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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Consultation procedure Public Assessment Report (CPAR)

Consultation on an ancillary medicinal substance incorporated in a medical device

Medical device: Gems Medium Suite

Ancillary medicinal substance: Human Serum Albumin

Procedure No. EMEA/H/D/003740/0000



Table of contents

1. Background information on the procedure	4
1.1. Submission of the dossier	4
1.2. Steps taken for the assessment of the product	4
1.3. Manufacturers	5
1.4. Remarks to the notified body	6
1.5. Recommended measures to the notified body	6
2. Scientific overview and discussion	7
2.1. General information	7
2.2. Quality documentation	7
2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself ...	7
2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device	10
2.2.3. Discussion and conclusion on chemical, pharmaceutical and biological aspects	14
2.3. Non-clinical documentation	15
2.3.1. Discussion and conclusion on the non-clinical documentation	15
2.4. Clinical evaluation	16
2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body	16
2.4.2. Clinical safety of the ancillary medicinal substance incorporated in the medical device	17
2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device.....	18
2.4.4. Discussion and conclusion on the clinical evaluation	19
2.5. Overall conclusions	20
2.6. Recommendation	21

LIST OF ABBREVIATIONS

ART	Assisted Reproductive Technology
BLM	Blastocyst Media
BSE	bovine spongiform encephalopathy
CE	Conformité Européenne
CGH	Comparative genomic hybridization
CLM	Cleavage Media
EC	European Commission
ET	embryo transfer
HAV	Hepatitis A Virus
HIV-1	Human Immunodeficiency Virus 1
HSA	Human Serum Albumin
IUI	intra-uterine insemination
IVF	In-Vitro Fertilisation
MEA	Mouse Embryo Assay
MEV	Mouse Encephalomyelitis Virus
NAT	Nucleic Acid Test
OAB	Octapharma AB, Stockholm, Sweden
OPG	Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria
ORB	Oocyte Retrieval Buffer
PETG	Polyethylene Terephthalate Glycol
Ph. Eur.	European Pharmacopoeia
PMF	Plasma Master File
PPV	Porcine Parvovirus
PRV	Pseudorabies Virus
PVP	Polyvinylpyrrolidone
QOS	Quality Overall Summary
REO	Reovirus type 3
SBV	Sindbis Virus
S(m)PC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The notified body BSI submitted to the European Medicines Agency (EMA) on 05 June 2013 an application for consultation on Human Serum Albumin Solution incorporated as ancillary medicinal substance in the medical device Gems Medium Suite, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Andrea Laslop

CHMP peer reviewer: Ondřej Slanař

- The application was received by the EMA on 05 June 2013.
- The procedure started on 25 September 2013.
- The Rapporteur's first assessment report was circulated to all CHMP members on 13 December 2013. The Co-Rapporteur's first assessment report was circulated to all CHMP members on 13 December 2013.
- During the meeting on 20-23 January 2014, the CHMP agreed on the consolidated list of questions to be sent to the applicant. The final consolidated list of questions was sent to the applicant on 23 January 2014.
- During the CHMP meeting on 17-20 March 2014, the CHMP agreed on a clock-stop extension of three months, requested by the Applicant on 14 March 2014.
- The applicant submitted the responses to the CHMP consolidated list of questions on 27 July 2014.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of questions to all CHMP members on 27 August 2014.
- During the CHMP meeting on 22-25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During the CHMP meeting on 20-23 October 2014, the CHMP agreed on a clock-stop extension of one month, requested by the Applicant on 03 October 2014.
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues on 13 November 2014.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP members on 01 December 2014.
- During the CHMP meeting on 15-18 December 2014, the CHMP agreed on a second list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP consolidated second list of outstanding issues on 22 January 2015.

- The Rapporteurs circulated the joint assessment report on the applicant's responses to the second list of outstanding issues to all CHMP members on 03 February 2015.
- During the CHMP meeting on 23-26 February 2015, the CHMP agreed on a third list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated third list of outstanding issues on 25 March 2015. Additional information was received on 17 April 2015 and 20 April 2015.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the third list of outstanding issues to all CHMP members on 08 April 2015. An updated assessment report was circulated on 20 April 2015.
- During the meeting on 20-23 April 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the committee, issued a positive opinion for quality and safety including the clinical benefit/risk profile of Human Serum Albumin Solution as ancillary medicinal substance used in Gems Medium Suite on 23 April 2015.

1.3. Manufacturers

Manufacturers of the active substance used as ancillary medicinal substance

Octapharma AB
 Elersvagen 40
 SE-112 75 Stockholm
 Sweden

Octapharma Pharmazeutika Produktionsges.m.b.H.
 Oberlaaer Strasse 235
 A-1100 Vienna
 Austria

Manufacturers of the finished product used as ancillary medicinal substance

Octapharma AB
 Elersvagen 40
 SE-112 75 Stockholm
 Sweden

Octapharma Pharmazeutika Produktionsges.m.b.H.
 Oberlaaer Strasse 235
 A-1100 Vienna
 Austria

Octapharma GmbH
 Niederlassung Dessau
 Otto-Reuter-Strasse 3
 06847 Dessau-Rosslau

Germany

Manufacturer responsible for batch release

Octapharma AB
Elersvagen 40
SE-112 75 Stockholm
Sweden

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna
Austria

Manufacturer of the medical device

Genea Biomedx UK Ltd
10-18 Union Street
London SE1 1SZ
United Kingdom

In accordance with Council Directive 93/42/EEC, as amended, a sample from each batch of bulk and/or finished product of the human blood derivative shall be tested by a state laboratory or a laboratory designated for that purpose by a member state.

1.4. Remarks to the notified body

N/A.

1.5. Recommended measures to the notified body

As discussed at CHMP, it would be recommended that the notified body request the following from the medical device manufacturer for device approval:

Area¹	Description
Quality "For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device"	Final real-time stability data up to 38 weeks for blastocyst medium, vitrification cryobase, vitsol 2, sperm buffer with pentoxifylline, should be presented after completion of the study to confirm the stability of the albumin content.

¹ Areas: quality, safety, including clinical benefit/risk profile.

2. Scientific overview and discussion

2.1. General information

During the consultation procedure the media family name has been changed to Gems Medium Suite from Genea BioPlatforms Solutions and Ready Sperm IVF media.

The Gems Solutions form a suite of sterile liquid media used for In Vitro Fertilisation and Assisted Reproductive Technologies. The media are designed to sustain and allow development of human gametes for in vitro fertilisation and subsequent embryo development. Their intended use is: storage, manipulation, in-vitro culture and transfer of human gametes and embryos. Several of the media contain human serum albumin as ancillary medicinal substance at concentrations between 4 and 20 mg/ml. Some of the media contain gentamycin and pentoxifylline as additional ancillary medical substances which are not part of this consultation procedure. Human serum albumin acts as carrier protein, binds to fatty acids, trace minerals, vitamins, growth factors and steroids. The functions of human serum albumin in the media are:

- environmental pH buffering
- colloid osmotic regulation
- membrane stabilisation
- scavenger and nutrient
- prevention of embryos and gametes from sticking to the devices used to collect and culture embryos.

Albunorm 25 % produced by Octapharma is used as albumin source. Octapharma has Marketing Authorisations for Human Serum Albumin 25% for 12 EEA countries. The use of a pharmaceutical grade human serum albumin provides consistency between batches while ensuring an appropriate safety profile.

2.2. Quality documentation

2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself

Introduction

Albunorm 25% is prepared from human plasma and removal/inactivation of viruses is achieved by cold ethanol fractionation and final container pasteurisation. Albunorm 25% is a human albumin solution for intravenous use. It is in compliance with the European Pharmacopeia (Ph. Eur.) requirements.

Drug substance

Nomenclature and structure

Adequate information on nomenclature and structure of the active substance are provided in the dossier.

Manufacture, Process controls, Specifications, Stability

The active substance human albumin is isolated and purified by cold ethanol fractionation from a pool of human plasma. This is a continuous manufacturing process and details on manufacture, specification and stability are provided in the Drug product section.

Control of materials

The starting material for the manufacture of Alburnorm 25% is human plasma. The plasma complies with the Ph. Eur. monograph "Human plasma for fractionation". Collection and testing of individual donations as well as testing of plasma pools for viral markers are documented in the Octapharma Plasma Master File (PMF). The PMF is annually recertified and the respective PMF certificate with its appended evaluation report is fully applicable to Octapharma's active substance human albumin. The PMF certificate and evaluation report submitted with this application for consultation procedure were issued on 15 March 2013 (EMA/H/PMF/ 000008/05/AU/010).

Drug product

Description of the Drug Product and Pharmaceutical Development

Adequate information on the composition of the drug product has been provided.

Alburnorm 25% is a solution for infusion, used for intravenous administration. It is a clear, slightly viscous liquid, almost colourless or slightly yellow or green solution. The pH and osmolality of the preparation are within defined ranges. The drug product contains the stabilisers caprylic acid and N-acetyl-DL-tryptophan.

The pharmaceutical development has been sufficiently described. N-Acetyl-DL-tryptophan and caprylic acid are used as stabilisers for pasteurisation. As reported in the literature, polymer formation occurs readily at lower concentrations while higher concentrations provide little additional stabilization. Sodium and potassium are osmotic and electrolytic components. Sodium is added to maintain the osmolality of the albumin solution at plasma level (according to Ph. Eur. 2.2.22). Water for injections is the solvent of the final product solution.

Manufacture and process controls

Manufacturers

The drug product (human albumin solution 25%) is manufactured from the starting material human plasma at two manufacturing sites (Octapharma AB (OAB) in Sweden and Octapharma Pharmazeutika Produktionsgesellschaft (OPG) in Austria). An additional site is used for Packaging and Labelling for drug product manufactured at both manufacturing sites (Octapharma GmbH Dessau, Germany). A contract analytical laboratory (Med. University of Vienna, Austria) is used to support the quality control of the drug product. This contract analytical laboratory is qualified and audited by Octapharma. GMP certificates were provided for these sites.

Description of manufacturing process, process control and validation

Sufficient details of the manufacturing process of Alburnorm 25%, from the starting material to the drug product, have been provided both as flow charts and in a narrative format.

Briefly, the active substance human albumin is isolated and purified by cold ethanol fractionation from a pool of human plasma. The protein fractions precipitate in the course of this process and after each precipitation stage they are separated from the protein solution either by centrifugation or filtration. After suspension of fraction V, the solution is ultrafiltered in order to remove the ethanol and precipitation salts and to reduce the volume of the solution. A subsequent diafiltration removes the residues of ethanol and reduces the aluminium content. Bulk pasteurisation is carried out before sterile filtration and filling to allow the use of the same filling line for different products. Final container

pasteurisation is performed in order to fulfil requirements for virus removal and/or inactivation. After final container pasteurization, the vials are incubated and subsequently subjected to visual inspection.

Controls of critical steps and intermediates

The manufacturing process is adequately controlled by in-process testing at critical steps throughout the process. The validated test methods used for in-process control during the production are identical at both manufacturing sites. Viral marker and NAT testing of plasma pools are described in the currently approved Plasma Master File (PMF).

Validation

A comprehensive validation from plasma pool to filling has been performed. The results indicate a well-controlled and harmonised process at the two production sites. The information provided is considered appropriate.

Control of excipients

All excipients comply with the current edition of the European Pharmacopoeia (Ph. Eur.). Quality control and compliance are either guaranteed by the respective manufacturers, or the required tests are performed by Octapharma.

Specifications

The finished product specification for Alburnorm 25% fulfils the requirements of the Ph. Eur. monograph 01/2013:0255. The stated limits are both release and shelf life limits. Analytical methods are sufficiently described and validated.

Batch analysis

Batch data were submitted for six batches (two produced at the Austrian and four produced at the Swedish manufacturing site). All data were within the drug product specifications.

Characterisation of impurities

A comprehensive characterization of impurities of the entire production process up to final product was performed. The samples were tested for total protein and other proteins. The successful removal of process-related impurities was demonstrated for different batches manufactured at both production sites. The results demonstrate equivalent impurity profiles (impurities originating from the starting material human plasma) for the harmonised manufacturing process for the final product manufactured at the two Octapharma production sites.

Container closure system

Final containers are of pharmacopoeia quality. The compatibility between the product and the container was demonstrated in the stability studies.

Alburnorm 25% final product is supplied in bottles of glass type II (Ph. Eur.), closed with bromobutyl-stoppers of type I (Ph. Eur.) and sealed with a flip-off cap. Detailed information about infusion bottles and stoppers has been provided.

With respect to the two intermediates in the manufacturing process of Alburnorm 25%, i.e. fraction V and bulk solution, the information on primary packaging material has been provided and is considered acceptable.

Stability

The proposed shelf life for Alburnorm 25% (when protected from the light in the currently proposed packaging format) is supported by the presented stability data.

Furthermore, submitted stability data support storage of the two intermediates, fraction V and bulk solution, under the following conditions

Facilities and Equipment

Comprehensive information on facilities and equipment has been provided for both sites involved in the manufacturing process of Alburnorm 25% final product.

Adventitious agents' safety

Non-viral adventitious agents

In accordance to the Guideline on the investigation of manufacturing processes for plasma derived medicinal products with regard to vCJD risk (CPMP/BWP/5136/03), the capacity of the Alburnorm 25% manufacturing process to remove prions was validated for the precipitation of fraction I+II+III and for the precipitation of fraction IV. The validation studies were performed with hamster-adapted scrapie 263K using an appropriately scaled down process. The reduction factors, obtained in two independent spiking runs, are acceptable.

Viral adventitious agents

Collection and testing of individual plasma donations as well as the testing of plasma pools for viral markers are documented in the Octapharma Plasma Master File (PMF, see above section on Drug Substance – Control of materials).

The capacity of the Alburnorm 25% manufacturing process to remove/inactivate both enveloped and non-enveloped viruses was investigated for the following steps: precipitation of fraction I+II+III, precipitation of fraction IV and pasteurisation in the final glass container. The following viruses were used:

- Enveloped viruses: Human Immunodeficiency Virus (HIV-1), Pseudorabies Virus (PRV), and Sindbis Virus (SBV)
- Non-enveloped viruses: Reovirus type 3 (REO), Mouse Encephalomyelitis Virus (MEV), Hepatitis A Virus (HAV) and Porcine Parvovirus (PPV)

The choice of viruses is considered adequate. To demonstrate reproducibility, two independent spiking runs were carried out. All viral validation studies were performed using small-scale models that had been shown to be valid representations of the production process.

The reduction factors obtained for each investigated step and for each virus were reported along with the global reduction factors.

In general, the Alburnorm 25% manufacturing process shows a good capability to reduce the potential prions/viral load of adventitious agents. With regard to the potential risk of Parvovirus B19 transmission to pregnant women, embryo and foetus reference is made to Section 2.2.2.

2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

Qualitative and Quantitative particular of the constituents of the medical device

The proposed (trade) name of each solution of Gems Medium Suite is reported below together with the Alburnorm 25% content:

For gamete handling and preparation:

1. Oocyte Retrieval Buffer (HSA 0.00mg/mL)
2. Sperm Buffer (HSA 10.00mg/mL)
3. Sperm Buffer with Pentoxifylline (HSA 10.00mg/mL)
4. Sperm Wash Gradient 45% (HSA 10.00mg/mL)
5. Sperm Wash Gradient 90% (HSA 10.00mg/mL)
6. Sperm Wash Gradient (100%) (HSA 10.00mg/mL)
7. Sperm Medium (HSA 10.00mg/mL)
8. Sperm Medium with pentoxifylline (HSA 10.00mg/mL)
9. Polyvinylpyrrolidone (PVP) (HSA 10.00mg/mL)

For fertilisation and embryo development:

10. Fertilisation Medium (HSA 5.00mg/mL)
11. Cleavage Medium (HSA 5.00mg/mL)
12. Blastocyst Medium (HSA 5.00mg/mL)

For cryopreservation:

13. Sperm Cryopreservation Medium (HSA 4.00mg/mL)
14. Cleavage Stage Freezing Set Sol 1 (HSA 12.00mg/mL)
15. Cleavage Stage Freezing Set Sol 2 (HSA 10.70mg/mL)
16. Cleavage Stage Freezing Set Sol 3 (HSA 10.70mg/mL)
17. Cleavage Stage Thawing Set Sol 1 (HSA 11.10mg/mL)
18. Cleavage Stage Thawing Set Sol 2 (HSA 11.60mg/mL)
19. Cleavage Stage Thawing Set Sol 3 (HSA 12.00mg/mL)
20. Cleavage Stage Thawing Set Sol 4 (HSA 12.00mg/mL)
21. Blastocyst Stage Freezing Set Sol 1 (HSA 12.00mg/mL)
22. Blastocyst Stage Freezing Set Sol 2 (HSA 11.40mg/mL)
23. Blastocyst Stage Freezing Set Sol 3 (HSA 10.90mg/mL)
24. Blastocyst Stage Thawing Set Sol 1 (HSA 12.00mg/mL)
25. Blastocyst Stage Thawing Set Sol 2 (HSA 12.00mg/mL)
26. Blastocyst Stage Thawing Set Sol 3 (HSA 12.00mg/mL)
27. Blastocyst Stage Thawing Set Sol 4 (HSA 12.00mg/mL)
28. Vitrification Set VitSol 1 (HSA 18.30mg/mL)
29. Vitrification Set VitSol 2 (HSA 16.20mg/mL)
30. Vitrification Set VitSol 3 (DMSO) (HSA 0.00mg/mL)
31. Warming Set WarmSol 1 (HSA 20.00mg/mL)
32. Warming Set WarmSol 2 (HSA 20.00mg/mL)
33. Warming Set WarmSol 3 (HSA 20.00mg/mL)
34. VitBase (HSA 20.00mg/mL)

Description of method of manufacture

The media manufacturing process can be defined into 8 activity steps:

1. Batch allocation
2. Washing & sterilization
3. Dispensing
4. Formulation
5. Filtration
6. Filling
7. Batch release
8. Customer packing

Dialysis is performed to remove the potential for any small molecules in Alburnorm 25% which may be present in quantities sufficient to potentially impact optimal embryo development. Alburnorm 25% although stable, may release small quantities of ammonium during its ongoing shelf-life; this is part of the natural degradation process. The detection of the small quantities and subsequent impact for humans is unknown. There is a reported impact to embryos with elevated ammonium levels above 300µmol/L as defined in Gardner, DK, Lane, M. Ammonium Induces Aberrant Blastocyst Differentiation, Metabolism, pH Regulation, Gene Expression and Subsequently Alters Foetal Development in the Mouse. (2003) *Biology of Reproduction* 69, 1109-117. Dialysis has historically been performed on Alburnorm 25% utilised in embryo culture mediums within Genea Biomedx and other businesses. Dialysis has been performed as an industry standard for many years and has provided functionally acceptable material suitable for use in embryo culture. The rationale for dialysis of Alburnorm 25% has been considered acceptable.

Control of starting material

It is noted that, in line with European legislation, each Alburnorm 25% batch that is used for the production of Gems Medium Suite solution batches should be released by an Official Medicines Control Laboratory (OMCL; in accordance with Articles 111(1), 113, 114(1)-(2) and 115 of Directive 2001/83/EC as amended and section 8 of Annex II to Council Directive 93/42/EEC, as amended).

The manufacturer of the Alburnorm 25%, Octapharma, certified that responsibilities for traceability are defined and that data needed for full traceability are stored for at least 30 years according to Article 4 of Directive 2005/61/EC, Article 14 of Directive 2002/98/EC and GMP annex 14.

All compounds used in the production of media are assessed before being released for use (as per the certificates of Analysis (COA)).

Water is purified before use; the water system produces pyrogen and nuclease free water.

Control tests carried out at intermediate stages of the manufacturing process of the medical device

There are 4 QA inspection points in the manufacturing process. Records of these activities form part of the final work order documentation:

- a) Verification of the chemicals and weights of chemicals
- b) That there is no residue remaining in the falcon tubes
- c) pH and osmolality re-check at end of media production
- d) The final inspection showing that all the final external testing has passed and that the batch can be released from quarantine.

The device manufacturer has agreed to include a test for Albumin in the final device product. The absence of in-process controls is acceptable because Alburnorm 25% content is not a parameter to control the manufacturing process.

Final control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device

Prior to release of Gem Medium Suite solutions from quarantine i.e. ready for distribution, testing is performed to ensure that the medium meets the required specifications.

As requested, the Applicant agreed to include a test for Albumin in the final product testing of Gem Medium Suite solutions.

Gems Medium Suite is aseptic sterile filtered and supplied in an aseptic state SAL 10^{-3} . Every batch of media is sterility tested SAL 10^{-3} .

Genea has established documented procedures and work instructions for identification, packaging, storage and protection to preserve the conformity of product during internal processing through to delivery to the customer.

Stability

During the consultation procedure Genea Biomedx provided additional stability data of different media showing stability of Alburnorm 25% over a real time storage period.

In summary, acceptable data have been provided to support the stability of Alburnorm 25% when incorporated in the IVF media over the claimed shelf life. Final real-time stability data including any OOS results will be presented by Genea Biomedx after completion of the study (see RECOMMENDATION).

Viral safety

Since the use of the albumin in the medical device is very different from the normal use of albumin solutions (i.e. plasma expander) and it is known that parvovirus B19 presents a risk for pregnant women and the foetus, a viral risk assessment with a sufficient safety margin concerning Parvovirus B19 was requested from Genea Biomedx for Gems Medium Suite (Cleavage Medium and Blastocyst Medium). As the manufacturer of the medical device did not provide it, the Applicant was asked to at least provide the maximum amount of Gems Medium Suite that is administered during IVF treatment. Consequently, the Applicant provided the amount of the Gems Medium Suite solutions, Cleavage Medium and Blastocyst Medium, which are administered during the intrauterine embryo transfer of the IVF treatment. Based on this information and knowing that both Gems Mediums have a 5% content of Albumin, the assessor was able to calculate that in the worst case the risk of Parvovirus B19 transmission was considered negligible for this stage of the IVF treatment (intrauterine embryo transfer). However, in order to have a complete risk assessment, upon CHMP 3rd list of outstanding issues, the Applicant provided the possible risk (to women and gametes) of contamination with Parvovirus B19 also in relation to the albumin-content in media used in the other two phases of the IVF treatment, preparation of gametes and cryopreservation. In addition, with documentation provided by Octapharma the worst case scenario of Parvovirus B19 virus load per vial of Alburnorm 25% was given. Based on this information, the assessors calculated that the estimated virus load per IVF treatment in the worst case, i.e. exposure of gametes to 100 mg of Alburnorm 25% during the sperm thawing step, cannot be considered negligible, notwithstanding the fact that there are other steps of exposure to Alburnorm 25%, i.e. blastocyst culture step, cryopreservation, cryostorage and intrauterine embryo transfer.

However, from the evaluation of the Octapharma PMF CHMP knew that Octapharma performs Parvovirus B19 NAT on minipools and plasma pools used for the production of some products as defined in the respective MA dossiers. Therefore, the applicant was requested to submit written confirmation from Octapharma that plasma pools for the production of Alburnorm 25% batches used as ancillary substance in Gems Medium Suite solutions are tested by NAT for Parvovirus B19. In addition, Octapharma was requested to state which Parvovirus B19 NAT acceptance limit is applied for the plasma pools for manufacture of Alburnorm 25%. Furthermore, the Medical Device Manufacturer was

requested to confirm in writing that only these Albnorm 25% batches will be used for production of Gems Medium Suite solutions.

Subsequently, the applicant submitted the requested documentation. Octapharma Vienna, the European Albnorm 25% manufacturer has now confirmed that plasma pools used for the production of Albnorm 25% batches are NAT tested for Parvovirus B19 with a defined virus load acceptance limit. Based on this confirmation, a risk assessment was carried out by the assessor considering the Parvovirus B19 NAT acceptance limit. If the plasma volume necessary to produce one 100 ml vial of Albnorm 25% and the total reduction factor of the manufacturing process for Parvovirus B19 are taken into consideration, the risk can be considered negligible. In addition, the medical device manufacturer, Genea Biomedx, has confirmed in writing, that only Albnorm 25% batches, produced from plasma pools tested by Parvovirus B19 NAT and fulfilling the Parvovirus B19 NAT acceptance limit will be used for the production of Gems Medium Suite solutions. In conclusion, this outstanding safety concern is considered as resolved.

As requested, Octapharma has committed to inform Genea Biomedx of any changes with respect to Parvovirus B19 safety post opinion.

2.2.3. Discussion and conclusion on chemical, pharmaceutical and biological aspects

Ancillary medicinal substance or the ancillary human blood derivative itself

For the information regarding quality and safety of the plasma used as starting material for the manufacture of Albnorm 25%, reference is made to the Octapharma PMF, which is annually recertified.

Comprehensive details on the manufacturing process for Albnorm 25% from the starting material to final product have been provided. Control of critical steps and intermediates are considered satisfactory. Process validation demonstrated consistency of the manufacturing process. The Manufacturer provided the requested documents regarding the Reference standards and materials.

The final product complies with the Ph. Eur. monograph for human albumin solution (01/2013:0255).

Stability studies demonstrate that Albnorm 25% remains within specification under the proposed storage conditions in the proposed containers. The proposed shelf life in the currently proposed packaging format is supported by submitted stability data.

Based on the overall reduction factors obtained from the adventitious safety validation studies, it is considered that, in general, the Albnorm 25% manufacturing process shows a good capability to reduce the prions/viral load of potential adventitious agents.

Upon request, the Notified Body BSI provided additional information on the Parvovirus B19 testing of the starting material for the production of Albnorm 25% (see below). In addition, the manufacturer of Albnorm 25%, Octapharma, committed to inform the device manufacturer Genea Biomedx of any changes with respect to Parvovirus B19 safety post opinion.

Ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

With respect to the ancillary human blood product as incorporated in the medical device, the Manufacturer provided more detailed information about the manufacturing process of some Gems Medium Suite solutions which are considered representative for the manufacture of all solutions. This was considered acceptable.

As regards the request to include a test for Albumin content throughout the manufacturing process of Gems Medium Suite solutions, the device manufacturer agreed to include a test for Albumin only in the final product. It is considered acceptable that the test is not carried out also as in-process control considering that the Albumin content is not a parameter to control the medical device manufacturing process.

Genea Biomedx stated that Alburnorm 25% used in the production of Gems Medium Suite media remained within its shelf-life throughout the duration of the shelf-life of the medical device and also provided stability data for Albumin over a real time period of 20 weeks. Final real-time stability data up to 38 weeks will be presented by the Genea Biomedx after completion of the study (See RECOMMENDED MEASURES).

The manufacturer of Alburnorm 25%, Octapharma, also clarified that responsibilities for traceability are defined and that data needed for full traceability are stored for at least 30 years according to Article 4 of Directive 2005/61/EC, Article 14 of Directive 2002/98/EC and GMP annex 14.

As Parvovirus B19 is known to be harmful for pregnant women and the foetus, a virus risk assessment with regards to Parvovirus B19 for Cleavage Medium and the Blastocyst Medium was required. After several CHMP requests on this issue, the Applicant provided the confirmation from Octapharma, Vienna, that plasma pools used for the production of Alburnorm 25% batches are tested by NAT for Parvovirus B19 with a maximum acceptance limit. Based on this confirmation and the volume of different Gems Medium Suite solutions used at different steps of the IVF cycle as well as the Parvovirus B19 reduction factor of the virus inactivation/removal steps included in the Alburnorm 25% manufacturing process, the assessor calculated that the maximum exposure to Parvovirus B19 of gametes and patient during an IVF treatment. This risk can be considered negligible. In addition, the medical device manufacturer, Genea Biomedx, has confirmed in writing, that only Alburnorm 25% batches, produced from plasma pools tested by Parvovirus B19 NAT and fulfilling the Parvovirus B19 NAT acceptance limit will be used for the production of Gems Medium Suite solutions. In conclusion, this outstanding safety concern is considered as resolved.

The medical device manufacturer confirmed to follow the legal requirement for OMCL batch release of each Alburnorm 25% batch that is used for the production of Gems Medium Suite solution batches.

2.3. Non-clinical documentation

2.3.1. Discussion and conclusion on the non-clinical documentation

The lack of pharmacodynamic studies is acceptable, since the role of albumin in buffers and media for in vitro fertilization is considered to be well known. Various chemicals have been introduced in the Gems Medium Suite version 3), the role of each of these substances should be carefully evaluated by the BSI.

The lack of pharmacokinetic studies is acceptable since the absorption of albumin through the vaginal and endometrial tissue is considered negligible. Direct contact with vaginal and endometrial tissue during the IVF transfer procedure is limited to less than one minute, and the amount of media to which the embryo is exposed with is less than 0.5mL.

The metabolic fate of the 0.5mL of media is not expected to cause subsequent adverse effects caused by accumulation due to the minute volume of biologically tested media and the typical exposure to the patient of only once per menstrual cycle.

Toxicity tests performed by the Manufacturer are not conventional assays to address non clinical safety, but taking into consideration the type of the device, they are considered suitable to demonstrate the safety of the solutions in their whole formulation. Furthermore, some of them were used as functional tests to address not only safety, but also quality issues (e.g. stability).

Some Gems media/buffer solutions which are intended to be injected into the female genital tract contain new substances compared to similar marketed media. Although Alburnorm 25% is a well-known substance, in order to evaluate the local tolerance of whole solutions a biocompatibility evaluation was requested to the Manufacturer. Results from: test for genotoxicity, carcinogenicity and reproductive toxicity; test for in vitro cytotoxicity; test for irritation and delayed-type hypersensitivity, performed only on 4 selected media (chosen to be representative of the whole media) were considered acceptable by the Manufacturer. Alburnorm 25% was only present in 3 out of 4; the one w/o Alburnorm 25% contained only gentamicin. Alburnorm 25% ranged between 5 mg/ml and 20 mg/ml (the maximum amount). Pentoxiphylline was present together with Alburnorm 25% in 2 out of 4 media.

Considering the media as a whole, for the 3 media that will be exposed to the patient (i.e. the mother to be) (ORB, CLM and BLM) the risk of any toxicokinetic leachable and breakdown products is considered insignificant due to the low volume used.

The Manufacturer presented a review from the literature on "development and Safety" of culture media, however no specific data was shown on the assessment of toxicity and local tolerance. While safety in IVF procedures of Alburnorm 25% and gentamicin is confirmed by the long time they have been used in culture media, for pentoxifylline, not present in the previous version of the device, no toxicity and local tolerance aspects have been presented by the Manufacturer. However, for the scope of the consultation procedure on the blood derivative (human serum albumin) the issue on toxicity and local tolerance is considered solved.

Overall, the results of the extensive published literature support the safety and usefulness of human serum albumin as a supplement of ART solutions for sperm preparation, fertilisation, culture of embryos to cleavage and blastocyst stage of development and cryopreservation.

The evidence provided as part of the submission documentation related to the non-clinical part for this consultation demonstrates that the ancillary human blood derivative, Alburnorm 25% does not seem to present any risk associated with its use.

2.4. Clinical evaluation

2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body

The in vitro culture of cells of any type (including embryos) uses a liquid medium to provide the cells with the components necessary to ensure maintenance of their mitotic capability. Currently, most commercially available IVF media suites, including those produced for human embryo culture, contain HSA.

Proteins are a necessary ingredient for all types of culture media and perform several important physical roles. The presence of proteins prevents embryos and gametes 'sticking' to the devices used to collect and culture embryos. HSA is the predominant form of protein found in human fallopian tube secretions. It is well documented that HSA can act as an anti-oxidant and has the ability to absorb toxins that can be detrimental to the developing embryo. Albumin has been used in Genea Biomedx media in Australia for the last 25 years, and more specifically Alburnorm 25% from Octapharma for the last 3 years also in Europe.

Albunorm 25% is a component of the media suite for a number of different reasons.

Sperm Capacitation

HSA is an inducer of capacitation in sperm (acting as an acceptor for membrane cholesterol), an important initial reaction in normal sperm function. Without this acceptor, sperm cells cannot undergo their normal series of reactions to make them capable of fertilisation. Concentrations of HSA in the order 10 – 30 mg/ml are suggested to be the most effective.

Sperm medium (which is used to pre-incubate sperm before insemination) contains 10 mg/ml albumin and has been used clinically at Genea, since 1997. The initial results comparing the sperm medium with the previous formulation (HTF medium) have been published and supports the contention that the sperm medium allows adequate capacitation and hence fertilisation in a clinical setting.

Micronutrient

There is some evidence that embryos can directly sequester albumin and utilize the protein for metabolism. The concentrations that can be utilized by embryos are very low (of the order of pg) so that the concentrations in the media suite (10 mg/ml) will easily supply the micronutrient.

Toxin protectant for embryos

Concentrations of 1 – 10 mg/ml of human serum albumin can also play a passive role in the culture media suite. Serum albumin plays a role in protecting the embryos against adventitious toxins that may be introduced with the gametes themselves. Furthermore, the HSA prevents the embryos and gametes sticking to the plastic and glassware used to collect and culture embryos during the IVF process.

As regards the fact that no results were available on the Cryopreservation set, nor on the vitrification set on the outcome of the cryopreservation process, in terms of proof of pregnancies after embryo vitrification and warming, Genea Biomedx provided results from the new clinical trial "CT3004" started on 15th December 2011 and finished 6th February 2013. The study compared two different patient groups: "Trial" vs "Control", where the former was in house manufactured Gems media products and the latter in house manufactured previous version 2 (Cook) media products. The results reported a survival rate of D5 blastocysts after vitrification/warming in all ART cycles of 92.1% vs 93.7%, and a foetal heart pregnancy rate of 45.8% vs 51% in Trial and Control group, respectively, indicating a comparable performance between the 2 media products.

2.4.2. Clinical safety of the ancillary medicinal substance incorporated in the medical device

From the clinical results presented for version 3 media suite, no negative impact on implanted women was observed.

The potential risks to the mother and the embryo during the use of IVF Media products are due to bacterial contamination, viral infection and local irritant effects.

A risk analysis was performed during the clinical trial showing a low to medium risk rate, and no additional risk mitigation actions beyond those already employed for routine clinical laboratory practice were considered necessary.

During the development programme of the media suite, pre-clinical testing was performed on human donor sperm, mouse embryos and excess human research to test the safety and efficacy of the new additives to the media suite.

Bacterial endotoxin in IVF culture media has been cited as a potential cause of reduced success in IVF treatment with fewer ova fertilized, poorer quality of fertilized ova, and lower pregnancy rate; there is also a risk of a pyrogenic response in the mother. To minimise the risk of contamination of the mother with endotoxins during ART, the applicant states that Gems ART media are manufactured using aseptic techniques and as an additional measure a limit for bacterial endotoxin is set within the IVF media products. It is noted that endotoxin testing is now performed for every batch as part of the batch release test. Gentamicin sulphate is also incorporated into the ART media, as a preservative, to minimise any bacterial contamination. The adequacy of these measures is outside the scope of the consultation.

Potential viral infections, such as Parvovirus B19 in the mother would likely result in a transient and self-limited viral disease. Foetal exposure would routinely produce a failed implantation, however if implantation is successful, current evidence does not support Parvovirus as the cause of congenital malformation or developmental delay. Though Octapharma stated the reduction factor for Parvovirus B19, this would not be sufficient in the presence of plasma pools with a high Parvovirus B19 viraemic titer.

Upon request, the Notified Body BSI provided additional information on the Parvovirus B19 testing of the starting material for the production of Alburnorm 25%. In addition, the manufacturer of Alburnorm 25%, Octapharma, committed to inform the device manufacturer Genea Biomedx of any changes with respect to Parvovirus B19 safety post opinion.

A virus risk assessment with regards to Parvovirus B19 for Gems Medium Suite solutions was performed for the maximum dose administered during an IVF treatment. From this, it is concluded that the estimated risk for Parvovirus B19 transmission to the pregnant woman, embryo and foetus can be considered negligible).

2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device

The Genea Biomedx submitted data from 2 clinical trials (named "2005 CT" and "2012 CT"), conducted in accordance with ISO14155:2011 (Clinical investigation of medical devices for human subjects – Good clinical practice), in which different versions (version 2 and version 3) of Gems Medium Suite were used.

Usefulness

The indirect comparison of performance of version 2 media vs historical data as presented in "2005 CT" does not allow to draw any conclusion on the assessment of the usefulness of the albumin since the composition of the media used as comparison to Version 2 is not known.

The new clinical trial performed by the Genea Biomedx referred as CT 2012, was primarily aimed to compare the efficacy in terms of fertilization, cleavage and development, blastocyst stage growth and pregnancy rates of Genea media version 3 vs version 2 house-made by Genea; as third comparison version 2 manufactured by Cook was also considered. Overall, version 3 performed at least as well as version 2 house-made and Cook on all endpoints.

For the scope of this consultation on the ancillary role of Alburnorm 25% in final devices, it is not possible to draw any conclusion in terms of the contribution of Alburnorm 25% to the efficacy of finished devices since no comparator without Alburnorm 25% was used in this trial.

However, according to the relevant guidance document, i.e. MEDDEV 2.1/3 rev 3 (European Commission), it is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation, all aspects of usefulness could be addressed by experience and other information generally available. As Alburnorm 25% is a well-known substance contained in comparable medical devices containing the same amount of the Alburnorm 25% from the same source (for example: COOK IVF cell culture media,), and considering the extensive post-marketing use of both IVF manufactured media/buffer (e.g. Cook) and house-made preparations (e.g. Genea's former version), the usefulness of Alburnorm 25% in the medical device can be accepted.

Safety

From the new clinical data presented, no safety issues were raised with the use of Gems Medium Suite nor were adverse effects attributed to Alburnorm 25%.

The major risks of Gems Medium Suite are sensitivity to any of the ingredients, especially gentamicin and Alburnorm 25%, and the inherent risk involved with the use of any plasma derived product, i.e. viral contamination. Measures are put in place by the Genea Biomedx to minimise the possible risk of transmitting virus with Alburnorm 25% in Gems Medium Suite and risk analysis is reviewed whenever a change is made to the Genea solutions or when negative feedback is received to ensure any unanticipated risks arising from use are duly actioned.

Alburnorm 25% is not a new product. Reassuring data come from extensive post-marketing use of both IVF manufactured media/buffer (e.g. Cook) and house-made preparations (e.g. Genea's former version) having provided a known risk profile of Alburnorm 25%.

Since the use of the albumin in the medical device is very different from the normal use of albumin solutions (i.e. plasma expander) and it is known that parvovirus B19 presents a risk for pregnant women and the foetus, a virus risk assessment was performed for the maximum dose administered during an IVF treatment. From this, it is concluded that the estimated risk for Parvovirus B19 transmission to the pregnant woman, embryo and foetus is negligible (see above Section 2.2.2 – Viral safety).

In conclusion, the benefit/risk balance of Alburnorm 25% as ancillary component incorporated in the in the Gems Medium Suite device is considered positive.

2.4.4. Discussion and conclusion on the clinical evaluation

The Notified Body adequately justified the inclusion of Human Serum Albumin in the Gems media in terms of clinical usefulness. Furthermore, a review of relevant literature on the clinical usefulness of Alburnorm 25% in IVF media and supportive clinical trial data were submitted by the device manufacturer Genea Biomedx.

These showed a favourable performance in terms of fertilization, cleavage and development, blastocyst stage growth and pregnancy rates of Gems Medium Suite version 3 compared to version 2 house-made and the Cook version.

In line with MEDDEV 2.1/3 rev 3 guideline, since Alburnorm 25% is a well-known substance contained in several medicinal products as well as in comparable medical devices that have been on the market for several years, safety and usefulness of Alburnorm 25% included in Gems Medium Suite devices can be reasonably derived from experience gained so far and are thus considered acceptable.

The inherent risk involved with the use of any plasma derived product, i.e. viral contamination, should be adequately controlled by risk minimisation measures. The risk of Parvovirus B19 transmission during an IVF treatment can be considered negligible based on the risk assessment performed. Overall, the submitted information is considered acceptable to support a positive benefit/risk profile of the ancillary medicinal substance Alburnorm 25% incorporated in the range of Gems Medium Suite solutions from a clinical point of view.

2.5. Overall conclusions

While exhaustive details on the manufacturing process for Alburnorm 25% from the starting material to final product have been provided referencing to the EMA Octapharma PMF (EMA/H/PMF/000008/05/AU/010; PMF certificate from 15 March 2013), a number of deficiencies were noted with respect to the ancillary Alburnorm 25% as incorporated in the medical device. Many details on the manufacturing process for the Gems buffers/media have been provided by the Manufacturer such as the reason why albumin is pre-treated (i.e. dialysis) before addition to the other components of the Blastocyst Medium, information on the test for albumin at the end of stage of production.

Stability data of 4 different media (blastocyst medium, vitrification cryobase, vitsol 2, sperm buffer with pentoxifylline) show stability of human albumin over a real time period of 20 weeks. There is only one OOS result in the photostability study. Since the product is stored protected from light, this outcome is acceptable. Final real-time stability data up to 38 weeks for blastocyst medium, vitrification cryobase, vitsol 2, sperm buffer with pentoxifylline, should be presented after completion of the study (See RECOMMENDED MEASURE).

Since the use of the albumin in the medical device is very different from the normal use of albumin solutions (i.e. plasma expander) and it is known that parvovirus B19 presents, this point was raised as issue in several LoIs. Finally, the required documentation was received for a parvovirus B19 risk assessment for the maximum dose administered during an IVF treatment. From this, it is concluded that the estimated risk for Parvovirus B19 transmission to the pregnant woman, embryo and foetus can be considered negligible.

The clinical trial performed by the Genea Biomedx showed similar performance in terms of fertilization, cleavage and development, blastocyst stage growth and pregnancy rates of version 3 compared to version 2 house-made and Cook. Alburnorm 25% used as ancillary substance in both versions was from the same source and in similar amounts.

In another clinical trial to assess the performance of embryos following cryopreservation and vitrification, for both patients treated with "in house manufactured Gems media products" and "in house manufactured previous version 2 (Cook) media products", the survival rate of D5 blastocysts after vitrification/warming in all ART cycles and a foetal heart pregnancy rate were comparable.

Considering that Alburnorm 25% used as ancillary substance in the Gems Medium Suite device is from the same source and in similar amounts of that in the IVF media approved in Australia, US and recently in EU (Cook IVF media) that have been on the market for a long time, safety and usefulness of Alburnorm 25% included in Gems Medium Suite can be reasonably derived from experience gained so far.

In conclusion, the benefit/risk balance of Alburnorm 25% as ancillary component incorporated in the Gems Medium Suite device could be considered positive.

The adequacy of risk minimisation measures for bacterial contamination and endotoxins in the Gems Medium Suite is outside of the scope of this consultation.

2.6. Recommendation

Based on the CHMP review of data submitted, the CHMP considers that the quality and safety including the benefit risk profile of Alburnorm 25% used as ancillary medicinal substance in the Gems Medium Suite can be considered positive.