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

26 June 2001
CPMP/2020/01 corr

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
26 to 28 JUNE 2001 PLENARY MEETING

TECHNICAL REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 72th plenary meeting from 26 to 28 June 2001 in the new meeting room facilities.

Product related issues

Centralised procedures

Following an appeal procedure, the Committee adopted a positive opinion by majority vote for the medicinal product Foscan and recommended the granting of the marketing authorisation under exceptional circumstances. Foscan is indicated for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy. The applicant is Scotia Pharmaceuticals Limited and the active substance is temoporfin. For further details, please the see the Summary of Opinion which has been published on the EMEA Website: **http://www.emea.eu.int/pdfs/human/opinion/1739801en.pdf** .

The CPMP adopted two positive opinions by consensus on a "line extension" application (in accordance with Annex II of Commission Regulation (EC) No 542/95 as amended) related to one active substance (Part B).

An overview of centralised procedures since 1995 is given in **Annex 1**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the last CPMP plenary meeting in May 2001 is provided in **Annex 2**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Referral procedures

The CPMP adopted by consensus a positive opinion for a medicinal product which was referred to the EMEA for arbitration under Article 10 of Council Directive 75/319/EEC, as amended.

Scientific Advice procedures

The CPMP was informed of the outcome of the discussions of the Scientific Advice Review Group (SciARG) meeting, which was held on Monday 25 June 2001. Please also note the procedural announcement included in this report. For further details, please see **Annex 4**.

Other product related issues

As part of the Committee's ongoing scientific review of cardiovascular risks and third-generation oral contraceptives, the CPMP considered further information from marketing authorisation holders. The CPMP will continue its discussions at its next meeting on 24 to 26 July 2001.

Non-product related issues

A position statement from the EMEA/CPMP on the use of placebo in clinical trials with regard to the revised Declaration of Helsinki (EMEA/17424/01) is annexed to this report (see **Annex 6**).

CPMP Working Parties and Ad-Hoc Groups

The CPMP appointed Dr. Mike Morris as Vice Chairman of the Quality Working Party, Dr. Klaus Olejniczak as Vice Chairman of the Safety Working Party and Dr. Bertil Jonsson was appointed as Vice Chairman of the Efficacy Working Party.

The CPMP heard the report from the Ad Hoc Expert Group on post-marketing data requirements in pregnancy and adopted the Joint PhVWP/EWP Concept paper (CPMP/EWP/PhVWP/1417/01) on

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the development of a CPMP Note for guidance on the Use of medicinal products during pregnancy: Need for post-marketing data. An overview of guidance documents adopted during the meeting or released for consultation to Interested Parties is attached as **Annex 5**.

Organisational Matters

The fifth meeting of the CPMP Ad Hoc Group on Organisational Matters (ORGAM) was held on 25 June 2001 and the following topics were discussed:

- The accelerated review procedure: A revision of the current guidance document is expected to be finalised shortly.
- The streamlining of CPMP oral explanations: It was agreed that a guidance document for industry should be prepared including recommendations whereby companies will be requested to provide, 14 days in advance of the planned oral explanation, any "material" presentation including strategic statements, updated product information and where applicable, updated post-authorisation commitments proposals.
- Appeal procedures: It was re-emphasised that a new Rapporteur and Co-Rapporteur should be systematically appointed.
- Article 10 referral procedure: Proposals were presented to streamline the evaluation procedure with emphasis on minimising the duration of clock stops during such procedure.
- Article 11 referral procedure: Proposals on data requirements to be submitted when starting an Article 11 referral procedure were also discussed and an updated SOP document will be prepared.

PROCEDURAL ANNOUNCEMENT

The CPMP agreed to replace the August 2001 plenary meeting by written procedures to be established for certain ongoing applications.

Companies intending to submit Scientific Advice requests in August 2001 should notify the EMEA Secretariat by 18 July 2001. Confirmation of the start of the procedures will be stated in the July 2001 CPMP Technical Report.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 25 June 2001, which is attached as **Annex 7**. During his last presentation the current MRFG Chairperson, Thomas Salmonson, announced that the project for harmonisation of SPCs will continue, as agreed at the Heads of Agencies meeting on 12-13 June 2001.

The June 2001 MRFG meeting was the last meeting under the Swedish Presidency. Belgium will take over the Chairmanship as of July 2000.

Next meetings

The CPMP was informed of the following meetings/conferences:

- Joint meeting of GCP Inspectors, Clinical assessors and CPMP members to be held at the EMEA on 4 September 2001.
- Ad-Hoc Expert Group on terminology in Pharmacogenetics (PGxWG) to be held on 4 July 2001.

The 73rd plenary meeting of the CPMP will be held from 24 to 26 July 2001.

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This Technical Report and other documents are available on the Internet at the following address:
http://www.emea.eu.int

EMEA CENTRALISED PROCEDURES

	1995-2000			2001			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Scientific Advice	74	122	196	8	27*	35	231
Follow-up to scientific advice	15	11	26	3**	2	5	31

* Including one Protocol Assistance requests.
** Including one Protocol Assistance request.

	1995-2000			2001			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	97	182	279	17	15	32	311
Withdrawals	12	37	49	1	7	8	57
Positive CPMP opinions	64	112	176	9	7	16	192[1]
Negative CPMP opinions[2]	1	3	4	0	1	1	5[3]
Marketing authorisations granted by the Commission	56	95	151	9	20	29	180[4]

	1995-2000			2001			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	265	551	816	96	132	228	1044
Positive opinions, variations type II	159	224	383	50	84	134	517
Negative opinions, variations type II	0	2	2	0	1	1	3
Extensions (Annex II applications)	34	20	54	0	4	4	58

[1] 192 positive opinions corresponding to 150 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 180 Marketing Authorisations corresponding to 137 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE MAY 2001 PRESS RELEASE

Brand name	Nespo
INN	darbepoetin alfa
Marketing Authorisation Holder	Amgen Europe
ATC code	B03XA
Indication	Treatment of anaemia associated with chronic renal failure
CPMP Opinion date	01/03/2001
Date of Commission Decision	08/06/2001

Brand name	Aranesp
INN	darbepoetin alfa
Marketing Authorisation Holder	Amgen Europe
ATC code	B03XA
Indication	Treatment of anaemia associated with chronic renal failure
CPMP Opinion date	01/03/2001
Date of Commission Decision	08/06/2001

OUTCOME OF THE JUNE 2001 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type I Variation applications following Type II procedure	
Number of Opinions	**Outcome**
6	Positive by consensus

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
15 (SPC/PL update)	Positive by consensus
11 (Pharmaceutical Aspects)	Positive by consensus
1 (Extension of indications)	Positive by consensus

Opinion for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Norvir (ritonavir) Abbott Laboratories Ltd.	Positive by consensus	----

OUTCOME OF THE JUNE 2001 CPMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indication(s)	Topic				
		Type of Request		Pharma-ceutical	Pre-Clinical	Clinical
		New	Follow-up			
Chemical	Imaging of suspected acute deep venous thrombosis (DVT) in the lower extremities	**X**				**X**
Biological	Prevention or treatment of HIV-1 infection	**X**			**X**	
Chemical	Treatment of traumatic Brain injury	**X**				**X**
Chemical	Treatment of depression with psychotic features	**X**				**X**

In addition to the adoption of the above final Scientific Advice letters, the Committee accepted five new requests for Scientific Advice and one follow-up Scientific Advice.

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE JUNE 2001 CPMP MEETING

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/373/01 draft	Draft Concept paper on the development of a CPMP Note for guidance on Risk assessment of medicinal products on human reproductive and development toxicities	Adopted in June 2001

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/2284/99	Points to consider on Clinical investigation of medicinal products for the management of Crohn's disease	Adopted in June 2001

PHARMACOVIGILANCE WORKING PARTY

Reference number	Document	Status
CPMP/PhVWP/1618/01	European Concept paper on Compliance with pharmacovigilance regulatory obligations	Released for 3 months' consultation in June 2001
CPMP/EWP/PhVWP/11417/01	Joint PhVWP/EWP Concept paper on the Development of a CPMP Note for guidance on the Use of medicinal products during pregnancy: Need for post-marketing data	Adopted in June 2001

ICH

Reference number	Document	Status
CPMP/ICH/1840/01	ICH Topic M2: Electronic Common Technical Document (e-CTD) (CPMP/ICH/1840/01) – The step 2 eCTD for testing – specification document	Released for 3 months' consultation in June 2001

ANNEX 6 to CPMP June 2001
EMEA/17424/01
London, 28 June 2001

EMEA/CPMP POSITION STATEMENT ON THE USE OF PLACEBO IN CLINICAL TRIALS WITH REGARD TO THE REVISED DECLARATION OF HELSINKI

The scientific committee of the European Agency for the Evaluation of Medicinal Products, the Committee for Proprietary Medicinal Products (CPMP), is responsible for providing scientific opinions to the European Commission for the granting of Marketing Authorisations for medicinal products within the European Union (EU).

In the EU, the requirements and standards for clinical trials using medicinal products are set out in Regulations, Directives and Guidelines. According to Council Directive 65/65/EEC of 26 January 1965 as amended, marketing authorisations may be granted provided that quality, safety and efficacy of medicinal products have been satisfactorily demonstrated by the applicant. Granting marketing authorisations to new medicinal products when their benefit to risk balance is at least the same as that of established therapies, if any, is a basic public health principle. These criteria form the basis of the CPMP's scientific opinions. The legislation provides for flexibility in the type and design of trials required for the demonstration of efficacy and safety. Council Directive 75/318/EEC as amended, states that "*in general clinical trials shall be done as 'controlled clinical trials' and if possible, randomised; any other design shall be justified. The control treatment of the trials will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo"*.

Guidance on the design of trials in support of a marketing authorisation application is provided in the CPMP guidelines, either harmonised globally through the International Conference on Harmonization (ICH), or in the European Union (this is one task of the Efficacy Working Party of the CPMP). In this respect, guidance on the choice of control groups is provided by the ICH E10 guideline and the various guidelines developed for particular therapeutic classes.

Council Directive 75/318/EEC also specifies that "*all clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinski*".

A revised version of the Declaration of Helsinki was issued recently (October 2000) and it remains a vital expression of medical ethics whose aims deserve unanimous support. Section 29 in particular states[1] that "*The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not preclude the use of placebo, or no treatment in studies where no proven prophylactic, diagnostic or therapeutic method exists."* A strict interpretation of the Declaration appears to rule out clinical trials that use a placebo control arm whenever authorised therapeutic methods already exist, preferring active controls.

Although the efficacy of some new medicinal products can be satisfactorily demonstrated without the use of a placebo, for others the judicious use of placebo remains essential to demonstrate their value. Where medicinal products do exist for a given indication, active controlled trials are encouraged provided that a methodologically acceptable demonstration of efficacy and safety can be obtained. However, trials that seek to prove that a new agent and an active control have similar efficacy are inherently less reliable than trials that seek to prove the superiority of the new agent to a comparator, whether inactive or active. Increasing the size of trials does not alleviate this problem. In some areas of medicine this lack of reliability means that it is only possible to obtain convincing scientific evidence of the efficacy of a new medicinal product by means of superiority trials. The use of an active control in such an area of medicine would mean that a new product would always have to demonstrate an improvement in efficacy over a currently authorised treatment. This may be too restrictive as, for example, granting an authorisation to a new medicinal product with similar efficacy and improved safety, may also be in the best interest of patients.

[1] this was maintained with small modifications from the 1996 version

There are a number of conditions that govern and restrict the use of placebo in order to avoid un-ethical use. First and foremost, the period during which a placebo is administered must not entail any additional risk of irreversible harm to the patient. Also, the patient included in the trial, or his/her legal representative, must receive and understand appropriate information on the trial, and give informed written consent. The patient's right to withdraw at any time, but still receive conventional treatment must be respected. It is acknowledged that un-ethical abuses of placebo in trials of medicinal products may occur in any country, and this potential for abuse should be eliminated. Similar ethical standards should be applied in trials performed in the European Union as well as in foreign countries. These aspects fall within the responsibilities of Ethics Committees reviewing protocols of clinical trials; they are also emphasized in ICH E6 guideline on Good Clinical Practice and in the recent Council Directive 2001/20/EC on Good Clinical Practice[2].

Forbidding placebo-controlled trials in therapeutic areas where there are proven prophylactic, diagnostic or therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest as there is a need for both new products and alternatives to existing medicinal products. Reliable scientific evidence of efficacy and safety ensures that a reliable evaluation of the balance of benefits and risks for a particular medicinal product can be made, avoiding erroneous decisions of either withholding or mistakenly granting a marketing authorisation. Provided that the conditions that ensure the ethical nature of placebo-controlled trials are clearly understood and implemented, it is the position of the CPMP and the EMEA that continued availability of placebo-controlled trials is necessary to satisfy public health needs.

[2] In the 'Whereas' of the Directive: "*The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration"*. and in article 3, "*A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored."*

Report from the meeting held on 25 June 2001

General issues

Harmonisation of SPC's

The MRFG will continue the project for harmonisation of SPC's within the given framework as decided by the Heads of Agencies meeting on 12–13 June 2001(for more information, see Heads of Agencies Press Release).

Pack-sizes in the Mutual Recognition Procedure

Applicants are recommended to apply for all pack-sizes already within the initial marketing authorisation application. The MRFG would like to remind applicants that it is not acceptable to apply for an additional pack-size through a national procedure for a medicinal product authorised through Mutual Recognition Procedure. Moreover, all authorised pack-sizes should be mentioned in the SPC.

Point of time for applications for variations after granting a marketing authorisation for a medicinal product applied through a Mutual Recognition Procedure

In order to clarify what was published in the May 2001 MRFG Press Release, the MRFG confirmed that a variation application could not be submitted before day 120 if not all CMS's have granted the marketing authorisation, i.e. the applicant may apply for a variation after day 120 when adequate translated SPC, labelling and PIL reflecting the Day 90 MR agreement have been delivered to all CMS's.

MRFG Best Practice Guide for Handling of Renewals in the Mutual Recognition Procedure

The revision of the above mentioned document was adopted by the MRFG for publication on the Heads of Agencies Website.

Position Paper on Repeat Use of the Mutual Recognition Procedure

The revision of the above mentioned document was adopted by the MRFG for publication on the Heads of Agencies Website.

Change in the EU-Presidency

The June MRFG meeting was the last under the Swedish Presidency. Belgium will take over the Chairmanship as of July 2000. Ms Natacha Grenier will be the next chairperson. She should be contacted in future in case of questions regarding the MRP.

Meeting schedule

The next MRFG meeting will be held on 23 July 2001.

The MRFG agreed that there would be no MRFG meeting held in August 2001.

Mutual Recognition Monitoring

The MRFG noted that 42 new mutual recognition procedures were finalised during the month of May 2001, as well as 99 type I and 49 type II variations.

The status as of 31 May 2001 of procedures under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type I variations finalised	Procedures from Type I variations pending	Procedures from Type II variations finalised	Procedures from Type II variations pending	Arbitrations referred to CPMP
2001	131	130	530	93	185	202	--

45 new procedures (regarding 66 products) started in May 2001. The categories of these procedures are as follows:

6 new active substances (first authorisation in the European Community after RMS approval) including **2** multiple applications and **1** repeat use.

20 known active substances (already authorised in at least one member state), including **2** multiple applications and **2** repeat use.

14 abridged applications including **1** repeat use and **3** multiple applications.

5 line extension applications.

The new procedures started this month relate to 15 full dossiers, 15 generics, 4 fixed combination applications, 10 bibliographic application and 1 informed consent.

The procedures consisted of 43 chemical substances and 2 biological-blood product[1].

39 of these procedures were prescription-only medicinal products in the reference Member State and 6 were Non-prescription (including OTC) medicinal products[2] .

1. As considered by RMS.
2. In this category products are classified as prescription-only or Non-prescription (OTC) products when the RMS has approved them accordingly, although the legal status is not part of the Mutual Recognition Procedure.

Number of countries involved in the new applications procedures started in May 2001

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (2)	1
DE (2)	1
DE (2)	6
DE (3)	7
DE (1)	6
DE (1)	6
DE (1)	6
DE (1)	6
DE (1)	10
DE (1)	5
DE (1)	15
DE (1)	1
DK (3)	10
DK (1)	4
DK (1)	15
DK (1)	2
DK (1)	1
DK (1)	1
DK (4)	5
FR (1)	11
FR (1)	11
FR (8)	16
FR (1)	5

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
IR (1)	2
IR (1)	2
IR (1)	2
IR (1)	2
NL (2)	10
NL (2)	5
NL (3)	4
NL (1)	10
NL (1)	11
NL (1)	1
NL (1)	1
NO (4)	3
SE (2)	3
SE (1)	5
SE (1)	5
SE (1)	16
UK (1)	15
UK (1)	10
UK (1)	5
UK (1)	6
UK (1)	15
UK (1)	15

All documents mentioned in this press release can be found at the MRFG website at the European Medicines Authorities Windows under the heading SOP.

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

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*Alternatively, you could visit the **MRFG web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*

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