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EMEA/CHMP/461473/2007

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: Medicult a/s HSA containing media*

Ancillary medicinal substance: Human albumin solution

EMEA/H/D/830

Applicant: DGM, DS Certificering A/S

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

*Note: the name of Medicult a/s HSA-containing media was changed to Origio a/s HSA-containing media in a post consultation procedure.

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Administrative information

Invented name of medical device:	Medicult a/s HSA containing media
INN (or common name) of the ancillary medicinal substance:	Human albumin solution
Applicant for medical device CE certification:	Medicult a/s
Notified body:	DGM, DS Certificering A/S
Applied intended purpose of the device:	In vitro maturation, culture and cryopreservation of human gametes and embryos
Intended purpose of the ancillary medicinal substance in the device:	• pH buffer • colloid osmotic regulation • membrane stabilisationer, • carrier of growth promoting substances (amino acids, vitamins, fatty acids) • scavenger and nutrient
Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:	1-10 mg/ml

1. Background information on the procedure

1.1. Submission of the dossier

The Notified Body DGM, DS Certificering A/S submitted to the European Medicines Agency (EMEA) on 02 February 2007 an application for Consultation on Human Albumin as ancillary medicinal substance(s) used in a medical device Medicult a/s HSA containing media, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

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

Rapporteur: Dr. David Lyons Co-Rapporteur: Dr Ian Hudson

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 02/02/2007.
- Additional information was submitted on 02/03/2007.
- The procedure started on 21/03/2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8/6/2007 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 29/5/2007.
- During the meeting of the Biologics Working Party on July 2007, experts were convened to address questions regarding the quality aspects raised by the CHMP.
- During the meeting in July 2007, the CHMP agreed on the consolidated List of Questions to be sent to the Notified Body. The final consolidated List of Questions was sent to the Notified Body on 17/07/2007.
- The Notified Body submitted the responses to the CHMP consolidated List of Questions on 10/8/2007.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the List of Questions to all CHMP members on 17/09/2007.
- During the CHMP meeting in October 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing by the Notified Body.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the list of outstanding issues dated 30/11/2007.
- During the meeting of the Biologics Working Party on December 2007, experts were convened to address questions regarding the quality aspects raised by the CHMP.
- During the meeting in December 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on the quality, safety and usefulness of Human Albumin as ancillary medicinal substance(s) used in Medicult a/s HSA containing media in December 2007.

2. General conditions for the use of ancillary medicinal substances in medical devices

2.1. Manufacturers

Manufacturer of the active substance used as ancillary medicinal substance

Talecris Biotherapeutics, Inc
86368 US 70 West Clayton, North Carolina 27520, USA

Manufacturer responsible for import and batch release in the European Economic Area

Bayer Biologicals S.r.l.
Bellaria, 35, I-53010 Torri-Sovicille (SI), Italy

Manufacturer of the devices

Medicult a/s
Møllenhaven 12, DK-4040 Jyllinge Denmark

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.

2.2. Recommended measures to the Notified Body

The Notified Body should request a commitment to the manufacturer of the medical device to report any out of specification result during the planed stability tests.

The manufacturer is recommended to substitute “Human Albumin Solution” or “Human Albumin” in place of “Human Serum Albumin (HSA)” in the label and information of each medium.

3. Scientific discussion

3.1. Introduction

The In Vitro Fertilisation (IVF) Medicult a/s HSA containing media is classified as a medical device according to the relevant Commission Directives (90/385/EEC, 93/42/EEC). The Medicult solutions incorporate human salbumin as a medicinal substance with ancillary action. The Notified Body, DGM, DS Certificering A/S, is consulting the CHMP regarding the quality, safety and usefulness of the albumin component in the Medicult a/s HSA media according to Directive (2000/70/EC).

MediCult a/s provides a complete range of media products for Assisted Reproduction Technologies (ART). MediCult a/s ART media are designed for use in the following IVF procedures: oocyte retrieval, oocyte in-vitro maturation, sperm preparation, culture microtechniques-sperm selection, sperm immobilization, removal of cumulus, cryopreservation of spermatozoa & embryos and culture of embryos and blastocysts.

The intended purpose of the range of MediCult a/s HSA-containing ART media includes retrieval and washing of oocytes, preincubation of immature oocytes, maturation of oocytes, isolation of viable spermatozoa, sperm washing, fertilization, culture of embryos, transfer of embryos, slow down

movement of sperm, biopsy for pre-implantation diagnosis, freezing of human spermatozoa, testicular tissue, embryos and blastocysts and thawing of embryos and blastocysts.

The intended purpose of HSA in IVF media is to act during different steps of the IVF cycle including pH buffer, colloid osmotic regulation, membrane stabilization, carrier of growth promoting substances (amino acids, vitamins, fatty acids, etc), scavenger and nutrient. In sperm preparation media, Human Albumin is intended to confer protective properties that help to maintain mobility and viability.

The albumin used for this purpose is Human Albumin, low aluminium (L/A) 25% from Talecris. The albumin is licensed in Germany and Greece under the names of Plasbumin and Human Albumin L/A respectively.

Human Albumin L/A 25% is manufactured according to Cohn-Oncley fractionation and in compliance with the Ph. Eur. monograph "Human Albumin Solution". The plasma used for the production of Human Albumin L/A 25% is covered by Talecris's Plasma Master File (PMF), which is assessed in the centralised PMF certification process. The initial PMF certificate was issued in February 2005 and updated in November 2006.

Composition and intended use of the HAS containing solutions of the medical device

Product type and Name	**Catalogue Ref. number**	**Intended use**
Flushing medium	1076,1084	Flushing medium is for retrieval holding and washing oocytes
Medicult a/s IVM System (LAG medium and IVM medium)	8221	LAG medium is for pre-incubation of immature oocytes
Suprasperm System	1092	Suprasperm system is for isolation of viable spermatozoa by the density gradient method
Sperm Preparation medium	1069,1070	Sperm preparation medium is for washing of spermatozoa and isolation of motile vibale spermatozoa by swim-up method
Universal IVF Medium	1030,1031	Universal IVF medium is for fertilization and culture until 2-8 cell stage. Universal IVF medium can also be used for embryo transfer
Embryo-Assist	1214,1213	For fertilisation and culture until the 2-8 cell stage. Embryo-Assist can also be used for embryo transfer
Blast-Assist	1216,1215	Blastocyst is for culture from the 4-8 cell stage through to blastcyst stage
ISM 1	1050,1150	ISM 1 is for fertilisation and culture until 2-8 cell stage
ISM 2	1051,1151	ISM2 is for culture from the 4-8 cell stage through to the blastocyst stage
UTM	1052,1152	UTM is for transfer of embryos and blastocysts
PVP medium	1089	PVP medium is for slowing down the movement of spermatozoa for ICSI
PVP clinical grade	1090	PVP clinical grade is for slowing down the movement of the spermatozoa for ICSI
Biopsy medium	1052	Biopsy medium is for blastmere biopsy of cleavage stage embryos for pre-implantation genetic diagnosis
Sperm Slow	1094	Sperm slow is for slowing down the movement of the sperm to allow for the selection of the most mature, viable spermatozoa for ICSI
Sperm Freezing media	1067	Sperm freezing medium is for freezing of spermatozoa and tissue from testicular biopsies
Embryo freezing pack	1026	Pack is for freezing of zygotes and cleavage stage embryos
Embryo Thawing pack	1098	Embryos thawing pack is for thawing of human zygotes and cleavage stage embryos frozen using Embryo Freezing Pack

Blastfreeze	1053	Blastofreeze is for freezing of Blastocysts
BlastThaw	1054	Thawing of blastocysts frozen using BlastFreeze

Quality aspects

3.2. Medicinal product before incorporation in the medical device

Introduction

Description

Albumin 25% L/A is a clear, slightly viscous pale yellow to amber coloured liquid. The active substance is human albumin. The albumin content in the product is not less than 96%. The composition is formulated to comply with the Ph.Eur. monograph 'Human Albumin Solution'.

Excipients

Sodium caprylate and N-acetyl-DL-tryptophan are used as excipients to stabilise the albumin and to reduce the formation of aggregates.

Specifications for N-acetyl-DL-tryptophan and sodium caprylate were provided and comply with Ph. Eur.

Container Closure System

The container of the product to be distributed to EU is a clear type II glass vial (USP/EP). The stopper compounds have been verified to meet the specifications of the current European Pharmacopoeia.

Active Substance

For the purpose of this report, the drug substance is defined as the sterile albumin bulk material prior to sterile filling.

- **General Information**

Nomenclature

The Ph. Eur. name of the active ingredient is Human Albumin Solution (Albumini Humani Solutio).

Structural Formula

A short description of the albumin molecule has been provided. Albumin consists of one single polypeptide chain of 585 amino acids cross linked by 17 disulfide bridges. The protein has a high degree of alpha helical structures and is folded into three domains. Each cylinder like domain has a hydrophobic inner space where hydrophobic substances such as fatty acids can bind. The outer surface of the molecule is mainly polar.

General Properties

The active substance human albumin is derived from human plasma.

- **Manufacture**

Definition of a batch

A fractionation batch is defined as the final Fraction V paste which is derived from Cohn fractionation of an amount of starting plasma.

A purification batch is defined as the final albumin bulk derived from the purification of an amount of Fraction V paste. The final bulk is sterile and contains stabilisers and electrolytes.

Description of Manufacturing Process and Process Controls

The manufacture of the sterile bulk is basically performed in two separate sequential processes: Cohn-Oncley fractionation followed by further purification steps.

The fractionation is a well-established method and consists of steps from plasma pooling to final Fraction V step. A series of cold alcohol precipitation steps, in which differences in pH, temperature and alcohol concentration are used, to separate the different protein fractions in plasma to obtain fraction V paste.

The purification consists of steps from suspension of fraction V paste to the sterile bulk and follows a series of standard pharmaceutical industry unit processes which include low temperature, pH control, filtration, centrifugation and acetone suspension.

There is no reprocessing of any of the fractionation steps. According to the manufacturer, in some cases, there is an option for reprocessing/reworking of the final bulk solution in case a compromise in bulk sterility occurs.

Control of materials

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material has already been approved in the centralised PMF certification procedure. Talecris PMF (formerly Bayer PMF) first certificate was granted for the PMF in February 2005 (EMEA/H/PMF/000004/04) and was re-certified in November 2006 (EMEA/H/PMF/000004/04/AU/003). Only plasma certified by the centrally approved PMF is used for the production of human albumin incorporated in the Medicult a/s HSA containing media.

The safety of the albumin with regard to potential Parvovirus B19 transmission requires special consideration. The applicant proposed a NAT limit for parvovirus B19 for the production for plasma pool. The limit is considered acceptable to guarantee the safety of the albumin taking into account the Parvovirus clearance of the manufacturing process of the albumin.

All raw materials used in the fractionation and purification steps of the manufacturing process meet the requirements of the European Pharmacopoeia (EP) and/or the United States Pharmacopoeia (USP). The specifications established by Talecris Biotherapeutics (formerly Bayer) have been provided. No animal derived materials are used in the manufacture of human albumin.

Control of Critical Steps and Intermediates

The control of the manufacturing process is deemed acceptable and relevant in-process controls are in place.

Microbiological quality is monitored throughout processes to ensure the necessary controls are in place to minimize potential product contamination. Information on all processing steps/conditions, the specification limits, reaction times, viral removal capacity and options for process-interruptions or storage time of intermediates are sufficiently provided.

Process Validation

The manufacturing process has been sufficiently validated and consistency of the production process has been adequately demonstrated. At least three consecutive qualification runs were performed for each system of the albumin product stream. Performance qualification of the process was carried out using approved batch production records.

Critical process steps, operating parameters and intermediate test data were evaluated to determine that each process step was consistent and that the final output of each process system met a set of pre-established acceptance criteria. All acceptance criteria were met and the performance qualification

demonstrated that the manufacturing process produces intermediates and final product that meet the pre-determined specifications and quality attributes.

Manufacturing Process Development

The method developed by Cohn for the cold ethanol fractionation of plasma to albumin was first published in 1946. Since that time a number of modifications have been introduced. These include changing the ethanol concentration, acetone drying of the albumin powder, incorporation of a pasteurisation step and the inclusion of caprylate as a stabiliser.

Impurities

More than 30 lots from each tested intermediate were analysed for the fractionation and purification steps of the process and the results verified consistency and reproducibility of the production process. The applicant has demonstrated the removal of expected impurities in the starting material as well as process related impurities.

- **Specification**

The sterile bulk before filling specification has been set at not less that 96% albumin. Protein composition of the drug substance is determined by state of the art methods. The method has been validated and full details have been provided.

Data from three batches were provided and all results complied with the set specification.

- **Stability**

The stability studies of the finished product support the current shelf life of the active substance and intermediates.

A protocol has been submitted for a proposed stability study designed to monitor the intermediates and the active substance maximum storage times.

Drug Product

- **Pharmaceutical Development**

The Cohn fractionation of human plasma to albumin was first described in 1946. Modifications have since been introduced including the use of pasteurisation to reduce the risk of hepatitis and the inclusion of caprylate as a stabiliser of the albumin protein.

Most of the description of pharmaceutical development is based on literature data since the Cohn-Oncley process is a well-established process. The excipients used are also well known and it is therefore acceptable that the applicant refers to the literature.

The suitability of the container system has been demonstrated. The stoppers have been verified to meet the specifications of the current European Pharmacopoeia.Safety of the closure system has been demonstrated by data on the stopper composition and data on aqueous extraction and toxicological studies.

The integrity of the closure system has been demonstrated.

- **Manufacture of the Product**

Batch formula

A batch is defined as the final uniform albumin bulk derived from the purification of an amount of fraction V paste.

Description of the manufacturing process and in-process controls

Production of the drug product from sterile albumin bulk consists of aseptic filling into final container, pasteurisation, incubation of final container after which the vials are stored. A flow chart of the process has been provided.

Reprocessing of the bulk is allowed when a compromise in bulk sterility is suspected caused by operator or equipment error.

A description of the packaging procedure, integrity and other testing have been provided.

Process validation

Full descriptions of the validation of procedures and equipment have been provided. The clean rooms are GMP certified.

Control of excipients

Specifications for N-acetyl-DL-tryptophan and sodium caprylate used as stabilisers in the finished product were provided. Both specifications comply with Ph. Eur.

Product Specification

Methods used for the release of the drug product are either Ph. Eur. methods or equivalent to Ph. Eur. methods. Validation reports were provided for test methods, which are not performed according to the Ph. Eur. methods.

Container Closure System

The container consists of bottles of glass and halobutyl isoprene rubber blend stoppers are used as closure. Both bottles and stoppers meet the requirements of the Ph. Eur. An cap is also used to seal the stoppers.

Stability of the Product

Results from four manufacturing batches support the assigned shelf life. The end of shelf life acceptance criteria ensure continued compliance with the Human Albumin Solution monograph of the European Pharmacopoeia.

Facilities and Equipment

A detailed description of the production facilities has been provided. The facility has undergone complete validation and is operated in accordance with current GMP. The buildings and equipment used to produce the product are dedicated to plasma product production.

Adventitious Safety Evaluation

Adventitious Agents

No materials of bovine or other TSE-susceptible animal species are used in production.

The Albumin 25% is produced from human plasma. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. The exclusion criteria have been described in the Plasma Master File (PMF) and were considered adequate and in line with Position Statement CPMP/BWP/2879/02. Intermediates of other suppliers are not used for production of the drug product.

The manufacturing process was investigated on its capacity to remove TSE agents. These investigational studies provide evidence that significant removal of prions can be expected from the manufacturing process.

Adventitious Viruses

Four steps of the production process were extensively validated for their virus inactivation/removing capacity including robustness studies. Enveloped viruses are effectively inactivated. Non-enveloped viruses have been demonstrated to be removed successively.

The applicant proposed NAT for parvovirus B19 of the production plasma pool as discussed in the Adventitious Agent Safety Evaluation section of this report. Viral validation studies in the manufacturing process of the albumin performed by the manufacturer estimated the clearance of parvovirus. The limit set for the plasma pools is considered acceptable to guarantee the safety of the albumin.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines and Ph. Eur. monograph for human albumin. The information provided in the application showed a consistent batch-to-batch production of Human Albumin L/A 25% achieving an adequate quality for the drug substance and the drug product. The manufacturing process of the drug substance and drug product were described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications.

The capacity and robustness of the manufacturing process to inactivate and remove viruses has sufficiently been investigated and, in summary, the virus safety of Human Albumin L/A 25% has adequately been demonstrated. No materials of bovine or other TSE-susceptible animal species are used in production. The Human Albumin L/A 25% is produced from human plasma in the USA. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. In addition, investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process.

3.3. Medicinal product in the context of its use in the medical device

Introduction

Medicult a/s media are comprised of different media used for handling gametes and embryos during In Vitro Fertilisation (IVF) and contain a protein supplement for culture medium. This protein supplement is human albumin, which has an ancillary effect, with the purpose to assist the function of the medical device.

The quality, safety and usefulness of the albumin as component of the solution are evaluated in the following part of the CHMP assessment report.

Quality, Safety and Usefulness

- **General Information**

The Medicult a/s media consists of several solutions or kits of solutions intended for use during the different stages of ART during the preparation, cultivation and storage of gametes and embryos. The solutions are supplemented with Human Albumin at the production site. There is no manipulation of the Human Albumin before adding it to the medical device solution. The Human Albumin used as ancillary medical substance is Human Albumin L/A 25% from Talecris and is manufactured according to the Ph Eur monograph Human Albumin Solution.

Medicult a/s ART media are designed for used in the following IVF procedures: oocyte retrieval, oocyte in-vitro maturation, sperm preparation, culture microtechniques (sperm selection, sperm

immobilisation, removal of cumulus), cryopreservation of spermatoza &embryos, culture of embryos and blastocysts.

The intended purpose of the range of MediCult a/s HSA-containing ART media includes: retrieval and washing of oocytes, preincubation of immature oocytes, maturation of oocytes, isolation of viable spermatozoa, sperm washing, fertilization, culture of embryos, transfer of embryos, slow down movement of sperm, biopsy for pre-implantation diagnosis, freezing of human spermatozoa, testicular tissue, embryos and blastocysts, thawing of embryos and blastocysts.

Historically, different kinds of media have been used in Artificial Reproduction Technologies (ART). For the purpose of culturing embryos these media have been supplemented to a great extent with proteins. Until the 1990s the most commonly used protein source in media for human IVF was human serum, obtained from the patient herself, human donors or fetal cord (Bungum M 2002). Since the 1990s serum has been replaced with various preparations of Human Albumin obtained from more highly defined sources. This was to attempt to reduce the risks of transmission of viral disease.

The role of the albumin in the media is extensive (Blake et al.). Albumin is intended to function as a pH buffer, a colloid regulator, a membrane stabiliser, a carrier of growth-promoting substances such as amino acids, vitamins, fatty acids, a scavenger and a nutrient.

The presence of the albumin in sperm preparation media is intended to confer properties to maintain the motility and viability. Albumin is intended to act as a potent inhibitor of lipid peroxidation, sperm capacitation and /or the acrosome reaction.

- **Qualitative and quantitative particulars of the constituents**

Product Name	Intended Purpose
IVM® System LAG Medium(vial 1) IVM® Medium (vial 2)	Pre-incubation of immature oocyte Maturation of mature oocyte
Flushing Medium	Retrieval, holding and washing of oocyte
Flushing Medium with 10 IU/ml Heparin	
Sperm Preparation Medium with Phenol Red	Washing of spermatozoa and isolation of motile viable spermatozoa by swim-up method
Sperm Preparation Medium	
SupraSperm® System 55% solution 80%	Isolation of viable spermatozoa by density gradient method
Universal IVF Medium with Phenol Red	Fertilisation and culture until 2-8 cell stage. Can also be used for embryo transfer
Universal IVF Medium	
EmbryoAssist™	
EmbryoAssist™ with Phenol Red	
BlastAssist®	Culture from 4-8 cell stage through to blastocyst stage
BlastAssist® with Phenol Red	
ISM1™	Fertilisation and culture until 2-8 cell stage
ISM1™ with Phenol Red	
ISM2™	Culture from 4-8 cell stage through to blastocyst stage
ISM2™ with Phenol Red	
UTM™	Transfer of embryos and blastocysts
UTM™ with Phenol Red	
PVP Medium	Slowing down movement of sperm to allow selection of most mature, viable spermatozoa for Intra Cytoplasmic Sperm Injection (ICSI)
PVP Clinical Grade	
SpermSlow™	
Sperm Freezing Medium	Freezing of spermatozoa and tissue from testicular biopsies
Biopsy Medium	Blastomere biopsy of cleavage stage embryos for pre-implantation genetic diagnosis

Embryo Freezing Pack	Vial 1 Vial 2 Vial 3	Freezing of zygotes and cleavage stage embryos
Embryo Thawing Pack	Vial 1 Vial 2 Vial 3 Vial 4	Thawing of human zygotes and cleavage stage embryos frozen using Embryo Freezing Pack
BlastFreeze™	Vial 1 Vial 2	Freezing of blastocysts
BlastThaw™	Vial 1 Vial 2	Thawing of blastocysts frozen using BlastFreeze

With the exception of IVM medium, all the products are provided as sterile solutions which are ready-to-use and obviate the need for preliminary dilution and mixing.

- **Description of method of manufacture**

Production is carried out in clean rooms which are classified according to EN ISO 14644-1. It is stated that the production facility has undergone complete validation and is operated in accordance with GMP.

The production of respective solutions is performed by adding the different ingredients to water for injection, mixing and adjusting pH before filtering the solution into container. Human Albumin is added at the end of the process. There is no manipulation of the Human Albumin before adding it to the medical device solution at the production site. The batch number of the Human Albumin is recorded. The sterile filling is a standard procedure according to GMP regulations.

The medical devices are manufactured in a plant designed for production of sterile products. The materials are weighed in an EN ISO 14644-1:1999 class 8 room. Liquid raw materials are measured and mixed with all raw materials in the class 7 mixing room. The filling operation takes place in a class 5 filtration room and is conducted in accordance with the requirements of EN 13824:2005. The solutions are filled into sterile Nalge Nunc bottles or filled directly into the final vials.

- **Controls of starting materials**

The Human Albumin complies with the Ph. Eur. monograph on Human Albumin Solution, which specifies quality requirements for a product normally administered intravenously. The Shelf Life specifications for Human Albumin 25% have been provided. The shelf life of the albumin is checked before addition to ensure that the expiry date of the albumin is not earlier than that of the medical device.

The manufacturer of the device committed that only Official Control Authority Batch Release (OCABR) lots of Human Albumin L/A 25% solution each albumin batch to be used for manufacture of the device.

The several other Medicult media components are stated to be of Ph.Eur. monograph quality where possible, or to satisfy in-house or supplier acceptance criteria. The water used is water for injection.

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

Not applicable

- **Control tests on finished product**

Tests for compliance with specifications are apparently conducted on each batch of each medium before release.

Additional analyses are conducted on media depending on their intended function.

The company has developed a method to measure albumin concentration in the media. The optimisation of this method has been described in the documentation provided.

The assay has been competently validated for its analytical performance. The manufacturer has clarified the limits of the content of human albumin to be included in the batch release specifications.

- **Stability**

The proposed shelf lives for the media range from 13 to 26 weeks, apparently when stored under ambient conditions.

Stability studies have been carried out on all the albumin-containing media solutions. The products were tested according to release specifications and some products were tested against additional parameters. To justify the shelf-lives the company has provided the results of real time studies based on the testing of physico-chemical and functionality parameters.

The stability studies do not include any test for albumin. Upon request, Medicult has committed to performing “new stability tests on products representative for the products range of human albumin-containing ART media. The studies will include human albumin analyses as well as the release tests throughout the shelf life”.

The company has provided the protocol of the stability study of six-representative media.

The stability limits for the albumin test were provided in the protocols..The company justifies the limits based on the fact that the performance of the ART media product is not sensitive to the exact concentration of albumin. The company stated that it will narrow these limits when more experience is gained.

CHMP notes that the Notified Body should request a commitment to the manufacturer of the medical device to report any out of specification result during the stability tests.

- **Toxicity**

Human albumin is known for its lack of intrinsic toxicity and immunogenicity.

In respect to toxicity, the Applicant refers to the EMEA Guideline (CPMP/PhVWP/BPWG/2231/99 rev.2) “Core SPC for Human Albumin Solution”, stating that:

1) Human albumin is a normal constituent of human plasma and acts like physiological albumin.

2) To date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.

3) No signs of acute toxicity have been described in animal models.

The biological safety tests successfully completed using HSA-containing ART Media are summarized in the QFI Report “Assessment of Biological Safety Status for the MediCult a/s Media Range, Sterilizing Filters, Media Containers and Accessories, and Compliance to Relevant Standards” (Ref: QFI0440/060926-01).

- **Reproductive function**

Human albumin is not considered a reproductive toxicant.

In respect to the reproduction toxicity, the applicant refers to the “Expert Opinion on toxicity testing of media for in-vitro fertilization” (containing HSA) issued by Danish Toxicology Centre, dated 10 August 2005, stating that “testing for reproductive toxicity and developmental toxicity refers to possible effects in young/full grown individuals when repeatedly exposed. Furthermore, no test guidelines exist for endpoints addressing effects in gametes and embryos”. The Report concludes that a Genotoxicity

test would be more appropriate in detecting toxicity to embryos and sperm cells, and hence to reproductive function. MediCult a/s have completed a Genotoxicty test, amongst several other biological safety tests (see Toxicity). This is considered acceptable.

- **Embryo/foetal and perinatal toxicity**

The applicant has not included any information regarding this section. This is considered acceptable, according to the EMEA Guideline CPMP/PhVWP/BPWG/2231/99 rev.2 “Core SPC for Human Albumin Solution” specifically stating that “to date, human albumin has not been reported to be associated with embryo-foetal toxicity”.

- **Mutagenic potential**

The EMEA Guideline CPMP/PhVWP/BPWG/2231/99 rev.2 “Core SPC for Human Albumin Solution” specifically states that “to date, human albumin has not been reported to be associated with mutagenic potential”.

Anyway, a specific Mutagenicity Test using a MediCult a/s media was conducted indicating that this media was non-mutagenic under the test conditions.

- **Carcinogenic potential**

Carcinogenicity is not considered a relevant test in the ISO 10993-1: 2003 Standard for devices with limited exposure to the patient.

Furthermore, the EMEA Guideline CPMP/PhVWP/BPWG/2231/99 rev.2 “Core SPC for Human Albumin Solution” specifically states that “to date, human albumin has not been reported to be associated with oncogenic potential”.

- **Pharmacodynamics**

Human albumin accounts qualitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity in the liver. The most important physiological functions of human albumin results from its contribution to oncotic pressure of the blood and transport function. Albumin stabilizes circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins. The role of protein in embryo culture medium may not only be as nitrogen source, but also as chelator to toxic metal ions. Human albumin binds other components and presents them to the embryo (transport protein), a source of amino acids, small ionic molecules and lipids, binds toxic species and sustains embryo growth.

- **Pharmacokinetics**

MediCult a/s IVF flushing and transfer media are the only MediCult a/s HSA-containing ART media to be in contact with the human body. Human embryos contained in the MediCult a/s HSA-containing ART media are transferred to the uterus transcervically using a small transfer catheter.

Direct contact of the MediCult a/s HSA-containing ART media with vaginal and endometrial tissue during the IVF transfer procedure takes less than one minute, and the quantity of media associated with the embryo(s) 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.

The maximum level of human albumin to which the patient will be exposed during the transfer procedure is 5 mg/ml for duration of less than one minute. Patients may also be exposed to a maximum of 1 mg/ ml of human albumin contained in the vial (flushing medium during retrieval of oocytes).

Under normal conditions, the total exchangeable albumin pool is 4-5g/kg body weight of which 40-50% is present intravascularly and 55-60% in the extravascular space. Abnormal distribution may occur in conditions such as severe burns or septic shock.

Under normal conditions, the average half-life of albumin is about 19 days. In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first 2 hours following infusion.

- **Local tolerance**

The EMEA Guideline CPMP/PhVWP/BPWG/2231/99 rev.2 states that “to date, human albumin has not been reported to be associated with embryo-foetal toxicity”.

Moreover, all MediCult ART media which are in contact with uterine and vaginal mucosa have been tested in local tolerance studies. For assessing local tolerance delayed contact hypersensitivity in guinea pigs together with vaginal irritation test in rabbits have been performed. The investigations have been performed according to ISO 10993 Biological Evaluation of Medical Devices-Part 10.

- **Clinical documentation**

The MediCult a/s HSA-containing ART media range has been formulated to mimic physiological milieu at the various stages of embryological development or for specific purposes such as cryopreservation of zoogametes or their recovery. The media solutions are designed to support complete pre-implantation development for the embryo following IVF in preparation for implant into the host. Medicult a/s HSA-containing ART media have been placed on the market since 1988 and they have been evaluated in several clinical studies.

Overall, an extensive scientific literature supports the clinical use of HSA containing ART media for oocyte preparation and in-vitro maturation, sperm preparation, culture microtechniques, cryopreservation of spermatozoa and embryos, culture of embryos to cleavage and blastocyst stage of development. The clinical documentation submitted covers all Medicult a/s HSA containing media proposed for the CE marking and within the scope of the Product Design Dossier. Articles were examined on the basis of study objectives, type of ART media studied, indications/procedure, intended purpose, number of patients, outcome and eventual complications.

Product-related main studies are summarized below. There is no indication from the appended studies that the product is any less useful and safe compared to other similar media.

- Flushing medium

Biljan et al performed a randomised trial to compare heparinised normal saline with heparinised Earle’s medium, which Medicult a/s flushing medium is comparable to. Ziebe et al performed a prospective randomised multi-centre study comparing MediCult a/s SynVitro Flush not containing human albumin to MediCult a/s Flushing Medium containing HSA. Both studies showed that the use of Medicult a/s HSA containing flushing medium leads to results comparable to that obtained with other not containing HSA in-house or commercially available flushing medium, in terms of oocyte recovery and fertilization rate (Biljan et al) or of average number of oocytes collected and inseminated, cleavage rate, average number of good embryos replaced and cryopreserved and ongoing pregnancy rate (Ziebe et al.). No adverse incidents occurred during oocyte recovery in either of the two groups.

BlastAssist®

MediCult a/s BlastAssist ART medium is a new culture medium supporting blastocyst development when used in combination with EmbryoAssist.

The BlastAssit medium is designed for the culture of human embryos to the blastocyst stage. Extending the culture period from the 2-3 days before transfer to 5 or 6 days allows for a more physiological synchronisation of the embryo stage. Furthermore it provides greater opportunities for selection of more viable and genetically normal embryos, because only embryos capable of converting from development dependent on stored maternal message to an activated embryonic genome will be capable to develop to the blastocyst stage and beyond (Jones et al).

Chesmore et al performed a randomised clinical study to evaluate two different types of culture media systems (MediCult a/s BlastAssist® System and Vitrolife G-series) for human in vitro fertilisation using sister oocytes to measure fertilisation rates (IVF and ICSI), cleavage and blastocyst development. MediCult a/s medium significantly increased cell division and promoted blastocyst development and formation.

In the study performed by Nilsson et al, single blastocyst transfer in 306 IVF patients (women under 39 years old) was performed. The embryos were cultured in BlastAssist®, resulting in pregnancy rate Takahashi performed a comparative study to evaluate two culture media, MediCult a/s BlastAssist System and G1.2/2.2 (IVF Science Scandinavia) for human embryos culture. A total of 105 patients who experienced repeated failures of conventional IVF/ICSI and underwent IVF (n=50) or ICSI (n=55) was enrolled in the study. A significantly higher percentage of blastocyst were obtained from culture in MediCult a/s BlastAssist, resulting in an higher percentage of good quality blastocysts, than in G1.2/2.2 medium. The authors concluded that the MediCult a/s BlastAssist medium better supports human blastocyst development than G1.2/2.2.

EmbryoAssist™

MediCult a/s EmbryoAssist is a new culture medium supporting cleavage stage embryo development. A clinical investigation (Hindkjær 2005) was performed by MediCult a/s to compare the EmbryoAssist and Universal IVF medium (MediCult a/s) for day 2 transfer patients and evaluate embryo development.

The principal objective of this study was to show that embryo development is significantly better supported in an enriched medium such as EmbryoAssist compared to MediCult a/s Universal IVF medium. Implantation and pregnancy rates were also observed to evaluate safety of EmbryoAssist.

The study shows similar fertilisation rate (54.7% in EmbryoAssist v 50.8% in Universal IVF medium), confirming that EmbryoAssist does not have any negative influence on oocyte fertilisation and embryo development potential. Performance of the media measured as fertilisation rate and embryo development indicated that EmbryoAssist does not influence the fertilisation potential of the oocytes. Fertilization rate, pregnancy and implantation were similar in the two groups. EmbryoAssist was shown to better support the development of good quality embryos for transfer and cryopreservation.

ISM1™, ISM2™ and UTM™

MediCult a/s has developed ISM media system for embryos culture, consisting of three media (ISM1™, ISM2™ and UTM™) designed to work as a sequential system. ISM1™ is used for fertilization and culture until the 6-8-cell stage and ISM2™ is used for extended culture until blastocyst formation. UTM™ is used as a transfer medium.

Several published studies have documented the efficacy of the ISM series.

Fechtali et al performed a prospective trial on sibling oocytes to compare the effects on two different media FertiCult (FertiPro) and ISM1™ (MediCult a/s). The study indicated that the two commercial media with different composition are equally able to sustain fertilisation but embryonic development

and embryo quality at day 2 seemed to be considerably enhanced when the embryos were cultured in ISM1™ during IVF or ICSI therapy. A multi-centre study conducted in University Hospital, Odense, Denmark; University Hospital, Uppsala, Sweden and Novum Clinic, Warsaw, Poland (unpublished data) compared sibling oocytes cultured in ISM1™ versus Universal IVF Medium. The study resulted in more "good quality embryos" and in better embryo development in ISM1™ group. Other randomised trials (i.e. Frydman et al.) have demonstrated excellent clinical pregnancy rates with the use of MediCult a/s ISM™ System.

Findikli et al performed a prospective randomised study to compare the efficiency of two different sequential media systems (Medicult a/s ISM1/ISM2 or G1.2/G2.2) for the cultivation of sibling embryos until blastocyst stage. Oocytes were randomly divided in two groups and cultured with either sequential media until media transfer. There was no statistically significant difference in the rate of fertilization, blastulation rate and embryo development on the second day of cultivation. On the 3rd day of cultivation, the mean number of blastomere was significantly higher in embryos cultivated within ISM1.

- Freezing and thawing media

Cryopreservation is an unavoidable option in stimulated IVF/ICSI and at the same time a tool in the prevention of multiple pregnancies. Cryopreservation of embryos increases the success rate of assisted conception treatments for infertile couples and is now an integral part of assisted reproduction techniques. A successful freezing and thawing procedure ensures the maintenance of the structural integrity of cells as well as its functional characteristics. MediCult a/s freeze and thaw media include Sperm Freezing Medium, Embryo Thawing pack BlastThawTM and Embryo Freezing pack BlastFreezeTM.

Sperm Freezing Medium

MediCult a/s has introduced a medium for cryopreservation of human spermatozoa and tissue from testicular biopsies. MediCult a/s Sperm Freezing Medium has been compared to other commercially available products in several studies.

Nallella et al. evaluated the ability of three cryoprotectants to preserve sperm quality, the Tris yolk buffer (TYB; Irvine Scientific), Sperm Freezing Medium (MediCult a/s) and Enhance Sperm Freeze (Conception Technologies). Data from these studies show that cryopreservation of human semen with the MediCult a/s Sperm Freezing Medium is comparable to other commercially media to preserve sperm quality. Dafopoulos et al described a simplified method for freezing of testicular tissue with the use of MediCult a/s Sperm Freezing Medium and assessed the cumulative clinical pregnancy rate. The freezing of testicular tissue resulted in satisfactory outcome after ICSI in cases of non-obstructive azoospermia. In conclusion the HAS containing Sperm Freezing Medium from MediCult a/s has been proved to be useful for the cryopreservation of human spermatozoa and tissue from testicular biopsies.

Embryo freezing and thawing media

MediCult a/s Embryo Freezing and Thawing pack are used for freezing and thawing human zygotes and cleavage stage embryos (day 2/3). The embryo survival rate and the pregnancy rate, obtained using MediCult a/s Embryo Freezing and Thawing media, vary between different studies: Best et al reported embryo survival rates between 54% - 59% and pregnancy rates between 11%-14%; Blin et al reported thawing survival rate of 93.9% and pregnancy rate of 12.6% (freezing at day 2) versus

20.2% (freezing on day 3); Ziebe et al reported an embryo survival rate of 57% and an overall ongoing pregnancy rate on 15%. Horne et al performed a randomized study to describe and compare the relative merits of embryo cryopreservation at the pronucleate (PN) and early cleavage (EC) stage and to determine the effect on the pregnancy rate in both the initial IVF cycle and the subsequent transfer of thawed embryos, reporting embryo survival rates between 74,4 and 77,4 %.

The results obtained from the above mentioned studies demonstrate the effectiveness of MediCult a/s HSA containing Embryo Freezing and Thawing media for the cryopreservation of pronuclear and cleavage stage human embryos

BlastFreeze™ and BlastThaw™

Blastocysts are easier to freeze than cleavage stage embryos for two main reasons: the cytoplasmic volume of the cells is lower thus the nucleocytoplasmic ratio is higher and as the number of cells is higher the embryo may recover even if some cells have been destroyed during the freezing and thawing procedures. MediCult a/s BlastFreezeTM and BlastThawTM are based on Earle's Balanced Salts Solutions and sucrose in different concentrations. Several studies demonstrate cryosurvival of blastocysts and pregnancies achieved after blastocysts cryopreservation in Medicult media. Virant-Klun et al evaluated the clinical role of blastocyst freezing and thawing after prolonged culturing in BlastAssist® medium, where the BlastFreezeTM and BlastThawTM media were used for the freeze and thaw process. The results showed a blastocyst survival rate of 81%, an implantation rate of 18% and a clinical pregnancy rate/ blastocyst transfer on 29.5%. No special blastocyst selection was made prior to freezing. Comparing these results with the ultra rapid freezing method (vitrification) of human blastocysts, using cryoloops and a base medium containing DMSO as the cryoprotectant, no significant difference were shown in the survival and implantation rates. Although there was a significant higher percentage of miscarriage for the cryoloop vitrification (28% versus 8%) compared to BlastFreezeTM and BlastThawTM (Mukaida et al; Virant-Klun et al).

Both studies involved large numbers of blastocyst freeze-thaw cycles. From the results obtained, it can be concluded that MediCult a/s HSA containing BlastFreezeTM and BlastThawTM are useful for freezing and thawing human blastocyst embryos.

- Media used for microtechniques

The mechanical insertion of a spermatozoon into the cytoplasm of the oocyte is called IntraCytoplasmic Sperm Injection (ICSI). The ICSI technique has demonstrated clear advantages in both fertilization and pregnancy rates compared to previously used microinjection techniques. Successful ICSI requires the injection of an immobilized spermatozoon.

MediCult a/s has a series of ready-to-use products based on high quality formulations and raw materials to help in processing gametes prior to ICSI, particularly intended to facilitate sperm immobilization. These products are PVP medium, SpermSlow™ and PVP Clinical Grade.

MediCult a/s PVP Medium and PVP Clinical Grade have been used in different ICSI studies but the individual products have not been evaluated in separate trials.

Studies performed by Kastrop et al., Kattera and Chen, Nicopollus et al, show fertilization rates after ICSI with the use of MediCult a/s PVP media ranging from 48% to 70.3%. Barak et al compared the efficacy of a hyaluronate solution to PVP medium in facilitating the injection of spermatozoa during the ICSI procedure. The fertilization rate for PVP was 71.3% versus 72.4% for hyaluronate.

In another similar study Menezo et al compared the PVP Clinical Grade from MediCult a/s to a hyaluronan solution. The results showed no significant difference in the implantation and pregnancy rate. PVP Medium, PVP Clinical Grade and SpermSlowTM from MediCult a/s can be successfully used to retard the movement of sperm as required for ICSI.

- Sperm Preparation

Sperm Preparation Medium

The MediCult a/s Sperm Preparation Medium is one of the first commercial sperm preparation media used in human IVF. Matyas et al performed a large study of testicular biopsy samples incubated in Medicult Sperm Preparation media summarizing a five years experience of testicular spermatozoa isolation for intracytoplasmic sperm injection in Hungary.

Testicular spermatozoa were successfully retrieved from the extracted testicular tissue in 218 cycles of 146 patients. Simultaneously, or one day later a total of 1668 oocytes were collected from 146 women.

A total of 1293 oocytes that had reached nuclear maturity were injected with testicular spermatozoa. Fertilisation rate was 55.4% and cleavage rate was 85.8%. A percentage of 27.7% clinical pregnancies was achieved with an implantation rate of 14.8%.

Biopsy Medium

MediCult a/s has developed Biopsy medium to facilitate the easy access of single blastomeres of live embryos for pre-implantation genetic diagnosis (PGD). Biopsy medium can be used with both BlastAssist and ISM series media and the effects of Biopsy Medium are completely reversible in both formulations. The MediCult a/s Biopsy Medium has been tested at the Centre of Pre-implantation Diagnosis at Arhus University Hospital in Denmark (unpublished data). The results showed a pregnancy rate per cycle started and per embryo transfer consistent with rates observed for PGD cycles.

3.4. Overall conclusion on clinical documentation

Human albumin is a protein used in IVF media. Protein in embryo culture medium acts as a nitrogen source and a chelator to toxic metal ions. The most commonly-used protein sources in IVF and embryo culture are human serum albumin or patient's serum (Laverge et al). Human albumin has been a component of MediCult ART media since the beginning of assisted reproduction technology. The extensive review of relevant scientific and clinical literature indicates that additional benefits for the MediCult a/s HSA-containing ART media. Moreover, 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 Human Albumin as a supplement of MediCult a/s HSA-containing media for Assisted Reproductive Technologies (ART).

- **Labelling**

The applicant has enclosed the instructions for use.

In the labelling and instructions for use reference is made to "Human Serum Albumin". It is noted that the Ph. Eur. monograph is "Human Albumin Solution".

The manufacturer is recommended to substitute “Human Albumin Solution” or “Human Albumin” in place of “Human Serum Albumin (HSA)” in the label and information of each medium.

Discussion on Quality, Safety and Usefulness

- **Quality**

Medicinal product before incorporation in the medical device

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines and Ph. Eur. monograph for human albumin. The information provided in the application showed a consistent batch-to-batch production of Human Albumin L/A 25% achieving an adequate quality for the drug substance and the drug product. The manufacturing process of the drug substance and drug product were described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications.

The capacity and robustness of the manufacturing process to inactivate and remove viruses has sufficiently been investigated and, in summary, the virus safety of Human Albumin L/A 25% has adequately been demonstrated. No materials of bovine or other TSE-susceptible animal species are used in production. The Human Albumin L/A 25% is produced from human plasma. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. In addition, investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process.

Medicinal product in the context of its use in the medical device

In general, the quality aspects of the incorporation of Human Albumin as ancillary medicinal substance in Medicult ART media were sufficiently addressed.

The manufacturing process is described and critical steps are performed under sterile conditions. The controls of starting materials are adequate. The manufacturer of the medical device has developed and validated a method to test albumin concentration at the lot release of the media and has committed to perform the human albumin test at the batch release of each media.

The company has provided stability data of the solutions to support the stability of the media throughout the shelf life. These tests do not include a test for albumin and the company has committed to performing new stability tests which include a test of human albumin on six product representative of the range of media. The protocols of the study were provided and are considered as adequate. The notified body is recommended to request a commitment to the manufacturer of the medical device to report any out of specification result during the planned stability tests.

- **Safety and Usefulness**

Medicinal product in the context of its use in the medical device

Albumin is universally added to most of IVF culture media because it is widely considered to be of benefit. The putative role of albumin in culture media is extensive, including:

- pH buffer
- Colloid osmotic regulation
- Membrane stabilisation
- Carrier of growth promoting substances (amino acids, vitamins, fatty acids, etc)
- Scavenger

- Nutrient

Until the 1990s the most commonly used protein source in media for human IVF was human serum, obtained from the patient herself, human donors or foetal cord. Since then serum has been replaced as a protein source with various preparations of human serum albumin, as a higher defined protein source. This was to attempt to reduce the risks of transmission of viral disease.

Albumin is the major soluble protein constituent of human blood, and also the most abundant macromolecule in the human oviduct. Whitten, Biggers and Whittingham performed landmark mouse embryology experiments, including serum in the culture media both as a protein source and agent to prevent the adherence of embryos to each other as well as to the plastic culture vessels.

The reason for including protein to culture media for human IVF is historical and stems from the early mouse work previously referred to. It is possible to culture viable mouse embryos to the hatching stage in vitro in a protein free media. There have also been human pregnancies reported in such systems. Nevertheless, it has been demonstrated that at the blastocyst stage of development albumin is endocytosed into the embryo from the medium.

Whilst albumin may not be a direct source of nutrients to the cell, it has the potential to assist growth by binding growth promoting substance and releasing them to the cell. In addition the presence of albumin in media facilitates the handling of embryos in vitro. The role of albumin as a source of nutrients has been studied in the mouse embryo model.The available scientific literature supporting the role of albumin in embryo development has been extensively discussed by the applicant.

Clinical safety

Some safety data are presented i.e. adverse event rate throughout an ART cycle. The main safety consideration regarding the use of human albumin is any potential infective risk.

The measures taken with respect to transmissible agents for the manufacture of Human Albumin for Medicult IVF media satisfy the current requirements and do not raise any safety concerns.

Clinical usefulness

An extensive literature of published papers and abstracts, using Medicult culture media, has been presented. Comparative studies comparing efficacy of Medicult IVF media to other IVF media were submitted. The role of albumin in culture media has been discussed.

It is difficult to link usefulness to the Human albumin component of the media alone as there are many other components in the media. Nevertheless, on the basis of the theoretical considerations (from literature review and historical data) and existing clinical practice with generally favourable results when using Medicult a/s IVF media, the usefulness of HSA as an ancillary medical substance in this medical device is considered sufficiently supported.

3.5. Overall conclusions and recommendation

Quality

The quality of Human Albumin 25% before and after the incorporation in the Medicult ART media has been sufficiently demonstrated.

The capacity and robustness of the manufacturing process of the Human Albumin 25% to inactivate and remove viruses has been sufficiently investigated and. In summary, the virus safety of the Human albumin L/a 25% has been adequately demonstrated. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. Investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process of Human Albumin 25%.

The manufacturer has included albumin tests to guarantee the quality of the albumin at the batch release of the media and during the shelf life.

Safety

Consideration of safety of Human Albumin is mainly pertaining to any risk of virus or prion transmission, and the special consideration for possible damage to the foetus due to early viral infection of the embryo with parvovirus B19.

Data presented in the quality part demonstrate a sufficient safety margin for HSA used in Medicult a/s IVF media with respect to parvovirus B19 and other blood borne viruses.

Usefulness

The usefulness of Human Albumin in Medicult a/s IVF media series can be theoretically supported for several reasons. Proteins added to media seem to be both necessary and useful for good results of the in vitro fertilization technique.

An extensive scientific literature supporting the clinical use of HSA containing ART media for oocyte in-vitro maturation, sperm preparation, culture microtechniques, cryopreservation of spermatozoa and embryos, culture of embryos to cleavage and blastocyst stage of development has been presented.

However, this clinical documentation cannot demonstrate, in a direct way, the claimed HSA beneficial properties, i.e. being a surfactant, a chelating agent, a nutritive source for the embryo, a pH buffering agent, a mediator of spermatozoa capacitacion, nor can directly support HSA usefulness in the various types of solution when used for their specific purposes.

Nevertheless, on the basis of the theoretical considerations (from literature review and historical data) and existing clinical practice with generally favourable results when using Medicult a/s IVF media, the usefulness of HSA as an ancillary medical substance in this medical device is considered sufficiently supported.

Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality, safety and usefulness of Human Albumin used as ancillary medicinal substance in the Medicult a/s IVF media was favourable therefore granted a positive opinion in the consultation procedure.

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