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

21 December 1998
CPMP/2866/1998

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 44th plenary meeting from 15 December to 17 December.

The CPMP welcomed Dr Patrick Waller from United Kingdom as a new member, replacing Dr Susan Wood (†), and elected him chairman of the Pharmacovigilance Working Party.

Centralised Procedures

The Committee adopted the following opinions[1]:

- Three positive opinions on centralised applications:

  - One positive opinion was adopted by consensus relating to one medicinal product containing a new active substance (Part B), a luteinising hormone releasing hormone (LHRH) antagonist indicated for the prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

  - One positive opinion was adopted by consensus relating to one medicinal product (Part A), a blood coagulating factor indicated for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A (congenital factor VIII deficiency or classic haemophilia).

  - One positive opinion was adopted by majority vote relating to one medicinal product containing a new active substance (Part A), indicated to promote the healing of diabetic ulcers.

- Two positive opinions on applications (line extensions) in accordance with Annex II of the Commission Regulation (EC) No 542/95:

  - One positive opinion was adopted by consensus relating to one application for an additional strength concerning an already centrally authorised medicinal product (Part B), an antiviral indicated for the treatment of HIV infected patients.

  - One positive opinion was adopted by majority vote relating to one application for an additional strength concerning an already centrally authorised medicinal product, (Part A), an immuno-modulating agent indicated for condyloma acuminatum and multiple sclerosis.

- Ten positive opinions by consensus for centralised type II variations.

[1] Note for Editors:
Applicants may appeal any CPMP opinion, provided they notify the EMEA in writing of their intention to appeal within 15 days of receipt of the opinion. In line with the decision of the Management Board at its 30 September meeting, further information on opinions adopted by the CPMP will be made available 60 days after adoption of the final opinion.

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- Two positive opinions by consensus following the annual re-assessment for two products (Part B) indicated for the treatment of HIV infected patients and nephropathic cystinosis respectively.

Since the CPMP meeting in November 1998, the Committee noted the withdrawal of four applications for three active substances (one Part A and two Part B).

The CPMP adopted three lists of questions (one Part A and two Part B). Two of the medicinal products were considered to be approvable and one non-approvable based on the information available.

The Committee heard six oral presentations/clarifications from applicants concerning ongoing centralised procedures.

Rapporteurs and Co-Rapporteurs were appointed for four applications forthcoming in the centralised procedure within the next four months (Part A). Rapporteurs were also confirmed for two Annex II applications expected to be submitted under the centralised procedure within the next four months (one Part A/one Part B).

The Committee adopted a response to the International Society of Drug Bulletins (ISDB) comments concerning quality and content of EPARs, to be made public (EMEA/42941/98).

An overview of centralised applications is given in Annex I.

Since the CPMP meeting in November 1998, the European Commission has granted a marketing authorisation for:

- Prometax (rivastigmine), a parasympathomimetic indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia
- Pritor (telmisartan), an angiotensin II antagonist indicated for the treatment of essential hypertension
- Micardis (telmisartan), an angiotensin II antagonist indicated for the treatment of essential hypertension
- Telmisartan Boehringer Ingelheim (telmisartan), an angiotensin II antagonist indicated for the treatment of essential hypertension

See Annexes II & III for details.

Scientific Advice

The Committee:

- Accepted four new requests for scientific advice as justified. Co-ordinators were appointed.

- Adopted three scientific advice letters by consensus on manufacturing, preclinical and/or clinical issues, biotechnology and development plans concerning three new medicinal products (Part A) intended for:
  - Replacement therapy in patients with diagnosed human growth hormone (hGh) deficiency
  - treatment of acromegaly
  - treatment on insulin dependent diabetes

- Adopted two follow-up scientific advice by consensus on manufacturing concerning two new medicinal products (Part B) intended for the treatment of respiratory infections, and treatment of cytomegalovirus (CMV)-retinitis in patients with AIDS, respectively.

Referrals

Referral under Article 7(5) of Commission Regulation (EC) No 541/95
A positive opinion for a variation type II referred to the EMEA under the mutual recognition procedure was adopted by majority vote and will be forwarded to the Commission.

Working Parties, Ad Hoc Expert Groups and Organisational Matters

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

QUALITY WORKING PARTY

A Concept Paper addressing the revision of the Note for Guidance on radiopharmaceuticals (CPMP/QWP/2809/98) was adopted.

SAFETY WORKING PARTY

The SWP workplan for 1999 (CPMP/SWP/2623/98) was adopted.

EFFICACY WORKING PARTY

The following documents were adopted for coming into operation in June 1999:

- Points to Consider on clinical investigation of slow-acting anti-rheumatic medicinal products in rheumatoid arthritis (CPMP/EWP/556/95)
- Note for Guidance on clinical investigation of medicinal products in the treatment of Parkinson's disease (CPMP/EWP/563/95)

The EWP Workplan for 1999 (CPMP/EWP/2963/98) was also adopted.

The following document was released for 6 months' consultation:

- Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). The CPMP noted the recent judgement of the European Court of Justice in an Article 177 Reference in Case C-368/96: The Queen and The Licensing Authority ex parte: Generics (UK) Limited, which includes a new definition of "essential similarity", which will have implications for the wording and interpretation of this Note for Guidance. This judgement has not been taken into account in the current draft so far.

PHARMACOVIGILANCE WORKING PARTY

The PhVWP workplan for 1999 (CPMP/PhVWP/2607/98) was adopted.

Mutual Recognition

The CPMP noted the report from the mutual recognition facilitation group (MRFG) 14 December 1998, which is circulated together with this Press Release (Annex IV).

Prof. R. Bass
Head of Human Medicines Evaluation Unit

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

CENTRALISED APPLICATIONS TO THE EMEA

	Part A	Part B	Total
Scientific advice	33	45	78
Follow-up to scientific advice	9	4	13

	Part A	Part B	Total[1]
Applications submitted since 1 January 1995	62	115	177
Withdrawals	11	19	30
Positive CPMP opinions	35	65	100[2]
Negative CPMP opinions	1	2	3[3]
Marketing authorisations granted by the Commission	28	60	88[4]

	Part A	Part B	Total
Variations type I	99	168	267
Positive opinions, variations type II	41	77	118
Negative opinions, variations type II	0	2	2
Extensions	25	6	31

1 These figures include the 18 former concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996
2 100 positive opinions corresponding to 76 substances
3 3 negative opinions corresponding to 2 substances
4 88 marketing authorisations corresponding to 67 substances

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure since the November 1998 Press Release

PRODUCT	**Brandname**	**PROMETAX**
	INN	rivastigmine
	Part A/B	B
COMPANY ORIGIN	**Country**	Switzerland
MARKETING AUTHORISATION HOLDER	**Name**	Novartis
THERAPEUTIC AREA	**ATC Code**	N07 AA
	Indication	symptomatic treatment of mild to moderately severe Alzheimer's dementia
PRESENTATION	**Pharmaceutical form**	hard capsules
	Strength	1 mg, 1.5 mg, 3 mg, 4.5 mg, 6 mg
	Number of presentations	20
EMEA/CPMP	**Validation**	24/07/98
	Date of opinion	17/09/98
	Active time	53 days
	Clock stop	0 days
COMMISSION DECISION	**Opinion receipt date**	01/10/98
	Date of Commission decision	04/12/98

PRODUCT	**Brandname**	**PRITOR**
	INN	telmisartan
	Part A/B	B
COMPANY ORIGIN	**Country**	UK
MARKETING AUTHORISATION HOLDER	**Name**	Glaxo Group Ltd
THERAPEUTIC AREA	**ATC Code**	C09CA0
	Indication	treatment of essential hypertension
PRESENTATION	**Pharmaceutical form**	Tablets
	Strength	40 mg, 80 mg
	Number of presentations	10
EMEA/CPMP	**Validation**	24/10/97
	Date of opinion	23/07/98
	Active time	188 days
	Clock stop	84 days
COMMISSION DECISION	**Opinion receipt date**	20/09/98
	Date of Commission decision	11/12/98

PRODUCT	**Brandname**	**MICARDIS**
	INN	telmisartan
	Part A/B	B
COMPANY ORIGIN	**Country**	Germany
MARKETING AUTHORISATION HOLDER	**Name**	Boehringer Ingelheim International GmbH
THERAPEUTIC AREA	**ATC Code**	C09CA0
	Indication	treatment of essential hypertension
PRESENTATION	**Pharmaceutical form**	Tablets
	Strength	40 mg, 80 mg
	Number of presentations	10
EMEA/CPMP	**Validation**	24/10/97
	Date of opinion	23/07/98
	Active time	188 days
	Clock stop	84 days
COMMISSION DECISION	**Opinion receipt date**	05/10/98
	Date of Commission decision	16/12/98

PRODUCT	**Brandname**	**TELMISARTAN BOEHRINGER INGELHEIM**
	INN	telmisartan
	Part A/B	B
COMPANY ORIGIN	**Country**	Germany
MARKETING AUTHORISATION HOLDER	**Name**	Boehringer Ingelheim International GmbH
THERAPEUTIC AREA	**ATC Code**	C09CA0
	Indication	treatment of essential hypertension
PRESENTATION	**Pharmaceutical form**	Tablets
	Strength	40 mg, 80 mg
	Number of presentations	10
EMEA/CPMP	**Validation**	24/10/97
	Date of opinion	23/07/98
	Active time	188 days
	Clock stop	84 days
COMMISSION DECISION	**Opinion receipt date**	05/10/98
	Date of Commission decision	16/12/98

PROMETAX*

International Nonproprietary Name (INN): **Rivastigmine**

On 4 December 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Prometax, which contains rivastigmine. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 16 September 1998. The Marketing Authorisation Holder responsible for this medicinal product is Novartis Europharm Limited, United Kingdom.

The approved indication is the symptomatic treatment of mild to moderately severe Alzheimer's dementia. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in the EPAR and is available in all European Union official languages.

The active substance of Prometax, rivastigmine, is a non-competitive acetylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic mediated cognitive deficits associated with Alzheimer's disease.

In clinical trials Prometax demonstrated statistical efficacy, in patients with mild to moderately severe dementia of the Alzheimer's type, when compared to placebo in the three domains, cognition, global assessment of improvement and activities of daily living. These studies showed that Prometax provided clinically relevant improvement in approximately 2 to 12% of responders, depending on the various definitions.

The most frequent adverse events observed during treatment were asthenia, anorexia, dizziness, nausea, somnolence and vomiting. Female patients were found to be more susceptible to nausea, vomiting, loss of appetite and weight loss. Other common adverse effects include abdominal pain, accidental trauma, agitation, confusion, depression, diarrhoea, dyspepsia, headache, insomnia, upper respiratory tract infection and urinary tract infection.

The CPMP, on the basis of efficacy and safety data submitted, considered that there was a favourable benefit to risk balance for Prometax and recommended that the Marketing Authorisation should be granted.

PRITOR*

International Nonproprietary Name (INN): **Telmisartan**

On 11 December 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Pritor, which contains telmisartan. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 23 July 1998. The Marketing Authorisation Holder responsible for this medicinal product is Glaxo Group Ltd, United Kingdom.

Pritor tablets are used for the treatment of high blood pressure. This is also known as essential hypertension. High blood pressure, if not treated, can damage blood vessels in several organs such as the heart, the kidneys, the brain and the eyes. In some instances this may lead to heart attacks, heart or kidney failure, strokes or blindness. There are usually no symptoms of high blood pressure before damage occurs.

Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in the EPAR, and is available in all European Union official languages.

Pritor belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a substance occurring in the body, which tightens your blood vessels making it harder for the blood to

* This text is the Abstract of the complete EPAR

pass through them and causing your blood pressure to increase. Pritor blocks this effect of angiotensin II, causing the blood vessels to relax, and so lowers your blood pressure.

Efficacy and safety of Pritor were assessed in 14 clinical trials in about 3000 patients with high blood pressure. Telmisartan lowered blood pressure to the same extent as all the other drugs, such as atenolol, lisinopril, enalapril .

Side-effects with Pritor were usually brief and mild in nature. In some patients, the following side-effects were reported: headache, cold or flu-like symptoms, dizziness, leg cramps, back pain, joint pain, tiredness, sinusitis, diarrhoea, stomach ache, muscle pain, cough, chest pain, urinary tract infection, feeling sick, sore throat. Gastro-intestinal bleeding was also reported but occurred mainly in patients who had gastric or duodenal ulcers or some other gastric problem.

The CPMP, on the basis of the efficacy and safety data submitted, concluded that there was a favourable benefit/risk ratio of Pritor and recommended that the Marketing Authorisation should be granted.

MICARDIS*

International Nonproprietary Name (INN): **Telmisartan**

On 16 December 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Pritor, which contains telmisartan. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 23 July 1998. The Marketing Authorisation Holder responsible for this medicinal product is Boehringer Ingelheim International GmbH, Germany.

Pritor tablets are used for the treatment of high blood pressure. This is also known as essential hypertension. High blood pressure, if not treated, can damage blood vessels in several organs such as the heart, the kidneys, the brain and the eyes. In some instances this may lead to heart attacks, heart or kidney failure, strokes or blindness. There are usually no symptoms of high blood pressure before damage occurs.

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The CPMP, on the basis of the efficacy and safety data submitted, concluded that there was a favourable benefit/risk ratio of Pritor and recommended that the Marketing Authorisation should be granted.

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TELMISARTAN BOEHRINGER INGELHEIM*

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On 16 December 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Pritor, which contains telmisartan. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 23 July 1998. The Marketing Authorisation Holder responsible for this medicinal product is Boehringer Ingelheim International GmbH, Germany.

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The CPMP, on the basis of the efficacy and safety data submitted, concluded that there was a favourable benefit/risk ratio of Pritor and recommended that the Marketing Authorisation should be granted.

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MRFG
Mutual Recognition Facilitation Group

Report from the meeting held on 14 December 1998

The MRFG noted that 21 new mutual recognition procedures have been finalised during the month of November 1998 as well as 32 type I and 17 type II variations.
The status as of 30 November 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
1998	169	30	298	78	198	147	1N.A. 4 var.

9 new procedures (regarding 23 products) have been started in November 1998. 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	1	0	0	0	0	4

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 new applications procedures in November 1998

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	1
DE (2)	3
DE (1)	4
FR (5)	5
NL (4)	1
NL (1)	13
SE (1)	4
UK (1)	3
UK (4)	14

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
UK (4)	14

General issues

- The Group adopted the *Member States' Standard Operating Procedure on simultaneous applications* (*Article 7 paragraph 2 of Directive 65/65/EEC)* (MS SOP Art. 7). It will be put on the MRFG Website for information.

- As anticipated in the November MRFG press release, Companies should contact the RMS in advance of the submission of a variation dossier in order to receive the MRP variation number. This number should be put in all application forms so that the variation is clearly identified among the Member States. For this purpose, the *Procedure for validation of Mutual Recognition Procedures for variations* has been revised in accordance with this new requirement and it will be published on the MRFG Website.

- It has been clarified by the Commission that in cases where an application is withdrawn in a CMS before the end of a MRP, it is possible for that CMS to trigger Art. 11 or 12 referrals in order to obtain a scientific answer to serious public health concerns. It is not possible nevertheless to trigger Art. 10 referral in such a case.

- As already stated in the *Break-out session protocol*, the latest time for the organisation of a break-out session should be the Wednesday before the plenary MRFG meeting.

- The December meeting was the last under the Austrian Presidency. Germany will take over the Chairmanship from the 1st January 1999 and Dr. Birka Lehmann will become the next chairperson. She should be contacted in future for details of the MRFG procedure and for information about press releases.

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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*Or you could visit the **MRFG web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*
http://heads.medagencies.org/