(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 June 2005 (30.06.2005)

PCT

(10) International Publication Number
WO 2005/058334 A1

(51) International Patent Classification[7]: A61K 35/16, A61P 7/02

(21) International Application Number: PCT/EP2004/053608

(22) International Filing Date: 20 December 2004 (20.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03029359.1 19 December 2003 (19.12.2003) EP

(71) Applicant *(for all designated States except US)*: **OCTAPHARMA AG** [CH/CH]; Seidenstr. 2, CH-8853 Lachen (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HEGER, Andrea** [AT/AT]; Kaiser-Ebersdorferstr. 11/4/7, A-1110 Wien (AT). **RÖMISCH, Jürgen** [AT/AT]; Laxenburgerstr. 152/2/6, A-2331 Vösendorf (AT). **SVAE, Tor-Einar** [AT/AT]; Karlsgasse 9, A-2340 Mödling (AT). **MARGUERRE, Wolfgang** [DE/DE]; Philosophenweg 21, 69120 Heidelberg (DE).

(74) Agents: **MEYERS, Hans-Wilhelm** et al.; Patentanwälte von Kreisler Selting Werner, Postfach 10 22 41, 50462 Köln (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A UNIVERSALLY APPLICABLE VIRUS INACTIVATED BLOOD PLASMA PRODUCED FROM PORTIONS OF NON-CAUCASIAN PLASMA

(57) Abstract: A blood plasma for human use pooled from donors which belong to 10 % or more to a non-Caucasian population, the plasma obtainable by mixing blood or blood plasma of blood groups A and B, optionally AB without admixing substantial amounts of blood or blood plasma of blood group 0 characterized in that four to eight parts of blood or blood plasma from donors having the blood group A, more than three parts to seven parts of blood or blood plasma from donors having the blood group B, zero to two parts of blood or blood plasma from donors having the blood group AB.

WO 2005/058334 A1

A universally applicable virus inactivated blood plasma produced from portions of non-Caucasian plasma

The present invention relates to a blood plasma pooled from donors which are substantially of non-Caucasians, a pharmaceutical preparation comprising the blood plasma of the invention and the use of the blood plasma of the invention for the manufacturing of a medicament.

Background of the invention

Blood groups and the inherent inter-individual differences in human blood were discovered by Karl Landsteiner. The ABO blood group system comprises 4 main phenotypes; 0, A, B, and AB, the phenotype being governed by codominant alleles at the ABO locus on chromosome 9.

Transfusion of ABO-identical or compatible plasma, such as FFP of specific blood groups is an effective and generally well tolerated treatment of various types of complex or isolated coagulation factor deficiencies, in thrombotic thrombocytopenic purpura, and in repeated large volume plasma exchange. However plasma transfusion in principle carries some risk of adverse events among recipients, which include both transmission of infectious and non-infectious diseases.

Non-infectious adverse events typically occur when immunologic incompatibility between e.g. transfused donor red blood cells and recipient antibodies produce accelerated destruction of transfused cells. According to Landsteiner's law, any human individual has antibodies in plasma if the corresponding antigen is absent from the red blood cells. For example, by infusing plasma from a group A donor to a group B patient, anti-B antibodies from donors plasma will react with and lead to destruction of the patient's red blood cells. Similarly, plasma from a group B donor, which contains anti-A

antibodies, is incompatible with a blood group A patient; and plasma from a group 0 donor, which contains both anti-A and anti-B antibodies, is incompatible with a patient having blood group A, B, or AB. Therefore, the blood types must be matched to avoid a reaction based on ABO incompatibility.

In addition to non-infectious adverse events, many infectious agents, including viruses, bacteria, and parasites, can be transmitted through blood transfusion. Well recognized viruses include hepatitis A virus (HAV), hepatitis B Virus (HBV), hepatitis C Virus (HCV), human immunodeficiency virus types 1 and 2 (HIV-1/2), and human parvovirus (PV). The risk of transmission of viral infections is minimized by the introduction of donor screening and new test procedures, and in particular, by the introduction of virus inactivation and/or virus removal procedures. Such procedures include virus inactivation by solvent detergent treatment (EP-A-0 131 740), irradiation, and pasteurization, or virus removal by nanofiltration.

Solvent detergent treated human plasma with specific blood groups, such as Octaplas® of blood groups A, B, 0, or AB (Octapharma AG Switzerland), was already developed as an alternative to FFP in order to prevent virus transmission.

Universally applicable plasma in principle can be obtained by using only AB plasma, which contains neither anti-A nor anti-B antibodies (IgM and IgG), thus is compatible with any patient regardless of his blood group. However, the frequency of AB donors (4%) is limited. A plasma suitable for universal transfusion is obtained, if anti-A and/or anti-B antibodies from blood group B and A donors, respectively are removed and/or neutralised by optimal mixing of plasma with the different blood groups. Such neutralization of antibodies was already described (WO-A-99/07390) by mixing 6 to 10 parts of blood or blood plasma of blood group A, 1 to 3 parts of blood or blood plasma of blood group B, and optionally 0 to 1.5 parts of blood or blood plasma of blood group AB without admixing substantial amounts of blood or blood plasma derived from blood group 0.

All human races in principle share the same blood system, although the frequency of the four main ABO blood groups varies in populations throughout the world. Measuring the titres of anti-A and anti-B antibodies, it was surprisingly found that not only the frequency of ABO blood groups but also the titers of blood group specific antibodies differ between different ethnic groups. In the Caucasians, in general, the titers of anti-A in group B and group 0 subjects tend to be higher than the titers of anti-B in group A and group 0 subjects. On the contrary, in people with non-Caucasian background, such as African-American, Hispanic or Native-American donors, anti-B is almost as high as anti-A titers. Consequently, mixing Caucasian plasma with a considerable portion of non-Caucasian origin at the above mentioned ratios, no optimal neutralization of blood group specific antibodies was found. For example, by mixing of 7 parts of blood group A plasma with 3 parts of blood group B plasma, a considerable portion of which was collected from non-Caucasian donors, high anti-B titres, both of IgM and IgG-type, were found in the plasma pool mixture.

Description of the invention

One object of the invention was to develop a further applicable virus inactivated blood plasma, which is produced by optimal mixing of blood plasma of different blood groups, obtained from blood or plasma of Caucasian origin and portions of non-Caucasian donors, such as donors of African-American, Hispanic and native American origin, facilitating an optimal neutralization of blood group specific antibodies in the mixture.

This object is solved by a blood plasma for human use pooled from donors which belong to 10 % or more to a non-Caucasian population, the plasma obtainable by mixing blood or blood plasma of blood groups A and B, optionally AB without admixing substantial amounts of blood or blood plasma of blood group 0 which comprises

- four to eight parts of blood or blood plasma from donors having the blood group A,
- more than three to seven parts of blood or blood plasma from donors having the blood group B,
- zero to two parts of blood or blood plasma from donors having the blood group AB.

Fractions of blood group 0 can be present in the plasma of the invention so long as these fractions do not introduce antibodies exceeding substantially the overall A or B blood group antigen concentration.

In the blood plasma product of the invention, ABO blood group specific antibodies are essentially neutralized by free blood group substances by an optimal mix of different blood groups, and therefore, this plasma can be transfused regardless of the patient`s ABO blood group. Therefore, the blood plasma of the invention further reduces both, the risk of transfusion related infections as well as ABO incompatibility related fatalities.

In another embodiment of the invention the blood plasma mixture is composed of

- five to six parts of blood or blood plasma derived from donors with blood group A,
- four to five parts of blood or blood plasma derived from donors with blood group B,
- zero to one part of blood or blood plasma derived from donors with blood group AB, and
- substantially no blood or blood plasma derived from donors with blood group 0.

The ABO blood group specific antibody titre of the blood plasma of the invention is in particular lower than 16 for anti-A and anti-B IgM antibodies, and lower than 64 for anti-A and anti-B IgG antibodies. In another mixture of

the blood plasma of the invention, the titre of the anti-A and anti-B IgM antibodies is lower than 8, and the titre of anti-A and anti-B IgG antibodies is lower than 32, employing assays known to a skilled person and described in the European Pharmacopeia (indirect Coombs Test).

Preferably, the blood plasma of the invention is inactivated by the method of EP-A-131740, known as solvent/detergent treatment, irradiation, pasteurisation and/or nanofiltration. A typical solvent/detergent-treatment is for instance use of detergents such as oxyethylated polyphenols, like Triton-X-100, and/or polyoxyethylene derivatives of fatty acids such as Tween 80 and tri-N-butylphosphate (TNBP), or combinations thereof. Also medium to long-chain fatty acids or salts thereof, both saturated and unsaturated, preferably caprylic acid or its salts, can be used for virus inactivation. Other methods are irradiation, pasteurization or nanoflitration. All these methods are known to the person skilled in the art.

Preferably, the blood plasma of the invention is frozen or lyophilized.

The blood plasma of the invention shows coagulation activities comparable to fresh frozen plasma.

The present invention is further illustrated by the following example.

Example 1

190 kg of fresh frozen plasma of blood group A, 156 kg of plasma of blood group B, and 34 kg plasma of blood group AB, all obtained in a considerable portion from non-Caucasian donors, are mixed after thawing at +37 °C. The obtained plasma mixture is virus inactivated by using the solvent detergent method. After removal of the virus inactivating reagents and freeze-drying, the amount of free anti-A and anti-B antibodies of both IgM and IgG-type is measured. The titre of anti-A and anti-B antibodies of IgM-type is lower than 8 and the titer of anti-A and anti-B antibodies of IgG-type is lower than 32.

Example 2

205 kg of fresh frozen plasma of blood group A, and 137 kg of plasma of blood group B, all obtained in a considerable portion from non-Caucasian donors, are mixed after thawing at +37 °C . The same procedure as in example 1 was used. The titre of anti-A and anti-B antibodies of IgM-type are lower than 8 and of IgG-type lower than 32.

Claims

1. A blood plasma for human use pooled from donors which belong to 10 % or more to a non-Caucasian population, the plasma obtainable by mixing blood or blood plasma of blood groups A and B, optionally AB without admixing substantial amounts of blood or blood plasma of blood group 0 characterized in that

   - four to eight parts of blood or blood plasma from donors having the blood group A,
   - more than three parts to seven parts of blood or blood plasma from donors having the blood group B,
   - zero to two parts of blood or blood plasma from donors having the blood group AB.

2. The blood plasma according to claim 1 virus-inactivated by any virus inactivation or virus removal method.

3. The blood plasma according to claim 2 wherein the blood plasma was inactivated by solvent/detergent treatment, irradiation, pasteurisation and/or nanofiltration.

4. The blood plasma according to claim 3 wherein the virus inactivation was performed by using detergents such as oxyethylated polyphenols, like Triton-X-100, and/or polyoxyethylene derivatives of fatty acids such as Tween 80 and tri-N-butylphosphate (TNBP), or combinations thereof.

5. The blood plasma according to claim 3 virus inactivated by treatment with long-chain fatty acids, such as caprylic acid or the respective salts.

6. The blood plasma according to any of the forgoing claims substantially free of virus inactivating agents.

7. The blood plasma of any one of the foregoing claims having ABO blood group specific antibody titre lower than 16 for anti-A and anti-B IgM antibodies, and lower than 64 for anti-A and anti-B IgG antibodies.

8. The blood plasma of any of the foregoing claims in liquid, frozen, dried, or lyophilised form.

9. A pharmaceutical composition comprising the blood plasma of any one of the claims 1 to 8.

10. Use of the blood plasma of any of the foregoing claims for the manufacturing of a medicament for the treatment of coagulation factor deficiencies, thrombotic purpura, and in repeated large volume plasma exchange.

11. A process for manufacturing the blood plasma of any one of the claims 1 to 8 by admixing

- four to eight parts of blood or blood plasma from donors having the blood group A,
- more than three parts to seven parts of blood or blood plasma from donors having the blood group B,
- zero to two parts of blood or blood plasma from donors having the blood group AB.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/053608

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/16 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/07390 A (OCTAPHARMA AG ; SVAE TOR EINAR (NO); MARGUERRE WOLFGANG (SE)) 18 February 1999 (1999-02-18) claims page 3	1-11
X	DATABASE WPI Section Ch, Week 200219 Derwent Publications Ltd., London, GB; Class B04, AN 2002-140576 XP002280416 & CN 1 321 468 A (DU Z) 14 November 2001 (2001-11-14) abstract	1-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2005	22/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	THALMAIR, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BERKOW R ET AL: "THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, FIFTEENTH EDITION. PASSAGE TEXT" MERCK MANUAL OF DIAGNOSIS AND THERAPY, RAHWAY, MERCK & CO, US, 1987, page 1132, XP002054540 the whole document	1-11
A	BURNOUF T ET AL: "L'INACTIVATION DES VIRUS DANS LES FRACTIONS PLASMATIQUES A USAGE THERAPEUTIQUE VIRAL INACTIVATION ON PLASMA FRACTIONS FOR THERAPEUTIC USE" JOURNAL OF EXPERIMENTAL AND CLINICAL HEMATOLOGY / NOUVELLE REVUE FRANCAISE HEMATOLOGIE, SPRINGER INTERNATIONAL, XX, vol. 29, no. 1, 1987, pages 93-96, XP000573465 ISSN: 0029-4810 the whole document	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/053608

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-11

It is not specified in claim 1 in which ratio the used parts of the different blood groups have been derived from Caucasian or non-Caucasian donors.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/053608

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9907390 A	18-02-1999	EP 0896824 A1	17-02-1999
		AT 225665 T	15-10-2002
		AU 742427 B2	03-01-2002
		AU 9256998 A	01-03-1999
		BG 64350 B1	30-11-2004
		BG 104117 A	29-12-2000
		BR 9811839 A	15-08-2000
		CA 2299421 A1	18-02-1999
		CN 1272061 A	01-11-2000
		CZ 20000370 A3	13-09-2000
		DE 69808620 D1	14-11-2002
		DE 69808620 T2	26-06-2003
		DK 991416 T3	10-02-2003
		EA 3182 B1	27-02-2003
		WO 9907390 A1	18-02-1999
		EP 0991416 A1	12-04-2000
		ES 2185218 T3	16-04-2003
		HK 1026146 A1	21-02-2003
		HU 0004795 A2	28-04-2001
		ID 24308 A	13-07-2000
		JP 2001513507 T	04-09-2001
		NO 20000578 A	27-03-2000
		NZ 502661 A	30-03-2001
		PL 338794 A1	20-11-2000
		PT 991416 T	28-02-2003
		TW 555563 B	01-10-2003
		US 2002182195 A1	05-12-2002
CN 1321468 A	14-11-2001	WO 02083157 A1	24-10-2002