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

26 October 1998
CPMP/2244/1998

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 42nd plenary meeting from 20 October to 22 October 1998.

The CPMP noted with great sadness the death on 30 September 1998 of Dr. Susan Wood, one of the UK CPMP members and Chairperson of the CPMP Pharmacovigilance Working Party. Dr. Jefferys, UK CPMP member paid tribute to her achievements and outstanding contribution to public health internationally and the CPMP observed a minute's silence in her memory.

The CPMP welcomed Dr. Gro Ramsten Wesenberg from Norway who attended the meeting as an observer.

Centralised Procedures

The Committee adopted the following Opinions[1]:

- Positive Opinions on Centralised Applications:
  - One positive Opinion was adopted by consensus relating to a Medicinal Product containing a new active substance (Part B), an anti-allergic, indicated for the symptomatic treatment of seasonal allergic conjunctivitis.
  - One positive Opinion was adopted by consensus relating to a Medicinal Product containing a new active substance (Part B), an antineoplastic agent, indicated for the treatment of patients with recurrent glioblastoma multiforme.
- Negative Opinions on Centralised Applications:
  - Two negative Opinions were adopted by majority of votes relating to two Medicinal Products containing the same new active substance (Part B), a nervous system drug.
  - One negative Opinion was adopted by majority of votes relating to a Medicinal Product containing a new active substance (Part A), an antithrombotic agent.
- One Positive Opinion by consensus for a Centralised Type I Variation following the Type II procedure.
- Five positive Opinions by consensus for Centralised Type II Variations.
  - One of the Variations is a follow-up to two urgent safety restrictions concerning serious cases of abnormal hepatic function including fulminant hepatitis observed in patients treated with Tasmar (Tolcapone). Details of the amendments introduced were described in the EMEA Press Release dated 15 October 1998 (EMEA/36027/98).

    Following assessment of the cases of hepatic reactions, the Committee concluded that the benefit / risk evaluation of Tasmar currently remains positive. The Committee confirmed the need for intense monitoring of the situation to ensure prompt action if necessary. The Marketing Authorisation Holder, Roche Registration Ltd. will report all hepatobiliary adverse reactions on an expedited basis, regardless of severity. In addition, the quality of reporting will be improved and relevant information will be submitted as soon as it becomes available.

[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 1998 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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Roche will communicate amended information to EU health professionals without delay in all EU languages and will submit as of November monthly reports to the EMEA/CPMP.

- One positive Opinion by consensus following the annual re-assessment for a Medicinal Product (Part A), an immunostimulating agent, authorised in 1997 under exceptional circumstances for the treatment of ambulatory relapsing multiple sclerosis. The positive benefit/risk evaluation was reconfirmed.

Since the CPMP meeting in September 1998, the Committee noted the withdrawal of three applications (one Part A and two Part B), due to a lack of efficacy and/or safety data.

One Centralised Procedure has commenced.

The Committee heard five Oral Presentations/Clarifications from Applicants.

An overview of Centralised Applications is given in Annex I.

Since the CPMP meeting in September 1998, the European Commission has granted Marketing Authorisations for:

- Aldara and Zartra (Imiquimod), indicated for topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients
- Humaspect (Votumumab), indicated as a radiopharmaceutical agent for tumour detection indicated in patients with histologically proven carcinoma of the colon or rectum for imaging of recurrence and/or metastases
- Simulect (Basiliximab), indicated for the prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation concomitantly with cyclosporin and corticosteroids
- Comtan (Entacapone), indicated for use as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa in patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.
- Karvezide and Co-Aprovel (Irbesartan / Hydrochlorothiazide), indicated for the treatment of essential hypertension.

See Annexes II & III for details.

Scientific Advice

The Committee:

- Accepted three new requests for Scientific Advice as justified. Co-ordinators were appointed.
- Adopted ten Scientific Advice by consensus on manufacturing, preclinical and/or clinical issues, biotechnology and development plans concerning ten new products, one for Part A, nine for Part B intended for:
  - the treatment of Fabry's and Gaucher's diseases
  - the treatment of glaucoma
  - the treatment of acromegaly
  - the prophylaxis of acute rejection in patients receiving allogeneic kidney, lung, heart and liver transplants and the treatment and/or prevention of chronic rejection in lung, heart and kidney transplantation
  - the rapid control of agitation and disturbed behaviours in patients with schizophrenia
  - the treatment of mild to moderate and severe asthma
  - the prevention of coronary restenosis and reduction of the frequency of cardiovascular deaths, myocardial infarctions and repeated revascularisation in patients who have undergone PTCR with or without stenting
  - the treatment as an adjunctive therapy to aspirin and heparin / prevention of thrombosis-induced ischaemic coronary events in patients with acute coronary syndromes
  - the treatment of respiratory infections
  - the treatment of schizophrenia.

Referrals

Referral under Article 12 of Council Directive 75/319/ EEC, as amended
A procedure relating to Medicinal Products containing Vigabatrin has been initiated by Finland. A Rapporteur and a Co-Rapporteur were appointed.

On 22 September 1998 the European Commission adopted Decisions for Medicinal Products containing terfenadine, which were addressed to the Member States concerned for compliance within 30 days. These Decisions endorse the following CPMP Opinions further to the Referral by France to the CPMP in February 1997:

- The Marketing Authorisations for all terfenadine 120 mg tablet and all terfenadine-pseudoephedrine tablet formulations should be withdrawn.
- The Marketing Authorisations for all Terfenadine 30 mg tablet, 60 mg tablet and 6 mg/ml oral suspension formulations should be varied and the Summary of Product Characteristics amended.

Copies of the final Opinions are available on the EMEA Website.

Working Parties, Ad Hoc Expert Groups and Organisational Matters

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

QUALITY WORKING PARTY

The Committee agreed to the Quality Working Party's proposal to apply the Note for Guidance on residual solvents (CPMP/ICH/283/95) to existing marketed Medicinal Products with a two-year's transition period until July 2000.

BIOTECHNOLOGY WORKING PARTY

The following document was adopted:

- Position Statement on Polysorbate 80 (CPMP/BWP/1952/98)

The following document was released for 3 months' consultation:

- Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via Medicinal Products (CPMP/BWP/1230/98, rev. October 1998)

EFFICACY WORKING PARTY

The following document was released for 3 months' consultation:

- Points to Consider on the Clinical Investigation of Medicinal Products in the Treatment of Patients with Chronic Obstructive Pulmonary Disease (CPMP/EWP/562/98, draft 3)

AD HOC EXPERT GROUP MEETING ON UPDATE OF GUIDANCE ON SPCS

The document "Consolidated Proposal for the Wording of the SPC" was adopted and will be forwarded to the European Commission.

ORGANISATIONAL MATTERS

The Committee adopted:

- Standard Operating Procedure on the Release of Assessment Reports to Applicants / Marketing Authorisation Holders (EMEA/SOP/H/001/98)
- Dates for the CPMP meetings in 2000:

18-20 January	30 May - 1 June	19-21 September
15-17 February	27-29 June	17-19 October
14-16 March	25-27 July	14-16 November
25-27 April	22-24 August	12-14 December

The Working Group on Quality Review of Documents, composed of representatives of the national competent authorities in the Member States, the European Commission, the Luxembourg Translation Centre and the EMEA adopted at their 16-17 July 1998 meeting the template for the Medicinal Product literature (Summary of Product Characteristics, Labelling and Package Leaflet). This literature is attached to the Scientific Opinions of the CPMP.
The template is in line with the Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use adopted by the Pharmaceutical Committee at their 23-24 September 1998 meeting. It is now available in all EU official languages, together with reference documents and shortcuts to relevant legislation, on the EMEA website. Applicants are advised to use these templates for the submission of all new draft product literature.

Mutual Recognition

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) which met on the 19 October 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	29	44	73
Follow-up to Scientific Advice	9	2	11

	Part A	**Part B**	**Total***
Applications submitted since 1 January 1995	61	108	169
Withdrawn	7	15	22
Positive CPMP Opinions	31	62	**93
Negative CPMP Opinions	1	2	***3
Marketing Authorisations granted by the Commission	28	56	****84

	Part A	**Part B**	**Total**
Variations type I	95	141	236
Variations type II	40	60	100
Extensions	23	4	27

* These figures include the 18 ex-concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996
** 93 positive Opinions corresponding to 70 substances
*** 3 negative Opinions corresponding to 2 substances
**** 84 Marketing Authorisations corresponding to 65 substances

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

PRODUCT	**Brandname**	**ALDARA**
	INN	Imiquimod
	Part A/B	B
COMPANY ORIGIN	**Country**	France
MARKETING AUTHORISATION HOLDER	**Name**	Laboratoires 3M Santé
THERAPEUTIC AREA	**ATC Code**	L03 AX
	Indication	Topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients
PRESENTATION	**Pharmaceutical form**	cream
	Strength	12.5 mg
	Number of presentations	1
EMEA/CPMP	**Validation**	20/06/97
	Date of Opinion	27/05/98
	Active time	209 days
	Clock stop	132 days
COMMISSION DECISION	**Opinion receipt date**	30/06/98
	Date of Commission Decision	18/09/98

PRODUCT	**Brandname**	**ZARTRA**
	INN	Imiquimod
	Part A/B	B
COMPANY ORIGIN	**Country**	France
MARKETING AUTHORISATION HOLDER	**Name**	Laboratoires 3M Santé
THERAPEUTIC AREA	**ATC Code**	L03 AX
	Indication	Topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients
PRESENTATION	**Pharmaceutical form**	cream
	Strength	12.5 mg
	Number of presentations	1
EMEA/CPMP	**Validation**	20/06/97
	Date of Opinion	27/05/98
	Active time	209 days
	Clock stop	132 days
COMMISSION DECISION	**Opinion receipt date**	30/06/98
	Date of Commission Decision	18/09/98

PRODUCT	**Brandname**	**HUMASPECT**
	INN	Votumumab
	Part A/B	A
COMPANY ORIGIN	**Country**	The Netherlands
MARKETING AUTHORISATION HOLDER	**Name**	Organon Teknika
THERAPEUTIC AREA	**ATC Code**	V09IA01
	Indication	Radiopharmaceutical agent for tumour detection indicated in patients with histologically proven carcinoma of the colon or rectum for imaging of recurrence and/or mestases.
PRESENTATION	**Pharmaceutical form**	Solution for injection
	Strength	12 mg
	Number of presentations	1
EMEA/CPMP	**Validation**	22/11/96
	Date of Opinion	27/05/98
	Active time	145 days
	Clock stop	407 days
COMMISSION DECISION	**Opinion receipt date**	10/07/98
	Date of Commission Decision	25/09/98

PRODUCT	**Brandname**	**SIMULECT**
	INN	Basiliximab
	Part A/B	A
COMPANY ORIGIN	**Country**	UK
MARKETING AUTHORISATION HOLDER	**Name**	Novartis Europharm Ltd
THERAPEUTIC AREA	**ATC Code**	L04A A02
	Indication	Prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation concomitantly with cyclosporin and corticosteroids
PRESENTATION	**Pharmaceutical form**	powder and solvent
	Strength	20 mg
	Number of presentations	1
EMEA/CPMP	**Validation**	24/10/97
	Date of Opinion	25/06/98
	Active time	188 days
	Clock stop	28 days
COMMISSION DECISION	**Opinion receipt date**	03/08/98
	Date of Commission Decision	9/10/98

PRODUCT	**Brandname**	**COMTAN**
	INN	Entacapone
	Part A/B	B
COMPANY ORIGIN	**Country**	Finland
MARKETING AUTHORISATION HOLDER	**Name**	Orion
THERAPEUTIC AREA	**ATC Code**	N04B X02
	Indication	Parkinson's disease and end-of-dose motor fluctuations
PRESENTATION	**Pharmaceutical form**	Film coated tablets
	Strength	200 mg
	Number of presentations	4
EMEA/CPMP	**Validation**	18/04/97
	Date of Opinion	27/05/98
	Active time	214 days
	Clock stop	188 days
COMMISSION DECISION	**Opinion receipt date**	03/07/98
	Date of Commission Decision	22/09/98

PRODUCT	**Brandname**	**KARVEZIDE**
	INN	Irbesartan / hyrdrochlorothiazide
	Part A/B	B
COMPANY ORIGIN	**Country**	France
MARKETING AUTHORISATION HOLDER	**Name**	Sanofi Pharma Bristol-Myers Squibb SNC
THERAPEUTIC AREA	**ATC Code**	C09DA
	Indication	treatment of essential hypertension.
PRESENTATION	**Pharmaceutical form**	Tablet
	Strength	150/12.5 mg, 300/12.5 mg
	Number of presentations	6
EMEA/CPMP	**Validation**	19/12/97
	Date of Opinion	23/07/98
	Active time	153 days
	Clock stop	63 days
COMMISSION DECISION	**Opinion receipt date**	21/08/98
	Date of Commission Decision	17/10/98

PRODUCT	**Brandname**	**COAPROVEL**
	INN	Irbesartan / hyrdrochlorothiazide
	Part A/B	B
COMPANY ORIGIN	**Country**	France
MARKETING AUTHORISATION HOLDER	**Name**	Sanofi Pharma Bristol-Myers Squibb SNC
THERAPEUTIC AREA	**ATC Code**	C09DA
	Indication	Treatment of essential hypertension.
PRESENTATION	**Pharmaceutical form**	Tablet
	Strength	150/12.5 mg, 300/12.5 mg
	Number of presentations	6
EMEA/CPMP	**Validation**	19/12/97
	Date of Opinion	23/07/98
	Active time	153 days
	Clock stop	63 days
COMMISSION DECISION	**Opinion receipt date**	21/08/98
	Date of Commission Decision	15/10/98

ALDARA*

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

On 18 September 1998**,** the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Aldara, which contains imiquimod. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 27 May 1998. The Marketing Authorisation Holder responsible for this medicinal product is Laboratoires 3M Santé, France.

The approved indication is the topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients. 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 Aldara, imiquimod, is an immune response modifier. In animal models imiquimod is effective against viral infections and acts as an antitumor agent principally by induction of alpha interferon and other cytokines. It appears that while imiquimod does not have a direct anti-viral activity it stimulates body responses which help fight the viral infection.

In clinical trials Aldara 5% cream given three times weekly for 8 hours a day was superior to both vehicle and 1% imiquimod cream both in terms of total and partial clearance of anogenital warts. The duration of application is limited to 16 weeks. There were no efficacy or safety data to assess the value of repeat applications of imiquimod in recurrent anogenital warts.

The most frequent adverse drug reactions observed during treatment were application site reactions at the wart treatment site, such as itching, burning and pain. Some systemic adverse reactions, including headache, flu-like symptoms, and myalgia were also reported.

In uncircumcised male patients with warts under the foreskin, the safety data although limited show that there is a likelihood of local skin reactions, including stricture of the foreskin requiring circumcision. Aldara is therefore not recommended for the treatment of uncircumcised male patients with warts under the foreskin unless the benefit is felt to outweigh the risk.

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

ZARTRA*

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

On 18 September 1998**,** the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Zartra, which contains imiquimod. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 27 May 1998. The Marketing Authorisation Holder responsible for this medicinal product is Laboratoires 3M Santé, France.

The approved indication is the topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients. 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 Zartra, imiquimod, is an immune response modifier. In animal models imiquimod is effective against viral infections and acts as an antitumor agent principally by induction of alpha interferon and other cytokines. It appears that while imiquimod does not have a direct anti-viral activity it stimulates body responses which help fight the viral infection.

In clinical trials Zartra 5% cream given three times weekly for 8 hours a day was superior to both vehicle and 1% imiquimod cream both in terms of total and partial clearance of anogenital warts. The

* This text is the Abstract of the complete EPAR

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In uncircumcised male patients with warts under the foreskin, the safety data although limited show that there is a likelihood of local skin reactions, including stricture of the foreskin requiring circumcision. Zartra is therefore not recommended for the treatment of uncircumcised male patients with warts under the foreskin unless the benefit is felt to outweigh the risk.

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

HUMASPECT*

International Non-proprietary Name (INN): Votumumab

On 25 September 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product HumaSPECT, which contains votumumab. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 27 May 1998. The Marketing Authorisation Holder responsible for this medicinal product is Organon Teknika BV, The Netherlands.

The approved indication is for the imaging of recurrence and/or metastase in patients with histologically proven carcinoma of the colon or rectum as an adjunct to standard non-invasive imaging techniques, such as ultrasonography or CT scan. 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 HumaSPECT, votumumab, is a human monoclonal antibody directed against cytokeratin tumour associated antigens found in human large bowel adenocarcinoma and is presented as a radiopharmaceutical imaging agent..

Clinical trials were designed to investigate the imaging activity of HumaSPECT in patients with a prior histological diagnosis of colonic cancer in whom recurrence or metastasis was strongly suspected. Analysis was made for standard diagnostic parameters, i.e. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. Special attention was paid to the parameters resectable, non-resectable and no evidence of disease. These studies showed that HumaSPECT had a good accuracy and sensitivity and meets efficacy and safety standards in the treatment of patients having histologically proven carcinoma of the colon or rectum.

The most common adverse reaction observed during treatment was fever. Other mild or moderate adverse events considered related to HumaSPECT were: increase in blood pressure, hypotension, abnormal liver function tests, bradycardia, nausea, vomiting, injection site reaction, hyperbilirubinaemia.

The CPMP, on the basis of the overall benefit/risk ratio considered that HumaSPECT showed a satisfactory safety profile and adequate evidence of efficacy and therefore recommended that the Marketing Authorisation should be granted.

SIMULECT*

International Non-proprietary Name (INN): Basiliximab

On 9 October 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Simulect, which contains basiliximab. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 24 June 1998. The Marketing Authorisation Holder responsible for this medicinal product is Novartis Europharm Ltd, UK.

* This text is the Abstract of the complete EPAR

The approved indication is for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation. 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 Simulect, basiliximab, is a monoclonal chimeric mouse-human antibody directed against the a-chain of the interleukin-2 receptor and inhibits the immunocompetent cells which are involved in the acute rejection of the transplant.

Clinical trials were designed to investigate the efficacy of Simulect in prophylaxis of organ rejection in *de novo* renal transplantation. These studies showed that Simulect, used concomitantly with ciclosporin for microemulsion and corticosteroids, significantly reduces the incidence of acute rejection episodes both within 6 and 12 months after transplantation. There was no significant difference between Simulect and placebo treated patients in graft survival after 6 and 12 months.

Simulect does not show any additional adverse event to those which organ transplantation patients experience as a consequence of their underlying disease and the concurrent administration of immunosuppressants and other medications. The most commonly reported events in both Simulect and placebo treatment groups were constipation, urinary tract infection, pain, nausea, peripheral oedema, hypertension, anaemia, headache, and hyperkalaemia.

The CPMP, on the basis of the overall benefit/risk ratio considered that Simulect showed a satisfactory safety profile and adequate evidence of efficacy in reducing the rate of acute rejection and therefore recommended that the Marketing Authorisation should be granted.

COMTAN*

International Non-proprietary Name (INN): Entacapone

On 22 September 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Comtan, which contains entacapone. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 27 May 1998. The Marketing Authorisation Holder responsible for this medicinal product is Novartis Europharm Limited.

The approved indication is for the use as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa in patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations. 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 Comtan, entacapone, is an orally active, nitrocathecol derivative with a selective and reversible inhibitory effect on the enzyme catechol-O-methyl transferase (COMT), which enhances brain levels of L-dopa when co-administered with L-dopa and a peripheral decarboxylase inhibitor (benserazide or carbidopa).

The most prominent undesirable effects caused by entacapone are abdominal pain and diarrhoea. In the majority of the cases these undesirable effects were graded mild or moderate. As expected, the frequency of dopaminergic undesirable effects is increased by entacapone.

The CPMP, on the basis of the efficacy and safety data submitted, considered that entacapone displayed a positive benefit/risk ratio in patients with Parkinson's disease and end-of-dose motor fluctuations and therefore recommended that a Marketing Authorisation should be granted.

KARVEZIDE*

International Non-proprietary Name (INN): Irbesartan / Hydrochlorothiazide

On 17 October 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Karvezide which contains irbesartan and hydrochlorothiazide. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 July 1998. The

* This text is the Abstract of the complete EPAR

Marketing Authorisation Holder responsible for this medicinal product is Bristol-Myers Squibb Pharma EEIG, United Kingdom.

Karvezide 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.

Karvezide is a combination of two active substances, irbesartan and hydrochlorothiazide.

Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a substance occurring in the body, which tightens blood vessels making it harder for the blood to pass through them and causing blood pressure to increase. Irbesartan blocks this effect of angiotensin II, causing the blood vessels to relax, and so lowers blood pressure.

Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.

Efficacy and safety of Karvezide were assessed in clinical trials in about 3000 patients with high blood pressure. The two active ingredients in Karvezide work together to lower blood pressure further than if either was given alone.

Side effects with Karvezide were generally rare and of a temporary nature. They were generally mild and do not normally require treatment to be interrupted. Symptoms or feelings most often reported by patients taking Karvezide or placebo (sugar tablets) included: headache, dizziness, fatigue, nausea/vomiting or abnormal urination. Of these, only fatigue was reported more often by patients taking Karvezide compared to patients taking placebo. Furthermore, as for any combination of two active substances, side effects associated with each individual component cannot be excluded.

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

COAPROVEL*

International Non-proprietary Name (INN): Irbesartan / Hydrochlorothiazide

On 15 October 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product CoAprovel which contains irbesartan and hydrochlorothiazide. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 July 1998. The Marketing Authorisation Holder responsible for this medicinal product is Sanofi Pharma Bristol-Myers Squibb SNC, France.

CoAprovel 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.

CoAprovel is a combination of two active substances, irbesartan and hydrochlorothiazide.

Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a substance occurring in the body, which tightens blood vessels making it harder for the blood to pass through them and causing blood pressure to increase. Irbesartan blocks this effect of angiotensin II, causing the blood vessels to relax, and so lowers blood pressure.

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Efficacy and safety of CoAprovel were assessed in clinical trials in about 3000 patients with high blood pressure. The two active ingredients in CoAprovel work together to lower blood pressure further than if either was given alone.

Side effects with CoAprovel were generally rare and of a temporary nature. They were generally mild and do not normally require treatment to be interrupted. Symptoms or feelings most often reported by patients taking CoAprovel or placebo (sugar tablets) included: headache, dizziness, fatigue, nausea/vomiting or abnormal urination. Of these, only fatigue was reported more often by patients taking CoAprovel compared to patients taking placebo. Furthermore, as for any combination of two active substances, side effects associated with each individual component cannot be excluded.

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

MRFG
Mutual Recognition Facilitation Group

Report from the meeting held on 19 October 1998

The MRFG noted that 21 new mutual recognition procedures have been finalised during the month of September 1998 as well as 50 type I and 13 type II variations.
The status as of 30 September 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	142	33	234	71	157	126	4 var

15 new procedures (regarding 29 products) have been started in September 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]
3	3	3	4	0	0	2

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

Each application can be classified in only one category.

Number of countries involved in the started new applications procedures in September 1998

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (4)	(13)
DE (1)	(2)
DE (1)	(4)
DK (2)	(4)
DK (2)	(4)
DK (2)	(13)
IT (1)	(14)
NL (2)	(14)
SE (1)	(14)

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
SE (3)	(14)
SE (3)	(13)
UK (1)	(10)
UK (1)	(13)
UK (1)	(9)
UK (4)	(13)

General issues

- The Group discussed with representatives from the European Commission several questions to the Commission Communication, some items should be highlighted in this Report.
  - If two medicinal products from the same Company have the same active substances, the same strength and the same pharmaceutical form, they have to be considered as the same product, therefore Art. 7a of the Council Directive 65/65/EEC, as amended, has to be triggered. Differences in excipients and indications do not prevent Member States to trigger art. 7a if there are no therapeutic implications. The outcome of the Mutual Recognition Procedure will be a harmonised SPC.
    The Group worked out a SOP for National Authorities when art. 7a has to be triggered, the final version will be published after the next MRFG meeting for information only. It should be applied to all applications nevertheless national procedures are still possible in two cases:
    - Applications in accordance to art. 4.8 a ii) of the Council Directive 65/65/EEC, as amended, so called bibliographic applications;
    - So called "line extensions" of non-harmonised national marketing authorisations.
  - For "line extensions" a Mutual Recognition Procedure can also be used if the existing dossiers are harmonised before the starting of the procedure. If the applicant chooses to submit a stand-alone application, it should be considered a valid application for all Concerned Member States. Nevertheless if the applicant chooses the Mutual Recognition Procedure for the Concerned Member States, he cannot use the national procedure in parallel.
  - Concerning the Mutual Recognition Procedure for an application which has earlier been withdrawn from a Concerned Member State, there is the clear statement that a second (a third....) round of applications following Mutual Recognition is possible. Only national applications are not possible for the same medicinal product.
  - The Marketing Authorisation Holder of "ex-concertation" products which falls under the scope of Part A of the Annex to Council Regulation (EEC) 2309/93, as amended, are obliged to switch to a Centralised Procedure as soon as they want to introduce a proteinaceous constituent obtained by rDNA technology or to change the expression system of a biotech active substance. In all other cases the products will remain in the Mutual Recognition Procedure.

- The MRFG adopted the list of MRFG Contact Points and this list will be published on the MRFG Website. The list is going to be provided to assist the pharmaceutical companies submitting applications through the MRP. The persons listed should only be approached for questions on a particular application. They should not be approached for agreed information on questions about the Mutual Recognition Procedure.

- Due to the positive experience with the automatic validation for new application over a 6-month trial period the Group decided to continue with this procedure for the future. Concerning the automatic validation for Type II variations which was limited during the trial phase only to cases where safety issues were identified by the RMS, the Group decided that it should be extended to all Type II variations from the 2nd November 1998. The revised SOPs will be published on the MRFG Website.

- The Group recognised the great success of the fast track procedure for Influenza Vaccines which was used this year for the first time. It has been used to harmonise the licensing of six different applications of Influenza Vaccines.

- The Group and representatives from the European Commission met again with the three trade associations EFPIA, AESGP and EGA and had extensive discussion on several items, especially focusing on the Commission Communication.

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/