26 January 2017
EMA/CHMP/878394/2016
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

LifeGlobal Media

International non-proprietary name: human serum albumin

Procedure No. EMEA/H/D/004287/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Ag	Antigen
ART	Assisted Reproductive Technology
BSE	bovine spongiform encephalopathy
CARTR Plus	Canadian Assisted Reproductive Technologies Register Plus
EC	European Commission
ET	embryo transfer
FDA	Food and Drug administration
HAV	Hepatitis A Virus
HBC	Hepatitis B Virus core Antigen
HbsAg	Hepatitis B Virus surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIMS	Heat inactivated maternal serum
HIV-1	Human Immunodeficiency Virus 1
HPLC	High Performance Liquid Chromatography
HSA	Human Serum Albumin
HTF	Human tubal fluid
HTLV	Humanes T-lymphotropes Virus
ICSI	Intracytoplasmic sperm injection
IUI	intra-uterine insemination
IVF	In-Vitro Fertilisation
MA	Marketing Authorization
MEA	Mouse Embryo Assay
MDM	medical Device Manufacturer
PGD	Preimplantation genetic diagnosis
Ph. Eur.	European Pharmacopoeia
PPV	Porcine Parvovirus
S(m)PC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The notified body BSI Group submitted to the European Medicines Agency (EMA) on 3 August 2015 an application for consultation on Human Serum Albumin (HSA) incorporated as ancillary medicinal substance in the medical device LifeGlobal Media, 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 and the evaluation teams were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Andrea Laslop

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 3 August 2015.
- The procedure started on 1 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 December 2015The Co-Rapporteur's first assessment report was circulated to all CHMP members on 18 December 2015
- During the meeting on 28 January 2016, 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 28 January 2016 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 9 August 2016
- The Rapporteurs circulated the joint assessment report on the applicant’s responses to the list of questions to all CHMP members on 19 September 2016 .
- During the CHMP meeting on 13 October 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant .
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues on 16 December 2016.
- The Rapporteurs circulated the joint assessment report on the applicant’s responses to the list of outstanding issues to all CHMP members on 9 January 2017 .
- During the meeting on 23-26 January 2017 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 as ancillary medicinal substance used in LifeGlobal Media.

1.3. Manufacturers

Manufacturers of the active substance used as ancillary medicinal substance

Octapharma AB
Elersvagen 40
11275 Stockholm
Sweden

Manufacturers of the finished product used as ancillary medicinal substance

Octapharma AB
Elersvagen 40
11275 Stockholm
Sweden

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

Manufacturer responsible for batch release

Octapharma AB
Elersvagen 40
11275 Stockholm
Sweden

Manufacturer of the medical device

Life Global Group LLC
393 Soundview Road
Guilford, CT 06437
USA

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.

2. Scientific overview and discussion

2.1. General information

LifeGlobal Media w/HSA is qualified as a medical device made up of medical devices which are media and solutions used in the area of human assisted reproductive procedures (ART).

The Notified Body, British Standards Institutions (BSI), is consulting the CHMP for a scientific opinion regarding the quality, safety and usefulness only of the HSA component of the device (human blood derivative) in accordance with Directive 93/42/EEC, as amended. As per MEDDEV 2.4/1 Rev 9, devices incorporating, as an integral part (i.e. physically or chemically combined at the time of administration) a

human blood derivative for the purpose of assisting the functioning of that device, are regarded as a Class III medical device, Rule 13.

The claimed ancillary roles of HSA into the medicinal device are:

1) binding of endogenous growth factors generated by embryos themselves and the chelation of heavy metals that may be present as contaminants in media components.

2) surfactant to facilitate embryo and gamete manipulation by preventing them from adhering to glass or tissue culture equipment. The protein has amphiphilic properties, which makes it suitable as an additive to inhibit adsorption of the active protein to the container, via competitive adsorption mechanisms. HSA also has a high glass transition temperature, which in combination with its amphiphilic nature, makes it an ideal excipient for cryoprotection.

The LifeGlobal Media w/HSA contains 2 ancillary substances HSA and Gentamicin Sulphate, of which only HSA is a human blood derivative.

The HSA contained in the Life Global Media is manufactured by Octapharma; other medical devices containing HSA by the same manufacturer has been previously assessed by the EMA.

For ancillary medicinal substances, other than human blood derivative or medicinal products that fall within the scope of Annex I of Regulation EC 726/2004 (gentamicin in this device), the choice of the consultation of EMA or of another Competent Authority for medicinal products is at discretion of the Notified Body in agreement with the medical device manufacturer. Based on the information provided, the consultation procedure for gentamicin is at the MHRA.

2.2. Quality documentation

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

Introduction

Albunorm 25 % manufactured by Octapharma is used as the source of albumin. Octapharma holds valid Marketing Authorisations for Albunorm 25% in several EU Member States. Pharmaceutical grade human serum albumin was selected for use as it provides consistency between batches while ensuring an appropriate safety profile.

The albumin is manufactured from human plasma derived from appropriately screened donor pools and processed for the removal/inactivation of transmissible agents. The plasma starting material is subject to the authorised EMA Plasma Master File (PMF) certification procedure - EMEA/H/PMF/000008/05/AU/014/G, last re-certified on 01 April 2016. A letter of confirmation has been provided by the PMF holder, Octapharma, to notify the medical device manufacturer in case of modification to the PMF or product recalls due to look back procedures. Furthermore, Octapharma confirmed that LifeGlobal would be informed in case of modification of the manufacturing process or specifications of the Albumin according to Annex I of Directive 2001/83/EC as amended.

Albunorm 25% is a solution containing plasma proteins in a concentration of 250 g/l with a content of human albumin of at least 96%. Albunorm 25% is a solution for infusion, used for intravenous administration filled in Type II (Ph. Eur.) glass bottles containing 50 ml and 100 ml. The bottles are closed with type I (Ph. Eur.) bromobutyl rubber stoppers. All excipients are declared to be of Ph. Eur. quality.

The final product complies with the current Ph. Eur. monograph for human albumin solution 0255.

Active substance

Nomenclature and structure

Adequate information on nomenclature and structure of the active substance human albumin is provided in the dossier.

Manufacture, Process controls, Specifications, Stability

The manufacture of human albumin solution for injection is described as a 'continuous' process from fractionation of the plasma starting material to the filling and sealing of the finished product vials. Therefore, details on manufacture, process controls, specifications and stability are provided in the finished product section.

Control of materials

The starting material for the manufacture of Albunorm 25% is human plasma. The plasma complies with the Ph. Eur. monograph "Human plasma for fractionation". All information on quality and safety of the plasma is included in the Octapharma PMF. The PMF is annually recertified and the respective certificate of compliance with the Community legislation (EMEA/H/PMF/000008/05/AU/014/G, last re-certified on 01 April 2016) is fully applicable to Octapharma's active substance human albumin.

Finished product

Description of the Finished Product and Pharmaceutical Development

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

Albunorm 25% is prepared from human plasma and is virus-inactivated by cold ethanol fractionation and final container pasteurisation.

Albunorm 25% is a solution for infusion, used for intravenous administration filled in Type II (Ph. Eur.) glass bottles containing 50 ml and 100 mL and closed with type I (Ph. Eur.) bromobutyl rubber stoppers. The bottles are sealed with tamper evident aluminium seal-off caps.

Albunorm 25% has a plasma protein concentration of 250 g/l with a content of human albumin of at least 96% and contains the following excipients: N-Acetyl-DL-tryptophan, caprylic acid, sodium, potassium and water for injections. All excipients are declared to be of Ph. Eur. quality. The final product complies with the current Ph. Eur. monograph for human albumin solution 0255.

Table 1. Description and composition of the finished product

Name of Active Ingredients	Quantity per 1000 ml	Function	Reference to Standards
Plasma proteins with at least 96% human albumin	250 g	Active Ingredients	Internal
Name of Excipients	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Sodium[1]	144-160 mmol	osmotic and electrolyt component	Ph. Eur
N-acetyl-DL-tryptophan	16-24 mmol	Stabiliser	Ph. Eur.
Caprylic acid	16-24 mmol	Stabiliser	Ph. Eur.
Water for injections	ad 1000 ml	Solvent	Ph. Eur.
Name of other Components	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Potassium[2]	≤ 12.5 mmol	osmotic and electrolyt component	Ph. Eur

[1]Sodium is added to the solution as sodium chloride and also as part of different buffer solutions. The quantity of sodium chloride varies depending on the sodium content on the solution in order to adjust to the requested final concentration of 144-160 mmol sodium per l protein solution.
[2]Potassium is a component of the human plasma starting material and not actively added as excipient.

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 a final concentration of 144 – 160 mmol/l to maintain the osmolality of the albumin solution at plasma level (according to Ph. Eur. 2.2.22). Water for injection is the solvent of the final product solution.

Manufacture and process controls

Manufacturers

Albunorm 25% is manufactured by Octapharma at the facility located in Octapharma AB (OAB), Sweden. An additional site for Packaging and Labelling for all manufacturing sites is Octapharma GmbH Dessau, Germany. A contract analytical laboratory (Med. University of Vienna) is used to support the quality control of the finished product.

Manufacturer Octapharma Stockholm

Octapharma AB
Elersvägen 40
112 75 Stockholm
Sweden

Additional sites for packaging and labelling for all manufacturing sites

Octapharma GmbH
Subsidiary Dessau
Otto-Reuter-Str. 3
06847 Dessau
Germany

Description of manufacturing process, process control and validation

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

The active substance human albumin is isolated and purified by the cold ethanol fractionation process from a pool of human plasma. In this process, after separation of the cryoprecipitate by centrifugation and optional adsorption of Vitamin K coagulation factors by chromatography or filtration, the relevant fractions are obtained through ethanol precipitations. After each precipitation stage the fractions are separated from the protein solution either by centrifugation or filtration. Following the 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. Stabilisers are added and the final sodium content is adjusted. Subsequently, the protein solution is adjusted to an albumin content of 25%. Bulk 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 the requirements for virus removal and/or inactivation.

Control of critical steps and intermediates

During manufacturing, two intermediates (fraction V and albumin bulk solution) can be stored at the conditions supported by stability data.

Details have also been provided on use, cleaning and regeneration of columns. Compositions of buffers or solutions have been provided in a tabular format. The in-process controls and their respective acceptance criteria are satisfactorily described and considered acceptable.

Validation

A comprehensive validation from plasma to filling has been performed and the information provided is appropriate. The results indicate a well-controlled process. Adequate validation was performed and submitted.

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 Albunorm 25% fulfils the requirements of the relevant Ph. Eur. monograph.

The description of the analytical procedures and acceptable validation reports were provided. Satisfactory information on the reference standards used for the analysis of the finished product has been provided.

Batch analysis

Batch analysis data for six batches, four of which were manufactured at the intended manufacturing site, have been provided and the results demonstrate good batch-to-batch consistency.

Characterisation of impurities

A comprehensive characterization of impurities of the entire production process up to final product was performed demonstrating successful removal of process-related impurities and considered acceptable. All samples were tested for total protein and accompanying proteins like Fibrinogen, IgA, IgG, IgM, α1 Antitrypsin, α 1 Acid glycoprotein, Antithrombin III, Haptoglobin and Transferrin.

Container closure system

Albunorm 25% is supplied in colourless glass bottles of glass type II (Ph. Eur.) and closed with bromobutyl rubber stoppers of type I (Ph. Eur.). The bottles are sealed with tamper evident aluminium seal flip-off caps.

Components used in the packaging of albumin finished product are of pharmacopoeial quality and are latex-free and not of animal origin. Details of the suppliers are given. The compatibility between the product and the container was demonstrated in stability studies.

For the primary packaging material for the intermediates has provided the following information:

- Fraction V: material specifications for polyethylene (PE)-bags and PE-hoses respective Certificates of Analysis and two reports addressing the leachability profile of this type of material.
- Bulk solution: material specifications for bags, respective Certificates of Analysis and two reports addressing the compatibility and leachability profile of this type of material.

Appropriate information on the primary packaging for all intermediates was provided including reports addressing the compatibility and leachability profile for the type of material used.

Stability

Real time/real condition stability data of four production scale batches for 36 months and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Stability data of two production scale batches manufactured at a manufacturing site not applied for was also provided as supportive information. The proposed shelf life of Albunorm 25% of 36 months when stored protected from light at 2 °C to 25 °C is supported by the presented stability data.

At the time the dossier was presented, the long-term stability study was ongoing to cover up to 60 months. In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Facilities and Equipment

Comprehensive information on facilities and equipment has been provided in Section 3.2.A.1 for the OAB site involved in the manufacturing process of Albunorm 25% final product.

Adventitious agents' safety

Materials of Biological Origin

The starting material of Albunorm 25% is human plasma. There are no other substances of animal or human origin used in the manufacture of Albunorm 25%.

Non-viral adventitious agents

Prion Safety Studies:

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 process to remove prions has been validated.

In the summary table the study results of the following production steps are summarised:

- Cold ethanol fractionation – precipitation of Fraction I+II+III

- Cold ethanol fractionation – precipitation of Fraction IV

The study has been performed with hamster-adapted scrapie 263K. It could be demonstrated that the precipitation procedures significantly remove prions from the concentrate. The reduction factors, obtained in two independent spiking runs, are acceptable as they range between 2.8 and 3.9 log.

TSE Compliance:

In compliance with Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), it was confirmed that no starting materials derived from bovine origin are used for the continuous production of Albunorm 25% from human plasma to the final product.

Optional adsorption of Vitamin K dependent coagulation factors or Antithrombin III during the manufacture of Albunorm 25% can be performed using suitable chromatography matrices either by batch or by column chromatography. These chromatography matrices comply with the above-mentioned guideline.

Viral adventitious agents

[1] 6.35 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

The capability of Albunorm 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 cold ethanol fractionation consists of stepwise cold ethanol precipitations of proteins by modifying the alcohol concentration, pH, ionic strength, and the temperature. The use of cold ethanol fractionation is known to reduce virus titers by two distinct mechanisms: fractional separation (partitioning) and, to a lesser extent, inactivation.

The main pasteurization of Albumin in the full-scale production process is performed in the final glass container at 60°C ± 0.5°C for 10 hours (as requested by European guidelines). Both lipid enveloped viruses and non-enveloped viruses are known to be irreversibly destroyed (inactivated) by this heating steps.

The studies were performed with both:

- 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 representation of the production process.

The reduction factors obtained for each investigated step and for each virus were provided and considered acceptable, along with the global reduction factors. In general, Albunorm 25% manufacturing process shows a good capability to reduce the potential prions/viral load of adventitious agents.

Octapharma has confirmed that plasma pools used for the production of Albunorm batches used as ancillary substance in LifeGlobal media are tested by NAT for Parvovirus B19 and are accepted with a maximum virus load of 100 IU/µl.

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

HSA is included as a surfactant in LifeGlobal Media w/HSA to prevent adherence of gametes and embryos to pipettes, culture dishes and other materials.

All of the devices in the LifeGlobal Media w/HSA medical device group are aqueous solutions containing various concentrations of inorganic salts, energy substrates, amino acids, gentamicin sulfate, and/or cryoprotectants. The products designed for handling, washing, manipulation, and/or cryopreservation of gametes and embryos include HEPES as the buffer. The products designed for the culture of gametes and embryos are bicarbonate-buffered, to be used in an atmosphere containing an appropriate concentration of CO2.

Qualitative and quantitative particulars of the constituents of the medical device

LifeGlobal Media w/HSA is a Media Culture System intended for use in various procedures ancillary to in vitro fertilization (IVF) and culture of human gametes and embryos (refer to the table below).

Table 5. Overview of the intended use of LifeGlobal products w/HSA

Product Name and Cat. Nos.	Intended Use
global® total® w/ HSA *HGGT-030 ml, HGGT-060 ml, HGGT-100 ml*	*Culture of human embryos from zygote to blastocyst, embyo transfer*
global® total® w/ HEPES w/ HSA *(HGTH-050 ml,HGTH-100 ml, HGTH-250 ml)*	*Human oocyte and embryo washing and manipulation, fertilization by intracytoplasmic sperm injection (ICSI), embryo transfer.*
global® total® for Fertilization w/ HSA *(HGTF-050 ml, HGTF-100 m, l)*	*Human embryo culture and fertilization*
LG PGD Biopsy Medium® *(LGGG*	*To facilitate the biopsy of cells from human cleavage-stage embryos for PGD.*
AllGrad Wash®® *(GALW)*	*Sperm washing and preparation for in vitro fertilization and for intra-uterine insemination*
global® DMSO Blastocyst Vitrification Kit *(DMVT)*	*Vitrification (ultra rapid freeaing) and crystorage of human blastocysts*
global® DMSO Blastocyst Vitrification Warming Kit *(DMWR)*	*Recovery and rehydration of human blastocysts.*
global® Blastocyst Fast Freeze Kit *(GVBI)*	*Cryopreservation of blastocysts*
global ®Blastocyst Fast Thawing Kit *(GBTH)*	*Thawing of vitrified blastocysts*

These procedures include: sperm washing and handling, intra-cytoplasmic sperm injection (ICSI), embryo biopsy for pre-implantation genetic diagnosis, sperm freezing, and blastocyst vitrification and thawing. The media products will be used in an IVF laboratory environment for assisted reproduction procedures by trained medical practitioners. Global® total® w/HSA and global® total® w/HEPES w/HSA might be introduced into the uterus. The remaining devices are used for in vitro procedures only and would never be introduced into the uterus or elsewhere into the human body.

HSA 25% is included as a surfactant in LifeGlobal Media w/HSA to prevent adherence of gametes and embryos to pipettes, culture dishes and other materials. The concentration of HSA 25% in the different media is shown in the table below.

Table 6. Overview of concentrations of Albunorm 25% as used in LifeGlobal Media

Product Name	Antibiotic	HSA
global® total® w/ HSA	Gentamicin (10 µg/ml)	10 g/l
global® total® for Fertilization w/ HSA	Gentamicin (10 µg/ml)	10 g/l
global® total® w/ HEPES w/ HSA	Gentamicin (10 µg/ml)	10 g/l
LG PGD Biopsy Medium	Gentamicin (10 µg/ml)	5 g/l
global® Blastocyst Fast Freeze® Kit		
Fast Freeze® Solution 1 (F1)	Gentamicin (10 µg/ml)	20 g/l
Fast Freeze® Solution 2 (F2)	Gentamicin (10 µg/ml)	20 g/l
Fast Freeze® Solution 3 (F3)	Gentamicin (10 µg/ml)	20 g/l
global® Blastocyst Fast Freeze® Thawing Kit		
Fast Freeze® Thawing Solution 1 (T1)	Gentamicin (10 µg/ml)	10 g/l
Fast Freeze® Thawing Solution 2 (T2)	Gentamicin (10 µg/ml)	10 g/l
Fast Freeze® Thawing Solution 3 (T3)	Gentamicin (10 µg/ml)	10 g/l
Fast Freeze® Thawing Solution 4 (T4)	Gentamicin (10 µg/ml)	10 g/l
Fast Freeze® Thawing Solution 5 (T5)	Gentamicin (10 µg/ml)	10 g/l
global® DMSO Blastocyst Vitrification Kit		
Equilibration Solution (ES)	Gentamicin (10 µg/ml)	10 g/l
Vitrification Solution (VS)	Gentamicin (10 µg/ml)	10 g/l
global® DMSO Blastocyst Vitrification Warming Kit		
Warming Solution 1 (W1)	Gentamicin (10 µg/ml)	10 g/l
Warming Solution 2 (W2)	Gentamicin (10 µg/ml)	10 g/l
Warming Solution 3 (W3)	Gentamicin (10 µg/ml)	10 g/l
AllGrad Wash®	Gentamicin (10 µg/ml)	5 g/l

Description of method of manufacture

All products are prepared by simple mixing of the components, including HSA. All components are added in their original form, without any intermediate processing or modification, followed by sterilizing filtration (using 0.22 µm gamma sterilized filters). Mineral oil products are filtered with pharmaceutical grade sterilizing filter. All other media products are filtered with pharmaceutical grade sterilizing filter. Products are aseptically filled into sterile PETG bottles and vials, and capping with sterile closures.

Control of starting material

The specifications for human albumin 25% manufactured at Octapharma are reported in the Certificate of Analysis provided by the Applicant. Confirmation has been provided by the Applicant that data needed for full traceability are stored for at last 30 years according to Article 4 of Directive 2005/61/EC, Article 14 of Directive 2002/98/EC and GMP annex 14.

An HPLC assay is used to test the identity (by retention time) and concentration (by peak area) of HSA in all incoming batches of source material for quality control purposes. The respective validation reports provided are acceptable.

The applicant provided an assessment of the potential risk posed by the possible contamination with parvovirus B19V. The calculation of the Estimated Worst Case Exposure to B19 per Procedure and Total Exposure is found satisfactory as it shows that the risk of contamination during the IVF is negligible.

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

There is no testing carried out at the intermediate stage.

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

Each lot of LifeGlobal Media w/HSA is tested for pH, osmolality, endotoxins, sterility, and by a one-cell mouse embryo assay (1-cell MEA), gentamicin content and protein (HSA) content.

The method has been appropriately validated.

The Applicant confirmed that the expiry date of the HSA 25% incorporated into any of the LG Media solution/medium batch is synchronised with, or longer than, the expiry date of the medical device so that the HSA 25% will remain within its shelf-life throughout the duration of the shelf-life of the medical device.

Stability

The stability of HSA in the final devices is assessed using both the same HPLC assay for concentration determination used to test incoming batches of Albunorm 25% and the colorimetric assay used for determination of protein (HSA) content of the final LifeGlobal Media w/HSA products. A validation report has been provided and found acceptable.

Stability Studies of Life Global Gamete and Embryo Culture and Handling Media Containing Human Serum Albumin

Based on stability studies performed for Global Total w/HSA and Global Total w/HEPES W/HSA for duration of 77 days, a shelf-life of 70 days at a temperature of 2-8°C is claimed by the applicant and found acceptable. The applicant states that these two media are representative also for Global® total® for Fertilization w/HSA, PGD Biopsy Medium, All Grad Wash® due to similar composition. This has been accepted, therefore the 70 days shelf life is also applicable to Fertilization w/HAS and PGD Biopsy Medium. However all Grad Wash required further studies since this medium shall be stored for up to one year (see supplementary stability study below).

All Grad Wash required further studies since this medium shall be stored for up to one year (see supplementary stability study below).

The Applicant has also provided for these media thawing/freezing stability data, stability data after exposure to light and stability data after repeated use of the media from the same bottle over one week.

A shelf life of 70 days for the above mentioned media is acceptable.

Supplementary Stability Tests of LifeGlobal Media containing Human Serum Albumin and gentamicin

Stability data of HSA 25% were obtained for Global Blastocyst Fast Freeze Kit, Global Blastocyst Fast Freeze Thawing Kit, Global DMSO Blastocyst Vitrification Kit, Global DMSO Blastocyst Warming Kit and AllGrad Wash. Samples of each product were taken at random from different batches, stored at 2-8°C protected from light, at the following time points: time of manufacture, mid-point though shelf life and after expiration. Based on the results, a shelf life of 1 year at a temperature of 2-8°C is claimed by the applicant and found acceptable.

The Applicant has clarified that the kit solutions for the Global Blastocyst Fast Freeze and Thawing kits, and the Global DMSO Blastocyst Vitrification and Warming kits are only manufactured in the 5 ml size used for the supplementary stability study. This therefore represents the worst (and only) case for those products. The 100 mL and 500 mL bottles of AllGrad Wash used in the supplementary stability study are the only sizes manufactured and therefore represent all cases. In addition, the Applicant has provided an acceptable justification for the missing in-use shelf life data for AllGrad Wash: this component contains similar concentrations of inorganic salts, glucose, lactate, pyruvate, phenol red, and HSA as Global Total w/HEPES w/HSA. They are packaged in the same PETG bottles with the same closures. Consequently, any effect (or lack of effect) of repeated sampling on Global Total w/HEPES w/HSA would be reflected in AllGrad Wash.

The formulation of All Grad Warming Kit is stated to be a simplification (without amino acids, with only 5mg/ml HSA) of Global Blastocyst Warming kit, and Global Blastocyst Fast Thawing kit. Therefore stability studies for Global Blastocyst Warming kit and Global Blastocyst Fast Thawing kit (according to the applicant) are also representative for All Grad Warming Kit. This approach was found acceptable.

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

The LifeGlobal media are manufactured using a 25% Albumin product manufactured by Octapharma (ancillary medicinal substance) and a mixture of physiologically balanced salt solutions which may contain amino acids, salts, gentamicin and glucose. Information regarding quality and safety of the plasma for the manufacture of HSA 25% is included in the EMA Octapharma PMF (EMEA/H/PMF/000008/05/AU/014/G that was last re-certified on 01 April 2016)

Exhaustive details of the manufacturing process for Albunorm 25% from the starting material to the final product have been provided. Controls of critical steps and intermediates are satisfactory. Process validation demonstrated consistency of the manufacturing process. The final product complies with the current Ph. Eur. monograph for human albumin solution. Albunorm 25% manufacturing process shows a good capability to reduce the potential prions/viral load of adventitious agents.

With respect to the ancillary human blood product as incorporated in the medical device, an analysis of the compatibility between HSA 25% and the other media components has been provided

To test the identity and concentration of HSA 25% in all incoming batches of source material for quality control purposes, an HPLC assay is used.

There are no in-process controls for HSA 25%. However, the proposed concentration of HSA in the finished device is checked on each finished product by means of a colorimetric method.

The data needed for full traceability is stored in compliance with the relevant European Directives.

Regarding the possible risk due to B19V contamination, there are measures in place in the manufacturing process of Albunorm 25% to reduce the viral load, including NAT testing of plasma pools with a maximum accepted virus load of 100 IU/µl. A statement had been provided by Octapharma indicating the estimated parvovirus B19V load per dose of Albunorm 25% while the Applicant has provided a risk assessment

where the total amount of Albunorm 25% used during the different phases of an IVF treatment is taken into account in order to calculate the maximum exposure of gametes, embryos and patient to parvovirus B19V during an IVF treatment. The Estimated Worst Case Exposure to B19 per Procedure and Total Exposure was found satisfactory as it shows that the risk of contamination during the IVF is negligible.

Human Albumin (25%) is mixed into the IVF media followed by membrane sterile filtration and filling. The quality of the IVF media is assured using a number of analytical tests, including a test for Human Albumin.

Stability data of Human Albumin is obtained using the HPLC method and the colorimetric method.

Based upon the submission of appropriate stability data, global total w/ HAS, global total w/ HEPES w/HSA, global total for Fertilisation w/ HAS and LG PGD Biopsy Medium have been granted a shelf life of 70 days at a temperature of 2-8°C.

Based on the submission of appropriate stability data, global Blastocyst Fast Freeze Kit, Global Blastocyst Fast Freeze Thawing Kit, Global DMSO Blastocyst Vitrification Kit, Global DMSO Blastocyst Warming Kit and AllGrad Wash have been granted a shelf life of 1 year at a temperature of 2-8°C.

2.3. Non-clinical documentation

Pharmacodynamics

No ad hoc pharmadynamics studies were submitted. HSA acts as surfactant to prevent the adhesion of gametes and embryos to pipettes and culture dishes. The (composition of the) solutions are, or are relatively simple modifications of, well-established commercial products that have been used for clinical ART laboratory procedures for many years. Those products were, in turn, derived from fundamental studies using mouse and/or other animal embryos.

The lack of pharmacodynamics studies is acceptable, since the role of HSA in buffers and media for in vitro fertilization is considered to be well known.

Pharmacokinetics

No ad hoc pharmacokinetics studies were submitted.

LG Media are for in-vitro use only. Consequently, pharmacokinetic considerations are not relevant to the HSA contained within those products. Given the small quantities of HSA introduced into the uterus, and the fact that HSA is normally found with the human uterine lumen, pharmacokinetic considerations are not functionally relevant to the HSA contained within those products.

The lack of pharmacokinetic studies is acceptable since the absorption of albumin trough the vaginal and endometrial tissue is considered negligible, therefore no further studies are requested.

Toxicity

Cytotoxicity

The cytotoxicity of each lot of each of the products listed in Table 5 is evaluated for cytotoxicity by mouse embryo assays (MEA). For quality control purposes, 80% of the embryos must develop to, or beyond, the expanded blastocyst stage. The consistent result of 90-100% expanded blastocysts indicates that these products are biocompatible with mammalian embryo development in vitro.

Global Total w/HSA and Global Total for Fertilization w/HSA: For each production lot, one-cell B6C3F1 X B6D2F1 mouse embryos are cultured in microdrops of the medium, under oil, under 5% CO 2 in air, for 96 hours. At the end of culture, the embryos are evaluated for development to the expanded blastocyst stage. Each assay includes a control group of embryos cultured in laboratory standard medium.

Global Total w/HEPES w/HSA and AllGrad Wash: For each production lot, one-cell B6C3F1 X B6D2F1 mouse embryos are exposed to Global Total w/HEPES w/HSA for 60 minutes, or AllGrad Wash for 30 minutes, and then cultured in laboratory standard medium and conditions for 96 hours. At the end of culture, the embryos are evaluated for development to the expanded blastocyst stage. Each assay includes a control group of embryos cultured in standard medium.

PGD Biopsy Medium: For each production lot, two-cell B6C3F1 X B6D2F1 mouse embryos are exposed to the medium for 30 minutes, and then cultured in laboratory standard medium and conditions for 72 hours. At the end of culture, the embryos are evaluated for development to the expanded blastocyst stage. Each assay includes a control group of embryos without exposure to PGD Biopsy Medium.

Global DMSO Blastocyst Vitrification and Warming Kits: For each production lot, the vitrification and warming solutions are tested together. One-cell B6C3F1 X B6D2F1 mouse embryos are sequentially exposed to the equilibration, vitrification and three warming solutions in the same manner as the solutions are used for human embryos. The embryos are then cultured in laboratory standard medium and conditions for 96 hours. At the end of culture, the embryos are evaluated for development to the expanded blastocyst stage. Each assay includes a control group of embryos cultured in laboratory standard medium.

Global Blastocyst Fast Freeze and Fast Freeze Thawing Kits: For each production lot, the Fast Freeze and Fast Freeze Thawing solutions are tested together. Expanded blastocyst B6C3F1 X B6D2F1 mouse embryos are sequentially exposed to the three freeze and five thawing solutions in the same manner as the solutions are used for human embryos. The embryos are then cultured in laboratory standard medium and conditions for 24 hours. At the end of culture, the embryos are evaluated for re-expansion. Each assay includes a control group of expanded blastocysts cultured in laboratory standard medium.

Carcinogenicity, germ cell mutagenicity, and teratogenicity

The Applicant declares that the potential for carcinogenicity of each component of the products listed in Table 5 was evaluated by reference to the IARC (International Agency for Research on Cancer) Monographs on the Evaluation of Carcinogenic Risks to Humans (http://monographs.iarc.fr). None of the components are classified by the IARC as being carcinogenic, probably carcinogenic, or possibly carcinogenic to humans.

The Applicant states that potential for germ cell mutagenicity, and teratogenicity was evaluated by reference to the information provided in the material safety datasheets provided by the supplier. None of the components carry any significant risk of germ cell mutagenicity, or teratogenicity.

Reproductive and developmental toxicity

The applicant declares that potential for reproductive or developmental toxicity of each component of the products listed in Table 5 was evaluated by reference to the information provided in the material safety datasheets provided by the supplier. None of the components are identified as having any potential for reproductive or developmental toxicity in their respective material safety datasheets.

Degradation products

The applicant declares that none of the components of the products listed in Table 5 are known to produce any significant accumulation of toxic products due to spontaneous degradation.

Compatibility with other substances

The applicant declares that all of the products listed in Table 5 are ready-to-use, and consequently there is no concern with compatibility with other substances.

All the provided toxicity tests performed by the Manufacturer are not conventional tests 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.

The lack of Carcinogenic, Reproductive and Developmental Toxicity Testing can be considered acceptable since the properties of HSA are well known and no further non clinical information is requested.

Local tolerance

Of the products listed in Table 5, only Global Total w/HSA, Global Total w/HEPES w/HSA, and AllGrad Wash are intended for uses that include exposure to the human body as they can be used for embryo transfer into the uterus. Embryo transfer into the uterus in 100 microlitres of Global Total w/HSA or Global Total w/HEPES w/HSA would represent a total dose of 1 milligram of HSA. AllGrad Wash may be used for intra-uterine insemination. The sperm are typically suspended in a maximum of 500 microlitres of medium for intra-uterine insemination. Intrauterine insemination in 500 microlitres of AllGrad Wash would represent a total dose of 5 milligrams of HSA. Global Total w/HEPES w/HSA and AllGrad Wash were evaluated for local tolerance in two in vivo tests performed by WuXi AppTec, St. Paul, MN, USA for Nelson Laboratories, Salt Lake City, USA.

All the local tolerance studies were conducted in compliance with ISO 10993-10:2010 (Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization) and ISO 10993-12:2012 (Biological Evaluation of Medical Devices, Part 12: Sample Preparation and Reverence Materials).

ISO Guinea Pig Maximization Sensitization Test (GLP – Method for Liquid Test Article)

For each of Global Total w/HEPES w/HSA and AllGrad Wash, guinea pigs were exposed in two induction phases to the undiluted test articles or normal saline (control). The challenge sites of each animal were observed for evidence of skin sensitization at 24 ± 2 and 48 ± 2 and then examined for signs of erythema and edema. Neither Global Total w/HEPES w/HSA nor AllGrad Wash elicited a sensitization response.

ISO Mucosal (Vaginal) Irritation Test (GLP – No Extraction)

The undiluted test solutions were applied to the vaginal vault of female albino rabbits. The dose amount for each animal was 1.0 mL, and test and control animals were dosed similarly. Each animal was dosed daily for five consecutive days. On Day 5, approximately 24 hours after the fifth dose, the vaginal tissue was harvested for histopathology analysis. The tissues were examined for irritant effect.

Both Global Total w/HEPES w/HSA and AllGrad Wash were classified as non-irritant.

In summary, the applicant declared that:

None of the ingredients of the products listed in Table 5 are likely to be toxic at the exposure levels associated with normal product use.
The products are not cytotoxic, based on the results of mouse embryo assays.
None of the components carry a known risk of carcinogenicity
None of the components carry any significant risk of genotoxicity.
None of the components carry a known risk of teratogenicity.
None of the components carry a known risk of reproductive toxicity.
None of the components carry a known risk of developmental toxicity,

Global Total w/HSA, Global Total w/HEPES w/HSA, and AllGrad Wash have no measurable allergenic potential or sensitizing capacity.
Global Total w/HSA, Global Total w/HEPES w/HSA, and AllGrad Wash have no measurable local irritation potential.

2.3.1. Discussion and conclusion on the non-clinical documentation

The lack of pharmacodynamic studies has been justified. The role of albumin in buffers and media for in vitro fertilization is considered to be well known. Since the solutions contain, besides HSA, gentamicin sulphate the applicant was requested to provide the MHRA non clinical assessment of this substance. Taking into consideration that gentamicin sulphate is contained at a concentration of 10 µg/ml to inhibit potential bacterial growth during normal handling and use, and that similar products are on the market containing gentamicin sulphate and HSA, at the same concentration and for the same intended use, it is possible to conclude that the safety of the products is not compromised.

The lack of pharmacokinetic studies is acceptable since the absorption of albumin through the vaginal and endometrial tissue is considered negligible.

Toxicity tests performed by the Manufacturer are not conventional tests 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. The lack of Carcinogenic, Reproductive and Developmental Toxicity Testing can be considered acceptable since the properties of HSA are well known. Studies aiming at demonstrating the local tolerance of the whole solutions which are intended to be injected into the female genital tract, have been performed. Results obtained demonstrate that Global Total w/HSA, Global Total w/HEPES w/HSA, and AllGrad Wash do not elicit any local sensitization nor irritation potential.

Based on the documentation provided, it can be concluded that the media present no unreasonable risk of harm and may be considered safe to use. Risks concerning the use of the various HSA-containing ART media have been reduced to an acceptable level and constitute no recognized risk for the gamete, embryo or patient when the intended promulgated use is followed.

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

There are no objections from a non-clinical point of view to acceptance of the currently proposed ancillary substance used in the medical device LifeGlobal Media.

2.4. Clinical evaluation

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

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 and it is not intended to have any additional pharmacological effect.

HSA is one of the most widely used and characterized proteins in the pharmaceutical field. LifeGlobal Media w/HSA consists in media and solutions intended for use in various procedures ancillary to in vitro fertilization and culture of human gametes and embryos. Some of these solutions contain two ancillary substances: gentamycin 10 µg/ml and human serum albumin (HSA) 25%.

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 HSA is a well-known substance contained in several medicinal products as well as in comparable medical devices (GEMS suite media, FertiPro N.V. HSA-containing media, PureSperm Wash) the notified body´s conclusion that inclusion of the ancillary human blood derivative, HSA, in the IVF media is acceptable in terms of usefulness.

The CE marked IVF Media on the market using HSA are already available. The notified body outlines the functions of HSA in ART media and solutions. The presence of the HSA in the LifeGlobal Media is the only difference between new and already commercialized IVF media.

The general information, as submitted, is considered acceptable. However, the Applicant did not submit any new data, but presented a summary of reports that refers to the use of LifeGlobal Media supplemented with HSA in ART, to support the authorization of the products listed in Table 5 in the European Union (CE marking). The Applicant justified the lack of new clinical reports stating that the Life Global products containing HSA, are, or are relatively simple modifications of commercial products that have been already used for clinical ART laboratory procedures. Considering the above, only the studies in which the LifeGlobal Media were supplemented with the same HSA amount of the products for which the authorization is sought have been considered relevant for the extrapolation of safety and efficacy profile.

Because most of the published studies did directly compare two or more IVF media, the Applicant reports as comparative reliable measure of efficacy of such media (i.e. embryo transfer number or implantation rate) values extrapolated from the Canadian Assisted Reproductive Technologies Register (CARTR) Plus 2013.

The selection of the CARTR data as the only dataset used for the purpose of the efficacy comparison has been justified based on the observation that the Canadian registry is the only national ART registry that reports implantation data extrapolated from fresh transfers (patients' own oocytes) across all maternal age groups, separated by day of transfer which is a prime determinant of the implantation rate.

Global Total w/HSA

For Global Total w/HSA, only 1 out of the 8 studies involving direct comparisons between Global medium supplemented with HSA and other commercially-available embryo cultured media has been evaluated, and only 5 out of 30 studies involving the use of Global medium supplemented with HSA for all of the embryos in the study have been assessed. Furthermore the 2 studies involving the use of Global Total for all the embryos in the study have not been considered due to the lack of a control.

Among all the submitted studies, the paper by Basile et al. "Type of culture media does not affect embryo kinetics: a time-lapse analysis of sibling oocytes" is the only one that allows to compare in vitro results of embryos cultured with different media. The results showed there is no difference in the morphokinetics of growing embryos using both Quinn's Advantage Cleavage and LG media in which HSA is added by the operator. However, as acknowledged by the authors themselves, the main limitation of the study, is that it was not powered to test differences in pregnancy rates between the two culture media. As also stated by the Applicant, implantation embryo rate is the only reliable measure of efficacy for these media. Overall the study could be considered supportive for the in vitro results and not for the clinical outcome: the rate of successful implantations.

Global Total w/HEPES w/HSA

The study objective was to verify if the storage time of vitrified human blastocysts negatively impacts on their survival, the implantation potential of embryos or the malformation rate of babies born. The study

did not plan a comparison between LG media and a comparator thus it is not possible to compare efficacy and safety of LF products versus IVF media already on the market.

Moreover i) all VIT solutions were prepared in HEPES-buffered Global medium containing 20% HSA and ii) after warming blastocysts were placed in 500 ml Global medium supplemented with 7.5% HSA for 15 min, before being transferred to new medium while the Global Total w/HEPES w/HSA (to be marked product) containing only 7.5 mg/mL HSA.

Aside from the amount of supplemented HSA is different from the 10 mg requested for the EU marketing; moreover, in the full article no specific mention is made to the added HSA amount in the Global Total w/HEPES embryo used to continue the embryo culture after the warming. No helpful information is retrievable from the study.

LG PGD Biopsy Medium

In the study by Sher G, et al. (2009) "Genetic analysis of human embryos by metaphase comparative genomic hybridization (mCGH) improves efficiency of IVF by increasing embryo implantation rate and reducing multiple pregnancies and spontaneous miscarriages" this medium is used to facilitate the biopsy of cells from human cleavage-stage embryos for PGD. Nevertheless, in the reported article there is no reference to the use of Life Global products. The PGD technique is performed on selected blastocysts but it is not clear which media are used for the in vitro diagnosis. As above no helpful information is retrievable from the study.

AllGrad Wash

The primary use of the product ALLGrad Wash® is for the washing sperm procedure. ALLGrad Wash® removes any particles of colloidal silica that may be present in the sperm pellet after centrifugation with ALLGrad® 45%, 90% and 100% used for the removal of dead sperm, debris, and other cells from human sperm cells prior to in-vitro fertilization or ICSI. ALLGrad Wash® may be also used to dilute ALLGrad® 100% stock solution.
In all clinical reports, the Applicant described the sperm collection and washing using the AllGrad Wash medium before ICSI or conventional IVF techniques. Clinical pregnancy rate (% of transfers) was the reference parameter derived from the Canadian Assisted Reproductive Technologies Register Plus (CARTR Plus) 2013 registry values.
Nevertheless, in the Magendzo A et al study the overall pregnancy rate per cycle reported (11.4%), obtained from stimulated women aged under 37 years is instead compared with the values reported by the De Brucker and Tourney study (13%). In this latter paper, the authors extrapolated their mean comparative value from a systematic retrospective analysis of 6 studies conducted to overview the impact of woman age on the outcome of intrauterine insemination (IUI) and to analyse whether ovarian superovulation may have any benefit on success rates.
ALLGrad Wash medium reference is reported in the retrospective report.

Global DMSO Blastocyst Vitrification and warming kits

LifeGlobal global® DMSO Blastocyst Vitrification Kit is indicated for vitrification (ultra-rapid freezing) and cryostorage of human blastocysts and is to be used in conjunction with the global® DMSO Blastocyst Vitrification Warming Kit. The warming kits are indeed used for the rehydration of human blastocysts that have been vitrified using the global DMSO Blastocyst Vitrification Kit.

For all the vitrification kits, embryos are sequentially exposed to 2 or 3 kit solutions containing 10 mg HSA and increasing concentrations of two cryoprotectants (DMSO & ethylene glycol, glycerol & ethylene

glycol, or ethylene glycol & propylene glycol).For all warming kits, embryos are sequentially exposed to 3 to 5 kit solutions containing HSA and decreasing concentrations of sucrose.

Vitrification is rapidly replacing slow cryopreservation as the method of choice for embryo freezing in clinical ART procedure. In contrast to slow cryopreservation methods, vitrification uses rapid cooling rates to preserve the embryo instantaneously and requires high concentrations of cryoprotectant combined with high cooling rates to transition from a fluid to solid state without a phase change thus avoiding intra or extracellular ice crystallization.

In the Reprod Biol Endocrinol paper by Desai, embryos were vitrified with Vitrification Solution #1 (VS1) consisted of 7.5% DMSO and 7.5% EG in Global medium with 20% serum protein substitute (SPS). Vitrification Solution #2 (VS2) contained 15% DMSO, 15% EG, 10 mg/ml Ficoll-70 and 0.65 M sucrose. The Applicant clarified that the 20% v/v Sage SPS used as protein supplement in the vitrification and thawing solutions used in the Report Biol Endocrinol paper by Desai contains a final concentration of 8.8 mg/ml HSA and a mix of 1.2% α and β globulins. The HSA concentration contained in the SPS supplement is approximately equal to the 10 mg/ml HSA contained in the Global DMSO Blastocyst Vitrification and Warming Kits, so supporting the efficacy of vitrification and thawing solutions when using the Global DMSO Blastocyst Vitrification and Warming Kits.

Clinical Efficacy and Safety of Global Blastocyst Fast Freeze and Fast Freeze Thawing Kits

Global® Blastocyst Fast Freeze® Kit is DMSO-free and uses regular sealable straws. It is a three-step cryopreservation process. It uses glycerol and ethylene glycol as cryoprotectants and uses global® w/ HEPES base medium and also contains 20 mg/ml HSA.

Global Blastocyst Fast Freeze® Thawing Kit is a five-step gradual rehydration process through reducing concentrations of sucrose in a global® w/ HEPES base medium containing 10 mg/ml HSA.

The use of both kits demonstrate a better Implantation Rate (% of blastocysts transferred) respect to comparative products as reported by Reed ML and al study (39.6% LifeGlobal Media vs 22.2% and 27.5%, Irvine and Vitrolife respectively).

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

In the Notified Body report some potential risks that could arise to the mother and the embryo during ART using IVF media systems are outlined. With regard to HSA, the possible risk identified is the potential transmission of infections. Therefore, it is a prerequisite for a positive safety profile that all quality issues with regard to virus safety are resolved. In particular, with respect to the possible risk due to contamination, the Applicant was asked to provide a risk assessment where the estimated B19V load per dose of Albunorm 25% and the total amount of Albunorm 25% used during the different phases of an IVF treatment are taken into account in order to calculate the maximum exposure of gametes, embryos and patient to B19V during an IVF treatment. The applicant responded by providing the correct estimated number of virus particles per vial of Albunorm (N) obtained by using the reduction factor for PPV reported in the original dossier (5.77 log). The corrected value for N was used in a revised calculation of the Estimated Worst Case Exposure to B19 per Procedure and Total Exposure that is found satisfactory as it shows that the risk of contamination during the IVF is negligible.

The Manufacturer did not address the safety profile of HSA in the submitted clinical reports. Bacterial contamination, viral infection and local irritant effects are among the possible safety issues associated with the use of IVF media particularly when human blood derivative are contained. Based on the

Non-clinical documentation provided, it can be concluded that the media present no unreasonable risk of harm and may be considered safe to use. Risks concerning the use of the various HSA-containing ART media have been reduced to an acceptable level and constitute no recognized risk for the gamete, embryo or patient when the intended promulgated use is followed.

The Manufacturer did not address the safety profile of HSA in the submitted clinical reports. Bacterial contamination, viral infection and local irritant effects are among the possible safety issues associated with the use of IVF media particularly when human blood derivative are contained. Based on the Non-clinical documentation provided, it can be concluded that the media present no unreasonable risk of harm and may be considered safe to use. Risks concerning the use of the various HSA-containing ART media have been reduced to an acceptable level and constitute no recognized risk for the gamete, embryo or patient when the intended promulgated use is followed.

Post-marketing surveillance of IVF manufactured media/buffer will allow monitoring of the safety profile of the devices.

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

In submitting the required information for the consultation for the LG range of IVF Media devices containing HSA the conclusion has been reached that inclusion of the ancillary human blood derivative is acceptable. The discussions provided by both the medical device manufacturer and Notified body on albumin's physiological roles and the established use of HSA supplementation of ART media, in addition to the literature evidence provided by the medical device manufacturer, together sufficiently demonstrated the usefulness of HSA added to the ART media.

The Notified Body has also evaluated the potential risks associated with the safety of the medical device and is satisfied that the combination of production controls and finished product testing is appropriate to minimize any known risks to the female recipient of the ART media. Given the demonstrated benefits of HSA, the usefulness of its addition to ART media associated with its use in assisted reproduction techniques, the benefit-risk of HSA supplementation of the LifeGlobal ART media is considered positive.

Addition of HSA in the In-Vitro Fertilization media is endorsed in terms of usefulness.

2.4.4. Discussion and conclusion on the clinical evaluation

The LG products containing HSA are (relatively) simple modifications of well-established commercial products that have been used for clinical ART laboratory procedures for many years. No new data about LG products w/HSA were submitted by the device manufacturer.

To support the clinical usefulness and the benefit of the HSA supplied media, the Applicant provided literature articles, short summaries of unpublished data regarding some clinical studies conducted in different IVF centres of USA. Despite the great number of studies submitted, only few clinical studies directly compare LG products and similar ART products. However, all the studies did not use for the IVF procedures the ready to use LifeGlobal media w/HSA. For this reason it is not easy to compare results obtained using the LifeGlobal media in which HSA was added by the operator and those obtained using the ready to use LifeGlobal media supplemented with HSA. Moreover, the Applicant reported values extrapolated from the Canadian Assisted Reproductive Technologies Register (CARTR) Plus 2013 as comparative reliable measure of efficacy of such media (embryo transfer number or implantation rate).

The selection of the CARTR data as the only dataset used for the purpose of the efficacy comparison has been justified based on the observation that the Canadian registry is the only national ART registry that reports implantation data extrapolated from fresh transfers (patients' own oocytes) across all maternal age groups, separated by day of transfer which is a prime determinant of the implantation rate. The Applicant has also provided the requested characterization of the population from which implantation rates are derived. The revised report (Clinical Reports of the Use of LifeGlobal ART Media Supplemented with Human Serum Albumin, 2016) contains a table showing the numbers of cycle starts, oocyte retrievals, and transfers, and implantation rates, divided by maternal age.

Nevertheless, it is recognised that the use of HSA in IVF media is a consolidated procedure. Therefore, the HSA addition in the ready to use LifeGlobal Media is considered justified in terms of usefulness as it is expected to represent a clinical benefit by enabling the implantation rate.

Finally, the Applicant declares no evidence of any adverse events affecting either the patients or the babies born that could be attributed to the use of LifeGlobal Media supplemented with HSA. No evidence of any events relevant to the risk analysis for all the media emerged from both the articles and summaries presented.

Overall, the submitted information is considered acceptable to support a positive benefit/risk profile of the ancillary medicinal substance HSA incorporated in the range of LifeGlobal Media from a clinical point of view.

2.5. Overall conclusions

The CHMP consider that the application in the present consultation regarding the medical device LifeGlobal Media incorporating the ancillary medicinal substance human serum albumin, is approvable.

2.6. Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality and safety including the benefit risk profile of human serum albumin used as ancillary medicinal substance in the LifeGlobal Media was favourable and therefore granted a positive opinion in the consultation procedure.