The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

24 October 97
CPMP/921/97

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 31st plenary meeting on 21-22 October 1997. This meeting was followed on 23 October 1997 by a Joint EFPIA/EMEA Information Day on Performance Assessment of the European Registration Systems (see Statement attached).

Centralised Procedures

The Committee adopted by consensus the following opinions and other measures:

- one positive opinion on a centralised application for a biological/biotechnology product (Part A) indicated for active immunisation against hepatitis B, diphtheria and tetanus in infants for primary vaccination and for booster;
- six positive opinions on centralised applications relating to products containing four new active substances (Part B);
· indicated for pain relief in patients with skeletal metastases;
· the treatment of HIV-1 infected patients (the assessment period for this application was 125 days and the opinion was given under exceptional circumstances);
· the treatment of various bacterial infections.

- an opinion on an extension for an already centrally authorised product, concerning new formulations;
- one positive opinion for a centralised type I variation following the type II procedure and two positive opinions for centralised type II variations.

Since the CPMP meeting in September 1997, the European Commission has granted a marketing authorisation for SIFROL (pramipexole) indicated for the treatment of idiopathic Parkinson's disease (14 October 1997). A summary concerning this product is given in Annex III.

An overview of centralised applications is given in Annex I and II.

Scientific Advice

The CPMP following oral consultation with the companies adopted by consensus two scientific advice on clinical development, one concerning cardiovascular indications and the other concerning the possibility of bridging studies. Three new requests for scientific advice were accepted as justified, and co-ordinators were appointed.

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Working Parties

The CPMP heard reports from its Quality, Biotechnology, Safety, Efficacy and Pharmacovigilance Working Parties.

Quality Working Party:

The following document was adopted:
· Reduced stability testing plan - bracketing and matrixing (CPMP/QWP/157/96); Annex to Note for Guidance on Stability Testing: Stability Testing of New Active Substances and Medicinal Products

The following document was released for 6-month consultation:
· Note for Guidance on dry powder inhalers (CPMP/QWP/158/96)

Efficacy Working Party:

The following document was adopted:
· Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Acute Respiratory Distress Syndrome (CPMP/EWP/504/97)

Pharmacovigilance Working Party:

Following the discussion about fenfluramine and dexfenfluramine containing medicinal products at the September meeting the matter was referred to the Committee within the scope of Article 15 (a) of Directive 75/319/EEC.

Biotechnology Working Party:

The following document was released for 3-month consultation:
· Addendum to Note for Guidance on Plasma-Derived Medicinal Products: The introduction of genomic amplification technology (GAT) for the detection of Hepatitis C Virus RNA in plasma pools (CPMP/BWP/390/97).

Mutual Recognition

The Committee noted the report from the Mutual Recognition Facilitation Group (MRFG) (20 October 1997) which is circulated together with this press release.

Prof. R. Bass
Head of Human Medicines Evaluation Unit

Annex I: Centralised Applications: Statistics
Annex II: New Community Marketing Authorisations
Annex III: Product Summary for SIFROL

This press release and other documents are available on the Internet at the following address: http://www.eudra.org/emea.html

ANNEX I to **CPMP - October 97**
Press Release

CENTRALISED APPLICATIONS TO THE EMEA

	CENTRALISED		TOTAL*
	Part A	***Part B***	
Applications submitted since 01.01.95	45	77	122
Withdrawn	1	7	8
Review ongoing	18	35	53
Opinions given by CPMP	26	35	61**
Marketing Authorisation granted by Commission	24	26	50***

* These figures include the 18 ex-concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996
** 61 Opinions corresponding to 48 substances
*** 50 Marketing Authorisations corresponding to 41 substances

	PENDING		FINAL		TOTAL
	Part A	***Part B***	***Part A***	***Part B***	
Variations type I	10	27	52	43	132
Variations type II	2	9	17	26	54
Extensions	16	2	10	2	30
Scientific advice	6		39		45

Updated 22 October 1997

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ANNEX II to **CPMP - October 1997**
Press Release

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure

Status: October 1997

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Trans-mission to COM b) Date of decision c) Date of notification d) OJ No.
a) **SIFROL** b) pramipexole c) Part B	a) Boehringer Ingelheim b) DE	a) N04BC b) Treatment of idiopathic Parkinson's disease	a) Tablets b) 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, 1.5 mg c) 10 Presentations	a) 18.06.96 b) 18.06.97 c) 208 Days d) 157 Days	a) 05.08.97 b) 14.10.97 c) d)

ANNEX III to **CPMP - October 1997**
Press Release

SIFROL

International Non-proprietary Name (INN): **pramipexole**

On 14 October 1997, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product SIFROL, which contains pramipexole. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 18 June 1997. The Marketing Authorisation Holder responsible for this medicinal product is Boehringer Ingelheim International GmbH, Germany.

The approved indication is for the treatment of signs and symptoms of advanced idiopathic Parkinson's disease in combination with levodopa, i.e. over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations). Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which is available in all eleven European Union official languages.

The active substance of SIFROL, pramipexole is a amino-benzothiazole derivative. It has been shown to be a selective and specific full dopamine (DA) receptor agonist with high affinity and selectivity for the DA D2 receptor subfamily, and particulary the D_3 receptor subtype.

Clinical trials were performed in advanced idiopathic Parkinson's disease patients showing end-of-dose phenomena on optimized L-dopa therapy. In this patient population, a clinically relevant benefit of pramipexole was demonstrated for up to 6 months in comparison to placebo.

In general, the side-effect profile of pramipexole is typical of a DA agonist, including hallucinations, sleep disturbances and gastrointestinal effects. Owing to a suspected potential of pramipexole to cause ocular toxicity ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities should occur. An increased dyskinesia frequency, particulary in women could not be excluded, and therefore L-dopa dose adjustments may be required. By these precautions and recommendations, which are included in the SPC, the potential safety concerns were considered to be adequately addressed.

The CPMP, on the basis of efficacy and safety data submitted, considered that SIFROL showed adequate evidence of efficacy and a satisfactory safety profile and therefore recommended that the Marketing Authorisation should be granted.

This text is also published as Abstract of the EPAR for SIFROL.

Mutual Recognition Facilitation Group

Report from the meeting held on 20 October 1997

The MRFG noted that 25 new mutual recognition procedures have been finalised in the last month as well as 13 type I and 8 type II variations.
The status as of 20 October 1997 of procedures under mutual recognition is as follows:

Year	New applications finalised	New applications in process	Type I variations finalised	Type I variations pending	Type II variations finalised	Type II variations pending	Arbitrations referred to CPMP
1997	88* + 25= 113	48	75	12	94	47	1 N.A. + 1 Var.

* the new applications finalised last month during the year 1997 were 88 and not 98 as stated in the September Press Release.

	New applications finalised	Type I variations finalised	Type II variations finalised	Arbitrations referred to CPMP
1995	10	16	17	1 N.A.

	New applications finalised	Type I variations finalised	Type II variations finalised	Arbitrations referred to CPMP
1996	84	49	73	1 N.A. + 1 Var.

11 new procedures (regarding 17 products) have been started since 22 September. The categories of these procedures are as follows:

New active substance[1]	Line extensions[2]	Fixed combinations	Generics	Herbal products[3]	OTC[4]	Others[5]
4	3	0	2	0	0	2

1. When in one of the involved Member States it concerns a new active substance according to the definition in the Notice to Applicants Part IIA;
2. Line extensions are those applications which extend a range of products, e.g. an additional strength, or a new pharmaceutical form from the same Marketing Authorisation Holder;
3. In this category products are classified as herbals when the RMS has considered them as herbal product;
4. In this category products are classified as OTC products when the RMS has approved it for OTC use, although the legal status is not part of the Mutual Recognition Procedure;
5. When the product is not classified in the previous six categories.

Each application can be classified in only one category.

Number of countries involved in the started procedures since 22 September 1997:

Reference Member State (number of products involved in the procedure)	Number of CMS involved in the procedure
DE (1)	13
DE (1)	11
DE (1)	8
DE (1)	4
FI (1)	13
FI (2)	13
NL (1)	5
SE (3)	7
SE (1)	3
SE (2)	14
UK (3)	1

General issues

- The Eudratrack system commenced operation on the 15th October 1997. This is an important development for the Mutual Recognition procedure and will progressively allow more standard information to be made available to the industry, professions and the public. The system will be closely monitored by the group for a 3 month trial period.
- The group was pleased to welcome the European Commission to the meeting. In future the Commission will regularly attend the meetings. This will allow procedural matters to be resolved more rapidly and such clarifications will be made available in the press report if appropriate.
- The group continued to monitor the role and the outcome of the break-out sessions and withdrawals. The group agreed to undertake a series of diagnostic reviews and will consider the implications of these on future practise.
- The group reviewed and reconfirmed the procedure for handling influenza vaccines through the Mutual Recognition system for the season 1998/99. A draft core SPC has been circulated to the Member States and the European Vaccines Manufacturers (EVM) for comments.
- At the November meeting the group will consider a proposal for the format of the response document of the applicant after day 60.

Information on the above mentioned issues can be obtained by the presiding chair of the MRFG:

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EMEA EFPIA

JOINT EMEA/EFPIA PRESS RELEASE

Outcome of the 4th Info-Day held on 23 October 1997 in London on

'PERFORMANCE REVIEW OF THE EUROPEAN REGISTRATION SYSTEM'

The fourth in a series of EFPIA-Info days organised by EFPIA with the collaboration of the EMEA and the European Commission was held in London on 23rd October 1997.
Over 260 delegates attended this meeting, including representatives from EMEA (CPMP members and EMEA staff) and, of course, a large number of industry representatives.

The first part of the session addressed the performance of the Centralised procedure and the results of a joint EFPIA/EMEA survey. Although the sample size was still small (20 finalised procedures were included), a high level of satisfaction was expressed by all respondents to the survey; Rapporteurs, Co-rapporteurs and EMEA project managers on one side and companies on the other.

The results presented were discussed during a panel discussion and a number of areas for improvement were identified. These included issues at the time of the oral explanations, the quality of the translations as well as the mechanism for their submission and assessment, clarification of questions from the CPMP, the avoidance of slippage and the time taken by companies to respond to these questions.

The CPMP Chairman referred to a general need for companies to be more focused during oral explanations and lack of professionalism in exceptional cases. From an operational perspective, companies expressed the wish for time-tables to be more strictly adhered to and greater privacy when preparing for oral explanations.

Companies were encouraged by EMEA/CPMP to avail themselves of pre-submission and scientific advice in order to prevent difficulties at a later stage.

However, the overall attitude was positive and all parties expressed their commitment to continue to work together towards better performance. EMEA and EFPIA have already organised a series of work-shops aiming to resolve many of these issues, the results of which will be made public. The questionnaire for the survey will be improved and used as a prospective tool involving all parties in order to continue to measure progress.

A discussion on the performance of the decision-making procedure from opinion to decision followed. It was clear that improvements in this part of the procedure were necessary, particularly with respect to control of linguistic issues and translation, management of the process within the EMEA and the practical difficulties presented by the formal Commission process. It was suggested that EMEA should be made responsible for the entire decision-making process in the case of

variations, possibly extending this to the entire decision-making process at the time of the review of the European authorisation system by Council and Parliament at the turn of the century.

The afternoon session addressed the performance of the Mutual Recognition Procedure (MRP). It was clear that the MRP had got off to a rather slower start than had been predicted, but that efforts were now being made to identify key concerns and to improve performance.

A presentation was made on the Eudratrack system which commenced operation on 15 October 1997. Industry and authorities expressed confidence that this new IT tracking system would improve communication both within the Mutual Recognition Procedure and externally and enable better management of the system.

The impact of the authorities' 'Best Practice Guide' of September 1996 had recently been evaluated by an EFPIA study of users of the MRP. Results of this survey were encouraging, pointing to an absence of arbitrations, improvements in timings for receipt of questions and overall consistency in national SmPCs. However, the absence of a true "Mutual Recognition Spirit" as evidenced by withdrawals and some national post-marketing commitments remains an issue of concern.

Experience on referrals for mutual recognition procedures presented by the EMEA reveals that despite the fact that, to date, there has been a relatively small number of arbitration cases, it has proved that the system facilitates the achievement of speedy consensus at CPMP level.

A 'Best Practice Guide' prepared by the industry was publicly launched at the meeting. Industry was also encouraged by the prospect of greater commitment by Heads of National Agencies which was expressed during the meeting and the recognition by them of the need to devote sufficient resources to ensure the success of the MRP.

The recent move to issue regular Press Releases by the MRFG, circulated together with the CPMP Press Release, was also welcomed by industry as a sign of a move towards better transparency and commitment to the procedure.

The Commission mentioned some of the elements which will be part of its forthcoming Communication: Clarification of Part A of the Annex to Reg. 2309/93; introduction of a biotechnological step into the manufacturing process of authorised products, interpretation of parts of the legislation affecting the MRP after 1/1/98. Both Member State representatives and industry participants expressed concern about the difficulties in planning in the absence of a clear view of what this interpretation would mean in practice.

In his closing remarks, EFPIA's director general referred to the twin pillars of the European system and the confidence he had that these would work together in harmony.