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

27 February 1998
CPMP/209/98

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 35th plenary meeting on 24-25 February 1998.

Centralised Procedures
The Committee adopted by consensus the following Opinions:

- One positive Opinion on a Centralised application relating to a product containing a new active substance (Part B) indicated for *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection.
- Three positive Opinions for Centralised type II Variations.
- One positive Opinion following the annual re-assessment for a product indicated for the treatment of patients with relapsing - remitting multiple sclerosis.

The Committee noted the withdrawal of two applications.

Since the CPMP meeting in January 1998, the European Commission has granted a Marketing Authorisation for QUADRAMET (Samarium [^{153}Sm]), a therapeutic radiopharmaceutical indicated for pain palliation, for PRIMAVAX (combined vaccine indicated for the active immunisation against Diphtheria, Tetanus and Hepatitis B, for VIRAMUNE (nevirapine) indicated for the treatment of HIV-1 infected adults, and for MIRAPEXIN (pramipexole) indicated in idiopathic Parkinson's Disease (Annexes II & III).

An overview of Centralised Applications is given in Annex I.

Referral under Article 7(5) of Commission Regulation (EC) 541/95
One positive Opinion for a Type II Variation under the Mutual Recognition Procedure, referred to the EMEA, was adopted by majority and will be forwarded to the Commission.

Referral under Article 12 of Council Directive 75/319/EEC
Following a Referral under Article 12 initiated by France in February 1997, the CPMP adopted a final Opinion by majority for Terfenadine containing medicinal products for transmission to the Commission.

Scientific Advice
The CPMP adopted Scientific Advice in response to three requests, by consensus, on preclinical and/or clinical issues concerning new products indicated for the treatment of chronic lymphocytic leukaemia, diabetic peripheral neuropathy and breast cancer. Scientific Advice was also adopted on the follow-up for a product indicated in the treatment of irritable bowel syndrome.

New variant Creutzfeldt-Jakob Disease and plasma-derived medicinal products
The CPMP adopted a position statement on new variant Creutzfeldt-Jakob Disease and plasma-derived medicinal products (CPMP/201/98) (Annex IV).

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8551
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

Medicinal products containing Aprotinin and pulmonary surfactant of bovine origin

On 23 February 1998 the CPMP became aware of the action taken by the Italian Ministry of Health regarding the suspension from the Italian market of medicinal products containing substances sourced from bovine lung.

The CPMP currently has no new information to question the continued marketing of these products. The CPMP has urgently requested the Italian authorities to provide full information as to why they have taken the reported action. The Committee will keep this topic under active review.

Working Parties

The CPMP re-appointed the Chairpersons of the Working Parties (Biotechnology Working Party: Giuseppe Vicari, Efficacy Working Party: Alfred G. Hildebrandt, Pharmacovigilance Working Party: Sue Wood, Quality Working Party: Jean-Louis Robert, Safety Working Party: Per Sjöberg). Reports from all Working Parties were heard.

Efficacy Working Party

The following document was adopted and will come into operation in August 1998.

- Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95)

ICH

The following document was released for five months consultation:

- Note for Guidance on Specifications: test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96), ICH topic Q6B.

Mutual Recognition

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) (23 February 1998) which is circulated together with this press release (Annex V)

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 Applications		Total*
	Part A	Part B	
Applications submitted since 1 January 1995	**49**	**93**	**142**
Withdrawn	**3**	**10**	**13**
Opinions given by the CPMP	**26**	**40**	**66****
Marketing Authorisations granted by the Commission	**24**	**31**	**55*****

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

** 66 Opinions corresponding to 53 substances

*** 55 Marketing Authorisations corresponding to 46 substances

	Final		Total
	Part A	Part B	A + B
Variations type I	**68**	**73**	**141**
Variations type II	**19**	**37**	**56**
Extensions	**10**	**2**	**12**
Scientific Advice	**50**		**50**

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure

Since January 1998 Press Release

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) Opinion received on b) Date of decision c) Date of notification d) OJ No.
a) **Quadramet** b) samarium [^{153}Sm] c) Part B	a) Cis bio International b) FR	a) V10BX02 b) Therapeutic radiopharma-ceutical for pain palliation	a) Solution for injection d) 1.5 ml, 2.3 ml, 3.1 ml b) 3 Presentations	a) 18.12.96 b) 22.10.97 c) 198 Days d) 95 Days	a) 26.11.97 b) 05.02.98 c) d)
a) **Primavax** b) combined vaccine c) Part A	a) Pasteur Merieux MSD b) FR	a) J07CA b) Bacterial and viral combined vaccines	a) Suspension for injection b) 0.5 ml c) 2 Presentations	a) 21.01.97 b) 22.10.97 c) 201 Days d) 68 Days	a) 21.11.97 b) 05.02.98 c) d)
a) **Viramune** b) nevirapine c) Part B	a) Boehringer Ingelheim b) DE	c) JO5AX04 d) Treatment of HIV-1 infected adults	a) Tablets d) 200 mg b) 2 Presentations	a) 20.06.97 b) 22.10.97 c) 125 Days d) None	a) 20.11.97 b) 05.02.98 c) d)
a) **Mirapexin** b) pramipexole c) Part B	a) Pharmacia & Upjohn b) SW	a) N04BC b) Treatment of idiopathic Parkinson's disease	a) Tablets b) 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, 1.5 mg c) 10 Presentations	a) 18.06.96 b) 18.06.97 c) 208 Days d) 141 Days	a) 05.08.97 b) 23.02.98 c) d)

QUADRAMET

International Non-proprietary Name (INN): **Samarium [^{153}Sm] lexidronam pentasodium**

Abstract

On 5 February 1998 the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Quadramet, which contains samarium [^{153}Sm] lexidronam pentasodium INN, also referred to as samarium [^{153}Sm]-EDTMP sodium. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 October 1997. The Marketing Authorisation Holder responsible for this medicinal product is CIS bio international S.A., France.

The approved indication is for the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases which take up technetium [^{99m}Tc]-labelled biphosphonates on bone 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 Quadramet emits therapeutic β-radiation useful in the palliative treatment of bone pain, and γ-radiation capable of visualisation by a γ-camera. Three well-conducted Phase III clinical trials were designed to investigate the safety and efficacy of Quadramet in the proposed indication. These studies showed that:

- Quadramet given by slow intravenous injection, is effective in relieving pain from bone metastasis.
- A dose of 1.0 mCi/kg (37 MBq/kg) of Quadramet is significantly more effective than placebo.
- Approximately 55% to 65% of patients experience pain relief at 4 weeks after receiving 1.0 mCi/kg of Quadramet.
- Following administration of Quadramet at a dose of 1.0 mCi/kg, the onset of pain relief is apparent by week 1 or week 2 and the duration of relief is at least 8 weeks (median duration 3-4 months).

The only adverse pharmacological effect attributable to administration of Quadramet is reversible bone marrow suppression. The main adverse events are referred to in the SPC, Section 4.8 Undesirable effects: the adverse haematological events may have been related to the effect of Quadramet on bone marrow, whereas the other reported experiences were generally related to the patients' disease evolution or to concomitant medication.

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

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

PRIMAVAX

International Non-proprietary Name (INN): **Diphtheria, Tetanus and Hepatitis B vaccine**

Abstract

On 5 February 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product PRIMAVAX which is a combined trivalent vaccine containing active substances of 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 22 October 1997. The Marketing Authorisation Holder responsible for this medicinal product is Pasteur Mérieux MSD, France.

The approved indication is for the active immunisation against hepatitis B, caused by all known subtypes, diphtheria and tetanus in infants: for primary vaccination and for booster according to national vaccination policies. 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 substances of PRIMAVAX, diphtheria and tetanus toxoids and purified recombinant hepatitis B surface antigen, are non-infectious substances which protect infants from diphtheria, tetanus and hepatitis B by stimulating an immune response (immunogenic activity) against these diseases. PRIMAVAX is the combination of bacterial (diphtheria and tetanus) and viral (hepatitis B) components of authorised vaccines and is manufactured using established technology.

Clinical studies were designed to investigate the immunogenic activity and the potential for adverse reactions of the combined vaccine in infants. These studies showed that PRIMAVAX had an acceptable profile of adverse reactions and that it elicited an immune response comparable to that observed following simultaneous administration of the existing bivalent vaccine containing diphtheria and tetanus toxoids and the recombinant hepatitis B vaccine.

The most frequent undesirable effects observed in the first three days after any injection were local reactions such as pain, redness, induration and nodules and systemic reactions such as transient hyperthermia, irritability, drowsiness, unusual crying, vomiting and diarrhoea.

The CPMP, on the basis of the overall benefit/risk ratio considered that PRIMAVAX 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 Primavax.

VIRAMUNE

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

Abstract

On 5 February 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Viramune 200 mg tablets which contains nevirapine. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 22 October 1997. The Marketing Authorisation Holder responsible for this medicinal product is Boehringer Ingelheim International GmbH, Germany.

The approved indication is for use as part of combination therapy for the antiviral treatment of Human Immunodeficiency Virus (HIV) infected adult patients with advanced or progressive immunodeficiency. 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.

Viramune is the first representative of a new class of antiretroviral agents called non-nucleoside reverse transcriptase inhibitors authorised in the European Union. The active substance of Viramune, nevirapine, interferes with HIV replication by acting on the reverse transcriptase enzyme through a different mechanism compared to nucleoside analogues.

Clinical trials were designed to investigate the activity of 400 mg of Viramune daily administered in combination therapy with nucleoside analogues in HIV infected patients. These studies showed that in adults, triple combination of Viramune with nucleoside analogues (zidovudine and didanosine) demonstrated a significant advantage over double therapies on the basis of changes in biological markers such as decrease of the plasma viral load and increase of CD4 cell counts. The triple combination therapy showed also significant clinical benefit in terms of HIV progression events.

The most frequent and significant adverse events observed during treatment were rash, potentially severe when associated to fever or other general symptoms, and hepatic abnormalities. To decrease the incidence of rash, Viramune is recommended to be administered with a starting dose of 200 mg for two weeks, doubling the dose after that introductory period.

The CPMP, on the basis of the efficacy and safety data submitted that the provisional overall risk/benefit ratio for Viramune was favourable and recommended that the Marketing Authorisation should be granted under exceptional circumstances. The Marketing Authorisation Holder will submit a clinical programme for an expanded investigation of Viramune in combination therapy. Additional information will be provided on pharmaceutical, toxicological and clinical 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 Viramune.

MIRAPEXIN

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

Abstract

On 23rd February 1998, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product MIRAPEXIN, which contains pramipexole. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 18 June 1997. The Marketing Authorisation Holder responsible for this medicinal product is Pharmacia & Upjohn S.A., Luxembourg.

The approved indication is for the treatment of signs and symptoms of advanced idiopathic Parkinson's disease (PD) in combination with levodopa i.e. over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations). 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 MIRAPEXIN, pramipexole is an amino-benzothiazole derivative. It has been shown to be a selective and specific full dopamine (DA) receptor agonist with high affinity and selectivity for the DA D_2 receptor subfamily, and particularly the D_3 receptor subtype.

Clinical trials were performed in advanced idiopathic PD patients showing end-of-dose phenomena on optimized L-dopa therapy. In this patient population, a clinically relevant benefit of pramipexole was demonstrated for up to 6 months in comparison to placebo.

In general, the side-effect profile of pramipexole is typical of a DA agonist, including hallucinations, sleep disturbances and gastrointestinal effects. In addition, ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities should occur due to a suspected potential of pramipexole to cause ocular toxicity. An increased dyskinesia frequency, particularly in women could not be excluded, and therefore L-dopa dose adjustments may be required. By these precautions and recommendations, which are included in the SPC, the potential safety concerns were considered to be adequately addressed.

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

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

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

London, 25 February 1998
CPMP/201/98

CPMP POSITION STATEMENT ON NEW VARIANT CJD and PLASMA-DERIVED MEDICINAL PRODUCTS

SUMMARY

A workshop of international experts on transmissible spongiform encephalopathies (TSEs), convened under the auspices of CPMP, was held on 15 January 1998 to consider the available information on new variant Creutzfeldt-Jakob disease (nvCJD) and relevant TSEs. In the light of the emerging information, the CPMP has reached the following conclusions:

There is no evidence that sporadic, familial or iatrogenic Creutzfeldt-Jakob disease (CJD) are transmitted via blood transfusion or via plasma-derived medicinal products. Therefore, the CPMP reaffirms its recommendation that recall of plasma-derived products is not justified where a donor is later confirmed as having CJD.

It is now recognised that nvCJD has different characteristics to sporadic, familial and iatrogenic CJD. Knowledge of other TSE agents suggests that transmission of nvCJD by medicinal products derived from human blood or plasma is very unlikely. Nevertheless, since there is a lack of specific information on nvCJD, the CPMP considers that, as a precautionary measure, it would be prudent to withdraw batches of plasma-derived medicinal products from the market if a donor to a plasma pool is subsequently strongly suspected, by a recognised reference centre, of having nvCJD. However, consequences for essential medicinal products where alternatives are not available will need careful consideration by national authorities.

Since a recall involving albumin used as an excipient has the potential to cause major supply difficulties for essential products, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of cases of nvCJD have occurred.

1. Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease affecting approximately one person per million population per year. Cases can arise spontaneously (sporadic), may arise at higher frequency in families with certain genetic mutations (familial) or can result from exposure to infectious material (iatrogenic).

The CPMP has considered the risk of transmission of CJD via plasma-derived medicinal products on a number of occasions. The CPMP position adopted in December 1995[1] was based on both the epidemiological and experimental data available on CJD (sporadic, familial and iatrogenic) and concluded that recall of batches was not justified where a donor subsequently developed CJD.

In 1996, a few cases of a new variant (nv) form of CJD were identified[2]. Recent published studies provide strong evidence that nvCJD is distinct from sporadic CJD and is caused by the agent responsible for BSE in cattle[3,4.] The CPMP, therefore, considered that there was a need to review all available information (including unpublished/preliminary data) on nvCJD and on relevant transmissible spongiform encephalopathies (TSEs)[5]. A workshop of international experts, convened under the auspices of the CPMP, was held on 15 January 1998. This was followed, on 16 January, by a CPMP expert working group meeting to advise, in the light of the emerging information, on any implications for plasma-derived medicinal products. This CPMP position statement is based on the outcome of these meetings.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8551
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

2. Sporadic, Familial and Iatrogenic CJD

Investigations with sporadic CJD have failed to show any transmissibility by intravenous transfusion. Experimental infectivity studies with TSEs in animal models have only irregularly found evidence of low levels of infectivity in blood or its components. Many studies did not detect infectivity[6, 7, 8, 9] Such experimental studies are complex and can be difficult to interpret but these results infer that transmission by transfusion is highly unlikely.

Epidemiological studies have also been carried out, including the investigation of recipients of blood from donors who later developed CJD. There are no cases of CJD that have been causally linked to transfusion of blood or plasma-derived products. Case control studies and cohort studies have shown no association with transfusion of blood, its components, plasma fractions or plasma-derived medicinal products[9].

In conclusion, there is no evidence that CJD is transmitted via blood or plasma-derived products. Therefore, the recommendation from the CPMP that recall of plasma products is not justified where a donor is later confirmed as having CJD is still valid.

As a matter of principle, blood and plasma is collected from healthy donors and appropriate selection and exclusion criteria and screening tests are applied to ascertain this as far as is possible. For CJD, the Council of Europe recommends exclusion of individuals who have in the past been treated with extracts derived from pituitary glands, who have been recipients of dura mater grafts or who have a family history of CJD[10]. These exclusion criteria are also included in the European Commission proposal for a Council Recommendation on the suitability of blood and plasma donors and the screening of donations[11].

3. Characteristics of nvCJD

The clinical profile and progression of nvCJD are different from sporadic, familial and iatrogenic CJD[12, 13]. There are also differences in the neuro-histopathological profiles of the two diseases. nvCJD affects teenagers or young adults and so far all patients were under the age of 50 at the onset of the disease. Usually they present with psychiatric or sensory disturbances or a combination of both. These early non-specific clinical signs may last several months and the diagnosis of nvCJD may not be suspected for some time. Later during the course of the disease, clinical signs evolve into a more typical picture of CJD. The overall length of the clinical phase may be more than a year. In contrast, sporadic CJD has a relatively fast clinical course and an average age of onset of 65 years with only a small percentage of cases younger than 50 years of age.

So far there have been a total of 24 cases of nvCJD (23 cases in the UK and one case in France[14, 15]). Although the incidence does not appear to be rising, it is considered too early to predict the future trend for nvCJD.

4. Evaluation of Any Potential Risk of Transmitting nvCJD via Plasma-derived Medicinal Products

There is currently no information from any study as to whether infectivity of the nvCJD agent can be found in blood, plasma or plasma fractions and, if present, whether it can be transmitted by intravenous transfusion. The information known about other TSE agents suggests that transmission by transfusion is very unlikely. However, it has to be borne in mind that nvCJD has different characteristics to other forms of CJD.

Results from studies in animals suggest that the lymphoreticular system (tonsils, lymph nodes and spleen) may be involved in the replication of the agents of TSE although the extent of involvement varies[16, 17, 18]. Protease-resistant prion protein, the abnormal form of a cellular protein associated with TSEs, has been observed in samples of tonsil and spleen taken at necropsy in nvCJD cases but not in other CJD cases[6,19]. This finding may indicate an increased level of infectivity associated with the lymphoid system in nvCJD cases compared with other forms of CJD and, consequently, there may be an increased risk of infectivity being present in blood.

In conclusion, it is recognised that nvCJD is different to sporadic, familial and iatrogenic CJD. While knowledge of other TSE agents suggests that transmission of nvCJD by intravenous transfusion is very unlikely, in view of the lack of specific information on nvCJD, it is prudent to consider appropriate precautionary measures.

5. Precautionary Measures for nvCJD

Precautionary measures can be directed at selection/exclusion criteria for donors and screening tests for donations, processes of removal or inactivation of the agent, recall of batches where a donor subsequently develops nvCJD, and substitution with alternative non-plasma-derived products, where available.

5.1 Selection/exclusion criteria and screening tests for nvCJD

At the present time, there are no identifiable risk factors that can be used as exclusion criteria for nvCJD. There is also no laboratory test that could be used for screening of donors or donations.

5.2 Potential methods for inactivation/removal of the agent of nvCJD

At present there is no procedure that will inactivate the putative agent of nvCJD without destroying the activity of the product. The development of methods for the removal or inactivation of the agent of nvCJD is desirable. There are suggestions from experimental studies of the association of TSE infectivity with white blood cells[20, 21] and removal of this related cellular debris from plasma for fractionation might be beneficial.

5.3 Recall of batches where information becomes available post-donation

In view of the lack of adequate information on nvCJD, it is prudent to recall batches of plasma-derived medicinal products where a donor to a plasma pool subsequently develops nvCJD. Recall should also include medicinal products containing plasma-derived products as excipients. However, in both cases, consequences for essential medicinal products where alternatives are not available will need careful consideration by national authorities.

A case-by-case consideration would be appropriate where plasma-derived products have been used in the manufacture of other medicinal products.

CJD reference centres in Member States will be aware of strongly suspected cases of nvCJD some time before a definitive diagnosis is made. In these cases, if the patient has donated blood or plasma, the reference centres should inform the organisation involved in the collection of blood or plasma so that withdrawal can be actioned.

Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.

Albumin is used widely as an excipient in biological medicinal products. In this case it is usually present in small quantities. A single batch of albumin may be used to produce a number of batches of a medicinal product. Any recall of an albumin batch which has been used as excipient may result in a consequential recall of a number of products and could create severe shortages. To prevent this, in the short term, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of cases of nvCJD have occured.

Development of substitutes for plasma-derived albumin for excipient use is encouraged although it is recognised that this can be difficult and requires a long-term approach.

5.4 Substitution with alternative products

For plasma-derived medicinal products derived from plasma collected in countries where a number of cases of nvCJD have occurred, national competent authorities undertaking precautionary measures on

a case-by-case basis should take into account the therapeutic benefits, the purely theoretical risk, the processing of the product and the supply situation.

Use of recombinant products could be considered as an alternative treatment, where these are available. It is felt that this choice should remain within the remit of the physician, taking into account the needs of the individual patient. It should be noted that recombinant products are often stabilised with human albumin.

6. Recommendations and Proposals

6.1 As a precautionary measure, the CPMP considers it prudent to withdraw batches of plasma-derived medicinal products from the market if a donor to a plasma pool is subsequently strongly suspected or confirmed, by a recognised reference centre, of having nvCJD. This recommendation also includes medicinal products containing a plasma-derived product as an excipient. However, in both cases, consequences for essential medicinal products where alternatives are not available will need careful consideration by national authorities. A case-by-case consideration is recommended where plasma-derived products have been used in the manufacture of other medicinal products.

6.2 Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.

6.3 Since a recall involving albumin used as an excipient has the potential to cause major supply difficulties for essential products, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of cases of nvCJD have occurred.

6.4 Despite the absence of any evidence of a risk of transmission, manufacturers will be encouraged to investigate further precautionary measures that may be applicable in the manufacturing process of plasma-derived medicinal products including the development of methods to remove or inactivate the agent of nvCJD. Development of substitutes for plasma-derived albumin as an excipient for medicinal products is encouraged.

6.5 Knowledge of CJD and other human TSE agents, and nvCJD in particular, is still incomplete. All studies contributing to the further understanding of TSEs, including experimental and epidemiological studies, should be urgently promoted. These should include:

- Continued surveillance of CJD and extension of the European network of surveillance centres.
- Development of laboratory tests that can improve clinical diagnosis and of tests that could eventually be used for the screening of blood donations or donors.
- Further research into tissue distribution of infectivity in nvCJD as compared with other forms of CJD.

References

1. CPMP Press Release, December 1995, CPMP/938/95.
2. Will R.G., Ironside J.W., Zeidler M., Cousens S.N., Estbeiro K., Alperovitch A., Poser S., Pocchiari M., Hofman A., Smith P.G. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; **347:** 921-25.
3. Bruce M.E, Will R.G., Ironside J.W., McConnell I., Drummond D., Suttle A., McCardle L., Chree A., Hope J., Birkett C., Cousens S., Fraser H., Bostock C.J. Transmissions to mice indicate that "new variant" CJD is caused by the BSE agent. *Nature* 1997; **389:** 498-501.
4. Hill A.F., Desbruslais M., Joiner S., Sidle K.C.L., Gowland I., Collinge J. The same prion strain causes vCJD and BSE. *Nature* 1997; **389:** 448-450.
5. CPMP Press Release, November 1997, CPMP/1056/97.
6. Information presented to CPMP Expert Workshop on nvCJD, 15 January 1998.
7. Diringer, H. Sustained viremia in experimental hamster scrapie. *Arch. Virol.* 1984; **82:** 105-109.
8. Casaccia P., Ladogana A., Xi Y.G., Pocchiari M. Levels of infectivity in the blood throughout the incubation period of hamsters peripherally injected with scrapie. *Arch. Virol.* 1989; **108:** 145-149.
9. Ricketts M.N., Cashman N.R., Stratton E.E., ElSaadany S. Is Creutzfeldt-Jakob Disease transmitted in blood? *Emerging Infectious Diseases* 1997; **3:** 155-163.
10. Council of Europe Recommendation No R (95) 15 on the preparation, use and quality assurance of blood components, 4th edition; 1998, Council of Europe publishing.
11. Proposal for a Council Recommendation on the suitability of blood and plasma donors and the screening of donated blood in the European Community, COM(97) 605 final, 17.11.97.
12. Zeidler M., Stewart G.E., Barraclough C.R., Bateman D.E., Bates D., Burn D.J., Colchester A.C., Durward W., Fletcher N.A., Hawkins S.A., Mackenzie J.M., Will R.G. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. *Lancet* 1997; **350:** 903-907.
13. Zeidler M., Johnstone E.C., Bamber R.W.K., Dickens C.M., Fisher C.J., Francis A.F., Goldbeck R., Higgo R., Johnson-Sabine E.C., Lodge G.J., McGarry P., Mitchell S., Tarlo L., Turner M., Ryley P., Will R.G. New variant Creutzfeldt-Jakob disease: psychiatric features. *Lancet* 1997; **350:** 908-910.
14. UK Department of Health, monthly Creutzfeldt-Jakob figures, 2 January 1998.
15. Chazot G., Broussolle E., Lapras C.L. et al. New variant of Creutzfeldt-Jakob disease in a 26-year-old French man. *Lancet* 1996; **347:** 1181.
16. Klein M.A., Frigg R., Flechsig E., Raeber A.J, Kalinke U., Bluethmann H., Bootz F., Suter M., Zinkernagel R.M., Aguzzi A. A crucial role for B cells in neuroinvasive scrapie. *Nature* 1997; **390:** 687-690.
17. Brown, P. B lymphocytes and neuroinvasion. *Nature* 1997; **390:** 662-663.
18. Blättler T., Brandner S., Raeber A.J., Klein M.A., Vilgtländer T., Weissmann C., Aguzzi A. PrP-expressing tissue required for transfer of scrapie infectivity from spleen to brain. *Nature* 1997; **389:** 69-73
19. Hill A.F., Zeidler M., Ironside J., Collinge J. Diagnosis of new variant Creutzfeldt-Jakob disease by tonsil biopsy. *Lancet* 1997; **349:** 99-100.
20. Kuroda Y., Gibbs C.J. Jr., Amyx H.L., Gajdusek D.C. Creutzfeldt-Jakob disease in mice: persistent viremia and preferential replication of virus in low-density lymphocytes. *Infect Immun* 1983; **41:** 154-161.
21. Manuelidis E.E., Gorgacz E.J., Manuelidis L. Viremia in experimental Creutzfeldt-Jakob disease. *Science* 1978; **200:** 1069-1071.

MRFG
Mutual Recognition Facilitation Group

Report from the meeting held on 23rd February 1998

The MRFG noted that 7 new mutual recognition procedures have been finalised during the month of January 1998 as well as 8 type I and 6 type II variations.
The status as of 31st January 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	7	47	8	39	6	90	--

15 new procedures (regarding 29 products) have been started in January 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	2	5	0	0	2

The categories of the 279 procedures from new applications finalised and in process up to 31st December 1997 are as follows:

New active substance[1]	Line extensions[2]	Fixed combinations	Generics	Herbal products[3]	OTC[4]	Others[5]
86	38	22	52	3	6	72

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 January 1998:

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	7
DE (3)	1
DE (3)	14
NL (3)	5
SE (2)	14
SE (2)	14
UK (1)	10
UK (3)	3
UK (1)	14
UK (2)	13
UK (1)	14
UK (1)	13
UK (1)	1
UK (2)	6
UK (3)	5

General issues

- The Group was given a report on the progress of establishing Eudranet.
- The Group received a report from its Eudratrack subgroup. It was noted that progress had been made and that the system should be operational by May although problems remained with the extraction of statistical information from the database.
- The Group agreed a major initiative to further enhance the procedure by tackling delays in validation and check-in. From May 1st for a six-month trial the group will follow a procedure of automatic validation and check-in by default. This means that validation and check-in will be authorised within 10 days unless a Concerned Member State specifically raises an issue and gives full details to the RMS and the applicant company. This should at a stroke remove a source of significant delays for many procedures.
- The Group held a very constructive discussion on issues concerning the full operation of the MR procedure after the end of the transition. The discussion focused on a practical interpretation of identically and of how line extensions could use the MR procedure. A document will be shared with the European Commission following the March MRFG. A document on the handling of cross-referrals applications (clones) in the MR procedure is also being elaborated.
- The Group also commenced consideration on how SPCs might be made available for completed MR procedures and how fees and other national requirements might be made readily accessible to applicants.
- A two-day meeting of the MRFG will be held in May 1998 at the invitation of the UK to consider strategic issues in the MR procedure.
- The Group concluded its meeting with a very constructive discussion with the three European Trade Associations, EFPIA, AESGP and EGA. The Group will hold a further meeting with the three associations in June.

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

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