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

26 April, 1999
CPMP/1150/99 corr

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 48th plenary meeting from 20 April to 22 April, 1999.

Centralised Procedures[1]

The Committee adopted:

- Two positive opinions on initial centralised applications:
  - One positive opinion was adopted by consensus under exceptional circumstances relating to a medicinal product containing a new active substance (Part B), an antiviral agent indicated for the local treatment of cytomegalovirus retinitis in patients with AIDS.
  - One positive opinion was adopted by consensus under exceptional circumstances relating to a medicinal product containing a known active substance for a new indication (Part B), an antiviral agent indicated for the treatment of chronic hepatitis B.
- Five positive opinions by consensus for centralised type II variations.
- Two positive opinions by consensus following the annual re-assessment for two antiviral agents (Part B).

The CPMP adopted seven lists of questions (one Part A/six Part B) (concerning five active substances) of which five (one Part A, four Part B) products were considered to be approvable and two (Part B) non-approvable based on the information available to the CPMP at this time.

The Committee heard three oral presentations/clarifications from applicants concerning initial centralised applications and one oral presentation/clarification regarding a type II variation application.

A public statement concerning Viagra and Patrex (sildenafil) on potential interaction with ritonavir is published on the Internet (CPMP/1148/99).

An overview of centralised applications is given in Annex I.

Since the CPMP meeting in March 1999, the European Commission has granted marketing authorisations for:

- Beromun (Tasonermin) indicated as an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP).

[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.

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- Cetrotide (Cetrorelix) indicated for prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

- Refacto (Moroctocog alfa) 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).

- Regranex (Becaplermin) indicated, in association with other good wound care measures, to promote granulation and thereby the healing of full-thickness, neuropathic, chronic, diabetic ulcers less than or equal to 5 cm^2.

See Annexes II and III for details.

Scientific Advice

The Committee:

- Accepted six new requests from companies for scientific advice. Co-ordinators were appointed.

- Adopted five scientific advice letters on preclinical and clinical issues, concerning five new medicinal products, two Part A/three Part B, intended for:

  - treatment of acute schizophrenia
  - treatment of congestive heart failure
  - relief of symptoms in patients with chronic obstructive pulmonary disease
  - treatment of glioblastoma multiforme
  - treatment of osteoporosis in postmenopausal women.

Working Parties, Ad Hoc Expert Groups and Organisational Matters

The CPMP heard reports from its Quality, Biotechnology, Safety, Efficacy and Pharmacovigilance Working Parties, as well as from the Ad Hoc Expert Group on Update on Guidance of SPCs and the Ad Hoc Working Group on Blood Products.

BIOTECHNOLOGY WORKING PARTY

One document was adopted:

- Final EU recommendations for the influenza vaccine composition for the season 1999/2000 (CPMP/BWP/1021/99).

The following document was adopted for coming into operation in April 1999:

- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (CPMP/BWP/1230/98).

EFFICACY WORKING PARTY

One document was adopted*:*

- Concept paper on the development of a Committee for Proprietary Medicinal Products (CPMP) Points to consider on biostatistical/methodological issues arising from recent CPMP discussions on licensing applications: adjustment for multiplicity and related topics (CPMP/EWP/908/99).

The following document was released for 6 months' consultation:

- Note for guidance on clinical investigation of steroid contraceptives in women (CPMP/EWP/519/98 draft).

ORGANISATIONAL MATTERS

The following standard operating procedure was adopted and will be made available on the Internet:

- EMEA SOP on legal status for supply to the patient of centrally approved medicinal products (EMEA/SOP/003/95 rev.1)

The CPMP finalised the revision of Chapter IV of the Notice to Applicants for transmission to the European Commission.

ICH

The following document was released for 3 months' consultation:

- Recommendations on electronic transmission of individual case safety reports message specification (CPMP/ICH/285/95 draft) – ICH topic M2.

Consultation with Interested Parties

Continuing the cycle of meetings with interested parties, the CPMP and the EMEA Secretariat held discussions with European representatives from the consumers, health professionals and trade associations from the pharmaceutical industry on 21 April 1999.

Mutual Recognition

The CPMP noted the report from the mutual recognition facilitation group (MRFG) of 19 April 1999, which is circulated together with this Press Release (Annex IV).

Prof. Rolf 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

EMEA CENTRALISED PROCEDURES

	1995-1998			1999			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	**Overall Total**
Scientific Advice	33	45	78	8	12	20	98
Follow-up to scientific advice	9	4	13	1	1	2	15

	1995-1998			1999			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	62	115	177	7	9	16	193
Withdrawals	11	19	30	0	3	3	33
Positive CPMP opinions	35	65	100[2]	2	10	12	112
Negative CPMP opinions[3]	1	2	3[4]	0	0	0	3
Marketing authorisations granted by the Commission	28	60	88[5]	6	5	11	99

	1995-1998			1999			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	99	168	267	8	60	68	335
Positive opinions, variations type II	41	77	118	9	14	23	141
Negative opinions, variations type II	0	2	2	0	0	0	2
Extensions	25	6	31	1	2	3	34

[2] 100 positive opinions corresponding to 76 substances
[3] In case of appeal the opinion will not be counted again
[4] 3 negative opinions corresponding to 2 substances
[5] 88 marketing authorisations corresponding to 67 substances

Medicinal products granted a Community Marketing Authorisation under the Centralised Procedure since the March 1999 Press Release

PRODUCT	**Brand name**	**Beromun**
	INN	Tasonermin
	Part A/B	Part A
COMPANY ORIGIN	**Country**	DE
MARKETING AUTHORISATION HOLDER	**Name**	Boehringer Ingelheim International GmbH
THERAPEUTIC AREA	**ATC code**	L03AA
	Indication	As an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP).
PRESENTATION	**Pharmaceutical form**	Powder and solvent for solution for injection
	Strength	1 mg
	Number of presentations	1 presentation
EMEA/CPMP	**Validation**	24.10.97
	Date of opinion	19.11.98
	Active time	188 days
	Clock stop	201 days
COMMISSION DECISION	**Opinion receipt date**	15.1.99
	Date of Commission decision	13.4.99

PRODUCT	**Brand name**	**Cetrotide**
	INN	Cetrorelix
	Part A/B	Part B
COMPANY ORIGIN	**Country**	DE
MARKETING AUTHORISATION HOLDER	**Name**	Asta Medica
THERAPEUTIC AREA	**ATC code**	G03X
	Indication	Prevention of premature ovulation in patients undergoing fertilisation treatment
PRESENTATION	**Pharmaceutical form**	Powder and solvent for solution for injection
	Strength	0.25 mg, 3 mg
	Number of presentations	4 presentations
EMEA/CPMP	**Validation**	27.2.98
	Date of opinion	17.12.98
	Active time	173 days
	Clock stop	121 days

COMMISSION DECISION	**Opinion receipt date**	19.1.99
	Date of Commission decision	13.4.99

PRODUCT	**Brand name**	**Refacto**
	INN	Moroctocog alfa
	Part A/B	Part A
COMPANY ORIGIN	**Country**	USA
MARKETING AUTHORISATION HOLDER	**Name**	Genetics Institute of Europe B.V.
THERAPEUTIC AREA	**ATC code**	B02BD02
	Indication	Indicated for the control and prevention of haemorrhagic episodes
PRESENTATION	**Pharmaceutical form**	Powder and solvent for solution for injection
	Strength	250 IU, 500 IU, 1000 IU
	Number of presentations	3 presentations
EMEA/CPMP	**Validation**	27.2.98
	Date of opinion	17.12.98
	Active time	146 days
	Clock stop	148 days
COMMISSION DECISION	**Opinion receipt date**	3.2.99
	Date of Commission decision	13.4.99

PRODUCT	**Brand name**	**Regranex**
	INN	Becaplermin
	Part A/B	Part A
COMPANY ORIGIN	**Country**	BE
MARKETING AUTHORISATION HOLDER	**Name**	Janssen-Cilag International B.V.
THERAPEUTIC AREA	**ATC code**	D 03
	Indication	Indicated to promote healing of full thickness diabetic ulcers
PRESENTATION	**Pharmaceutical form**	Gel
	Strength	100µg/g
	Number of presentations	1 presentation
EMEA/CPMP	**Validation**	21.11.97
	Date of opinion	17.12.98
	Active time	188 days
	Clock stop	203 days
COMMISSION DECISION	**Opinion receipt date**	28.1.99
	Date of Commission decision	29.3.99

Abstracts for Products granted a Community Marketing Authorisation under the centralised procedure since the March 1999 Press Release

BEROMUN

International Non-proprietary Name (INN): Tasonermin

Abstract

On 13 April 1999, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Beromun, which contains tasonermin. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 19 November 1998. The Marketing Authorisation Holder responsible for this medicinal product is Boehringer-Ingelheim International GmbH, Germany.

The approved indication is as an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP). 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 Beromun, tasonermin is a non-glycosylated protein and is a cytokine belonging to the tumour necrosis alfa (TNF∝) family. It has immunomodulatory properties, and has cytotoxic antitumour effects.

Clinical trials were designed to investigate the safety and efficacy of Beromun an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP). During treatment the majority of patients experienced fever, usually of a mild to moderate degree. Other commonly (greater than 10 %) encountered systemic undesirable effects are nausea and /or vomiting, cardiac arrhythmias, fatigue, chills, liver toxicity, and infections. Commonly encountered (greater than 10%) regional (in the treated limb) undesirable effects include cutaneous reactions, oedema, pain in the perfused limb, nerve injury, and wound infection.

The CPMP, on the basis of safety, quality and efficacy data submitted, considered that Beromun showed a favourable benefit risk ratio for the approved indications, and therefore recommended that the Marketing Authorisation should be granted.

CETROTIDE

International Nonproprietary Name (INN): Cetrorelix (as acetate)

Abstract

On 13 April 1999, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Cetrotide, which contains cetrorelix (as acetate). This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 17 December 1998. The Marketing Authorisation Holder responsible for this medicinal product is ASTA Medica Aktiengesellschaft, Germany.

The approved indication is for prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques. 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 Cetrotide, cetrorelix (as acetate), is a LHRH (Luteinising hormone releasing hormone)-antagonist. It binds competitively to pituitary LHRH-receptors and effectively inhibits the release of LH from the pituitary gland; sex hormone levels are suppressed to castration levels in men.

In clinical studies, the efficacy of cetrorelix is comparable with published literature for LHRH-analogues in terms of achieved pregnancies. In a direct comparison of cetrorelix versus buserelin and versus triptorelin depot, its efficacy was very similar regarding prevention of LH surges, however, it was inferior in terms of pregnancy and delivery rates.

The main adverse events reported were injection site reactions and ovarian hyperstimulation. Systemic adverse events were rare, e.g. nausea, pruritus and headache. The administration of cetrorelix outside controlled ovarian stimulation (COS), i.e. in healthy women, results in symptoms of estrogen deficiency, withdrawal bleeding and hot flushes, whereas these symptoms are not expected in COS patients. Laboratory parameters did not change in a relevant manner. There were no serious safety concerns with regards to liver function tests, although a clear trend for a late increase in liver enzymes and alkaline phosphatase was noted. The SPC includes appropriate contraindications regarding moderate to severe renal and hepatic impairments.

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

REFACTO

International Nonproprietary Name (INN): Moroctocog alfa

Abstract

On 19 April 1999, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product ReFacto, which contains moroctocog alfa, recombinant coagulation Factor VIII. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 17 December 1998. The Marketing Authorisation Holder responsible for this medicinal product is Genetics Institute of Europe B.V., Germany.

The approved indications are 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). 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 ReFacto, moroctocog alfa, is a glycoprotein consisting of 1438 amino acids. produced by recombinant DNA technology. It has an amino acid sequence that is comparable to the 90 + 80 kDa form of factor VIII (i.e. B-domain deleted), and post-translational modifications that are similar to those of the plasma-derived molecule. This substance has functional characteristics comparable to those of endogenous factor VIII. ReFacto works by replacing factor VIII in haemophilia A patients to enable their blood to clot.

Clinical trials investigated use in previously treated patients (PTP) as well as previously untreated patients (PUP). The efficacy during surgical procedures was also evaluated. These studies showed that ReFacto was satisfactory in terms of efficacy and safety and effective haemostasis was achieved and maintained in the treated population.

Adverse events observed during treatment occurring in 72 cases during 32013 infusions (0.2%), which were probably or possibly related to therapy were: nausea, shortness of breath, venous access catheter complications, headache, numbness, increased liver enzymes, altered taste, fever, dizziness, chills, injection site reaction, sleepiness, tiredness, sweating, pain, severe allergic reaction, acne, itching, rash, blurred vision, loss of appetite, stomach pain, gastroenteritis, rapid heart beat, coughing, trauma, yeast infection, slight increase in heart enzymes, increased bilirubin, and muscle weakness.

The CPMP, on the basis of efficacy and safety data submitted, considered that ReFacto showed adequate evidence of efficacy for the approved indications, as well as a satisfactory benefit/risk profile and therefore recommended that the Marketing Authorisation should be granted.

REGRANEX

International Nonproprietary Name (INN): Becaplermin

Abstract

On 29 March 1999 the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Regranex, which contains Becaplermin. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 17 December 1998. The Marketing Authorisation Holder responsible for this medicinal product is Janssen-Cilag International N.V. Belgium.

The approved indication is for Regranex. 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 Regranex, Becaplermin, is a recombinant human platelet derived growth factor, produced by the yeast *Saccharomyces cerevisiae*. Becaplermin helps the growth of normal tissues in order to heal diabetic ulcers.

Clinical trials investigated the safety and efficacy of REGRANEX in diabetic adults aged 19 years or over who were suffering from at least one stage III or IV diabetic ulcers of at least 8 weeks duration. These studies showed that These studies demonstrated the efficacy and safety of REGRANEX in the treatment of patients having full-thickness, chronic, diabetic ulcers with a baseline surface area less than or equal to 5 cm^2, for a period not exceeding 20 weeks in total in any individual patient.

The following undesirable effects, which are not clearly related to the REGRANEX therapy, were observed during treatment : infection, skin ulceration and skin disorders (including redness and pain). Blisters and swelling were reported rarely.
The CPMP, on the basis of efficacy and safety data submitted, considered Regranex showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

Report from the meeting held on 19 April 1999

The MRFG noted that 10 new mutual recognition procedures were finalised during the month of March 1999, as well as 83 type I and 21 type II variations.

The status as of 31 March 1999 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
1999	26	32	181	67	72	127	--

15 new procedures (regarding 34 products) started in March 1999. The categories of these procedures are as follows:

New active substance[1]	Line extensions[2]	Fixed comb.	Generics	Herbal products[3]	OTC[4]	Blood products	Immuno-logicals	Others[5]
3	2	0	5	0	0	0	0	5

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 other eight categories.

Each application can be classified in only one category.

Number of countries involved in the new applications procedures started in March 1999:

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	5
DE (1)	5
DE (3)	12
DE (2)	2
DK (5)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
IR (1)	8
NL (2)	11
NL (2)	8
SE (6)	1
SE (1)	11
SE (1)	2
SE (1)	14
UK (2)	14
UK (3)	5
UK (3)	2

General issues

- The number of applications for new procedures within the MR procedure in 1999 is increasing (January: 5, February: 14 and March: 15)
- The MRP index will be launched on 20 April 1999 and can be accessed via the MRFG website at the European National Medicines Authority Window as detailed below
- Position papers on line extensions, informed consent applications and repeat use ("second wave") will be amended for finalisation in May
- The list of contact points has been updated and is available on the MRFG website.

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/**