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

25-09-97
CPMP/813/97

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 30th plenary meeting on 23-24 September 1997. The CPMP welcomed two new members, who are Prof. Winkler from Austria and Dr. Abadie from France succeeding Dr. Pittner and Dr. Le Courtois respectively.

An overview of applications is given in Annex I. A list of products recently granted marketing authorisations by the Commission and summaries concerning these products are given in Annex II and III.

Centralised Procedures

The Committee adopted by consensus a positive opinion on a centralised application for a product containing a new active substance (Part B) indicated for the treatment of HIV infection.

The Committee also adopted by consensus 6 positive opinions for centralised type I variations following the type II procedure and 5 positive opinions for centralised type II variations.

Since the CPMP in July 1997, the European Commission has granted marketing authorisations for Tasmar (tolcapone), for the use in patients with Parkinson's disease, Helicobacter Test INFAI (^{13}C-urea) for in vivo diagnosis of Helicobacter pylori infection, Infanrix-HepB (DTPa-HB vaccine) for active immunisation of infants against diphtheria, tetanus, pertussis and hepatitis B, Benefix (nonacog alpha) for control and prevention of haemorrhagic episodes and prophylaxis of haemophilia B, factor IX deficiency, Aprovel/Karvea (irbesartan) for the treatment of essential hypertension.

11 applications forthcoming in the centralised procedure within the next 6 months have been distributed to Rapporteurs and Co-Rapporteurs.

The Committee adopted the "Crisis Management Plan regarding Centrally Authorised Products for Human Use" (CPMP/388/97) and released this document for information and possible comments within three months.

The Committee adopted the document "Annual Reassessment after Specific Obligations and the Risk-Benefit Profile of Medicinal Products Authorised under Exceptional Circumstances" (CPMP/657/97).

Scientific Advice

The CPMP adopted by consensus two scientific advice following specific and justified requests on issues of clinical development and biotechnology presented to the Committee earlier by pharmaceutical companies.

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Working Parties

The CPMP heard reports from its Quality, Biotechnology, Safety, Efficacy and Pharmacovigilance Working Parties and the Ad Hoc Expert group on Antiretroviral Medicinal Products.

Efficacy Working Party:

The following document was adopted for coming into operation in March 1998:

- Note for guidance on involutional osteoporosis in women (CPMP/EWP/552/95)

Biotechnology Working Party:

The Biotechnology Working Party has reviewed the impact of the Commission Decision 97/534/EC of 30 July 1997. This review and information from the discussion held at the Pharmaceutical Committee on 17 September were considered by the CPMP. The EMEA has been requested by the Commission to co-ordinate the responses of Member States. The TSE guideline discussion will be continued and will be finalised when final interpretion of the Commission Decision is available.

Pharmacovigilance Working Party:

The Committee noted that fenfluramine and dexfenfluramine containing medicinal products have been withdrawn from the market of the Member States, following information from the USA which suggests that patients taking these products might be at risk of heart valve disorders.

ICH

The following ICH Guidelines Step 4 were adopted by the Committee for coming into operation in March 1998:

- E2B: Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95)
- E8: Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)
- Q3C: Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)
- Q5D: Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (CPMP/ICH/294/95)
- S1C: Addendum to Note for Guidance on Dose Selection for Carcinogenicity Studies of pharmaceuticals: Addition of a Limit Dose and Related Notes (CPMP/ICH/366/96)
- S1B: Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals (CPMP/ICH/299/95)
- S2B: Note for Guidance on Genotoxocity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (CPMP/ICH/174/95)
- S6: Note for Guidance on Preclinical safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)
- M3: Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95)

The following ICH Guidelines Step 2 were released for a six months consultation period:

- Q6A: Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug products: Chemical Substances (CPMP/ICH/367/96)
- S4A: Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) (CPMP/ICH/300/95)

The Committee noted reports from the ad hoc Working Party on Herbal Medicinal Products (10-11 September 1997) and from the MRFG (22 September 1997) which are circulated together with this Press Release.

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

	CENTRALISED		TOTAL*
	Part A	***Part B***	
Applications submitted since 01.01.95	43	69	112
Withdrawn	1	7	8
Review ongoing	17	33	50
Opinions given by CPMP	25	29	54**
Marketing Authorization granted by Commission	24	25	49***

* These figures include the 18 ex-concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996
** 54 opinions corresponding to 43 substances
*** 49 opinions corresponding to 40 substances

	PENDING		FINAL		TOTAL
	Part A	***Part B***	***Part A***	***Part B***	
Variations type I	5	15	51	42	113
Variations type II	5	8	14	26	53
Scientific advice	5		37		42

Updated 25 September 1997

ANNEX II to **CPMP - September 1997**
Press Release

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure

Status: September 1997

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Transmission to COM b) Date of decision c) Date of notification d) OJ No.
a) **Infanrix-HepB** b) DTPa-HB vaccine c) Part A	a) SmithKline Beecham Biologicals b) USA	a) J07CA b) Active immunisation of infants	a) Suspension for injection b) c) 6 Presentations	a) 15.02.96 b) 16.04.97 c) 199 Days d) 217 Days	a) 26.05.97 b) 30.07.97 c) 01.08.97 d) OJ No.C 263/3 of 29.08.97
a) **Helicobacter Test INFAI** b) ^{13}C-urea c) Part B	a) INFAI b) DE	a) VO4CX Helicobacter pylori Test	a) Powder b) 75 mg/vial c) 1 Presentation	a) 23.09.96 b) 16.04.97 c) 162 Days d) 28 Days	a) 05.06.97 b) 14.08.97 c) 15.08.97 d) OJ No.C 263/3 of 29.08.97
a) **Tasmar** b) tolcapone c) Part B	a) Hoffmann-La Roche b) CH	a) N04BX01 b) Use in Parkinson's disease	a) Tablets b) 100 mg, 200 mg c) 6 Presentations	a) 18.06.96 b) 19.03.97 c) 170 Days d) 90 Days	a) 23.04.97 b) 27.08.97 c) d)
a) **Benefix** b) nonacog alpha c) Part A	a) Genetics Institute b) USA	a) BO2BD04 b) Hemophilia B, factor IX deficiency	a) Powder for injection b) 250 IU, 500 IU, 1000 IU c) 3 Presentations	a) 23.09.96 b) 14.05.97 c) 162 Days d) 55 Days	a) 16.06.97 b) 27.08.97 c) d)
a) **Karvea** b) irbesartan c) Part B	a) Sanofi BMS SNC b) FR	a) C02EX Treatment of Hypertension	a) Tablets b) 75 mg, 150 mg, 300 mg c) 9 Presentations	a) 21.10.96 b) 14.05.97 c) 163 Days d) 27 Days	a) 16.06.97 b) 27.08.97 c) d)
a) **Aprovel** b) irbesartan c) Part B	a) Bristol-Myers b) BE	a) C02EX Treatment of Hypertension	a) Tablets b) 75 mg, 150 mg, 300 mg c) 9 Presentations	a) 21.10.96 b) 14.05.97 c) 163 Days d) 27 Days	a) 16.06.97 b) 27.08.97 c) d)

ANNEX III to **CPMP - September 1997**
Press Release
14 August 1997
CPMP/417/97

HELICOBACTER TEST INFAI

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

On 14 August 1997, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Helicobacter Test INFAI, which contains ^{13}C-urea. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 16 April 1997. The Marketing Authorisation Holder responsible for this medicinal product is INFAI, Institut für biomedizinische Analytik & NMR-Imaging GmbH, Germany.

The approved indication is for in vivo diagnosis of gastroduodenal *Helicobacter pylori* infection. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in this EPAR and is available in all European Union official languages.

The active substance of Helicobacter Test INFAI is ^{13}C-labelled urea, a non-radioactive stable isotope in the form of a crystalline powder. The product is intended for oral administration after reconstitution with tap water. The diagnostic principle is based upon the urease activity of *Helicobacter pylori*. In case of a *Helicobacter pylori* infection in the stomach, the ^{13}C-urea is metabolised by urease and $^{13}CO_2$ is liberated in the exhaled air. Since other urease producing bacteria are seldomly found in the gastric flora, the presence of urease activity in the stomach is indicative of the presence of *Helicobacter pylori.*

In four clinical trials with the specified parameters of test meal, dosage and cut-off point, a high diagnostic efficacy of the breath test was shown, independent of use after or before *Helicobacter pylori* eradication therapy. None of the clinical studies performed with the Helicobacter Test INFAI reported side effects due to ^{13}C-urea. In view of the fact that urea is physiologically abundantly present and only a small additional amount is to be administered once, it is considered that any additional risk is negligible for urea breath test.

Although Helicobacter Test INFAI is a diagnostic test to detect *Helicobacter pylori* infection with a high specificity and sensitivity, differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies. The suppression/eradication of *Helicobacter pylori* may lead to false negative or positive results, therefore the test should be used after at least 4 weeks without systemic antibacterial therapy and 4 weeks after the last dose of acid antisecretory agents.

The CPMP, on the basis of the efficacy and safety data provided by the company, recommended that the Marketing Authorisation should be granted for Helicobacter Test INFAI for in vivo diagnosis of gastroduodenal *Helicobacter pylori* infection.

This text is also published as Abstract of the EPAR for Helicobacter Test Infai.

ANNEX III to **CPMP - September 1997**
Press Release
30 July 1997
CPMP/395/97

INFANRIX HEPB

International Non-proprietary Name (INN): **Diphtheria, tetanus, acellular pertussis and hepatitis B vaccine**

On 30 July 1997, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product INFANRIX HepB, which is a combined, tetravalent vaccine containing the active substances of two previously authorised vaccines. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 16 April 1997. The Marketing Authorisation Holder responsible for this medicinal product is SmithKline Beecham Biologicals, Belgium.

The approved indication is for the active immunisation of all infants from the age of two months against diphtheria, tetanus, pertussis and hepatitis B. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in this EPAR and is available in all European Union official languages.

The active substances of INFANRIX HepB, diphtheria, and tetanus toxoids, three purified acellular pertussis antigens and purified recombinant hepatitis B surface antigen, are non-infectious substances which protect infants from diphtheria, tetanus, pertussis and hepatitis B by stimulating an immune response (immunogenic activity) against these diseases. INFANRIX HepB has been developed on the basis of the combination of an existing trivalent vaccine diphtheria-tetanus-acellular pertussis and the recombinant yeast-derived hepatitis B vaccine, where the active substances are produced using established technology.

Clinical trials were designed to investigate the immunogenic activity and the potential for adverse reactions of the combined vaccine in infants. These studies showed that INFANRIX HepB had an acceptable profile of adverse reactions and that it elicited an immune response comparable to that of the existing trivalent vaccine diphtheria-tetanus-acellular pertussis and the recombinant hepatitis B vaccine.

The most frequent adverse reactions observed during treatment were pain, redness, swelling, fever. Other general symptoms such as unusual crying, vomiting, diarrhoea, loss of appetite and restlessness.

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

This text is also published as Abstract of the EPAR for Infanrix-HepB.

ANNEX III to **CPMP - September 1997**
Press Release
27 August 1997
CPMP/108/97

APROVEL

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

On 27 August 1997, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Aprovel, which contains irbesartan. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 15 May 1997. The Marketing Authorisation Holder responsible for this medicinal product is Sanofi Pharma Bristol-Myers Squibb SNC.

Aprovel is indicated in the treatment of high blood pressure (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. There are usually no symptoms of high blood pressure before damages occur.

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

The active substance of Aprovel, irbesartan, belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Aprovel prevents the binding of angiotensin II to these receptors, causing the blood vessels to relax and the blood pressure to lower.

Clinical trials demonstrated that blood pressure is lowered and controlled with Aprovel.

Undesirable effects with Aprovel were generally rare, mild, of temporary nature, and did not normally require treatment to be interrupted. In the placebo controlled studies, undesirable effects occurred with similar frequency in patients taking Aprovel and in patients taking placebo.

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

This text is also published as Abstract of the EPAR for Aprovel.

ANNEX III to **CPMP - September 1997**
Press Release
27 August 1997
CPMP/107/97

KARVEA

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

On 27 August 1997, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Karvea, which contains irbesartan. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 15 May 1997. The Marketing Authorisation Holder responsible for this medicinal product is Bristol-Myers Squibb Pharma EEIG.

Karvea is indicated in the treatment of high blood pressure (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. There are usually no symptoms of high blood pressure before damages occur.

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

The active substance of Karvea, irbesartan, belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Karvea prevents the binding of angiotensin II to these receptors, causing the blood vessels to relax and the blood pressure to lower.

Clinical trials demonstrated that blood pressure is lowered and controlled with Karvea.

Undesirable effects with Karvea were generally rare, mild, of temporary nature, and did not normally require treatment to be interrupted. In the placebo controlled studies, undesirable effects occurred with similar frequency in patients taking Karvea and in patients taking placebo.

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

This text is also published as Abstract of the EPAR for Karvea.

ANNEX III to **CPMP - September 1997**
Press Release
24 September 1997
CPMP/549/97

BeneFIX

International Non-proprietary Name (INN): **nonacog alfa**

On 27 August 1997, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product BeneFIX, which contains coagulation factor IX produced by means of recombinant DNA technology. This decision was based on the favourable opinion under exceptional circumstances and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 14 May 1997. The Marketing Authorisation Holder responsible for this medicinal product is Genetics Institute of Europe.

The approved indication is for the control and prevention of hemorragic episodes and for routine and surgical prophylaxis in previously treated patients with haemophilia B (congenital factor IX deficiency or Christmas disease).

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

The active substance of BeneFIX, nonacog alfa, is a recombinant coagulation factor IX (produced by means of recombinant DNA technology) similar to the natural factor IX which is normally present in human blood and is necessary for the blood to form clots. In haemophilia B patients, because of a genetic defect this substance is not present or is present in a very insufficient amount: therefore it is necessary to provide these patients with a substitute of coagulation factor IX.

Clinical trials were designed to investigate previously treated patients (PTPs) with moderate or severe haemophilia B for treatment and prevention of bleeding and when they were to undergo elective, major surgical procedures that required factor IX replacement therapy. These studies showed that BeneFIX was adequate in terms of efficacy and safety in the treatment of patients having haemophilia B. The use of BeneFIX is indicated in haemophiliac patients previously treated with other medicinal products containing coagulation factor IX, for the control and prevention of haemorrhagic episodes and for routine and prophylaxis before surgery. The treatment with BeneFIX can be pursued in presence of a factor IX inhibitor (neutralising antibody) less than 5 Bethesda Units, if the patient continues to respond clinically with an increase in circulating factor IX.

Adverse reactions observed during treatment with BeneFIX were nausea, discomfort at the injection site, altered taste, burning sensation in jaw and skull, allergic rhinitis, lightheadedness, headache, dizziness, chest tightness, fever, phlebitis/cellulitis at injection site, drowsiness, dry cough/sneeze, rash and one single hive. In one case was observed the development of a factor IX inhibitor, an antibody which blocks the activity of the coagulation factor IX.

The CPMP on the basis of the overall benefit/risk ratio recommended that the Marketing Authorisation should be granted “under exceptional circumstances” because the indication for which the product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence under normal conditions of use.
The Marketing Authorisation Holder will submit the final reports of the ongoing clinical studies and the follow-up data of patients treated with BeneFIX. Additional information will be provided on pharmaceutical and biological aspects of this medicinal product. All additional studies will be carefully monitored and the results will be reviewed by the CPMP.

This text is also published as Abstract of the EPAR for BeneFIX.

AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS MEETING

10-11 SEPTEMBER 1997

EMEA, 7 Westferry Circus, Canary Wharf, London E14 4HB

On 10 and 11 September 1997 the EMEA hosted the second meeting of the ad hoc working group on herbal medicinal products chaired by Dr K. Keller (BfArM).

The working group completed its review of existing quality guidance, and in particular proposals for modification of the Note for Guidance "Quality of Herbal Remedies".

The group also reviewed current safety guidelines, especially commenting on the draft guideline "Non-clinical testing of substances with long-term marketing experience (old substances)", which could be developed for the evaluation of known herbal medicinal products.

Member States have in place some abridged procedure for applications containing bibliographical safety data for well known herbal medicinal products.

The chairman presented preliminary results on a small survey of the acceptability of ESCOP monographs in the different Member States. The working group will further discuss this matter at its next meeting (24-25 November 1997) during which it will also address the issue of the safety and efficacy of herbal medicinal products as well as ESCOP proposals on pharmacovigilance in relation to these products.

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Mutual Recognition Facilitation Group

Report from the meeting held on 22 September 1997

The MRFG noted that 21 new mutual recognition procedures have been finalised recently as well as 11 type I and 12 type II variations.
The status as of 22 September 1997 of procedures under mutual recognition is as follows:

Year	New applications finalised	New applications in process	Type I variations finalised	Type I variations pending	Type II variations finalised	Type II variations pending	Arbitrations referred to CPMP
1997	98	54	62	18	86	35	1 N.A. + 1 Var.

	New applications finalised	Type I variations finalised	Type II variations finalised	Arbitrations referred to CPMP
since 01.01.1995	182	127	176	3 N.A. + 2 Var.

Since 21 July for 29 new applications the procedures have been started with the following characteristics:

New active substance[1]	Line extensions[2]	Fixed combinations	Generics	Herbal products[3]	OTC[4]	Others[5]
11	2	3	3	0	2	8

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 strenght, 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 procedures since 21 July 1997:

Reference Member State (number of products involved in the procedure)	Number of CMS involved in the procedure
AT (1)	8
DE (1)	12
DE (2)	13
DK (1)	12
DK (4)	1
ES (2)	14
ES (2)	14
FI (2)	7
FI (2)	1
FR (1)	4
FR (1)	9
FR (1)	12
FR (1)	3
SE (2)	14
SE (1)	2
SE (1)	2
UK (1)	13
UK (6)	7
UK (2)	12
UK (3)	13

UK (1)	10
UK (1)	1
UK (1)	13
UK (2)	10
UK (1)	14
UK (3)	13
UK (3)	13
UK (1)	13
UK (1)	2

The validation time will be provided when EUDRATRACK is fully operational.

General issues

- The MRF Group met with three trade organisations for discussion of the Best Practice Guide for Industry and the MRFG press release.
- The Chairmanship will be taken over by Dr. D. Jefferys (UK) by 1st October 1997

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

Mrs G.M. Janse-de Hoog
Medicines Evaluation Board in The Netherlands
Tel. 31-70-3407422

MR Procedures finalised since 1st January 1995 until 22nd September 1997

New active substance	Line extensions	Fixed combinations	Generics	Herbal products	OTC	Others
58	21	13	36	1	5	51

Reference Member State	N. of products involved in the procedure	N. of Concerned Member States involved at the start of the procedure	Type of application
BE	2	14	LINE EXTENSION
BE	2	14	LINE EXTENSION
BE	2	12	LINE EXTENSION
BE	2	11	LINE EXTENSION
BE	2	2	GENERICS
BE	1	4	OTHERS
DE	4	12	NAS
DE	1	13	NAS
DE	1	11	NAS
DE	1	12	NAS
DE	1	6	OTHERS
DE	3	6	NAS
DE	2	12	NAS
DE	3	11	OTHERS
DE	3	12	NAS
DE	2	10	GENERICS
DE	2	14	NAS
DE	3	9	OTHERS
DE	3	14	NAS
DE	2	2	NAS
DE	3	3	NAS
DK	1	12	LINE EXTENSION
DK	1	1	LINE EXTENSION
DK	10	13	OTHERS
DK	1	10	GENERICS
DK	2	1	GENERICS

DK	2	10	GENERICS
DK	1	3	FIXED COMBINATION
DK	2	11	GENERICS
DK	1	4	OTHERS
DK	2	11	LINE EXTENSION
DK	1	6	GENERICS
DK	3	9	GENERICS
DK	3	11	GENERICS
DK	1	11	GENERICS
DK	2	3	GENERICS
DK	3	6	GENERICS
DK	1	8	OTHERS
DK	2	8	GENERICS
DK	1	2	GENERICS
DK	3	10	OTHERS
DK	6	1	GENERICS
DK	1	1	OTHERS
DK	4	2	OTHERS
DK	4	9	NAS
FI	1	5	OTHERS
FR	1	13	OTHERS
FR	5	12	NAS
FR	1	12	LINE EXTENSION
FR	1	7	NAS
FR	2	9	OTHERS
FR	3	14	OTHERS
FR	1	6	NAS
FR	1	13	NAS
FR	3	9	NAS
FR	2	13	NAS
FR	1	13	NAS
FR	5	13	NAS
FR	1	10	LINE EXTENSION
FR	1	10	OTHERS
IR	1	4	OTHERS
IR	2	11	OTHERS
IR	1	6	OTHERS
IR	1	12	LINE EXTENSION
IR	3	1	OTHERS
IT	4	1	OTHERS
NL	1	13	LINE EXTENSION
NL	5	5	NAS
NL	1	8	NAS
NL	1	14	NAS
NL	3	12	NAS
NL	1	8	NAS
NL	1	5	NAS
NL	3	13	FIXED COMBINATION
NL	3	12	FIXED COMBINATION
NL	2	9	OTHERS
NL	1	1	GENERICS
NL	1	2	GENERICS
NL	1	6	OTC
NL	4	5	OTHERS
NL	1	3	GENERICS
NL	2	13	LINE EXTENSION
NL	2	14	NAS
NL	1	10	FIXED COMBINATION
NL	3	13	GENERICS
NL	1	8	LINE EXTENSION

NL	1	5	OTHERS
NL	1	6	GENERICS
NL	1	9	LINE EXTENSION
NL	3	7	OTHERS
NL	2	7	OTHERS
NL	1	5	GENERICS
NL	2	2	OTHERS
NL	2	14	NAS
NL	1	5	GENERICS
NL	2	3	NAS
NL	2	1	NAS
SE	1	1	NAS
SE	1	11	NAS
SE	3	13	OTHERS
SE	3	1	NAS
SE	1	1	NAS
SE	1	1	NAS
SE	1	1	NAS
SE	1	1	NAS
SE	1	1	NAS
SE	3	1	GENERICS
SE	3	1	GENERICS
SE	3	1	GENERICS
SE	1	1	FIXED COMBINATION
SE	1	3	LINE EXTENSION
SE	2	12	NAS
SE	1	13	NAS
SE	1	2	HERBAL
SE	1	2	FIXED COMBINATION
SE	1	1	NAS
SE	2	11	NAS
SE	1	11	NAS
UK	2	12	LINE EXTENSION
UK	5	14	NAS
UK	5	14	LINE EXTENSION
UK	1	12	OTHERS
UK	1	1	NAS
UK	2	11	OTHERS
UK	5	5	OTHERS
UK	1	2	LINE EXTENSION
UK	8	11	OTHERS
UK	1	13	NAS
UK	2	14	NAS
UK	5	10	OTHERS
UK	1	5	NAS
UK	2	11	GENERICS
UK	2	11	OTHERS
UK	1	7	OTHERS
UK	2	5	GENERICS
UK	1	4	OTHERS
UK	1	4	GENERICS
UK	1	14	NAS
UK	1	7	OTHERS
UK	2	8	OTHERS
UK	2	6	GENERICS
UK	1	13	GENERICS
UK	3	4	OTHERS
UK	2	7	OTHERS
UK	1	13	FIXED COMBINATION
UK	1	13	FIXED COMBINATION

UK	1	3	NAS
UK	1	8	NAS
UK	1	13	OTC
UK	1	11	OTHERS
UK	1	14	NAS
UK	2	4	OTC
UK	2	4	OTC
UK	1	10	GENERICS
UK	1	12	FIXED COMBINATION
UK	2	8	OTHERS
UK	1	8	FIXED COMBINATION
UK	1	14	OTHERS
UK	6	14	NAS
UK	1	5	GENERICS
UK	1	11	FIXED COMBINATION
UK	1	11	OTHERS
UK	2	3	GENERICS
UK	2	3	GENERICS
UK	1	10	OTC
UK	1	10	GENERICS
UK	1	13	NAS
UK	2	14	NAS
UK	2	12	LINE EXTENSION
UK	2	1	GENERICS
UK	1	3	OTHERS
UK	1	13	OTHERS
UK	1	14	LINE EXTENSION
UK	1	8	FIXED COMBINATION
UK	5	14	OTHERS
UK	1	10	OTHERS
UK	1	8	OTHERS
UK	1	8	FIXED COMBINATION
UK	1	12	LINE EXTENSION
UK	1	14	OTHERS
UK	1	13	NAS
UK	1	3	OTHERS
UK	2	14	NAS
UK	3	14	NAS
UK	5	5	OTHERS