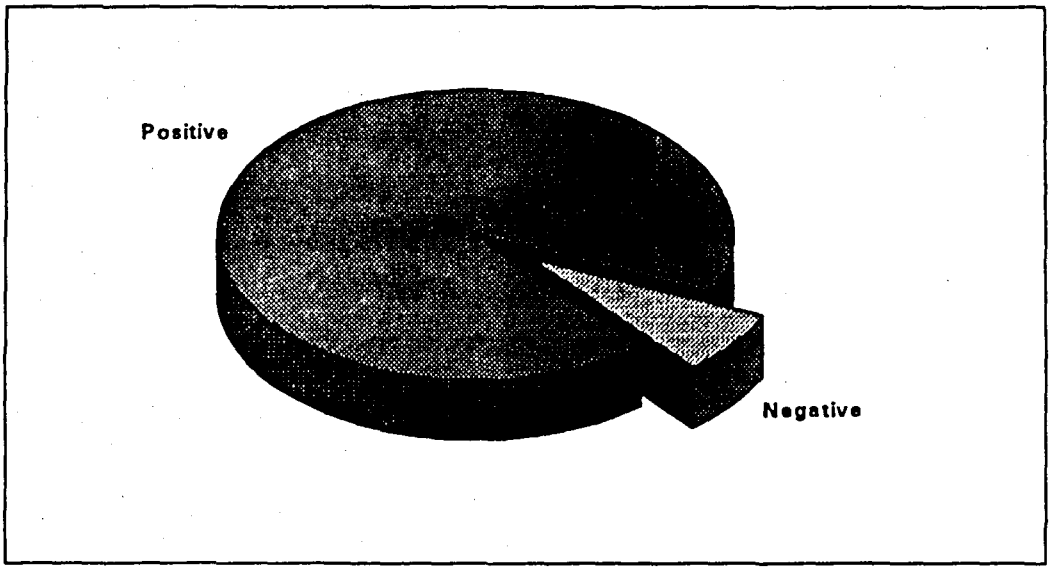
4.2 The extent to which the safeguard clause is used would seem to indicate that concerned Member States completely re-assess a multi-state application, looking for issues to raise. With the notable exception of Luxembourg, which recognises the authorizations of other Member States, the frequency of systematic objections has even increased for some Member States and only slightly declined for others.

Figure 5: Frequency of objections in the multi-state procedure



4.3 The CPMP has given 184 opinions for multi-state procedures up to and including December '92. Of these, 171 have been favourable and 13 unfavourable.

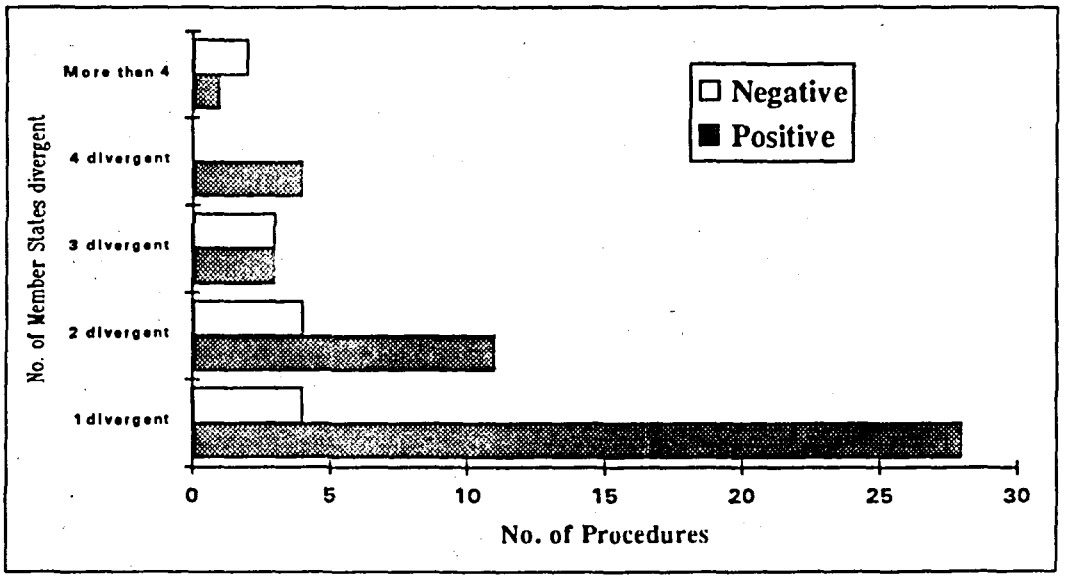
Figure 6: Outcome of multi-state opinions



4.4 However, as the opinion of the CPMP is not legally binding, the opinion does not always express a unanimous view. Therefore, the practice is to identify any Member State which diverges from the Committee opinion, giving reasons for such divergence.

Of the 171 positive opinions, 124 have been unanimous.

Figure 7: Divergence in multi-state opinions

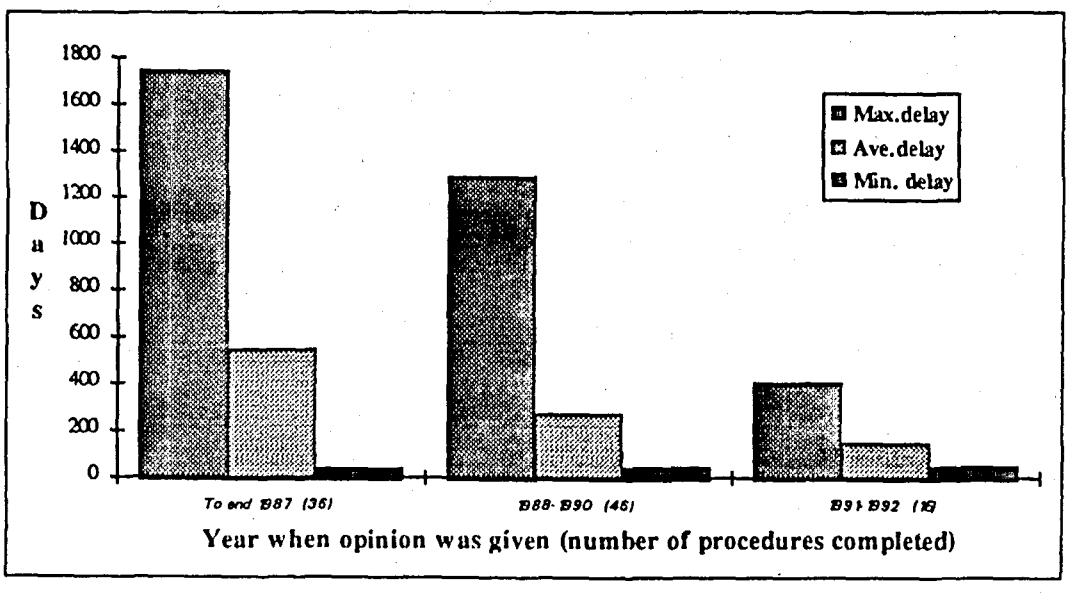


4.5 As already mentioned, a disadvantage of the current multi-state procedure is the delay in the issuing of the marketing authorization documents by the Member States following the CPMP opinion. Article 14.3 of Directive 75/319/EEC, as amended, requires notification by the Member states to the Committee of decisions on action arising from opinions of the CPMP. Unfortunately, delays considerably longer than the prescribed 60 days have been seen although some Member States have introduced administrative procedures to ensure a rapid and efficient processing of the opinion.

The multi-state procedure does not provide for an appeal mechanism, so that once an opinion is given, the national appeal procedures are used. Nonetheless the CPMP closely follows the outcome of final decisions of the concerned Member States until all concerned Member States have notified their final decision (see annex 4 for completed procedures).

Of those multi-state procedures which are now complete, i.e. those for which all concerned Member States have notified their decision with regard to the application as presented during the multi-state procedure, the delay following the opinion (from the date of the CPMP opinion to the date of the last notification by a concerned Member State) has exceeded the allowed 60 days of the Directive (Article 14.3 of Directive 75/319/EEC) as the following chart shows:

Figure 8: Delay of national notifications following multi-state opinions



Whilst the trend in the notification of decisions following CPMP opinion is in the right direction, clearly it is a matter which needs to be improved. In addition, figure 8 refers only to those procedures which are completed. Of the 184 opinions given by the CPMP in the multi-state procedure, 86 remain to be completed by the Member States, some for as long as 18 months.

In order to reduce this delay, the CPMP has taken the initiative of including with every opinion, a summary of product characteristics. Whilst every effort is made to achieve 'the' SPC, there are many instances where it is not possible to arrive at an agreement on the precise wording of the SPC.

5. EVALUATION OF THE MULTI-STATE PROCEDURE

On the basis of the experience outlined above, it is possible to identify some emerging trends and features of the multi-state procedure:

a) The Multi-state procedure remains attractive to industry, as confirmed by the continued increase in the numbers of applications.

b) The vast majority of opinions are positive, consistent with the philosophy of the Directive which provides for Member States to take into due consideration the marketing authorization of another Member State.

c) However, there are dissenting views in approximately 30% of cases. which means that the objective of the single market with free movement of products is not being achieved.

d) As the opinion is not legally binding, it is not always possible to resolve dissentions in an opinion.

e) The delays in notification of national action following the CPMP opinion, and the consequential delay in market access is a cost of 'non-Europe' for the pharmaceutical industry.

f) The experience gained in the multi-state procedure can provide invaluable pointers regarding the operation of the decentralized procedure in the future. Therefore the CPMP will draw on this experience in putting into practice the legally supported basis of mutual recognition in the decentralized procedure.

CHAPTER IV

CONCERTATION PROCEDURE

1. PRINCIPLES OF THE CONCERTATION PROCEDURE

1.1 The legal rules governing the concertation procedure are set out in Council Directive 87/22/EEC of 22 December 1986. A 'Notice to Applicants' explaining the concertation procedure was published in 1989 (Rules governing medicinal products in the European Community, Volume II) and is currently being revised. The revised document which will be referred to as Volume IIA is expected to be available in September '93.

1.2 The objective of the concertation procedure is to provide a mechanism of arriving at uniform decisions throughout the Community on applications for marketing authorizations for medicinal products developed by means of new biotechnology processes and other high technology medicinal products. This means that any questions relating to such products must be resolved at Community level within the CPMP before any national decision is reached concerning the marketing of the product concerned.

Moreover the Commission publishes a list of the products in respect of which the procedure has been used. Such products benefit from the ten year period of protection of innovation afforded by Article 4. 8 (a) of Directive 65/65/EEC as amended by Council Directive 87/21/EEC of 22 December 1986, from their first date of authorization in the Community. In the case of Zidoduvide which had already been authorized prior to the introduction of the procedure, the 10 years which starts from 20.6.90 only applies to the List B indication (asymptomatic patients). The first list was published in COM(39)91 of 15 February 1991 and is updated hereunder:

Figure 9: Products which have benefited from the concertation procedure

INN name	*Brand name*	*Authorization holder*	*First authorization*	*Member State*
OKT3	ORTHOCLONE	Cilag	3.6.86	Fr
rDNA Human Growth Hormone	NORDITROPIN	Nordisk Gentofte	28.4.88	Dk
rDNA Insulin	INSULIN	Novo Industri A/S	8.7.88	Dk
Erythropoetin	EPREX	Cilag	4.8.88	Fr
Mab purified Factor VIII	MONOCLATE P	Armour Pharmaceutical	3.10.89	It
rDNA Interleukin	PROLEUKIN	Eurocetus	23.6.89	Sp
Antimyosin Fab-DTPA	MYOSCINT	Centocor Europe	13.6.89	It
rDNA Hepatitis B vaccine	ENGERIX - B	Smith Kline French Labo	10.12.86	Be
Erythropoeitin	RECORMON	Boehringer Mannheim	1.3.90	Dk
rDNA Human Growth Hormone	GENOTROPIN	Kabi Biopharma	5.5.88	Be
Zidoduvine (asymptomatic patients)	RETROVIR*	Wellcome Foundation	20.6.90	Dk
Glucagon	HYPOGON*	Novo Nordisk	29.7.91	Dk
rDNA Human Growth Hormone	HUMATROPE	Lilly Industries	12.10.87	Dk
Alteplase, 10mg	ACTILYSE	Boehringer Ingelheim	10.6.87	Fr
rDNA Human Growth Hormone	ESKATROPE	SmithKline Beecham	28.8.91	Dk
Interferon alpha-2b (Hepatitis)	INTRON A	Schering Plough	24.1.85	Irl
r-metHug-CSF	NEUPOGEN	Hoffmann La Roche	15.3.91	UK
HA/1A monoclonal antibody	CENTOXIN	Centocor	2.4.91	Nl
Dental Tetracycline fibre	ACTISITE*	Alza	30.7.91	It
Immunoconjugate CYT-103	ONCOSCINT	Eurocetus	1.7.91	Be
rDNA Human Growth Hormone	SAIZEN	Ares Serono	21.5.91	It
Eflornithine	ORNIDYL*	Merrell Dow	29.3.91	Be

INN name	*Brand name*	*Authorization holder*	*First authorization*	*Member State*
Interferon 2 alpha (Hepatitis)	ROFERON A	Hoffmann La Roche	2.7.86	UK
Interferon alpha nl(ins)(Hepatitis)	WELLFERON	Wellcome Foundation	3.3.86	UK
rDNA Human Insulin	HUMULIN	Lilly Industries	1.9.82	Nl
GM-CSF Molgramostim	LEUCOMAX	Schering Plough/Sandoz	23.10.92	UK
Mab purified Factor IX	MONONINE	Armour	5.10.92	It
gamma Interferon	IMUKIN	Boehringer Ingelheim	20.7.92	It
Didanosine	VIDEX*	Bristol Myers Squibb	12.5.92	It
Pentostatin	NIPENT*	Parke Davis	5.1.93	It

* Products accepted by the CPMP as being within List B of the annex to Directive 87/22/EEC.

2. SCOPE

2.1 Medicinal products from new biotechnology processes as defined in the Annex to Directive 87/22/EEC are included as "List A products". The concertation procedure is obligatory for all medicinal products developed by means of the following biotechnological processes:

- recombinant DNA technology;
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryots, including transformed mammalian cells;
- hybridoma and monoclonal antibody methods

2.2 Medicinal products of high technology as defined in the Annex to Directive 87/22/EEC are eligible to be "List B products". High-technology products with novel characteristics as defined in List B of the Annex to Directive 87/22/EEC may, at the request of the applicant, be accepted for consideration under the concertation procedure.

The following categories are eligible for List B status:-

- ♦ medicinal products developed by other biotechnological processes which, in the opinion of the competent authority concerned constitute a significant innovation;
- ♦ medicinal products administered by means of new delivery systems which, in the opinion of the competent authority concerned constitute a significant innovation;
- ♦ medicinal products containing a new substance or an entirely new indication which, in the opinion of the competent authority concerned are of significant therapeutic interest;
- ♦ new medicinal products based on radio-isotopes which, in the opinion of the competent authority concerned constitute a significant innovation;
- ♦ medicinal products the manufacture of which employs processes which, in the opinion of the competent authority concerned constitute a significant technical advance such as 2-dimensional electrophoresis under micro-gravity.

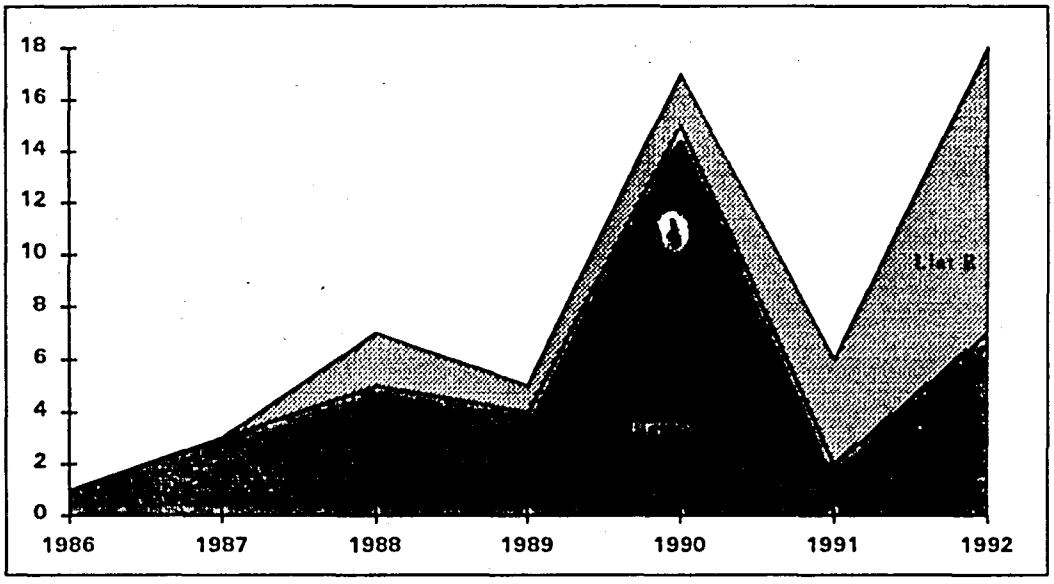
2.3 In order to maintain the same conditions of marketing for products which have been the subject of an opinion of the CPMP under the concertation procedure, the same application for amendment should be submitted to all Member States which have authorized the product. Normally, the Member State which acted as rapporteur for the original application would act as rapporteur for the variation, although this is not a requirement.

The procedure for the examination of a variation is identical whether the product is List A or B, and may include an accelerated procedure or a full procedure, depending on the nature of the variation. Very minor changes requiring only an assessment report from the rapporteur will usually follow a written procedure (within 30 calendar days). More major changes (such as a major new indication with considerable clinical data) may need a procedure almost as complex as a full application.

3. USAGE

3.1 Between 1.1.91 and 31.12.92, 19 new concertation procedures were started. This marked a significant increase in the usage of the procedure.

Figure 10: Usage of the concertation procedure



3.2 The concertation procedure may be used for medicinal products derived from biotechnology (obligatory), or at the choice of the applicant, for high technology products. In 1990 there was a surge of biotechnology applications, as most of those medicinal products derived from biotechnology which had been authorized by national procedure before the entry into force of Directive 87/22/EEC came within

the scope of the concertation procedure. This was due to the clarification issued by the CPMP in July '89 regarding amendments to any medicinal product derived from biotechnology. 1992 has seen a substantial growth in the number of high technology applications. Many of these would fall into the general meaning of 'orphan drugs' and it is an important signal that a centrally co-ordinated procedure for access to the single market favours even medicinal products for rare diseases which would not necessarily have a large market.

3.3 The CPMP has given 30 opinions in the concertation procedure. All of these have been positive. However, 3 applications were withdrawn by the applicant prior to opinion. Of these 30 opinions, 26 were unanimous. Of the 4 which were dissenting, two opinions had 1 Member State dissenting, one opinion had 2 Member States dissenting and in the case of one opinion, five Member States dissented.

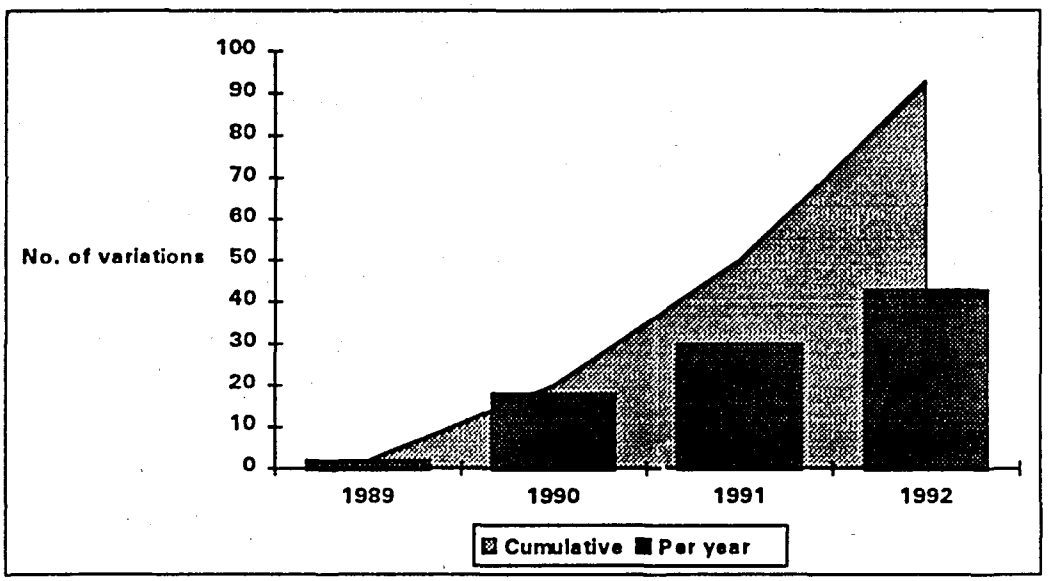
A major success of the concertation procedure is the extent to which 'the' summary of product characteristics (SPC) is achieved - in 21 of the 30 procedures. In these cases, the Member States agree a harmonized single SPC. Thus not only does the same physical product move throughout the market, but the same product information for health care professionals applies in all Member States.

3.4 Any amendment of the particulars and documents of the marketing authorization, or amendment to the approved summary of product characteristics, must be submitted to the competent authorities. In the case of medicinal products which have been considered through the concertation procedure, such amendments (often referred to as variations) avail of a co-ordinated procedure through the CPMP, thus ensuring the continued harmonization of the product and its particulars.

The innovative nature of medicinal products using the concertation procedure is such that improvements to the quality of the product are a frequent source of variations. So too is the extension of the clinical usage of the product. Pharmacovigilance data may, on occasions, lead to an amendment of the summary of product characteristics.

The many and diverse nature of variations in the concertation procedure has very substantially increased the work load of the CPMP.

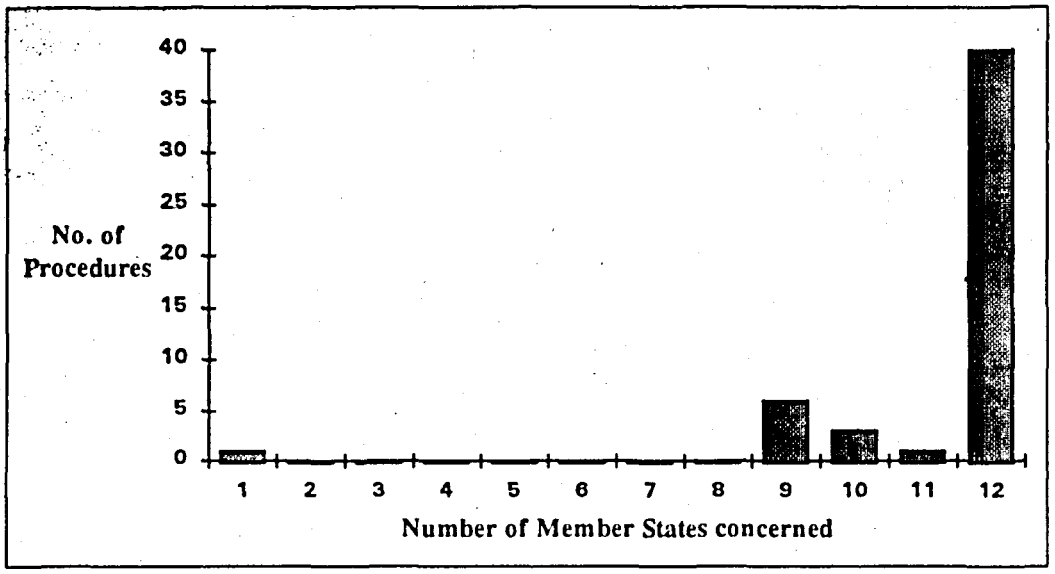
Figure 11: Extent of variations in the concertation procedure



3.5 Unlike the multi-state procedure, the concertation procedure does not set a minimum number of countries to which application must be made. Instead, application can be made to as few as 1 (there is an exemption from the procedure for List A products which are to be marketed during five years in only one Member State). However, all members of the CPMP must receive at least the summary of the dossier (Part I). In practice, almost all concertation procedures apply to all 12 Member States.

The concertation procedure also differs from the mulit-state one by virtue of the number of Member States actually concerned with each procedure. Whereas for the multi-state procedure the mean coverage is 6.3 Member States per procedure, in the concertation procedure it generally all 12 Member States, except in exceptional cases.

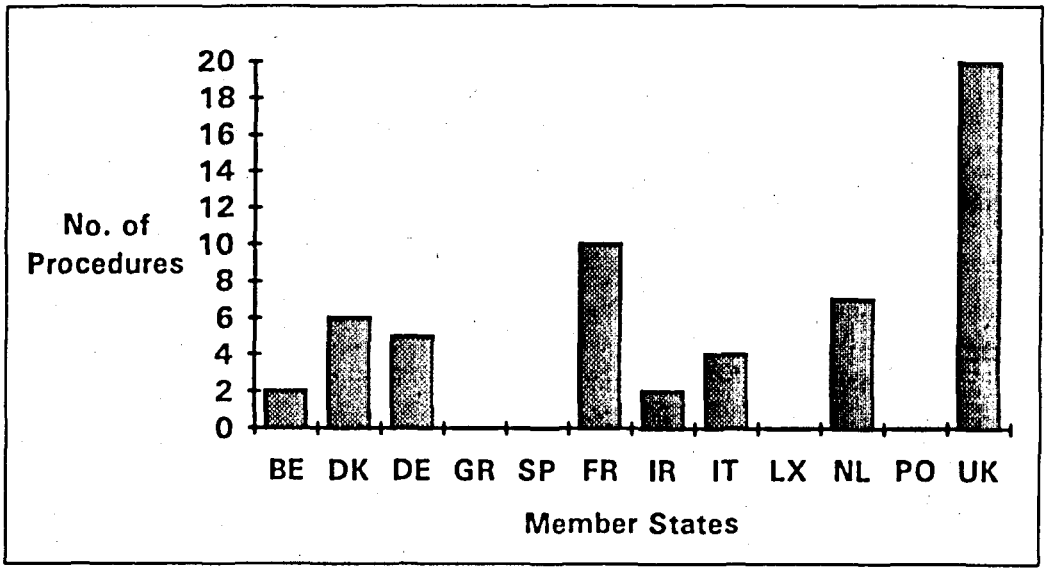
Figure 12: Coverage of Member States by concertation procedures



3.6 Another difference with the multi-state procedure is the fact that no decision on the application is made by any Member State prior to a concertation procedure. Thus the assessment of the application is done at the same time in all Member States and is led by a rapporteur. The applicant may choose the rapporteur by virtue of submitting the application in that Member State first. It is the practice, however, for applicants to liaise with the competent authority before commencing a concertation procedure and before making a submission.

The task of rapporteur is more evenly distributed between the Member States. Additionally, the role of co-rapporteur allows for a second Member State to support the first in the assessment of the application.

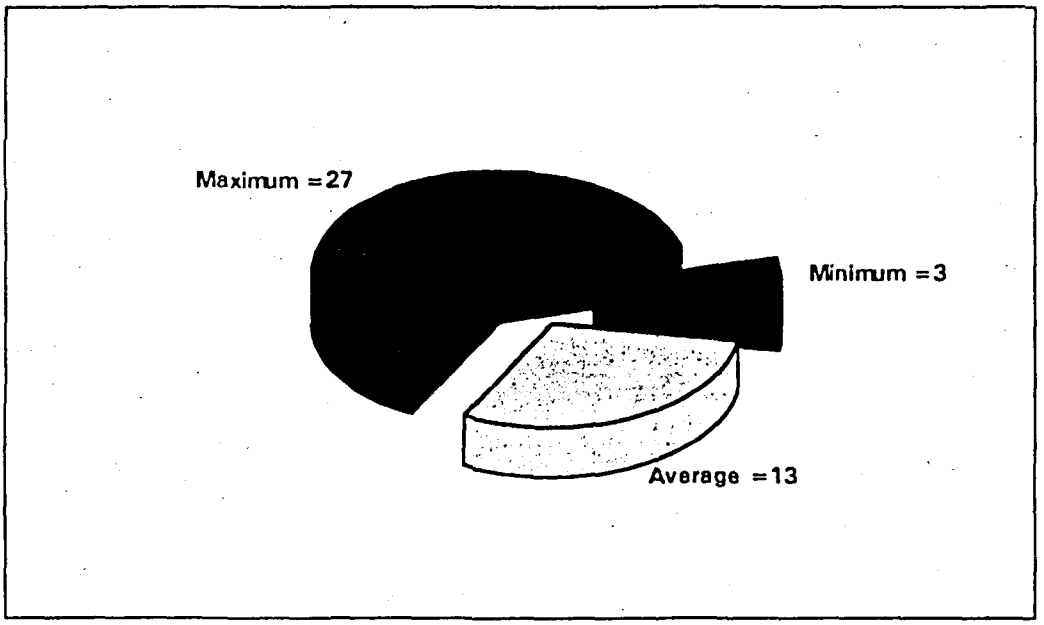
Figure 13: Rapporteurs in the concertation procedure



3.7 The duration of the concertaton procedure has been queried on many occasions. Previously it was not possible to give any indication as the number of procedures was too small to draw any reasonable conclusions. However, as 30 procedures have now reached an opinion, it is possible to provide an overview.

The length of the assessment phase, taking the date of submission of the applicant as day 1, up to the date of the opinion of the CPMP is summarized hereunder:

Figure14: Length of concertation procedures/months



3.8 However, of concern in the concertation procedure just as it is in the multi-state procedure, is the delay in notification of decisions following the CPMP opinion. Further, in the concertation procedure, a period of only 30 days is allowed for notification of such decisions. Given that only 5 out of the possible 30 procedures have been completed, it is possible to indicate the length of time between the date of the CPMP opinion and the date of notification of a decision by the last Member State concerned for these 5 procedures:

A = 57 months; B = 31 months; C = 29 months; D = 7 months; E = 29 months.

Since the concertation procedure deals with medicinal products derived from biotechnology and also high technology products, it is clearly in the interest of patients that this area is targeted as a priority aspect for improvement.

CHAPTER V

OTHER CPMP OPINIONS

1. REFERRALS TO THE CPMP

1.1 The CPMP may be called upon to give an opinion as to whether a particular medicinal product complies with the requirements set out in Directive 65/65/EEC. In addition to the multi-state and concertation procedures already described in Chapters III and IV, the CPMP may be requested to formulate an opinion on the basis of Articles 11 or 12 of Directive 75/319/EEC, as amended. It is the policy of the CPMP that opinions issued in accordance with articles 11 and 12 of Directive 75/319/EEC are made publicly available. Therefore, in annex 3, all such opinions issued during 1991-1992 are reproduced.

The synthesis of the different aspects (efficacy, safety, quality, and pharmacovigilance) involved in the establishment of the benefit/risk ratio of medicinal products means that there is a continuous exchange of information within the CPMP and its specialised working parties. Thus matters may be considered by the pharmacovigilance working party, one of the other specialised working parties (efficacy, safety, quality, biotechnology), or by an ad hoc group convened for that express purpose.

1.2 Article 11 of Directive 75/319/EEC allows either a Member State or the Commission to refer a matter to the CPMP for opinion. Such cases would arise when applications for a particular medicinal product have been submitted in several Member States and one or more have granted a marketing authorization while one or more have refused it. The referral could also occur where one or more Member States have suspended or revoked a marketing authorization while one or more Member States have not done so.

The person responsible for placing the medicinal product on the market is informed of any decision of the CPMP to issue a reasoned opinion, and may generally avail of the opportunity for written or oral explanation to the CPMP.

1.3 Article 12 of Directive allows the competent authorities of the Member States, in specific cases where the interests of the Community are involved, to refer a matter to the CPMP before reaching a decision on a request for a marketing authorization or on the suspension or revocation of an authorization.

The CPMP has identified a number of areas where, given the current state of scientific knowledge, it is considered that Article 12 should be used:

- in the case of products for the primary treatment of AIDS (which may, at the request of the applicant, use List B of the concertation procedure)

- for applications following the List B (concertation) procedure, where the CPMP has already accepted that the medicinal product is of Community interest, the withdrawal by the applicant of the application from the concertation procedure with reapplications on a national basis,

- in the case of information from pharmacovigilance, where the benefit/risk ratio of a medicinal product must be reassessed.

The CPMP may amend the above cases in the light of scientific progress, and this would be announced through the CPMP press release.

The CPMP considers that, when practical, the applicant or the marketing authorization holder would be offered the opportunity to make a submission, orally or in writing, before the CPMP issues its opinion.

2. PHARMACOVIGILANCE IN THE FRAMEWORK OF THE CPMP

2.1 The CPMP has for many years been concerned with issues of pharmacovigilance. The system of pharmacovigilance, which operates nationally, is concerned with the collection of information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and the evaluation of such information scientifically. In addition to the consideration of matters referred to it under Articles 11 or 12 of Directive 75/319/EEC, the CPMP exchanges information on all decisions taken (Articles 30 and 33 of Directive 75/319/EEC). Further, in Directive 89/341/EEC (Article 3) Member States must notify the World Health Organisation of measures taken by them or by manufacturers on action which may affect public health in third countries.

The consideration of pharmacovigilance issues by the CPMP comprises a number of specific areas of activity.

2.2 Pharmacovigilance Opinions

During the period under review, the Committee prepared 7 pharmacovigilance opinions, on the following substances, some of which were an updating of previous opinions e.g Glafenine, Flunarizine:

Opinion no.	Active Substance	Trade Name	Date
8 revision 1	Glafenine/floctafenine	Glifanan	13 2 1991
6 revision 1	Flunarizine	Sibelium	12 3 1991
6 revision 2	Flunarizine	Sibelium	11 9 1991
10	Fenoterol	Berotec	11 9 1991
11	Triazolam	Halcion	11 12 1991
8 revision 2	Glafenine	Glifanan	14 1 1992
12	Noscapine	Different in the Member States	4 12 1992

2.3 Rapid Alert

The procedure for rapid alerts which had been in operation since 1979 was updated in July '91 (III/3917/91). The rapid alert system has been used on 22 occasions.

These alerts concerned, for the most part, notifications of decisions taken at national level. As such, the evaluation process, which necessarily takes some time, had already been completed. Such evaluations however tended to be based on the data available to the relevant authority from its own market, without the benefit of input from other authorities. The CPMP is currently working on improving this system of alert so as to avail of data coming from all Member States in the assessment of pharmacovigilance information, prior to any decision being taken. A number of guidelines have been prepared to facilitate this.

In July '91, the CPMP adopted a guideline on the exchange of pharmacovigilance information (III/3366/91). The objective of this system is the exchange of any specific pharmacovigilance information that, after a first evaluation in the Member State, does not require urgent action but could facilitate the early detection of potentially important problems. This allows all Member States to share their information and to prepare a more informed position.

2.3 Causality Classification

A variety of different systems for the assessment of the likelihood of a causal relationship in case reports of suspected ADR's have been developed. Three major causality classifications have been recognised for use at Community level:

Category "A": reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable.

Category "B": reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence.

Category "C": reports where causality is, for one or another reason, nor assessable, e.g. because of insufficient evidence, conflicting data or poor documentation.
A fuller explanation of this system is given in 'Procedure for causality classification in Pharmacovigilance in the European Community (III/3445/91), which is reproduced in Chapter VI.

2.4 Pharmacovigilance Hearings

When considering pharmacovigilance information, the CPMP draws on the information available within the Member States, from international sources and generally invites the marketing authorization holder (or holders) to submit written explanations. In addition, before the finalization of a pharmacovigilance opinion, the applicant/marketing authorization holder may present orally before the Committee.

During the period under review, (1991-92) 2 pharmacovigilance hearings with the CPMP were held.

3. PROHIBITED MEDICINAL PRODUCTS (DIRECTIVE 75/319/EEC ARTICLE 33.4)

3.1 Article 33.4 of Directive 75/319/EEC requires the Commission to publish annually a list of the medicinal products prohibited in the Community.

Due to Directive 65/65/EEC, which provided that no medicinal product may be marketed until formal approval in the form of a marketing authorization has been given, all medicinal products must be deemed to be prohibited unless specifically authorized. For the purposes of compiling a useful listing therefore, the term 'prohibited' is taken as meaning those medicinal products which have been authorized and for which the authorization is withdrawn/revoked.

It should be noted that prohibitions are imposed by the Member States not by the Commission. Prohibition can take various forms, including outright revocation of the marketing authorisation, or temporary suspension for a period while precautionary measures/studies are carried out. In the latter case, the matter may be resolved quickly and the product either reinstated on the market or definitively withdrawn.

Until the Agency envisaged under the proposals for the future system for evaluation of medicinal products is in place, the role of the CPMP is limited to the consideration of reported adverse reactions to marketed products, which are referred to it in accordance with Articles 11 and 12 of Directive 75/319/EEC. Article 14.3 of the same directive requires Member States to inform the Committee of actions taken pursuant to the publication of an opinion. Therefore the following listing covers those products which have been 'prohibited' in one or more Member States, following a CPMP pharmacovigilance opinion.

3.2 Glafenine

In March '89, the Belgian authorities requested the Committee, in accordance with Article 12 of Directive 75/319/EEC, to give an opinion on Glafenine (GLIFENAN). Glafenine is a peripheral analgesic for which a number of side-effects, particularly anaphylactic reaction and intrarenal crystallisation, had been reported.

The CPMP considered the available information and issued a first opinion in December '89, recommending a number of safeguard measures including limiting the supply of Glafenine to non renewable prescription and amendments to the summary of product characteristics. This opinion was revised in February '91, when all Member States were invited to compile and report on the up-to-date situation. In the light of further information, both from the marketing authorization holder and competent authorities of the Member States, the Committee issued an opinion in January '92, concluding that the signal first identified in spontaneous surveillance had been confirmed by a Dutch epidemiological study, and that the risk of anaphylactic reaction with Glafenine was higher than for other analgesics. Thus

the benefit/risk ratio was considered to be negative and the marketing authorization should be withdrawn.

France and Portugal did not concur with the scientific assessment of the Committee. They did not share the conclusions of the Dutch epidemiological study and therefore considered that there was no new information available, and Glafenine, aside from anaphylactic reaction, had less of some other side-effects than other analgesics. Therefore the product was still considered by those 2 countries to have a favourable benefit/risk ratio when used as a second line treatment in patients where other analgesics were inappropriate.

Following the CPMP opinion of January '92, Italy, the Netherlands and Spain informed the Committee that the marketing authorizations for medicinal products containing Glafenine had been revoked. France suspended the marketing authorization for one year and Portugal notified a suspension of 90 days.

Belgium and Luxembourg had withdrawn the marketing authorizations in December '91; the company had withdrawn the product from the German market in 1983; and no application for marketing authorization had been submitted in Denmark, Ireland and the United Kingdom.

Therefore the substance is not presently marketed in the Member States.

3.3 Triazolam

On 2 October '92, Triazolam (HALCION) was temporarily suspended in the United Kingdom. The French and Dutch authorities immediately requested the Committee to give an opinion, in accordance with Article 11 of Directive 75/319/EEC. Triazolam is a short acting hypnotic for which a number of side-effects, including memory impairment and neuro-psychiatric effects, had been reported. Medicinal products containing 0.25 mg and 0.125 mg Triazolam were authorized in all

Member States, although the authorization of both dosage forms had been temporarily suspended in the UK on 2.10.91.

The CPMP, upon preliminary consideration, issued a Position Statement in October '91, recommending a number of safeguard measures including limiting the supply of Triazolam to small packs and amendments to the summary of product characteristics emphasising the short-term use of the product. The Committee considered it necessary to review the large volume of information submitted by the company, as well as data in the application dossier and information from pharmacovigilance. Therefore rapporteurs were appointed. The report of the rapporteurs was considered in December '91 when the Committee issued an opinion confirming the safeguard measures taken, particularly with regard to the maximum dosage of 0.25mg, the narrow and very precise indications as well as contra-indications for the product, the absolute importance of short term usage (not more than 10 days) which had been reinforced by the introduction of small pack sizes in all Member States.

The Committee further decided to complete the work done by the rapporteurs and invited them to fully assess the relative benefit/risk ratio of all short acting hypnotics. This review was undertaken by the ad hoc group on Hypnotics (see page 11). The report of the ad hoc group is expected to be finalized in 1993 and thereafter the CPMP will publish a scientific report.

Since the opinion, the UK has continued the suspension of both dosage forms and the matter is currently *sub judice*.

On 30.12.91, France suspended the 0.25 mg. presentation for one year; on 9.1.92, Spain suspended the 0.25 mg. presentation for six months and renewed this suspension for a further 6 months on 10.7.92. Both Member States nonetheless adhered to the continued the authorization of 0.25mg dosage recommendation (by virtue of the 0.125mg presentation, which is available on their markets).

Thus the 0.125 mg presentation is authorized in 11 Member States, while the 0.25mg is authorized in all except the UK, France and Spain. Pack sizes were reduced in all Member States and information on the product for both health care professionals and patients was strengthened.

3.4 Medicinal products of bovine origin

Following the adoption by the CPMP of the guideline 'Guidelines for minimizing the risk of transmission of agents causing spongiform encephalopathies via medicinal products' in December '91, a number of Member States suspended/withdrew medicinal products of bovine origin. In many cases it was possible to reformulate the product and therefore the suspension was lifted. The reformulation of a number of products is still on-going in the Member States. A report on the position is being prepared by Portugal and will be available during 1993.

3.5 Mumps vaccine

In September '92, the company SmithKline Beecham voluntarily withdrew all their vaccines (Pariorix, Rimparix and Pluserix) which contained the Urabe Am 9 strain. Data collected in active surveillance studies in the United Kingdom suggested a frequency of meningitis following vaccination that was higher than previously reported. However, the company liaised with the competent authorities of the Member States and the CPMP to ensure that the discontinuation of the products was implemented with the least possible disruption, in order to maintain public confidence in the national vaccination programme.

3.6 Herbal Remedies

In the course of its review of the proposals from ESCOP (see page 11), the CPMP compiled a listing of herbs and herbal derivatives which had been withdrawn for safety reasons from one or more Member State markets.

HERB/HERBAL DERIVATIVE	*PART OF PLANT*	*Reason for withdrawl*
Aconitum (all species)	ALL PARTS	Contains aconitine and other toxic alkaloids
Angelia archangelica L.	FRUIT, HERB	Contains phototoxic furanocumarins
Aristolochia (all species)	ALL PARTS	Contains aristolochin acids, strong carcinogen, genotoxicity
Artemisia cina (BERG.) WILLKOMM.	FLOWER BUD	Contains the toxic lactone santonin
Berberis vulgaris L.	BARK, ROOT BARK, ROOT	Contains the alkaloid berberine
Borago officinalis	HERB, FLOWERS	Contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties
Byronia (all species)	ROOT	Cytotoxic cucurbitacines
Chenopodium ambrosioides L. var. anthelminthicum (L.) A. GRAY	ESSENTIAL OIL	Contains the toxic principle ascaridole
Chrysanthemum vulgare (L.) BERNH.	FLOWER, HERB	May contain essential oil with neurotoxic thujone
Claviceps purpurea (FR.) TULASNE	SECALE CORNUTUM (SCLEROTIUM)	Contains toxic ergot-alkaloids
Convolvulus scammonia L.	RESIN	Drastic laxative with irritant properties
Croton tiglium L.	SEED, FATTY OIL FROM SEED	Contains tumour promoting phorbol diesters
Cynoglossum officinale L.	HERB	contains pyrrolizidine-alkaloids with genotoxic, carcinogenic and hepatotoxic properties
Dryopteris filix mas (L.) SCHOTT	RHIZOME	Constituents are highly toxic, especially with increased absorption
Exogonium purga (WEND) BENTH.	ROOT, RESIN	Drastic laxative action with irritant action

Juglans regia L.	**FRUIT-SHELL**	May contain the naphtoquinone juglone which is mutagenic and possibly carcinogenic
Juniperus sabina L.	**HERB**	Toxic herb
Ledum palstre L.	**HERB**	Contains essential oil which is a potent irritant of GI tract, kidneys and urinary tract
Mallotus phillipinensis (LAM.) MÜLLER-ARG.	**GLAND AND TRICHOMES (KAMALA)**	Drastic laxative action which may cause severe gastroenteritis, diarrhoea and vomiting when taken in higher doses
Ocimum basilicum L.	**ESSENTIAL OIL**	Contains high amounts of estragole which is genotoxic and a carcinogen in rodents
***Petasites hybridus* (L.) GAERT. MEYER et SCHREB.**	**LEAF**	Contains pyrrolizidine alkaloids with genotoxic, carcinogenic and hetatotoxic properties
Petroselinum crispum (MILL.) Nym. ex A.W.HILL	**FRUIT**	Contains significant amounts of essential oil with toxic apiole
***Pulsatilla vulgaris* MILLER**	**HERB**	Higher doses may irritate teh kidneys and urinary tract; pregnancy is an absolute contra-indication
Ruta graveolens L.	**HERB, LEAVES**	Causes phototoxic reactions, genotoxic, can be fatal
Rubia tinctorum L.	**ROOT**	Contains lucidin with genotoxic and probably carcinogenic activity
Sassafras albidum (NUTT.) NEES	**WOOD, ROOT**	Contains essential oil with carcinogenic and genotoxic safrole
Senecio (all species)	**HERB, ROOT**	Contains pyrrolizidine alkaloids with genotoxic carcinogenic and hepatotoxic properties
Strychnos nux-vomica L.	**SEED**	contains alkaloids, especially strychnine

Symphytum (all species) internal use	**HERB, LEAF, ROOT**	Contains pyrrolizidine alkaloids with genotoxic, carcinogenic and hepatotoxic properties
Teucrium chaùaedris L.	**HERB**	Hepatotoxicity
Tussilago farfara L.	**FLOWER, ROOT**	Contains pyrrolizidine alkaloids with genotoxic, carcinogenic and hepatotoxic properties
Vinca minor L.	**HERB, LEAF**	Haematological changes (leucocytopenia, lymphocytopenia, reduced globulin levels) have been observed in rabbits

A number of other herbs/herbal derivatives were also considered. Further examination of the benefit/risk of some other herbs/herbal derivatives, and under what conditions of use, will be undertaken during 1993.

CHAPTER VI

INTERNATIONAL ACTIVITIES AND TRADE

1. INTERNATIONAL EXCHANGE

1.1 The CPMP does not limit its considerations to developments within the European Community, but also monitors and reviews scientific innovations and developments internationally. Many countries and regions have expressed interest in the mechanisms and results of the harmonization activity of the Community.

Thus, for example, the standard application format (Notice to Applicants) adopted by the 12 Member States is now acceptable in all the member countries of the Nordic Council and the European Free Trade Association (EFTA), Australia, Canada, South Africa and most eastern European countries.

1.2 Therefore, the CPMP has introduced a practice of international consultation on all draft guidelines and technical standards. Thus many countries and regions in the world have the opportunity to comment on the technical and scientific requirements for the development of medicinal products in the EEC.

2. INTERNATIONAL CONFERENCE ON HARMONIZATION

2.1 The first International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH 1) took place in Brussels in November '91. This major international conference was jointly supported and organised by the Commission of the European Communities, the US Food and Drug Administration, the Japanese Ministry of Health and Welfare, together with the pharmaceutical industry as represented by the International Federation of Pharmaceutical Industry Associations, the European Federation of Pharmaceutical Industry Associations, the US Pharmaceutical Manufacturers Association and the Japanese Pharmaceutical Manufacturers Association.

The International Conference on Harmonization is distinctive in that it is supported both by regulators and the industry in order to facilitate greater harmonization of technical requirements in the three regions. ICH 1 in Brussels was a success as progress was made in all three areas of safety, quality and efficacy. Following on from this success, ICH 2 is currently being planned for Orlando in October '93.

To prepare for ICH 2, the Steering Committee mets on two occasions each year, along with more than 100 experts from the three regions. In March '93, the Steering Committee met in Brussels with the expert groups on quality, safety and efficacy to prepare positions before the conference in Orlando in October '93.

2.2 Eleven topics were considered and developed during ICH 1 and a further 17 will be prepared for ICH 2:

	Quality	Safety	Efficacy
ICH 1	Stability testing	Short and long term toxicity	Clinical safety
	Specifications	Reproductive toxicity	Special populations:Geriatrics
	Pharmacopoeias	Biotechnology	Good Clinical Practices
		Timing of toxicity studies	Dose Response studies
ICH 2	Stability II	Carcinogenicity	Population exposure in clinical trials
	Analytical validation	Genotoxicity	Clinical safety reports
	Impurity testing	Toxicokinetics	Clinical study reports
	Pharmacopoeial issues		Dose response studies
	Biotechnology		Ethnic factors in the acceptability of foreign data

With so many topics for consideration, the CPMP and its working parties have structured the discussions on ICH such that it now takes a regular place in the agendas of all meetings. A co-ordinator for the CPMP has been nominated for each of the symposia:

Quality:	Dr. A.C. Cartwright
Safety:	Professor R. Bass
Efficacy:	Professor J.M. Alexandre

The CPMP has further illustrated its commitment to international harmonization- by accepting to release for consultation three draft tripartite guidelines developed through the ICH process:

draft Stability testing of new drug substances and products (May '92);
draft Reproduction toxicity (December '92);
draft Clinical studies in special populations: Geriatrics (December '92).

3. COUNCIL OF EUROPE

3.1 The convention relating to the elaboration of a European Pharmacopoeia was signed in 1964 within the framework of the Council of Europe. The European Community gave legislative force to the standards of the European Pharmacopoeia in Directive 75/318/EEC as amended by Directive 91/507/EEC.

In November '89, a protocol for the accession of the EEC to the European Pharmacopoeia was opened for signature. The Protocol was ratified by all states which are parties to the Convention. Therefore, the Community will become a direct member of the Convention during 1993.

3.2 A framework agreement was set up in 1992, between the Commission and the Council of Europe, which provides for the development, over the next four years, of standards for biological medicines described in the European Pharmacopoeia.

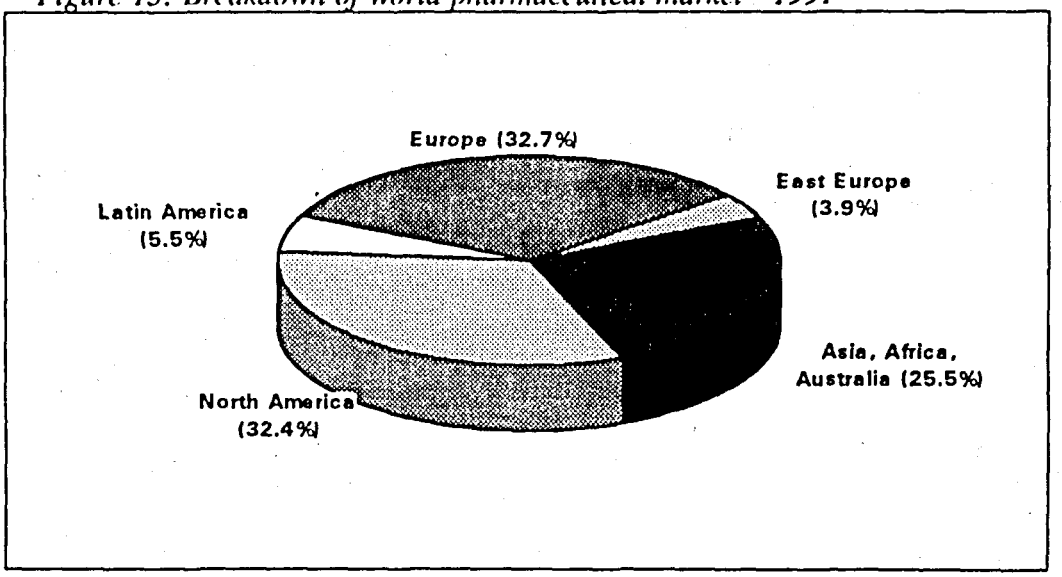
4. RELATIONS WITH EFTA/EEA

4.1 During 1991-92, experts from EFTA and the Nordic Council of Medicines attended all meetings of the Quality, Safety and Efficacy working parties of the CPMP. All draft texts for guidelines and technical requirements were also circulated to both bodies for consultation. This close co-operation facilitated the acceptance of the 'acquis communitaire' in the pharmaceutical sector during negotiations for the EEA (European Economic Area) agreement.

5. TRADE IN PHARMACEUTICALS

5.1 The total value of the world pharmaceutical market (excluding China and the former Soviet Union) in 1991 was estimated to have been around ECU 140 billion. Taken as a whole, the European Community constitutes the largest pharmaceutical market in the world, accounting for a third of the total[4].

Figure 15: Breakdown of world pharmaceutical market - 1991



4 EFPIA in Figures, 1991 - 1992

5.2 From the previous reports (cited above) and from the many economic analyses, approximately 67% of sales of medicinal products in the Community come from the Member States. This level has been relatively constant for the last decade.

Figures for the geographical distribution of exports (for bulk and finished pharmaceuticals) are given in annex 5, as well as trade and other statistics.

5.3 Article 15 of Directive 75/319/EEC requests that this report should cover the operation of the multi-state procedure and its effects on the development of intra-Community trade. Even though the numbers of multi-state and concertation procedures have continued to grow, they would represent less than 10% of the total number of applications made in the Community each year. Therefore the impact on intra-Community trade has not been possible to quantify, but it may be assumed not to be substantial.

However, what has been significant has been the progress in harmonization which in now complete. From the stand point of achieving the single market, there remains the finalization of the legislative support to the future system - which allows access to a single market either through the 'door' of a Member State or through a Community 'door'. Thereafter it will be up the pharmaceutical industry to avail of the opportunity of the largest single market for pharmaceuticals in the world.

Annexes

Annex 1

Chronological listing of pharmaceutical legislation relating to human medicinal products

EEC DIRECTIVES RELATING TO THE MARKETING AUTHORIZATION FOR MEDICINAL PRODUCTS FOR HUMAN USE

- COUNCIL DIRECTIVE 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° 22 of 9.2.65)

- COUNCIL DIRECTIVE 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° L 147 of 9.6.75)

- COUNCIL DIRECTIVE 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (O.J. n° L 147 of 9.6.75)

- COMMISSION DIRECTIVE 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (O.J. n° L 270 of 26.9.91)

- COUNCIL DIRECTIVE 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° L 332 of 28.11.83)

- COUNCIL DIRECTIVE 87/19/EEC of 22 December 1986 amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (O.J. n° L 15 of 17.1.87)

- COUNCIL DIRECTIVE 87/21/EEC of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° L 15 of 17.1.87)

- COUNCIL DIRECTIVE 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology (O.J. n° L 15 of 17.1.87)

- COUNCIL DIRECTIVE 89/341/EEC of 3 May 1989 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° L 142 of 25.5.89)

- COUNCIL DIRECTIVE 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens

- COUNCIL DIRECTIVE 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals

- COUNCIL DIRECTIVE 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma (O.J. n° L 181 of 28.6.89)

- COMMISSION DIRECTIVE 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use (O.J. n° L 193 of 17.7.91)

- COUNCIL DIRECTIVE 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use (O.J. n° L 113 of 30.4.92)

- COUNCIL DIRECTIVE 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use (O.J. n° L 113 of 30.4.92)

- COUNCIL DIRECTIVE 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets (O.J. n° L 113 of 30.4.92)

- COUNCIL DIRECTIVE 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use (O.J. n° L 113 of 30.4.92)

- COUNCIL DIRECTIVE 92/73/EEC of 22 September 1992 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products (O.J. n° L 297 of 13.10.92)

Annex 2

List of members of the CPMP, March '93

29 March 1993

COMITE DES SPECIALITES PHARMACEUTIQUES

COMMITTEE FOR PROPRIETARTY MEDICINAL PRODUCTS

Président / Chairman :

Professore Duilio POGGIOLINI — Direttore Generale del Servizio Farmaceutico, Ministero della Sanità
Viale della Civiltà Romana 7
I-00144 Roma EUR
Tel.: (39)(6) 592.58.63 / 592.55.25
Telex: 625205 MINSAN I
Telefax: (39)(6) 592.58.24

Vice-Présidents /
Deputy Chairmen :

M. le Professeur Jean-Michel ALEXANDRE — Président de la Commission d'enregistrement des médicaments
Ministère de la Santé et de l'action humanitaire
Direction de la Pharmacie et du Médicament
1, Place de Fontenoy
F-75700 Paris
Tel.: (33)(1) 40.56.47.09
Telefax: (33)(1) 40.56.53.55

M. Fernand SAUER — Chef d'Unité "Produits pharmaceutiques"
Commission des Communautés européennes
Direction générale du Marché intérieur et des Affaires industrielles
III/C-3
Tel.:(322) 295.51.80)

Secrétariat du Comité des spécialités pharmaceutiques /

Secretariat of the Committee for Proprietary Medicinal Products :

Mrs. Marie C. DONNELLY
Téléphone : (322) - 296.03.32
- 295.69.35
Commission des Communautés européennes
Direction générale du Marché intérieur et des
Affaires industrielles
Unité "Produits pharmaceutiques"
D.G. III C 3 - NERV 2/8

Rue de la Loi 200
B-1049 BRUXELLES

Telefax : 296.15.20

Telex : 21.877 COMEU B

LISTE DES MEMBRES / LIST OF MEMBERS

a) Représentants / Representatives :

b) Suppléants / Deputies :

BELGIQUE

a) M. F. GOSSELINCKX
Hoofdinspecteur-Directeur
Farmaceutische Inspectie
Rijksadministratief Centrum
Vesaliusgebouw
B-1010 Brussel
Tel.: (32)(2) 210.48.93
Telex: 25.768.MVGSPF B
Telefax: (32)(2) 210.48.80

b) M. Noël WATHION
Farmaceutisch Inspecteur
Farmaceutische Inspectie
(idem)
Tel.: (32)(2) 210.48.96

DANMARK

a) Mr. Henning HOVGAARD
Registreringschef, cand. pharm.
Sundhedsstyrelsen, Lægemiddelafdeling
Frederikssundsvej 378
DK-2700 Brønshøj
Tel.: (45) 44-94.36.77
Telex: 35333 IPHARM DK
Telefax: (45) 44-94.02.37

b) Mrs. Birgitte KRISTENSEN
Afdelingsforstander cand. pharm.
Sundhedsstyrelsen (idem)
Tel.: (45) 44-94.36.77

DEUTSCHLAND

a) Prof. Dr. Alfred G. HILDEBRANDT
Leiter des Instituts für Arzneimittel des
Bundesgesundheitsamtes
Seestraße 10
D-1000 Berlin 65
Tel.: (49)(30) 4502.1 / 4502-1203
Telex: (2627)(17) 308062 BGESA D
Telefax: (49)(30) 4502-1207

b) Frau Prof. Dr. med. Ursula GUNDERT-REMY
Leiterin der Abteilung
Experimentelle und klinische Pharmakologie
im Institut für Arzneimittel des
Bundesgesundheitsamtes
(idem)
Tel.: (49)(30) 4502.1189

ESPAÑA / SPAIN

a) Dr. F. GARCIA ALONSO

Dirección General de Farmacia y Productos Sanitarios, Ministerio de Sanidad y Consumo
Paseo del Prado, 18 - 20
E-28014 Madrid
Tel.: (34)(1) 420.20.68
Telex: 22.608 MSASS
Telefax: (34)(1) 420.32.17
ou 420 10 42 (Min. gen.)
ou 420 11 67
(questions communaut.)

b) Dra. Dolores SANDOVAL

Centro Nacional de Farmacobiologia
Majadahonda
28220 Madrid

Tel.: (34)(1) 638.51.55
Fax: (34)(1) 638.06.13

FRANCE

a) M. le Professeur Jean-Michel ALEXANDRE Direction de la Pharmacie et du Médicament
Ministère de la Santé et de l'action humanitaire
1, Place de Fontenoy
F-75700 Paris
Tel.: (33)(1) 40.56.47.09
Telefax: (33)(1) 40.56.53.55

b) M. le Professeur Jacques DANGOUMAU Agence du Médicament
Ministère des Affaires sociales, de la Santé et de la Ville
Tel.: (33) (1) ....

(Mme. Marie-Danièle Campion - Ministère des Affaires sociales, de la Santé et de la Ville - AGENCE DU MEDICAMENT - DIRECTION GENERALE - cellule Affaires Européennes et Internationales, 143-145 Bd. Anatole France, F-92200 SAINT-DENIS, Tel. 48 13 20 46, Fax 48 13 20 03)
M. Patrick LE COURTOIS - procedures: tél. 33 1 40.56.54.61, fax 40 56 45 71)

GREECE

a) Professor D. VARONOS

Chairman Registration Committee
E.O.F.
Mesogion 284
GR-155 62 Holargos
Tel.: (30)(1) (E.O.F.) 6525194-5 / 6525525-6-7
resp. (30)(1) 779.08.41 (University)
Telefax: (30)(1) 6545535

b) Mme. J. YOTAKI

Director Pharmaceutical Studies Division, E.O.F.
(idem)
Tel.: (30)(1) 65 26 216

IRELAND

a) Dr. Marie BURNS

Acting Medical Director
National Drugs Advisory Board
Charles Lucas House
63-64 Adelaide Road
Dublin 2
Tel.: (353)(1) 76.49.71 - 7
Telex: 90542 NDAB EI
Telefax: (353)(1) 76.78.36

b) Dr. Anthony O'BRIEN

Medical Assessor
National Drugs Advisory Board (Idem)
Tel.: (353)(1) 76.49.71 - 7

ITALIA

a) Dott. Romano CAPASSO

Consigliere Ministeriale
Direzione Generale Servizio Farmaceutico
Ministero della Sanità
Viale della Civiltà Romana 7
I-00144 Roma EUR
Tel.: (39)(6) 592.58.28
Telefax: (39)(6) 592.58.24

b) Dr. Marisa PAPALUCA

Medical Assessor
Operative Center for Community Procedures
Ministero della Sanità
Via della Sierra Nevada 60
I-00144 Roma EUR
Tel.: (39)(6) 592.58.26

LUXEMBOURG

a) Mme. Jacqueline GENOUX

Pharmacien-Inspecteur, Direction de la Santé
Division de la Pharmacie et des Médicaments
10, rue C.M. Spoo
L-2546 Luxembourg
Tel.: (352) 4.08.01
Telex: 2546 SANTE LU
Telefax: (352) 48.49.03

b) Mme. M. BACKES

Chef de Division Pharmacie et Médicaments (Idem)

NEDERLAND

a) Dr. J.F.F. LEKKERKERKER

Internist, Voorzitter College ter beoordeling van geneesmiddelen, Ministerie van Welzijn, Volksgezondheid en Cultuur
Postbus 5811
NL-2280 HV Rijswijk (ZH)
Tel.: (31)(70) 340.79.11
Telex: 31680 WVC RW NL
Telefax: (31)(70) 340.51.55

b) Dr. W.F. VAN DER GIESEN

Secretaris van het College ter beoordeling van geneesmiddelen (idem)
Tel.: (31)(70) 340.72.10
Telex and Telefax as above

PORTUGAL

a) Dr. J.A. ARANDA da SILVA

President of the Board of INFARMED
Instituto Nacional da Farmácia e do Medicamento - INFARMED
Av. Estados Unidos da America, 37
1700 Lisboa / Portugal
Tel.: (351)(1) 80 41 31
Telex: 15655 MAS P
Telefax: (351)(1) 84 80 331

b) Prof. Dr. José A. MORAIS

Ph.D., Assoc. Prof., Universidade de Lisboa, Faculdade de Farmacia,
Av. das Forças Armadas, 1600 Lisboa
Tel. 793.30.64, ext. 210
Fax 793.77.03

UNITED KINGDOM

a) Dr. Keith H. JONES

Director Medicines Control Agency
Department of Health
Medicines Control Agency
Market Towers, 1 Nine Elms Lane
London SW8 5NQ
Tel.: (44)(71) 273.0100
Telex: 883669 DHSSHQ G
Telefax: (44)(71) 273.0493

b) Dr. David JEFFERYS

Head, New Drugs and European Licensing
Department of Health
Medicines Control Agency (idem)
Tel.: (44)(71) 273.0200

Annex 3

Opinions of the CPMP in accordance with article 11 or article 12 of Directive 75/319/EEC (Pharmacovigilance)

1991 - 1992

COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 13 September 1989

RESTRICTED

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Pharmacovigilance Opinion No. 6 relating to **FLUNARIZINE**

Meeting of 13 September 1989

1. By letter of 28.2.89 the competent authority of Denmark requested the CPMP to give an opinion on Sibelium (Flunarizine), a peripheral vasodilator.

   The product is currently authorized in Belgium, Denmark, the Federal Republic of Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal.

2. The Committee considered the request at its meeting of 11-12 July 1989 and invited the company, Janssen Research Foundation (letter of Belgium of 24 July 1989) to supply additional pertinent information.

3. The Company's written submission was contained in a letter of 31.8.89 and a hearing before the Committee was offered (23.8.89).

4. During the hearing which took place in Brussels on 13th September 1989, 5 representatives of the company attended and made a presentation.

5. Having taken due account of the adverse drug reactions reported, the Committee considered that

   - Flunarizine should be contra-indicated in patients with a history of extrapyramidal symptoms, Parkinsonism, Alzheimer's disease and depression;

   - a special warning should be included in any information, mentioning that 'Flunarizine may induce extrapyramidal and depression symptoms and reveal Parkinsonism. It should be used with caution especially in the elderly';

   - all of the extrapyramidal and depressive symptoms should be adequately mentioned in the package leaflet.

6. The indications, especially central and peripheral vascular diseases, should be reviewed, taking into account the risks.

Provisional address: Rue de la Loi 200, B - 1049 Brussels. Telephone: direct line 23 . . . . . standard 235 11 11
Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 12 March 1991

Pharmacovigilance Opinion No. 6/1 on FLUNARIZINE

Meeting of 12th March 1991

WHEREAS the Committee for Proprietary Medicinal Products, at the request of Denmark (22.2.89), had considered the adverse event profile of the product Sibelium (Flunarizine); and following a hearing (13.9.89) with the company Janssen Research Foundation, had adopted an opinion (pharmacovigilance No. 6) on 13th September 1989.

WHEREAS, in the opinion of 13.9.89, the indications, especially central and peripheral vascular diseases, were to be reviewed taking into account the risks. Therefore a meeting of experts took place on 2.7.90, and the rapporteur (Belgium) circulated (29.10.90) an updated assessment report and the co-rapporteur (Denmark) also circulated an assessment report (15.8.90).

WHEREAS the product is not authorised in the United Kingdom;

WHEREAS the company circulated (22.1.91) additional documentation and a proposal for the summary of product characteristics, and 3 representatives attended a hearing on 13.2.91

1. The Committee considers that for the concerned Member States, on the basis of current data, only the indications "prophylaxis of migraine in patients with frequent and severe attacks, who have not responded satisfactorily to other treatment and/or in whom other therapy has resulted in unacceptable side-effects" and "symptomatic treatment of vestibular vertigo, due to diagnosed functional disorder of the vestibular system" may in principle be accepted.

2. There is a need for confirmatory extensive controlled, double blind clinical studies in order to support the benefit/risk ratio of flunarizine in both these indications. These studies should refine the optimal dosage regimen, and to better define the sequence of therapy e.g. for the maintenance treatment of migraine prophylaxis. In those Member States where these indications are not currently authorised, these studies would have to be assessed before such an indication could be accepted.

3. A summary of product characteristics is in annex.

4. The company is requested to establish an intensive drug monitoring program in order to estimate the incidence of the adverse reactions, their frequency as well as the population at risk.

5. The protocols and results of the on-going trials for migraine should be submitted.

6. The company is requested to confirm, in writing, that the company has withdrawn all other indications for this product in all Member States.

Rue de la Loi 200, B - 1049 Brussels.
Telephone: direct line 23 . . . . . standard 235 11 11 Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 11 September 1991

[redacted]

[redacted]

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Pharmacovigilance Opinion No. 6/2 on FLUNARIZINE

Meeting of 11 September 1991

WHEREAS the Committee for Proprietary Medicinal Products, at the request of Denmark (22.2.89), had considered the adverse event profile of the product Sibelium (Flunarizine); and following a hearing (13.9.89) with the company Janssen Research Foundation, had adopted an opinion (pharmacovigilance No. 6) on 13th September 1989.

WHEREAS, in the opinion of 13.9.89, the indications, especially central and peripheral vascular diseases, were to be reviewed taking into account the risks. Therefore a meeting of experts took place on 2.7.90, and the rapporteur (Belgium) circulated (29.10.90) an updated assessment report and the co-rapporteur (Denmark) also circulated an assessment report (15.8.90).

WHEREAS the product is not authorised in the United Kingdom;

WHEREAS the company circulated (22.1.91) additional documentation and a proposal for the summary of product characteristics, and 3 representatives attended a hearing on 13.2.91

1. The Committee considers that for the concerned Member States, on the basis of current data, only the indications "prophylaxis of migraine in patients with frequent and severe attacks, who have not responded satisfactorily to other treatment and/or in whom other therapy has resulted in unacceptable side-effects" and/or "symptomatic treatment of vestibular vertigo, due to diagnosed functional disorder of the vestibular system" may in principle be accepted.

2. There is a need for confirmatory extensive controlled, double blind clinical studies in order to support the benefit/risk ratio of flunarizine in both these indications. These studies should refine the optimal dosage regimen, and to better define the sequence of therapy e.g. for the maintenance treatment of migraine prophylaxis. In those Member States where these indications are not currently authorised, these studies would have to be assessed before such an indication could be accepted.

3. A summary of product characteristics is in annex.

4. The company is requested to establish an intensive drug monitoring program in order to estimate the incidence of the adverse reactions, their frequency as well as the population at risk.

5. The protocols and results of the on-going trials for migraine should be submitted.

6. The company is requested to confirm, in writing, that the company has withdrawn all other indications for this product in all Member States.

Rue de la Loi 200, B – 1049 Brussels.
Telephone: direct line 23 . . . . . standard 235 11 11 Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 13 December 1989

[redacted]

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Pharmacovigilance opinion No. 8 on GLAFENINE and FLOCTAFENINE

1. In March 1989, the Belgian authorities requested the Committee for Proprietary Medicinal Products, in accordance with Article 12 of Directive 75/319/EEC, to give a pharmacovigilance opinion on Glafenine and Floctafenine.

2. During its meeting on 14-15 November 1989 and on 12-13 December 1989, the Committee considered the spontaneous pharmacovigilance data which had been forwarded by the Member States, and agreed:

   I) The following amendments should be inserted in the Summary of Product Characteristics for Glafenine:

   Under 'Therapeutic Indications': Glafenine is reserved as a second line treatment, to be used only when other analgesic products are inappropriate.

   Under 'Contra-indication', the following to be added: Any known hypersensitivity to Glafenine and its derivatives is an absolute contra-indication to treatment.

   Under 'Particular precautions for use':
   - Glafenine must be stopped immediately as soon as the first sign of hypersensitivity becomes evident;
   - repeat prescriptions should be avoided;
   - Glafenine should not be given to patients for whom it is not prescribed;
   - it is necessary to drink copiously in order to reduce the risk of intrarenal crystallization.

   II) The supply of Glafenine should be subject to non renewal medical prescription (List 1 of the Council of Europe).

3. On the basis of the pharmacovigilance data currently available, the CPMP considers that Floctafenine appears to present a lower incidence of side-effects than Glafenine. With the exception of intrarenal crystallization, the risk profile however seems similar.

   The ADR of both Glafenine and Floctafenine would continue to be monitored and the position would be later reviewed by the CPMP, if necessary.

Provisional address: Rue de la Loi 200, B - 1049 Brussels. Telephone: direct line 23 . . . . . standard 235 11 11
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COMMISSION
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CONFIDENTIAL AND RESTRICTED

Brussels, 13 February 1991

[redacted]

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Pharmacovigilance Opinion No. 8/1 relating to GLAFENINE
Meeting of 13 February 1991

WHEREAS the Committee for Proprietary Medicinal Products adopted an opinion on GLAFENINE on 13.12.1989;

WHEREAS, in the short time since the adoption of that opinion, only limited results have been observed so far; whereas no unexpected data have been submitted to the Committee since December 1989:

1. The Committee considers that the opinion of 13.12.1989 remains unchanged.

2. In accordance with the opinion of 13.12.1989, the Committee wishes to continue its surveillance particularly with regard to adverse reactions, and therefore requests

   - the marketing authorisation holders to prepare a safety update, taking account of global data, especially identifying the data for the year 1990;

   - the Member States upon whose territory this product is marketed, to compile and report on the up-to-date situation.

3. The Committee will consider this information at its meeting in June 1991, following which its opinion would be finalised.

Rue de la Loi 200, B - 1049 Brussels.
Telephone: direct line 23 . . . . . standard 235 11 11 Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

COMMISSION
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Brussels, 14 January 1992

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
Pharmacovigilance opinion No. 8/2 on **GLAFENINE**
Brussels, 14 January 1992

WHEREAS, in March 1989, the Belgian competent authorities requested the Committee for Proprietary Medicinal Products, in accordance with Article 12 of Directive 75/319/EEC, to give a pharmacovigilance opinion on Glafenine, a peripheral analgesic, on which a number of side-effects, particularly anaphylactic reaction, and intrarenal crystallisation had been reported. France and the Netherlands agreed to act as rapporteurs;

WHEREAS Glafenine was authorised, at that time, in Belgium, Spain, Greece, France, Italy, the Netherlands and Portugal, as well as in approximately 75 countries outside the European Community. The company had withdrawn the product from the German market in August 1983, and no application had been made in Denmark, Ireland and the United Kingdom;

WHEREAS, during its meeting on 14-15 November 1989 and on 12-13 December 1989, the Committee considered the spontaneous pharmacovigilance data which had been forwarded by the Member States, and agreed a number of safeguard measures, including limiting the supply of Glafenine to non renewal medical prescription (List 1 of the Council of Europe), and amendments in the Summary of Product Characteristics:

> Under 'Therapeutic indications': Glafenine is reserved as a second line treatment, to be used only when other analgesic products are inappropriate.
>
> Under 'Contra-indication': the following to be added: Any known hypersensitivity to Glafenine and its derivatives is an absolute contra-indication to treatment.
>
> Under 'Particular precautions for use':
> - Glafenine must be stopped immediately as soon as the first sign of hypersensitivity becomes evident;
> - repeat prescriptions should be avoided;
> - Glafenine should not be given to patients for whom it is not prescribed;
> - it is necessary to drink copiously in order to reduce the risk of intrarenal crystallization.

WHEREAS, in December 1990, the Belgian competent authorities withdrew the marketing authorisation in Belgium for Glafenine. Luxembourg mutually recognised this action and also withdrew the marketing authorisation;

WHEREAS, at the meeting of 13 February 1991, the Committee reissued its opinion and invited the marketing authorisation holders to prepare a safety update, taking account of global data, especially identifying the data for the year 1990, and in order to continue its surveillance, particularly with regard to adverse reactions, requested the Member States upon whose territory this product was marketed to compile and report on the up-to-date situation;

Provisional address: Rue de la Loi 200, B - 1049 Brussels. Telephone: direct line 23 . . . . . standard 235 11 11
Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

WHEREAS, in May, the company Roussel-Uclaf submitted a safety update, which was further elaborated in September 1991;

WHEREAS the competent authority in the Netherlands had initiated a case-cohort epidemiological study, focussing on anaphylactic reaction only. The final results of this study were circulated to all members of the Committee on 13 November 1991, and to the company Roussel-Uclaf;

WHEREAS, at the meeting on 12 December 1991, the Committee considered the submissions of May, September and November 1991, and the company Roussel-Uclaf presented for a hearing;

WHEREAS the matter was further considered at a meeting of the Committee on 14 January 1992, when the company submissions of 5.12.91 and 10.1.92 were also reviewed;

1. The Committee considers that the signal first identified in spontaneous surveillance has been confirmed by the Dutch epidemiological study, and that the risk of anaphalactic reaction with Glafenine is higher than for other analgesics. Given the seriousness of the reaction, the benefit/risk ratio of the product is considered negative and the marketing authorization should be withdrawn.

2. France and Portugal do not concur with the scientific assessment of the Committee. They do not share the conclusions of the Dutch epidemiological study and therefore consider:

   - there is no new information available,

   - Glafenine, aside from anaphylactic reaction, has less of some other side effects than other analgesic/antiinflammatory compounds.

   Therefore the product is still considered to have a favourable benefit/risk ratio when used as a second line treatment in patients where other analgesics are inappropriate.

3. In accordance with Article 14(3) of Directive 75/319/EEC, as amended by Directive 83/570/EEC, all Member States shall inform the Committee, within 60 days, on what action they have taken on the Committee's opinion.

4. In accordance with Article 33(3) of Directive 75/319/EEC, as amended by Directive 89/341/EEC, Member States shall forthwith bring to the attention of the World Health Organisation any action which may affect the protection of public health in third countries, with a copy to the Committee.

COMMISSION
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Brussels, 11 September 1991
Rev. 1

[redacted]

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Inhaled fenoterol in the treatment of chronic and acute asthma

Pharmacovigilance Opinion No. 10

On 27.3.1991, Italy circulated a Pharmacovigilance request to all Member States regarding Fenoterol, and its authorization status.

The marketing authorization holder in the Netherlands and in Italy, Boehringer Ingelheim, proposed (5.7.1991) an alteration to the prescribing information, which raised a number of questions with regard to the use of fenoterol and the appropriate prescribing instructions for the product.

Germany, in July 1991, requested the Committee for Proprietary Medicinal Products for an opinion, in accordance with Article 12 of Directive 75/319/EEC. Germany and Italy have agreed to act as rapporteurs.

The authorisation holder was invited to present an overview of the benefit/risk profile of the product with particular regard to

* the use of fenoterol in the treatment and prophylaxis of asthma and in comparison with other treatments;

* the implications of reduced dosage, an alteration of indications and/or the method of administration on the benefit/risk profile of the product.

A preliminary discussion between the company, the Efficacy Working Party and some members of the Pharmacovigilance Working Party took place on 27.8.91, with a report to the CPMP in September 1991.

In September 1991, the CPMP considered the report (III/3520/91).

1. The Committee considers that in the light of the information available the summary of product characteristics (article 4(a) of Directive 65/65/EEC) should be amended, particularly in regard to:

   A. Indications

   A.1 100 mcg/puff

   a) Symptomatic treatment of acute asthma episodes

   b) Prophylaxis of exercise induced asthma

   c) Symptomatic treatment of bronchial asthma and other conditions with reversible airways narrowing e.g. chronic obstructive bronchitis. Concomitant anti-inflammatory therapy should be considered.

Rue de la Loi 200, B – 1049 Brussels.
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A.2 200 mcg/puff

The indications detailed in A.1, when not adequately controlled by the use of Berotec 100 mcg/puff as part of an appropriate therapeutic plan.

B. Dosage regimen (applies for both formulations)

a) **Acute asthma episodes**

1 puff of Berotec is sufficient for prompt symptom relief in many cases. In more severe cases, if breathing has not noticeably improved after 5 minutes, a second dose may be taken.

If an attack has not been relieved by 2 puffs, further puffs may be required. In these cases, patients should consult the doctor or the nearest hospital immediately.

b) **Prophylaxis of exercise induced asthma**

1-2 puffs for each administration, up to a maximum of 8 puffs per day.

c) **Bronchial asthma and other conditions with reversible airways narrowing**

If repeated dosing is required, 1-2 puffs for each administration, up to a maximum of 8 puffs per day.

C. Precautions/Warnings

Prolonged use:
- On demand treatment (symptom oriented) may be preferable to regular use.
- Particularly in the case of regular use, patients should be re-evaluated for the addition or the increase of anti-inflammatory therapy (e.g. inhaled corticosteroids) to control airway inflammation and to prevent long term damage.

2. The company is requested to submit an application for the 100 mcg/puff formulation in all Member States.

3. The protocols, results and timetable of on-going studies should be submitted as soon as available.

COMMISSION
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Brussels, 16 October 1991

[redacted]

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
Meeting of 16 October 1991

Position Statement on TRIAZOLAM

- WHEREAS, in accordance with Article 11 of Directive 75/319/EEC, the competent authorities in France (2.10.91) and in the Netherlands (4.10.91) requested the opinion of the Committee for Proprietary Medicinal Products regarding the medicinal product HALCION(R) (triazolam);

WHEREAS the company, Upjohn, circulated a revised Protocol 321 to all Member States;

WHEREAS the medicinal product containing 0.25 mg and 0.125 mg triazolam is authorised in Belgium, Denmark, Germany, Spain, Greece, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal and the United Kingdom. The authorisation of the medicinal product was suspended on 2.10.1991 in the United Kingdom initially for a period of 3 months (which may be renewed) and procedures to revoke that authorisation have been initiated.

WHEREAS in response to questions raised by Member States, the authorisation holder Upjohn submitted a large amount of information to all Member States on 11.10.91.

WHEREAS the Committee considered this medicinal product at its meeting on 16.10.91, at which time the company presented for a hearing.

WHEREAS the United Kingdom attended the meeting and presented the factual basis for its action, however in order not to prejudice the UK appelate procedure, it did not participate in the discussions leading to this Position Statement, which does not include the United Kingdom.

1. Given the large volume of information supplied on 11.10.91, the Committee considers it necessary to review these data, as well as data in the application dossier and information from pharmacovigilance. Rapporteurs have been appointed and will report in December 1991.

2. Upon preliminary consideration of the available data, evidence of new risks at recommended doses does not seem to be available.

3. The information on the only available presentations (0.25 mg and 0.125 mg) should be immediately strengthened (see Annex).

4. To emphasize that the product is for short-term use, the company has proposed introducing small pack sizes. The Committee considers that small packs (not more than 7 tablets) should be made available immediately.

5. The company has accepted to perform an extensive pan-European controlled comparative post-marketing safety and efficacy study immediately, and a draft protocol should be submitted to the Committee before December 1991.

6. The Committee will formulate its opinion in December 1991, taking into account the full review of all existing data.

Rue de la Loi 200, B - 1049 Brussels
Telephone: direct line 23 . . . . . standard 235 11 11 Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

Indication

add: Triazolam is only indicated when the sleeping disorder is severe, disabling or causing extreme distress.

Duration of use

Triazolam should not be used for more than 2-3 weeks, and treatment thereafter requires a complete re-evaluation of therapy.

Posology

The lowest effective dose should be used. For many patients a dose of 0.125 mg immediately before retiring may be sufficient. A dose of 0.25 mg should not be exceeded.

For elderly, debilitated patients and patients with disturbed liver/kidney function, the dose should not exceed 0.125 mg before retiring.

Safety and efficacy of triazolam have not been established for patients younger than 18.

Warning:

Triazolam should not be used in patients with any major psychiatric disorders.

COMMISSION
OF THE EUROPEAN
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Brussels, 11 December 1991

[redacted]

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

TRIAZOLAM

Pharmacovigilance Opinion No. 11

WHEREAS, in accordance with Article 11 of Directive 75/319/EEC, the competent authorities in France (2.10.91) and in the Netherlands (4.10.91) requested the opinion of the Committee for Proprietary Medicinal Products regarding the medicinal product HALCION(R) (triazolam);

WHEREAS the medicinal product containing 0.25 mg and 0.125 mg triazolam is authorised in Belgium, Denmark, Germany, Spain, Greece, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal and the United Kingdom. The authorisation of the medicinal product was suspended on 2.10.1991 in the United Kingdom initially for a period of 3 months (which may be renewed) and procedures to revoke that authorisation have been initiated. WHEREAS the United Kingdom attended the meeting; however in order not to prejudice the UK appelate procedure, it did not participate in the discussions leading to this Opinion;

WHEREAS in response to questions raised by Member States, the authorisation holder Upjohn submitted a large amount of information to all Member States on 11.10.91, and presented for a hearing on 16.10.91.

WHEREAS the Committee considered this medicinal product at its meeting on 16.10.91, at which time the company presented for a hearing;

WHEREAS, given the large volume of information supplied on 11.10.91 and in the light of the hearing, the Committee considered it necessary to review these data, as well as data in the application dossier and information from pharmacovigilance. Rapporteurs were therefore appointed.

WHEREAS, the Committee considered the report of the rapporteurs on 11.12.91, at which time the company presented again for a hearing and made further proposals (11.12.91);

1. The Committee confirms the safeguard measures as indicated in its position statement of 16.10.1991, particularly with regard to the maximum dosage of 0.25 mg, the narrow and very precise indications, as well as contra-indications, for this product, the absolute importance of short term usage (not more than 10 days), which has been reinforced by the introduction of small pack sizes in all Member States.

2. In order to complete the excellent work done by the rapporteurs, the Committee has invited them to fully assess the relative risk/benefit ratio of all short acting hypnotics.

3. The safety in clinical use of all hypnotics will continue to be monitored by the Committee.

Rue de la Loi 200, B – 1049 Brussels.
Telephone: direct line 23 . . . . . standard 235 11 11 Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

COMMISSION
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Brussels, 4 December 1992

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Pharmacovigilance Opinion No. 12 on NOSCAPINE
Meeting of 4 December 1992

In November 1989, the competent authorities of the Netherlands informed the Committee for Proprietary Medicinal Products (CPMP) of a publication which suggested a possible association of noscapine, an alkaloid of opium, with polyploidy. The matter was referred by the CPMP to the Safety Working Party which was requested to compile and consider all up-to-date scientific data.

WHEREAS, the Safety Working Party considered the question in January and May 1990, and indicated the need for further information on the mutagenic and genotoxic potential of noscapine; whereas, in October 1990, the company, Beecham Research, supplied additional information, which was considered;

WHEREAS, in March 1991, the United Kingdom agreed to act as rapporteur, and all assessment reports as well as the authorisation status of the substance in all Member States were reviewed. An expert report was prepared and submitted to the CPMP in May 1991, as well as a paper on 'Noscapine induced polyploidy in vitro'.

The UK assessment concluded that for anaesthetic products, such as Omnopon which was marketed in UK, the noscapine component carried no additive benefit in the product. It was the UK position that for such products there was no justification for tolerating any risk, even if this is largely derivative i.e. from in vitro data. This limitation was considered to apply especially to the women of reproductive capacity. Therefore, in the UK, the legal status of noscapine containing anti-tussive medicinal products was changed to "prescription only medicine (POM)" from General Sales List (for maximum dose 15 mg, daily intake 5 mg) on July 20th, 1992. As a result of actions taken by the manufacturer, noscapine is no longer a component in anti-tussive medicinal products on the UK market .

In the opinion of some Member States, exemplified by Denmark, where noscapine containing anti-tussive products are available without a prescription (OTC), the in vitro data was not convincing that a potential hazard existed with respect to human safety, and did not change the marketing situation. The results of further elucidation of the potential genotoxicity, studies of which were in process in Sweden, were awaited instead.

This new material became available at the beginning of 1992 and was evaluated in an extensive report by the Swedish Medical Products Agency. This report described polyploidy in general and the available information to elucidate the potential genotoxicity and reproductive toxicity of the substance and mentioned the information on carcinogenic activity.

Rue de la Loi 200, B - 1049 Brussels.
Telephone: direct line 23 . . . . . standard 235 11 11 Telex: COMEU B 21877 Telegraphic address: COMEUR Brussels

The assessment concluded that the only reliable results so far that indicated a relevant genotoxic potential of noscapine was the demonstrated spindle damaging effect and the polyploid/aneuploid inducing capacity at high concentrations in vitro. There were equivocal results concerning a clastogenic activity in vitro. However, it had been clearly shown that noscapine did not induce gene mutations in vitro and was without an aneugen and clastogenic activity in vivo. Based on these conclusions and the low systemic exposure in man, the Swedish Medical Products Agency did not consider it justified to undertake restrictive regulatory action on the use of noscapine in women of childbearing age, or on its general use by making it available on prescription only.

The CPMP concluded that the data presented and the assessment of safety performed did not present significant indications of potential hazardous effects in man from the use of the substance as an anti-tussive. The absence of any reported hazards, despite the extensive use for decades of noscapine in clinical practice was also noted. Furthermore, pharmacokinetic studies demonstrated a very low systemic exposure in man after taking therapeutic doses of the active substance in anti-tussive preparations.

In conclusion the CPMP does not propose restrictions at this time for anti-tussive medicinal products containing noscapine, although the different pattern of dosage and supply of such anti-tussives across the Community.

Annex 4

Multi-state procedures which have been completed

March 1993

COMPLETED MULTI-STATE PROCEDURES

AUT = autorisation REF(1) = refusal/withdrawal OR = country of origin * = not concerned

MEDICAMENT/ Opinion No./Date	PAYS / COUNTRIES											
	BE	DK	DE	ESP	FR	GR	IRL	IT	LUX	NL	PO	UK
Peppermint oil 76, 23.11.88	REF 23.12.88	REF 09.12.88	REF 10.01.89	REF 21.12.88	AUT 15.6.89	REF 22.12.88	*	REF 28.12.88	REF 29.12.88	REF 12.12.88	*	OR
Cefuroxime 77, 14.9.88	*	*	AUT 09.03.89	*	*	*	*	*	*	AUT 17.03.89	*	OR
Recomb.Human Growth Horm. 78, 15.2.89	*	*	AUT 22.02.89	AUT 16.04.89	AUT 03.04.89	*	AUT 23.02.89	OR	*	*	*	AUT 10.11.89
Enoximone 79, 14.12.88	*	*	AUT 25.08.89	AUT 21.12.88	OR	*	*	*	AUT 21.06.89	AUT 07.06.89	*	*
Disopyramide 80, 14.12.88	AUT 11.04.90	AUT 10.01.89	AUT 25.04.89	*	OR	*	AUT 20.04.89	*	*	AUT 20.02.89	*	AUT 01.03.89
Podophyllotoxin 81, 14.12.88	*	*	*	*	AUT 05.08.88	*	*	AUT 28.12.88	AUT 22.02.89	OR	*	AUT 18.01.89
5-asa 82, 14.12.88	AUT 11.04.90	OR	AUT 13.02.89	*	*	*	AUT 02.02.89	AUT 28.12.88	AUT 22.2.89	*	*	AUT 24.08.90
Loratadine 83, 15.2.89	OR	*	AUT 25.08.89	*	*	AUT 25.10.88	*	*	*	AUT 20.03.89	*	*
Gemeprost 84, 13.9.89	AUT 07.02.90	*	*	*	*	*	*	*	AUT 17.11.89	AUT 16.10.89	*	OR
Salbutamol 88, 15.2.89	*	*	AUT 16.06.89	*	*	*	*	*	AUT 17.11.89	*	*	OR

(1) An applicant may subsequently appeal the Member State ruling, using national procedures.

March 1993

COMPLETED MULTI-STATE PROCEDURES

AUT = autorisation REF(1) = refusal/withdrawal OR = country of origin * = not concerned

MEDICAMENT/ Opinion No./Date	PAYS / COUNTRIES											
	BE	DK	DE	ESP	FR	GR	IRL	IT	LUX	NL	PO	UK
Terodiline HCl 63, 15.6.88	AUT 05.01.89	*	AUT 13.12.89	AUT 17.06.88	REF 15.11.88	*	*	REF 13.07.88	AUT 19.08.88	*	*	OR
Cetirizine 64, 14.4.88	OR	AUT 28.04.88	*	*	*	AUT 01.03.88	AUT 15.08.88	AUT 13.03.89	*	AUT 25.08.88	*	AUT 16.09.88
Amino acids 65, 13.4.88	AUT 24.05.88	*	AUT 07.02.90	AUT 16.06.88	OR	*	REF 09.12.87	AUT 08.02.89	AUT 11.05.88	AUT 12.09.88	*	AUT 11.10.89
Dextrose 66, 17.2.88	AUT 15.09.89	AUT 25.04.88	REF 13.02.89	*	REF 10.07.89	AUT 01.08.88	AUT 03.02.89	*	AUT 30.03.88	AUT 23.05.89	*	OR
Fucidic acid 67, 15.6.88	AUT 26.09.88	OR	AUT 12.12.90	*	AUT 22.06.88	AUT 01.06.88	*	AUT 08.02.89	*	*	*	*
Acides amines 69, 15.6.88	OR	*	*	AUT 17.06.88	AUT 11.02.90	*	*	*	*	*	*	*
Enoxaparine 70, 15.6.88	AUT 23.08.88	AUT 14.6.89	AUT 18.01.89	AUT 17.06.88	OR	AUT 19.10.88	AUT 29.08.89	AUT 31.07.90	AUT 19.08.88	AUT 01.03.89	*	AUT 23.10.90
Rifampicin isoniazid/pyr. 71, 14.9.88	AUT 09.01.89	*	AUT 31.01.89	AUT 30.09.88	*	*	*	AUT 08.02.89	AUT 26.10.88	*	*	OR
Nizatidine 72, 15.6.88	*	*	AUT 15.12.88	*	*	AUT 01.07.88	*	*	*	*	*	OR
Atenolol 73, 14.9.88	*	*	AUT 17.08.89	*	*	*	*	*	AUT 26.10.88	*	*	OR

(1) An applicant may subsequently appeal the Member State ruling, using national procedures.

March 1993

COMPLETED MULTI-STATE PROCEDURES

AUT = autorisation REF(1) = refusal/withdrawal OR = country of origin * = not concerned

MEDICAMENT/ Opinion No./Date	PAYS / COUNTRIES											
	BE	DK	DE	ESP	FR	GR	IRL	IT	LUX	NL	PO	UK
Salbutamol Inhaler 42, 12.11.86	AUT 19.08.91	AUT 30.06.86	*	*	AUT 17.04.87	AUT 29.01.87	*	AUT 30.12.86	AUT 19.12.86	AUT 12.06.87	*	OR
Ketoprofen 43, 11.3.87	AUT 20.01.88	AUT 05.02.87	*	*	*	*	*	*	AUT 27.11.86	AUT 19.06.87	*	OR
Bisoprolol fumarate 44, 11.3.87	*	*	OR	AUT 16.06.87	*	AUT 12.01.88	AUT 18.06.87	AUT 01.03.89	AUT 19.12.86	AUT 06.10.87	*	AUT 18.12.87
Prazosin 45, 10.6.87	REF 17.08.87	*	AUT	AUT 23.03.87	AUT 14.02.90	REF 30.05.88	OR	REF 15.05.87	REF 10.07.87	REF 28.07.87	*	*
Fibr.extr. testa triticum 46, 16.9.87	*	*	REF 16.06.89	*	AUT 26.01.88	AUT 26.01.88	*	*	*	*	*	OR
Tixocortol pivalate 47, 14.10.87	*	AUT 28.10.87	*	*	OR	*	INF 03.11.92	*	AUT 06.01.88	*	*	REF 17.12.90
Iron gluconate 48, 7.7.87	AUT 19.01.88	*	OR	*	*	*	*	AUT 05.03.90	AUT 30.09.87	*	*	*
Inhaler salbutamol 49, 7.7.87	AUT 04.06.91	AUT 25.04.88	REF 12.10.88	AUT 21.10.87	AUT 30.06.87	AUT 11.03.88	OR	AUT 02.03.90	AUT 06.01.88	AUT 28.06.88	*	AUT 01.09.87
Selegiline HCl 50, 16.9.87	AUT 20.01.88	*	OR	AUT 09.10.87	*	*	*	*	AUT 06.01.88	REF 14.09.88	*	*
Tetratolol 51, 17.2.88	AUT 23.08.88	AUT 15.03.88	AUT 23.03.89	REF 09.03.88	OR	AUT 04.03.88	AUT 21.04.88	AUT 10.04.89	AUT 30.09.87	AUT 12.09.88	*	REF 17.12.90

(1) An applicant may subsequently appeal the Member State ruling, using national procedures.

March 1993

COMPLETED MULTI-STATE PROCEDURES

AUT = autorisation REF(1) = refusal/withdrawal OR = country of origin * = not concerned

MEDICAMENT/ Opinion No./Date	PAYS / COUNTRIES											
	BE	DK	DE	ESP	FR	GR	IRL	IT	LUX	NL	PO	UK
Metoclopramide HCl 52, 16.9.87	REF 21.11.87	AUT 30.09.87	REF 04.11.87	REF 09.10.87	*	REF 09.11.87	OR	REF 24.10.87	REF 06.01.88	AUT 19.05.88	*	*
Flumazenil 53, 14.10.87	AUT 18.01.88	AUT 28.10.87	AUT 31.10.88	AUT 21.10.87	OR	AUT 31.03.88	AUT 18.02.88	AUT 01.02.89	AUT 30.09.87	AUT 27.04.88	*	AUT 29.03.88
Fenticonazole 54, 16.12.87	*	*	AUT 31.01.91	*	*	*	AUT 18.02.88	OR	*	*	*	*
Propanolol HCl 55, 14.10.87	*	AUT 28.10.87	*	*	OR	AUT 22.01.88	AUT 18.02.88	REF 14.05.90	*	AUT 14.12.88	*	AUT 05.02.91
Leuproreline 56, 14.9.88	AUT 09.08 89	*	*	*	OR	*	*	AUT 13.02.89	*	*	*	*
Dihydrocodeine tatrate 57, 17.2.88	AUT 24.05.88	REF 26.09.89	AUT 28.12.88	AUT 04.03.88	AUT 31.01.89	AUT 09.08.88	*	REF 07.03.88	AUT 30.03.88	REF 06.02.89	*	OR
Ciprofloxacine 58, 16.12.87	*	*	*	AUT 04.02.88	*	AUT 06.04.88	*	*	*	*	*	OR
Mesalazine 60, 16.12.88	AUT 16.05.88	AUT 11.01.88	OR	*	*	AUT 05.02.88	*	*	*	AUT 18.03.88	*	AUT 21.03.89
Frusemide amiloride HCl 61, 17.2.88	AUT 01.07.88	AUT 29.03.89	*	*	*	AUT 17.05.88	*	AUT 02.02.89	AUT 30.03.88	*	*	OR
Zuclopethixol 62, 13.4.88	*	OR	*	*	*	AUT 25.02.88	*	AUT 20.05.88	*	*	*	*

(1) An applicant may subsequently appeal the Member State ruling, using national procedures.