ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS AND MARKETING AUTHORISATION HOLDER IN THE MEMBER STATE

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	UMAN BIG 180 I.E./ml Injektionslösung	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml
Denmark		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	UMAN BIG	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml
Germany		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	UMAN BIG	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml
Hungary		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	Umanbig 180 NE/ml	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml
Italy	Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY		UMAN BIG	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml
Poland		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	UMAN BIG	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Portugal		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	UMAN BIG	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml
Sweden		Kedrion S.p.A. Loc Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) - ITALY	Umanbig 180 IU/ml solution for injection	180 IU/ml	Solution for injection	Intramuscular use	180 IU/ml 540IU/3ml

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF UMAN BIG

UMAN BIG is a plasma derived medicinal product preparation of immunoglobulins (mainly IgG) with a specifically high content of antibodies against the hepatitis B virus surface antigen (HBsAg). UMAN BIG belongs to the pharmacological class of immune sera and human specific immunoglobulins for intramuscular administration and contains 100-180 g/l of plasma proteins with at least 90% of them representing Immunoglobulin G (IgG). Specific neutralizing antibodies against the Hepatitis B virus are present at a concentration of not less than 180 IU/ml. It has been marketed since 1979, for intramuscular use. UMAN BIG is manufactured from large pools of human plasma, through a consolidated and validated industrial process that ensures compliance with Ph. Eur. requirements, as well as reproducibility of quality characteristics, hence consistency of the biological response. The application for UMAN BIG 180 IU/ml solution for injection was submitted through the Mutual Recognition Procedure, on the basis of the marketing authorisation granted by the RMS (Italy) on the 2nd of June 1979.

The objecting member state Greece raised a potentially serious risk to public health related to the design of the submitted PK study designed to support the initial application, since the population enrolled in the PK study represents a different patient population from the population intended for the use of UMAN BIG and because the dosage administered was different from the posology indicated in the SPC. Greece considered that a change in liver function is a common cause of altered drug pharmacokinetics and that the dosage in the PK study was much higher than that recommended in the relevant core SPC and proposed SPC. Therefore the results of the study can not be extrapolated to the population intended for use and consequently, the protective anti-HBs level in the population intended for use is not known and neither whether the recommended dose in the core SPC could guarantee an appropriate antibody level to prevent hepatitis B in adults and hemodialysed patients as well as newborns of a hepatitis B virus carrier-mother. During the RMS procedure, the Applicant committed to carry out an observational study on newborns with mothers carrying the hepatitis B virus. The study protocol was submitted to the RMS and all CMSs.

Although the Reference Member State concluded that the objections raised had been resolved, the Objecting Concerned Member State was still of the opinion that a potential serious risk to public health was identified for this particular product, with regards to safety and efficacy. The procedure was therefore referred to the CHMP in October 2008. Following the referral to the CHMP, the Committee noted the position of the RMS and the objecting CMS and decided to adopt a List of Questions addressed to the Blood Products Working Party (BPWP), in order to receive the view of the working party, on both specific issues related to this specific product and on issues related to immunoglobulins in general.

Summary of the report from the BPWP and CHMP position:

1. Is a single PK study conducted in a population and dose regimen different from the one intended for the Marketing Authorisation adequate and sufficient to support efficacy in all indications foreseen in the European core SPC for immunoglobulins, with no specific efficacy clinical trial?

The Applicant stated that the only relevant measure of efficacy for this kind of product is the level of protective anti-HBs achieved in the plasma, since after the introduction of vaccination it is no longer feasible to assess the efficacy of the product on the basis of the incidence of new infections. In addition, the Applicant submitted several clinical studies conducted in populations that are representative of the populations indicated in the SPC as bibliographic reference, which confirm the efficacy of UMAN BIG in the claimed indications. The Applicant also demonstrated the impossibility to perform any clinical study in any of the populations included in the indication, apart from newborns, after the introduction of the vaccination.

The Applicant submitted data from study PK KB-036, which evaluates the PK profile of Hepatitis B

immunoglobulins in HBs-Ag-Negative patients who have received liver transplantation (OLT patients) in order to support the efficacy of the product. The study was performed in different populations and in much higher posology than recommended in the relevant core SPC because the Applicant considered that the indications, posology and pharmacokinetic information reported in the core SPC are not product specific, but rather that they apply to products complying with the relative European Pharmacopoeia monograph, such as UMAN BIG. The Applicant provided bibliographic data showing that the pharmacokinetics of UMAN BIG in the population in which the PK study was carried out is super-imposable to that of healthy volunteers; therefore the population of study KB 036, although representing a specific subset of patients, did not influence the results obtained. Literature references show also that the pharmacokinetic profile of UMAN BIG is comparable to that of other intramuscular Hepatitis B immunoglobulin products.

The Applicant provided comprehensive published data on the use of UMAN BIG in the prophylaxis of hepatitis B in newborns from HBsAg carrier mothers, demonstrating its efficacy in this particular subset of population. More than 1,000 Italian newborns included in the studies (published between 1983 and 2001) received UMAN BIG and the dose regimen and protective threshold (10 mIU/ml) are consistent with the provisions of the current core SPC and proposed SPC. There are enough data regarding the safety and PK of UMAN BIG in newborns, administered for the prevention of HBV transmission from HBsAg infected mothers. There is also convincing evidence that UMAN BIG, along with active anti-HBV immunization, prevented transmission of HBV to newborns from anti-HBe+ mothers. Finally, the papers quoted by the Applicant indicate that UMAN BIG prevented newborns from HBeAg infected mothers from becoming chronic HBsAg carriers.

The BPWP considered that UMAN BIG adheres to the Ph. Eur. Monograph (0722) and has shown a PK and safety profile within the expected ranges of an immunoglobulin, in a study in stabilized HBsAg/HBeAg negative post-liver transplant patients. Levels of antibodies of ≥100IU/ml were achieved. Furthermore, published data from non-sponsor driven studies using UMAN BIG in the prophylaxis of hepatitis B in approximately 1000 newborns of HBsAg carrier mothers was submitted. The dose regimen and protective threshold were consistent with the current core SPC. Based on the proof-of-principle applied to all immunoglobulins, the BPWP considered that submitting a single PK study is acceptable.

The CHMP noted that UMAN BIG is manufactured from large pools of human plasma, through a consolidated and validated industrial process and that the conformity of UMAN BIG to Ph. Eur. Monographs is well established. The PK KB-036 study demonstrates that the anti-HBsAg antibodies in UMAN BIG maintain the kinetic profile of the natural antibodies and that the entire production process does not affect their characteristics or the integrity of the immunoglobulin molecule and therefore does not alter the biological response. The PK behaviour, especially in terms of half life of the anti HB antibodies and maintenance of a protective antibody level titre can be considered as an acceptable surrogate marker of efficacy. The CHMP also noted the commitment to carry out an observational study on newborns with mothers carrying the hepatitis B virus. Therefore, the CHMP considered that these findings, together with the compliance with the Ph. Eur. requirements in terms of potency and the long lasting experience in clinical use, support the efficacy of the product and the indications applied for in the SPC and considered that submitting a single PK study is acceptable.

2. Are Post Marketing Safety (PMS) data generated in only one EU country adequate to define the safety profile of the product?

The Applicant provided a summary of the available post-marketing experience data for both UMAN BIG and IMMUNOHBs (a different brand name an identical product with the same pack sizes and concentration, produced by the same manufacturing sites, using the same manufacturing process), indicating that approximately 143,381,160 IU of IMMUNOHBs and approximately 11,695,680 IU of UMAN BIG have been sold worldwide between June 1995 and December 2007. The Applicant also provided exposure data, stating that a total of about 143,589 injections were given to patients. During this period, no notification of any adverse reaction related to the products IMMUNOHBs and UMAN BIG was received by the Applicant, either through the literature or the Regulatory Authorities,

Doctors, Pharmacists or Patients. A literature search on specific immunoglobulins for intramuscular administration has shown, in general, a satisfactory profile of tolerability and safety, even if mild to moderate adverse events have been observed. Limited cases of nausea, vomiting, hypotension, tachycardia, allergic or anaphylactic reactions have also been reported. Moreover, the potential risk of transmitting infective agents through administration of anti hepatitis B immunoglobulins is only theoretical due to the state of the art knowledge and procedures for quality control.

The Applicant concluded that no new information on tolerability is available to suggest a modification of the safety profile of UMAN BIG. According to the Applicant, the characteristics of the product, the available safety data, and the overall safety system in place do not warrant any recommendations for further risk minimisation activities.

The BPWP considered that post marketing safety data generated in only one EU member state can be adequate to define the safety profile of the product provided that the quality of the data and the Pharmacovigilance system is sufficient.

The CHMP noted that an active pharmacovigilance system is in place in Italy since 1975 guaranteeing a strict control of the adverse events linked to medicinal products and that the Italian pharmacovigilance database does not contain a single suspected adverse reaction signal related to UMAN BIG, which is consistent with the statement of the Applicant of the safety of UMAN BIG. Therefore, the CHMP was of the opinion that the submitted post marketing safety data are adequate to assess the safety profile of the product, even if they originate from a single EU member state.

3. Should non-clinical product-specific safety data be submitted for this product, in line with point 5.3 the Core SPC for human Immunoglobulin for IV administration? And if yes, what kind of non-clinical studies shall be performed?

The BPWP considered that data from pre-clinical studies do not provide any additional information concerning the actual immunoglobulin and that often, data on the excipients are necessary. UMAN BIG contains glycine as the excipient, a natural amino acid and therefore not expected to cause any problems.

The CHMP considered that based on the 28 years of clinical experience with the existing formulation of UMAN BIG, the safety in humans can be considered to have been extensively assessed. The CHMP was also of the opinion that a new pre-clinical investigation would not be justified at the moment, based on the extensive clinical use and the supporting pharmacovigilance data.

4. Does the BPWP consider necessary the development of a specific Note for Guidance on the Clinical Investigation of Human Plasma derived Hepatitis-B Immunoglobulins to outline requirements particularly with regard to the design of the clinical studies and the required safety data for the claimed indications?

The BPWP noted that a guideline would not be helpful for currently ongoing applications but that a combined Guideline on the data expected to support applications for specific immunoglobulins against hepatitis B, varicella, tetanus, tick-borne encephalitis and rabies, for which there is currently only a core SPC.

The CHMP fully endorses the development of a combined Guideline on specific immunoglobulins, in order to harmonise the requirements for granting marketing authorization.

In conclusion, the CHMP sought advice from the Blood Products Working Party on the four questions raised for discussion and noted the positive recommendation in favour of UMAN BIG expressed by the BPWP in a report dated 27 November 2008. The CHMP noted that no safety issues were raised in over 28 years of extensive clinical practice, following extensive use in the pre-and-post vaccination era and that the Italian pharmacovigilance database does not contain a single signal of any suspect

adverse reaction related to UMAN BIG. The CHMP also noted the commitment to carry out an observational study on newborns with mothers carrying the hepatitis B virus. The CHMP considered that efficacy in the sought indications has been demonstrated, based on the submitted PK study and the literature data. Therefore, the CHMP is of the opinion that the benefit/risk balance of the product can be considered to be positive and that the product is approvable.

GROUNDS FOR OPINION

Whereas

- the CHMP considered that the post marketing safety data submitted are adequate to establish the positive safety profile of UMAN BIG,

- the CHMP considered the efficacy profile of UMAN BIG to be satisfactory for the indications applied for in the SPC,

- the CHMP considered that the benefit/risk of UMAN BIG is positive,

the CHMP has recommended the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination Group procedure as mentioned in Annex III for UMAN BIG.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.