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

29 May 1998
CPMP/975/98

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 38th plenary meeting on 26-27 May 1998.

Centralised Procedures

The Committee adopted the following Opinions:

- Seven positive Opinions on Centralised Applications

  - Two positive Opinions were adopted by consensus relating to two Medicinal Products containing the same new active substance (Part B), an immunomodulating agent, indicated for the topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients.

  - Two positive Opinions were adopted by a majority of votes relating to two Medicinal Products containing the same new active substance (Part B), as an adjunct to standard preparation of levodopa/benserazide or levodopa/carbidopa, for use in patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

  - One positive Opinion was adopted by consensus relating to a Medicinal Product containing a new active substance (Part A), a diagnostic radiopharmaceutical agent for tumour detection indicated in patients with histologically proven carcinoma of the colon or rectum for imaging of recurrence and/or metastases.

  - Two positive Opinions were adopted by consensus relating to two Medicinal Products containing the same new active substance (Part B), an urological agent indicated for the treatment of erectile dysfunction.

- One positive Opinion was adopted by consensus relating to an extension for an already centrally authorised Medicinal Product containing an active substance (Part B), a selective immunosuppressive agent indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants.

- Five positive Opinions were adopted for Centralised type I Variations following the Type II procedure.

- Five positive Opinions were adopted for Centralised type II Variations.

Since the CPMP Meeting in April 1998, the Committee noted the withdrawal of three applications for Part B.

Five Centralised Procedures have been started after validation (two for part A and three for part B).

The Committee heard two Oral Presentations / Clarifications from Applicants.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 1
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

Rapporteurs and Co-rapporteurs were assigned for ten applications forthcoming in the Centralised Procedure within the next four months, four for Part A and six for Part B, including one double application for the same active substance.

An overview of Centralised Applications is given in Annex I.

Since the CPMP meeting in April 1998, the European Commission has granted a Marketing Authorisation for:

- Pylobactell (^{13}C-urea), indicated for the *in vivo* diagnosis of gastroduodenal Helicobacter pylori infection.
- Rebif (interferon beta-1a), for the treatment of multiple sclerosis.
- Exelon (rivastigmine), for the symptomatic treatment of mild to moderately severe Alzheimer's dementia (Annexes II & III).

Scientific Advice

The Committee :

- Accepted four new requests for Scientific Advice as justified. Co-ordinators were appointed.
- Adopted five Scientific Advice by consensus on preclinical and clinical issues as well as development plans concerning six new medicinal products (Part B) intended for the treatment of:
  - CMV retinitis in AIDS patients
  - Allergic rhinitis and chronic idiopathic urticaria
  - Hepatitis B and Herpes Simplex
  - Functional improvement in patients with severe dementia
  - Parkinson's disease

Working parties, Ad Hoc Expert Groups.

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

Recommendation on the use of reassortant RESVIR-13 for influenza vaccines
The CPMP considered and adopted the recommendations of the BWP on the use of the reassortant RESVIR-13 for influenza vaccines. (Annex IV).

Mutual Recognition

The CPMP noted the report from the Mutual Recognition Facilitation Group from the meeting held on 26 May 1998 which is circulated together with this press release (Annex V).

Meeting with Interested Parties
The regular meeting with Interested Parties was held in the afternoon of 27 May 1998.

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	26	33	59

	Centralised Applications		Total*
	Part A	Part B	
Applications submitted since 1 January 1995	54	99	153
Withdrawn	4	13	17
Opinions given by the CPMP	27	54	81**
Marketing Authorisations granted by the Commission	25	34	59***

	Part A	Part B	Total
Variations type I	83	115	198
Variations type II	24	47	71
Extensions	10	3	13

* These figures include the 18 ex-concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996

** 81 Opinions corresponding to 63 substances

*** 59 Marketing Authorisations corresponding to 50 substances

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

PRODUCT	**Brandname:**	**PYLOBACTELL**	**REBIF**	**EXELON**
	INN:	^{13}C-urea	Interferon beta-la	Rivastigmine
	Part A/B:	Part B	Part A	Part B
COMPANY ORIGIN	**Country:**	UK	CH	CH
MARKETING AUTHORI-SATION HOLDER	**Name:**	B.S.I.A. Ltd (UK)	Ares Serono (Europe) Ltd (UK)	Novartis Europharm Ltd (UK)
THERAPEUTIC AREA	**ATC Number.:**	V04CX	L03AA11	NO7 AA
	Indication:	*In vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection	Treatment of relapsing / remitting multiple sclerosis.	Symptomatic treatment of mild to moderately severe Alzheimer's dementia.
PRESENTATION	**Form:**	Soluble tablet	Solution for injection	Capsule, hard
	Dosage:	100 mg	6 MIU	1.5mg, 3mg, 4.5mg, 6mg
	Number of presentations:	1 Presentations	3 Presentations	12 Presentations
EMEA/CPMP	**Validation:**	18.12.96	22.07.96	18.04.97
	Date of Opinion:	19.11.97	17.12.97	28.01.98
	Active time:	163 Days	181 Days	186 Days
	Clock stop:	158 days	285 days	97 days
COMMISSION DECISION	**Opinion receipt date:**	13.02.98	13.02.98	04.03.98
	Date of Commission Decision:	07.05.98	04.05.98	12.05.98

EXELON

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

Abstract*

On 12 May 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Exelon, 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 28 January 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 Exelon, 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 Exelon 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 Exelon 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 Exelon and recommended that the Marketing Authorisation should be granted.

* This text is the Abstract of the complete EPAR

PYLOBACTELL

International Non-Proprietary Name (INN): **^{13}C-urea**

Abstract[*]

On 7 May 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Pylobactell, which contains ^{13}C-urea. This decision was based on the assessment report on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 19 November 1997. The Marketing Authorisation Holder responsible for this medicinal product is B.S.I.A. Ltd., United Kingdom.

The approved indication is for the *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection. 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 in this product is ^{13}C-urea, i.e. urea labelled with the non-radioactive stable isotope ^{13}C. It is presented in the form of a soluble tablet to be dissolved in water prior to oral administration. The diagnostic principle is based upon the urease activity of *Helicobacter pylori*. In the case of gastroduodenal *Helicobacter pylori* infection, the ^{13}C-urea is metabolised by urease and $^{13}CO_2$ is liberated in the exhaled air. Breath samples are collected and the $^{13}CO_2$ / $^{12}CO_2$ ratio is determined ; it is this ratio that provides a quantitative indicator of *Helicobacter pylori* infection. Since other urease-producing bacteria are seldom found in the gastric flora, the detection of $^{13}CO_2$ in the breath above a certain limit is indicative of the presence of duodenal *Helicobacter pylori* infection.

Two clinical trials in a total of 366 patients have supported the request for a Marketing Authorisation. In these trials a high diagnostic efficiency of the breath test following ingestion of ^{13}C-urea was shown, independent of use after or before *Helicobacter pylori* eradication therapy, and with due regard to the specified parameters of test meal, dosage and cut-off point of the assay. The clinical studies reported in the dossier used isotope ratio mass spectrometry (IRMS) to analyse breath samples, although any other objectively qualified method may be applied, provided it is suitably validated for use with this product by a competent laboratory. None of the clinical studies performed with the product reported side effects due to ^{13}C-urea. In view of the fact that urea is intrinsically present in the body and only a small additional amount is to be administered in the form of this product, it is considered to be safe. Although Pylobactell is a diagnostic test to detect *Helicobacter pylori* infection with a high specificity and sensitivity, differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies. It should also be kept in mind that the performance of the test will be affected by treatments which may interfere with *Helicobacter pylori* status or urease activity, e.g. antibiotics or proton pump inhibitors, and these restrictions are set out in the SPC.

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

.

[*] This text is the Abstract of the complete EPAR

REBIF

International Non-proprietary Name (INN): **Interferon beta-1a**

Abstract*

On 4 May 1998, the European Commission issued a marketing authorisation valid for the entire European Union for the medicinal product REBIF, which contains a human interferon beta-1a produced by DNA recombinant technology. This decision was based on the assessment report on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 28 January 1998. The pharmaceutical company responsible for the medicinal product REBIF is Ares-Serono (Europe) Ltd.

The approved indication is for “the treatment of ambulatory patients with relapsing-remitting multiple sclerosis (MS) characterised by at least 2 recurrent attacks of neurological dysfunction (relapses) over the preceding 2-year period. REBIF decreases the frequency and severity of relapses over 2 years". 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 REBIF is recombinant human interferon beta-1a. Interferons are substances naturally present in the human body and are involved in the regulation of immune system functions. The administration of REBIF provides an additional amount of interferon beta, which has proven useful in the treatment of a neurological disease termed "multiple sclerosis", for which there is no specific treatment available so far. In this disease the immune system does not function normally and there is chronic inflammation and abnormal functioning of the nerves of the central nervous system. A particular clinical form of this disease termed "relapsing-remitting multiple sclerosis" presents recurrent attacks of neurological dysfunction (relapses) followed by partial or complete recovery (remissions). Clinical studies have shown that the administration of REBIF to patients affected by this form of multiple sclerosis reduces the frequency (approximately 30% over 2 years) and severity of clinical relapses.

Common undesirable adverse effects were local inflammation at the injection site, usually mild and reversible, flu-like syndrome. The most commonly reported symptoms of the flu syndrome are muscle ache, fever, arthralgia, chills, asthenia, headache, and nausea. These symptoms decrease in frequency with continued treatment. Other less common adverse events reported in association with interferon beta include diarrhoea, anorexia, vomiting, insomnia, dizziness, anxiety, rash, injection site necrosis, vasodilatation and palpitation. Serious hypersensitivity reactions may occur.

The overall adverse effects profile was considered acceptable.

In assessing the benefit/risk balance, the CPMP judged from the scientific information available that there is adequate evidence for the efficacy and clinical safety of REBIF in the approved indication.

The CPMP recommended that the Marketing Authorisation should be granted under "exceptional circumstances" because of the current lack of information on a) the precise mechanism of action, not yet known, by which interferon beta-1a influences the relapses, b) conclusive data on the long term effects of REBIF on the progression of the disease and on disability pattern, which is not yet available. The Marketing Authorisation Holder will submit additional information on the clinical experience with this medicinal product on an ongoing basis. All new studies to be carried out will be carefully monitored and the results will be reviewed annually by the CPMP.

* This text is the Abstract of the complete EPAR

Influenza Vaccines

Having considered the outcome of the May CPMP Biotechnology Working Party's (BWP) the CPMP decided to follow the advice of the BWP on :

- Recommendation on the use of reassortant RESVIR-13.

  Recently the centre for Biologics Evaluation and Research Department (USA), prepared a new reassortant from the A/Sydney/5/97 virus; RESVIR-13.

  On the basis of cross-reactivity tests the BWP agreed that RESVIR-13 isantigenically similar to A/Sydney/5/97. Preliminary studies suggest that it would give significantly higher virus yields in eggs. RESVIR-13 would thus be suitable as an additional A/Sydney/5/97 (H3N2) like strain for vaccine production.

- The WHO recommendations already adopted by the CPMP on influenza virus strains acceptable for the purpose of vaccine production for the 1998 – 1999 season, have been transmitted to the concerned producing companies.

  Influenza A (H3N2) - A/Sydney/5/97 - : IVR-108 reassortant

  Influenza A (H1N1) - A/Beijing/262/95 - : X-127 reassortant

  Influenza B - B/Beijing/184/93 - : B/Harbin/7/94

MRFG
Mutual Recognition Facilitation Group

Report from the meeting held on 26 th May 1998

The MRFG noted that 15 new mutual recognition procedures have been finalised during the month of April 1998 as well as 24 type I and 19 type II variations.
The status as of 30th April 1998 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	54	52	78	47	61	109	--

21 new procedures (regarding 39 products) have been started in April 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]
6	4	6	3	0	1	1

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 April 1998:

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (5)	8
DK (1)	14
DK (1)	6
FI (1)	7
FR (2)	13
FR (2)	11
FR (1)	1
FR (2)	11
IT (1)	11
NL (2)	2
NL (1)	13
NL (4)	4
SE (1)	14

SE (1)	12
SE (1)	12
UK (1)	14
UK (1)	7
UK (2)	1
UK (4)	1
UK (4)	10
UK (1)	12

General issues

The Press Release of the informal MRFG meeting held in London on 8-9 May 1998 is attached (Annex I) to this document.

- The MRFG noted that 21 new procedures (regarding 39 products) had been started in April, 6 procedures were for new active substances.

- The group adopted a new procedure for the automatic validation of variations which will be introduced from the 1st of June. The protocol for this new procedure is attached to the Press Release and will also be available on the MRFG web site (http://heads.medagencies.org/). This new procedure complements the automatic validation procedure for new applications which was successfully introduced on the 1st of May 1998 (both the documents are attached as Annex II)

- The group discussed the development of an index of products which have used the MR procedure and how this could be included in the MRFG web site. It also discussed how SPCs might be made available through the Head of Agencies' Web site.

- The group was pleased to see that the number of withdrawals since January 1998 had fallen by around 50%. Discussions were held on how to reduce the number of withdrawals further. Consideration was also given to revising the protocol document for breakout meetings, which should additionally help to reduce the number of withdrawals.

- Discussions were held to prepare for the liaison meeting with the Trade Associations, which will be held in June.

- The first Break-out Session using video-conference facilities took place.

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

Dr David Jefferys
Medicines Control Agency
Market Towers
1 Nine Elms Lane
UK - London SW8 5NQ
Phone: +44.171.273.0454 or
+44.171.273.0451

*or you could visit the **MRFG Web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*

http://heads.medagencies.org/

Annex 1

PRESS RELEASE

INFORMAL MRFG MEETING HELD ON 7th & 8th MAY IN LONDON

The Mutual Recognition Facilitation Group (MRFG) held a two-day meeting on 7th and 8th May. This meeting was hosted by the Medicines Control Agency of the United Kingdom as part of the UK Presidency of the European Union. The meeting was held in the MCA's new conference facility.

The group considered a series of strategic and operational issues. These included the transparency and visibility of the Mutual Recognition procedure. The group had an in-depth discussion on the withdrawal of applications from individual Member States in the Mutual Recognition. A number of recommendations were agreed and these will be discussed with the *Heads of Agencies* group and are likely to result in modifications to the breakout protocol document and to the *Best Practice Guide.*

The meeting also considered the development of a Website and how this can be integrated into the forthcoming proposal from the Heads of Agencies group. Detailed discussions were also held on the subject of delays in licence issuance. Here a set of proposals were elaborated and these will be discussed further with the Trade Associations at a meeting which has already been arranged for June.

Annex 2
FINAL

PROCEDURE FOR AUTOMATIC VALIDATION OF MR PROCEDURES FOR NEW APPLICATIONS

This procedure has been agreed by the MRF Group for a trial period of 6 months to ensure that validation times are within those agreed in the Best Practice Guide. Completion of Eudratrack records by all involved is essential for the operation of this procedure.

The RMS should update the Eudratrack record with the date the AR was sent.

The APPLICANT should fax the date of dispatch and the address to which the dossier was sent to RMS and CMS. This should be done from the single central contact address NOT from individual local affiliates using a single fax document showing all the dispatch dates when dispatch is complete.

On receipt of each of the above, the CMS will update the Eudratrack record.

If, after 5 working days of notification of BOTH AR and dossier dispatch the Eudratrack record is not complete with respect of AR and dossier received date for each CMS, the RMS will notify (initially by fax) the CMS who have not completed the Eudratrack record that the clock will start at the end of the next 5 working day period unless notification of an invalid application is received.

The RMS will start the procedure 5 working days after this notification unless informed by a CMS that the application is not valid.

If a CMS has previously informed the RMS that the application is not valid, the clock will be started when that CMS informs the RMS when the application is valid.

The CMS must inform the RMS that the application has become valid within 5 working days of the missing information being supplied.

With the agreement of the applicant, the clock may be started at a later date in order to coincide with an MRF group at an appropriate point in the procedure.

FINAL

PROCEDURE FOR VALIDATION OF MUTUAL RECOGNITION PROCEDURES FOR VARIATIONS

An automatic validation procedure for new applications was agreed at MRFG with effect from 1 May 1998, for a 6 month trial period. Whilst experience is gained from this procedure, the following arrangements apply for variations.

Completion of Eudratrack records by all member states is essential for the operation of the procedure (see Behaviour Code for RMS and CMS).

- **Type I Variations**
  Existing arrangements for validation apply. See Notice to Applicants.

  CMS should notify receipt of a valid/invalid application within 10 working days. Complete Eudratrack record.

  Note: The new Variation Regulation amendments will not require confirmation of receipt of a valid application by CMS. RMS will notify the start of procedure. Automatic validation will therefore take effect from the date of implementation of the new legislation.

- **Type II Variations - Majority of applications where change request is initiated by the applicant**
  Existing arrangements for validation apply. See Notice to Applicants.

  CMS should notify receipt of a valid/invalid application within 10 working days. Complete Eudratrack record.

  Note: Experience from the automatic new application procedure will be gained before implementing for Type II variations.

- **Type II Variations - Where RMS identifies a safety need (including safety changes at the initiation of the applicant)**
  Note: Examples of such Type II safety variations are

  - Type II variations submitted following the introduction of an Urgent Safety Restriction.

  - Changes to the SPC involving safety information eg contraindications, warnings, undesirable effects.

Procedure to follow:

Submission of Variation application simultaneously to RMS and CMS by **applicant**.

The **applicant** should fax in a single document to the RMS and CMS all the despatch dates of the variation application when despatch is complete.

RMS completes Eudratrack record.

CMS to confirm receipt by updating the Eudratrack record.

If after 5 working days of notification of application despatch, some or all confirmations of receipt are still lacking, the **RMS** will notify (initially by fax) the CMS who have not sent their confirmation of receipt (completed the Eudratrack record) that the clock will start at the end of the next 5 working day period unless notification of an invalid application is received.

RMS notifies applicant and CMS of procedure start date. This is Day 0.

If a CMS has previously informed the RMS that the application is not valid, the clock will be started when that **CMS** informs the RMS when the application is valid.

The **CMS** must inform the RMS that the application has become valid within 5 working days of the missing information being supplied.

May 1998