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

21 September 1998

CPMP/2010/1998

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 41st plenary meeting from 15 September to 17 September 1998.

Centralised Procedures

The Committee adopted the following Opinions:

- Two positive Opinions on Centralised Applications:
  - One positive Opinion was adopted by consensus relating to a Medicinal Product containing an active substance (Part A), an anti-parathyroid hormone, indicated for the treatment of Paget's disease and hypercalcaemia in malignancy.
  - One positive Opinion was adopted by majority of votes relating to an active substance (Part B), already approved in a former Centralised Procedure, a parasympathomimetic, indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.
- Eight positive Opinions by consensus for Centralised Type II Variations, including two double applications.

Since the CPMP meeting in July 1998 the Committee noted the withdrawal of one Centralised Application (Part A).

Six Centralised Procedures have been started after validation. Four for Part A including one triple Application for the same new active substance and two for Part B.

The Committee heard two Oral Presentations/Clarifications from Applicants.

Rapporteurs and Co-Rapporteurs were assigned for five Part B applications forthcoming in the Centralised Procedure within the next four months. A Rapporteur was also assigned for three Extension Applications for three Medicinal Products currently in the Decision Making Process relating to the same active substance (Part B).

An overview of Centralised Applications is given in Annex I.

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

- Xenical (Orlistat), indicated for the treatment of obesity
- Evista and Celvista (Raloxifene), indicated for the prevention of non-traumatic vertebral fractures in postmenopausal women at an increased risk of osteoporosis
- NovoNorm (Repaglinide), indicated in patients with type 2 diabetes whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise

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- Fortovase (Saquinavir), indicated for the treatment of HIV-1 infected adult patients, in combination with antiretroviral agents
- Viagra and Patrex (Sildenafil), indicated for the treatment of erectile dysfunction

  In view of an anticipated rapid and high level of patient exposure, the Marketing Authorisation Holders of Viagra and Patrex have agreed to update the Committee on a monthly basis with data on safety and patient exposure to allow for a close review of the safety of these products.
- Comtess (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 established on those combinations.

See Annexes II & III for details.

Scientific Advice

The Committee:

- Accepted four new requests for Scientific Advice as justified. Co-ordinators were appointed.

- Adopted four Scientific Advice by consensus on manufacturing, preclinical and/or clinical issues, and development plans concerning four new products, two for Part A, two for Part B, intended for:

  - the prevention of the development of secondary cataract following primary extracapsular cataract surgery
  - the treatment of pulmonary hypertension
  - the treatment of chronic lymphocytic leukaemia in patients who are refractory to or who have relapsed following previous treatment
  - the prevention and treatment of postmenopausal osteoporosis.

Referrals

Referral under Article 7.5 of Commission Regulation (EC) No. 541/95, as amended
The Committee noted three Referrals for Arbitration to the CPMP of three Type II Variations relating to the harmonisation of the SPC / indications concerning the renewal of a Marketing Authorisation for a Medicinal Product already authorised through the former Concertation Procedure. A Rapporteur and a Co-Rapporteur were assigned.

The Committee noted the Referral for Arbitration to the CPMP of a Type II Variation relating to the extension for an indication, concerning the renewal of a Medicinal Product already authorised through the former Concertation Procedure. A Rapporteur and a Co-Rapporteur were previously assigned.

Referrals under Article 15(a) of Council Directive 75/319/EEC, as amended
The Committee noted the Referral under Article 15 (a) of Council Directive 75/319, as amended, by Austria for anorectics related to Amphetamine (Clobenzorex, Fenbutrazate, Fenproporex, Mazindol, Mefenorex, Norpseudoephedrine, Phenmetrazine, Phendimetrazine, Propylhexedrine). A Rapporteur and two Co-Rapporteurs were assigned.

ICH

The Committee heard a report from the Steering Committee and Expert Working Groups meeting, held in Tokyo from 31 August to 3 September 1998.

Working Parties, Ad Hoc Expert Groups and Organisational Matters.

The CPMP heard reports from its Biotechnology Working Party, from the EWP/QWP joint Group of Experts on Pharmacokinetic Issues and from the Ad Hoc Expert Working Group on Update of Guidance on SPCs.

EMEA AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

The CPMP was informed that the activities of the EMEA Ad Hoc Working Group on Herbal Medicinal Products had resulted in the release of new documents for consultation and in the revision of the proposals released for consultation in January 1998 (Annex IV).

Mutual Recognition

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) on 14 September 1998, which is circulated together with this Press Release (Annex V).

Prof. R. Bass
Head of Human Medicines Evaluation Unit

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

CENTRALISED APPLICATIONS TO THE EMEA

	Pending		Final		
	Part A	**Part B**	**Part A**	**Part B**	**Total**
Scientific Advice	**6**	**9**	**30**	**37**	**67**
Follow-up Scientific Advice	**0**	**0**	**9**	**2**	**11**

	Part A	**Part B**	**Total***
Applications submitted since 1 January 1995	**60**	**108**	**168**
Withdrawn	**6**	**13**	**19**
Opinions given by the CPMP	**31**	**60**	****91**
Marketing Authorisations granted by the Commission	**26**	**51**	*****77**

	Part A	**Part B**	**Total**
Variations type I	**94**	**124**	**218**
Variations type II	**38**	**57**	**91**
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

** 91 Opinions corresponding to 69 substances

*** 77 Marketing Authorisations corresponding to 72 substances

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

PRODUCT	**Brandname**	XENICAL
	INN	Orlistat
	Part A/B	B
COMPANY ORIGIN	**Country**	Switzerland
MARKETING AUTHORISATION HOLDER	**Name**	Hoffmann-La Roche
THERAPEUTIC AREA	**ATC Code**	A08A B01
	Indication	treatment of obesity
PRESENTATION	**Pharmaceutical form**	capsules
	Strength	120 mg
	Number of presentations	3
EMEA/CPMP	**Validation**	2/01/97
	Date of Opinion	25/03/98
	Active time	183 days
	Clock stop	255 days
COMMISSION DECISION	**Opinion receipt date**	5/05/98
	Date of Commission Decision	29/07/98

PRODUCT	**Brandname**	EVISTA
	INN	Raloxifene
	Part A/B	B
COMPANY ORIGIN	**Country**	United States
MARKETING AUTHORISATION HOLDER	**Name**	Eli Lilly Nederlands BV
THERAPEUTIC AREA	**ATC Code**	code pending
	Indication	prevention of non-traumatic vertebral fractures in postmenopausal women
PRESENTATION	**Pharmaceutical form**	film-coated tablets
	Strength	60 mg
	Number of presentations	4
EMEA/CPMP	**Validation**	25/07/97
	Date of Opinion	22/04/98
	Active time	188 days
	Clock stop	84 days
COMMISSION DECISION	**Opinion receipt date**	25/5/98
	Date of Commission Decision	05/08/98

PRODUCT	**Brandname**	CELVISTA
	INN	Raloxifene
	Part A/B	B
COMPANY ORIGIN	**Country**	United States
MARKETING AUTHORISATION HOLDER	**Name**	Eli Lilly Nederlands BV
THERAPEUTIC AREA	**ATC Code**	code pending
	Indication	prevention of non-traumatic vertebral fractures in postmenopausal women
PRESENTATION	**Pharmaceutical form**	film-coated tablets
	Strength	60 mg
	Number of presentations	4
EMEA/CPMP	**Validation**	25/07/97
	Date of Opinion	22/04/98
	Active time	188 days
	Clock stop	84 days
COMMISSION DECISION	**Opinion receipt date**	25/5/98
	Date of Commission Decision	05/08/98

PRODUCT	**Brandname**	NOVONORM
	INN	Repaglinide
	Part A/B	B
COMPANY ORIGIN	**Country**	Denmark
MARKETING AUTHORISATION HOLDER	**Name**	Novo Nordisk
THERAPEUTIC AREA	**ATC Code**	A10BX02
	Indication	type 2 diabetes
PRESENTATION	**Pharmaceutical form**	tablets
	Strength	0.5 mg, 1.0 mg, 2.0 mg
	Number of presentations	7
EMEA/CPMP	**Validation**	25/07/97
	Date of Opinion	22/04/98
	Active time	199 days
	Clock stop	97 days
COMMISSION DECISION	**Opinion receipt date**	05/06/98
	Date of Commission Decision	17/08/98

PRODUCT	**Brandname**	FORTOVASE
	INN	Saquinavir
	Part A/B	B
COMPANY ORIGIN	**Country**	Switzerland
MARKETING AUTHORISATION HOLDER	**Name**	Roche Registration Ltd.
THERAPEUTIC AREA	**ATC Code**	J05A E01
	Indication	treatment of HIV-1 infected adult patients
PRESENTATION	**Pharmaceutical form**	soft capsules
	Strength	200 mg
	Number of presentations	2
EMEA/CPMP	**Validation**	20/06/97
	Date of Opinion	22/04/98
	Active time	209 days
	Clock stop	97 days
COMMISSION DECISION	**Opinion receipt date**	25/05/98
	Date of Commission Decision	20/08/98

PRODUCT	**Brandname**	VIAGRA
	INN	Sildenafil
	Part A/B	B
COMPANY ORIGIN	**Country**	UK
MARKETING AUTHORISATION HOLDER	**Name**	Pfizer Ltd.
THERAPEUTIC AREA	**ATC Code**	G04 BE
	Indication	treatment of erectile dysfunction
PRESENTATION	**Pharmaceutical form**	film coated tablets
	Strength	50 mg
	Number of presentations	7
EMEA/CPMP	**Validation**	24/10/97
	Date of Opinion	27/05/98
	Active time	188 days
	Clock stop	28 days
COMMISSION DECISION	**Opinion receipt date**	26/06/98
	Date of Commission Decision	15/09/98

PRODUCT	**Brandname**	PATREX
	INN	Sildenafil
	Part A/B	B
COMPANY ORIGIN	**Country**	Italy
MARKETING AUTHORISATION HOLDER	**Name**	Roerig Farmaceutici Italiana S.p.A
THERAPEUTIC AREA	**ATC Code**	G04 BE
	Indication	treatment of erectile dysfunction
PRESENTATION	**Pharmaceutical form**	film coated tablets
	Strength	50 mg
	Number of presentations	7
EMEA/CPMP	**Validation**	24/10/97
	Date of Opinion	27/05/98
	Active time	188 days
	Clock stop	28 days
COMMISSION DECISION	**Opinion receipt date**	26/06/98
	Date of Commission Decision	15/09/98

PRODUCT	**Brandname**	COMTESS
	INN	Entacapone
	Part A/B	B
COMPANY ORIGIN	**Country**	Finland
MARKETING AUTHORISATION HOLDER	**Name**	Orion
THERAPEUTIC AREA	**ATC Code**	N04B X02
	Indication	for the use in patients with 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	16/09/98

XENICAL*

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

On 29 July 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Xenical, which contains orlistat. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 25 March 1998. The Marketing Authorisation Holder responsible for this medicinal product is Roche Registration Limited, United Kingdom.

The approved indication is for use in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m², or overweight patients (BMI ≥ 28 kg/m²) with associated risk factors. 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 Xenical, orlistat, is an inhibitor of gastrointestinal lipases and thereby impairs the metabolism of lipids in the intestinal lumen leading to a prevention of lipid absorption. It is presented as Xenical 120 mg hard capsules. The recommended dose of orlistat is one 120 mg capsule three times daily, which should be taken immediately before, during or up to one hour after each main meal.

In clinical studies carried out in obese patients, Xenical demonstrated a modest effect on body weight after 1-year of treatment in association with a mild hypocaloric diet, with the mean effect of –3.2 kg weight loss as compared to placebo. Responder rates were 20% of patients taking orlistat (120 mg t.i.d) as compared to 8% of patents taking placebo. During the second year, Xenical associated with an eucaloric diet did not prevent weight regain.

The most frequent adverse events observed during treatment were gastrointestinal in nature, notably oily spotting from the rectum, flatus with discharge, faecal urgency, fatty/oil stool, oily evacuation, increased defecation and faecal incontinence. The overall safety issues, together with appropriate warnings and precautions have been addressed in the SPC.

In order to select those patients likely to respond and not to unduly expose patients to Xenical, treatment should only be started if diet alone has previously produced a weight loss of at least 2.5 kg over a period of 4 consecutive weeks, and treatment should be discontinued after 12 weeks if patients have been unable to lose at least 5% of the body weight as measured at the start of drug therapy. The maximal duration of treatment should not be longer than 2 years.

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

CELVISTA*

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

On 5 August 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Celvista, which contains raloxifene. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 April 1998. The Marketing Authorisation Holder responsible for this medicinal product is Eli Lilly Nederland B.V., The Netherlands.

The approved indication is for the prevention of non traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis. 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.

* This text is the Abstract of the complete EPAR.

The active substance of Celvista, raloxifene (as hydrochloride), is a selective estrogen receptor modulator (SERM). It acts as an estrogen agonist on bone and lipid metabolism but not in uterine or breast tissues. Its biological actions are mediated through high affinity binding to estrogen receptors and regulation of gene expression.

In 3 clinical studies (2-years data), raloxifene demonstrated an effect on bone mineral density and resorption which is qualitatively similar to that of estrogen although of lesser magnitude, and clearly superior to placebo (calcium supplementation only). Raloxifene 60 mg/day prevents bone loss in postmenopausal women, who are at increased risk of developing osteoporosis and decreases the risk of incident vertebral fractures. There are no data on extravertebral fractures.

The treatment-emergent adverse events, which occurred significantly more often during raloxifene than placebo treatment, were venous thromboembolic events, superficial vein thrombophlebitis, vasodilatation (hot flushes), leg cramps and peripheral oedema. There were no differences in the incidence of reported uterine bleeding between the raloxifene and placebo groups. When comparing raloxifene treated patients (n=317) with continuous combined (n=110) or cyclic hormonal replacement therapy (HRT) (n=205) patients, the incidence of breast symptoms and uterine bleeding in raloxifene treated women was significantly lower than in women treated with either form of HRT. The long-term effect of Celvista on the risk of breast cancer is unknown. No data are yet available to demonstrate benefit of raloxifene on atherosclerotic cardiovascular disease. When determining the choice of raloxifene or estrogen (hormonal replacement therapy) for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on breast tissue, and cardiovascular risks and benefits.

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

EVISTA*

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

On 5 August 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Evista, which contains raloxifene. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 April 1998. The Marketing Authorisation Holder responsible for this medicinal product is Eli Lilly Nederland B.V., The Netherlands.

The approved indication is for the prevention of non traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis. 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 Evista, raloxifene (as hydrochloride), is a selective estrogen receptor modulator (SERM). It acts as an estrogen agonist on bone and lipid metabolism but not in uterine or breast tissues. Its biological actions are mediated through high affinity binding to estrogen receptors and regulation of gene expression.

In 3 clinical studies (2-years data), raloxifene demonstrated an effect on bone mineral density and resorption which is qualitatively similar to that of estrogen although of lesser magnitude, and clearly superior to placebo (calcium supplementation only). Raloxifene 60 mg/day prevents bone loss in postmenopausal women, who are at increased risk of developing osteoporosis and decreases the risk of incident vertebral fractures. There are no data on extravertebral fractures.

The treatment-emergent adverse events, which occurred significantly more often during raloxifene than placebo treatment, were venous thromboembolic events, superficial vein thrombophlebitis, vasodilatation (hot flushes), leg cramps and peripheral oedema. There were no differences in the incidence of reported uterine bleeding between the raloxifene and placebo groups. When comparing raloxifene treated patients (n=317) with continuous combined (n=110) or cyclic hormonal replacement

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therapy (HRT) (n=205) patients, the incidence of breast symptoms and uterine bleeding in raloxifene treated women was significantly lower than in women treated with either form of HRT. The long-term effect of Evista on the risk of breast cancer is unknown. No data are yet available to demonstrate benefit of raloxifene on atherosclerotic cardiovascular disease. When determining the choice of raloxifene or estrogen (hormonal replacement therapy) for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on breast tissue, and cardiovascular risks and benefits.

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

FORTOVASE*

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

On 20 August 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Fortovase 200 mg soft capsules, which contains saquinavir. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 April 1998. The Marketing Authorisation Holder responsible for this medicinal product is Roche Registration Limited, United Kingdom.

The approved indication is for use in combination with antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV-1) infected 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.

Fortovase is a new formulation containing a known protease inhibitor used in the treatment of HIV infection, saquinavir authorised in the European Union. The active substance of Fortovase, saquinavir, interferes with HIV replication by acting on the maturation of the virus, rendering the virus non-infectious. A hard capsule formulation containing a salt of saquinavir has already been granted a Marketing Authorisation for the same indication at the recommended dose of 600 mg three times a day. Fortovase comes in a soft gelatine capsule that delivers more saquinavir to the body than the currently available formulation. The recommended daily dose of Fortovase is increased compared to the already authorised formulation to 1200 mg three times daily within 2 hours after a meal. The advantage of this formulation is to achieve sufficient exposure to saquinavir during antiviral treatment that confers a higher initial suppression of multiplication of the virus.

The efficacy of Fortovase has been demonstrated in 5 clinical studies, including 3 ongoing comparative trials. The overall results at 16 weeks of a controlled clinical study confirm the superior antiviral efficacy of Fortovase at the recommended dose over the previous authorised formulation of saquinavir when both products are used in combination with other antiretroviral agents, yielding a higher proportion of patients with undetectable virus levels in the blood.

Fortovase is well tolerated. The most frequent adverse events observed during treatment are gastro-intestinal, including diarrhoea, nausea and abdominal discomfort. No new adverse events have been observed with Fortovase compared to the previous authorised formulation.

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

* This text is the Abstract of the complete EPAR.

NOVONORM*

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

On 17 August 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product NovoNorm, which contains repaglinide. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 April 1998. The pharmaceutical company responsible for this medicinal product is Novo Nordisk A/S.

The approved indication is for treatment of patients with Type 2 diabetes (Non-Insulin-Dependent Diabetes Mellitus) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in Type 2 diabetes patients who are not satisfactorily controlled on metformin alone.

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

The active substance repaglinide is a new chemical entity, a carbamoylmethyl benzoic acid derivative insulinotropic antidiabetic agent. Repaglinide lowers blood glucose acutely by stimulating the release of insulin from the pancreas.

A total of 2122 patients were exposed to NovoNorm in all clinical trials. In the pivotal long-term studies running for up to one year, 1796 patients were investigated: 1209 on repaglinide, 407 on glibenclamide, 81 on glipizide and 99 on gliclazide. These long-term clinical trials demonstrated that NovoNorm was at least as effective as these sulfonylureas for the treatment of patients with Type 2 diabetes previously treated with diet or any other oral anti-diabetic medicinal product. One study recruiting 83 patients substantiated the clinical use of repaglinide in combination with metformin. The recommended dosage in these studies was 0.5 to 4 mg 3 times daily administered before meals.

The clinical safety profile based on over 1600 patients treated with repaglinide was overall reassuring. This corresponded to 1205 patient years of exposure with repaglinide. The main reasons for withdrawal (13%) were hyperglycaemia (4%) and hypoglycaemia (1%).

There is as yet no clinical experience in treating patients with hepatic and severe renal insufficiency or in elderly greater than 75 years of age or in children and adolescents less than 18 years of age.

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

VIAGRA*

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

On 15 September 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Viagra, which contains sildenafil. 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 Pfizer Limited, United Kingdom.

The approved indication is for the treatment of erectile dysfunction (ED), which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. 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 Viagra, sildenafil (as citrate), is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa

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(a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response.

In clinical studies, the efficacy of Viagra was well established with regard to attaining and maintaining erections sufficient for sexual intercourse in male subjects with ED from a broad spectrum ofetiology over a 3 months follow-up period, including diabetics and patients with spinal cord injury. In order for sildenafil to be effective, sexual stimulation is required. In dose ranges from 25-100 mg, a significantly improved response to sildenafil was observed compared to placebo treatment.

Analysis of the overall number of adverse events as well as treatment related adverse events at the recommended doses (25-100 mg) showed a higher overall rate of incidence in subjects treated with sildenafil compared with placebo. Headache, vasodilation (flushing), dyspepsia, rhinitis and abnormal vision are the most frequently encountered side effects. The majority of the reported adverse events were mild or moderate in severity. No differences between sildenafil and placebo-treated subjects were observed in the overall safety database for mortality, all cardiovascular serious adverse events, and myocardial infarction rate (adjusted to 100 man years of treatment).

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

PATREX

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

On 15 September 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Patrex, which contains sildenafil. 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 Roerig Farmaceutici Italiana S.p.A, Italy.

The approved indication is for the treatment of erectile dysfunction (ED), which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. 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 Patrex, sildenafil (as citrate), is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa (a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response.

In clinical studies, the efficacy of Patrex was well established with regard to attaining and maintaining erections sufficient for sexual intercourse in male subjects with ED from a broad spectrum ofetiology over a 3 months follow-up period, including diabetics and patients with spinal cord injury. In order for sildenafil to be effective, sexual stimulation is required. In dose ranges from 25-100 mg, a significantly improved response to sildenafil was observed compared to placebo treatment.

Analysis of the overall number of adverse events as well as treatment related adverse events at the recommended doses (25-100 mg) showed a higher overall rate of incidence in subjects treated with sildenafil compared with placebo. Headache, vasodilation (flushing), dyspepsia, rhinitis and abnormal vision are the most frequently encountered side effects. The majority of the reported adverse events were mild or moderate in severity. No differences between sildenafil and placebo-treated subjects were observed in the overall safety database for mortality, all cardiovascular serious adverse events, and myocardial infarction rate (adjusted to 100 man years of treatment).
The CPMP, on the basis of efficacy and safety data submitted, considered that there was a favourable benefit to risk balance for Patrex and recommended that the Marketing Authorisation should be granted.

COMTESS*

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

On 16 September 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product COMTESS, 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 Orion Corporation, Finland.

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 COMTESS, 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.

* This text is the Abstract of the complete EPAR.

Proposals from the Ad Hoc Working Group on Herbal Medicinal Products released for consultation until 1 December 98 (EMEA/ad hoc HMPWG/33279/98).

- Proposal for new Guidance "Fixed combinations of herbal medicinal products with long-term marketing experience" - Guidance to facilitate mutual recognition and use of bibliographic data
- Comments and proposals for revision of the Notice to Applicants Volume 2B Parts I C 1 and II, including proposal for tabular formats specific to Herbal Medicinal Products

Final proposals from the Ad Hoc Working Group on Herbal Medicinal Products (revised after 3 month consultation) (EMEA/ad hoc HMPWG/114/98).

- Good Manufacturing Practice (GMP): Comments and proposals for revision
- Proposals for revision of Note for Guidance "Quality of Herbal Remedies"
- Proposal for new guidance: "Non-clinical testing of herbal drug preparations with long-term marketing experience" Guidance to facilitate mutual recognition and use of bibliographic data
- Notice to Applicants Volume 2A and Volume 2B Parts IB1, IC2, and III – Comments and proposals for revision
- Comments on Part 4 of Annex to Council Directive 75/318/EEC of 20 May 1975 "Clinical documentation"
- Proposal for a core-SPC for*Valerianae radix*

MRFG
Mutual Recognition Facilitation Group

Report from the meeting held on 14th September 1998

The MRFG noted that 34 new mutual recognition procedures have been finalised during the months of July and August 1998 as well as 65 type I and 34 type II variations.
The status as of 31st of August 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	121	41	184	71	144	109	4 var.

32 new procedures (regarding 60 products) have been started in July and August 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]
5	2	6	7	0	0	12

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 July and August 1998

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (01)	9
DE (01)	14
DK (01)	2
DK (04)	8
DK (01)	13
DK (04)	1
DK (01)	9
DK (01)	5
FI (02)	14
FR (01)	8
NL (02)	5
NL (01)	10
NL (01)	7
SE (01)	11

SE (01)	13
SE (01)	5
SE (01)	13
SE (01)	7
UK (01)	10
UK (04)	14
UK (01)	9
UK (04)	13
UK (02)	10
UK (01)	10
UK (06)	9
UK (02)	12
UK (03)	5
UK (02)	12
UK (04)	1
UK (02)	1
UK (01)	14
UK (01)	14

General issues

- A representative from the European Commission gave additional clarification on the questions raised by the MRFG about the Commission Communication paper dated 16th July 1998. Further answers will be expected after the outcome of the Pharmaceutical Committee meeting.

- The Eudratrack subgroup met with representatives from the Project Team of the MRFG Mutual Recognition Survey of the Trade Associations in order to consider the possibility to release EUDRATRACK data to the Trade Associations for the survey purposes.

- The Group adopted the meeting dates for next year. The calendar of 1999 MRFG meeting is available as an annex to this press release.

- The updated statistics including all new applications over the period January 1995 to July 1998 will be published on the MRFG Website.

- An amended version of the Best Practice Guide (change from day 60 to day 55 for the Communication by Member States of any serious public health concern) was adopted during the Heads of Agencies meeting in July 1998. This amended version is available on the MRFG Website.

All annexes 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/