8 August 2012
EMEA/CHMP/212141/2006

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: IVF Media GIII Series*

Ancillary medicinal substance: Human serum albumin

EMEA/H/D/000003

Applicant: Det Norske Veritas Certification AS

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

*Note. The name of GIII series was changed to G5 series in a post consultation procedure.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Administrative information

Invented name of medical device:	IVF Media GIII Series
INN (or common name) of the ancillary medicinal substance:	Human serum albumin
Applicant for medical device CE certification:	Vitrolife Sweden AB
Notified body:	Det Norske Veritas Certification AS
Applied intended purpose of the device:	Solutions used in In vitro fertilisation procedures
Intended purpose of the ancillary medicinal substance in the device:	Colloid osmotic regulation, pH buffer, membrane stabiliser, carrier of growth hormones, surfactant, scavenger and nutrient
Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:	Range from 2 to 25 mg/ml

1. Background information on the procedure

1.1. Submission of the dossier

The Notified Body Det Norske Veritas submitted to the European Medicines Agency (EMEA) on 5 October 2005 an application for Consultation on human serum albumin as ancillary medicinal substance used in a medical device IVF Media GIII Series, 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: Prof. Ingemar Persson Co-Rapporteur: Dr. Manfred Haase

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 5 October 2005.
- The procedure started on 26 October 2005.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 January 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 January 2006.
- During the meeting on 20-23 February 2006, 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 24 February 2006.
- The Notified Body submitted the responses to the CHMP consolidated List of Questions on 28 March 2006.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the List of Questions to all CHMP members on 15 May 2006.
- During the meeting on 26-28 June 2006, 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 serum albumin as ancillary medicinal substance used in IVF Media GIII Series on 28 June 2006. The Notified Body provided the letter of undertaking on the recommended measures to be fulfilled post-authorisation on 28 June 2006 (Annex 6).

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

2.1. Manufacturers

Manufacturer(s) of the active substance used as ancillary medicinal substance

Talecris Biotherapeutics
8368 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 device(s)

Vitrolife Sweden AB
Faktorvägen 13, SE-434 37 Kungsbacka, Sweden

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

As discussed at CHMP, it would be recommended that the Notified Body request the following from the Applicant for device approval:

Area[1]	Description	Due date[2]
Quality	The manufacturer of the active substance used as ancillary medicinal substance (Talecris) should commit to perform the planned stability study and to report any out of specification results to the Notified Body. The final study report should be submitted.	31/03/2007

1. Areas: Quality, Safety, Usefulness
2. Due date for the recommended measure or for the first interim report if a precise date cannot be committed to.

3. Scientific discussion

3.1. Introduction

The In Vitro Fertilisation (IVF) Media GIII Series is classified as a medical device according to the relevant Commission Directives (90/385/EEC, 93/42/EEC). The GIII series solutions incorporate human serum albumin (HSA) as a medicinal substance with ancillary action. The Notified Body, Det Norske Veritas, is consulting the CHMP regarding the quality, safety and usefulness of the albumin component in the GIII series solutions according to Directive (2000/70/EC).

The IVF Media GIII Series (GIII Series) consist of set of solutions or kits of solutions, which are used during the different stages of In Vitro Fertilisation (IVF) for preparation, cultivation and storage of gametes and embryos (see section 3.3: Medicinal product in the context of its use in the medical device - Qualitative and quantitative particulars of the constituents). The solutions are supplemented with HSA either at the production site or by the user. There is no manipulation of the HSA before adding it to the medical device solution.

The intended purpose of HSA in IVF media is to act during the different steps of the IVF cycle in the colloid osmotic regulation, as a pH buffer, membrane stabiliser, carrier of growth hormones, surfactant, and scavenger and as nutrient. The function of HSA is not differentiated between the different medical devices used for IVF procedures.

The albumin used for this purpose is Human Albumin, low aluminium (L/A) 25% from Talecris. The albumin is licensed in Germany under the name Human Albumin L/A 25 % Bayer and in Greece under the name Plasbumin. Other strengths of the albumin (5%, 20%) are also approved in Italy and Spain.

Human Albumin L/A 25% is manufactured according to the 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 is covered by Bayer'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 December 2005.

For the evaluation of the safety and usefulness unpublished and published data for the GIII Series were reviewed including data from two studies carried out by the medical device manufacturer.

3.2. Medicinal product before incorporation in the medical device

Introduction

Description

Human Albumin L/A 25% is a clear, slightly viscous, pale yellow to amber coloured solution. The active substance is human albumin. The albumin content in the product is not less than 96%.

Composition

Ingredient	Reference	50 ml Amount	100 ml Amount	Function
Protein[1]	EP	12.5 g	25 g	Active ingredient
Sodium caprylate	In-house			Stabiliser
N-acetyl-DL-tryptophan	EP			Stabiliser
Sodium[2]	In-house			Tonicity
Water for injections	EP			Solvent

Excipients

Sodium caprylate and N-acetyl-DL-tryptophan are used as excipients to stabilise the albumin and to reduce the formation of aggregates. The use of sodium caprylate to protect albumin solution was first published in 1944. The binding of N acetyl-DL-tryptophan to albumin and the stabilising capacity was first published in 1958. .

Container closure system

The container consists of glass vials. The stoppers are made of a halo butyl isoprene-blend elastomer. A flip-off seal is also used for sealing the vials.

Quality Aspects

Active Substance

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

Manufacturer(s)

In 2005 Bayer Corporation sold its plasma business to Talecris. Documentation clarifying and supporting Talecris' status as new owner of the facility in the USA was supplied.

Definition of a batch

The fractionation volume of a plasma pool is about 3600 l and yields approximately 270 kg paste V.

A purification batch is defined as the final albumin bulk derived from approximately 588 kg fraction V paste. The final bulk is a sterile solution and contains the appropriate stabilizers and electrolytes. A typical bulk size is about 800 kg.

Description of Manufacturing Process and Process Controls

The manufacturing of the drug substance has been adequately described and optional steps have been clearly indicated in the flow charts submitted. 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 the usual procedures in albumin purification with one exception: The manufacturer uses an additional acetone extraction step.

There is no reprocessing of any of the fractionation steps but according to the manufacturer, in some cases, the final bulk solution may be reprocessed beginning with reformulation and sterile filtration. Reprocessing of the bulk may only be performed when there is a potential compromise in sterility assurance due to equipment failure, or a breach in environmental conditions. Reprocessing of bulks that fail sterility testing is not allowed. The reasons for reprocessing of the bulk can also be accepted.

Control of Materials

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material for the drug substance has already been approved in the centralised PMF certification procedure. Only plasma certified by the centrally approved PMF is used for the production of human albumin incorporated in the IVF Media GIII Series.

Traceability is a key issue when plasma is used in the production of intermediates and drug products. There is a link, through the manufacturer of the Human Albumin to post-collection information on the

donors and to post-marketing data on the albumin and its starting material (plasma pool) until the expiry date of the medicinal device containing the albumin. The expiry date of the albumin is not earlier than that of the medical device.

All relevant contracts between the manufacturer of albumin and the manufacturer of the medical device regarding traceability will be updated accordingly. This work is already in progress and the documentation regarding manufacturing sites was updated in the dossier.

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 these 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 beginning has been sufficiently validated and consistency of the production process has been adequately demonstrated. At least three qualification batches were used for the validation of the fractionation and purification steps of the process.

Critical parameters, operating parameters and intermediate testing results were evaluated to ensure consistency of each production step and that the final output of each system met the pre-established acceptance criteria. The acceptance criteria have been set using results from process characterisation, small-scale studies and/or historical process data.

In addition, the applicant presented data from process characterisation studies on the fractionation process and the purification process.

The first study covered the fractionation process from pooled plasma to fraction V paste.

A validation study similar to that performed for the fractionation process was also performed for the purification process from fraction V paste to final container

Manufacturing Process Development

The manufacturing process is based on the Cohn-Oncely fractionation process first established in 1940s and later modified in 1950s including the addition of acetone drying. In the 1980s, filtration was introduced to reduce sodium citrate and aluminium levels in the albumin solution. The current formulation uses N-acetyl-DL-tryptophan and sodium caprylate to stabilise the albumin. The composition of Albumin L/A 25% is formulated to comply with the Ph. Eur. monograph “Human Albumin Solution”.

Impurities

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

Specification

Appropriate specifications for the drug substance were set and justified.

Analytical methods

The protein composition of the bulk is tested using an in-house method. The method has been sufficiently described and validated.

Batch analysis

Data from three batches of drug substance were provided. All results complied with the set specification.

Container closure system

Stainless steel tanks with varying size are used for storing final bulk product at 5 °C in a class C area. The tanks are kept under positive air pressure and each tank is sterilised before use.

Stability

The stability studies presented for the sterilised bulk are acceptable and well justified.

Drug Product

- Pharmaceutical Development

The process development started in 1940 as E .J. Cohn developed a method of plasma fractionation to obtain human albumin. In the meantime, changing the ethanol concentration, the introduction of acetone washing, using filtration for improved cleaning, the introduction of pasteurisation and the addition of stabilisers modified the process.

Most of the description of pharmaceutical development is based on literature data since the Cohn-Oncely 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.

Batch formula

A batch is defined as the final uniform albumin bulk derived from the purification of approximately 588 kg fraction V paste, which may be derived from maximum 12 plasma pools. The typical batch (bulk) size is 800 kg.

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.

Re-processing can only be allowed to correct potential compromise in bulk sterility due to technical failure. Re-filtration of the final bulk that fails the test for sterility is not allowed.

Descriptions of the primary and secondary packaging have also been provided.

Process validation

The validation of the aseptic filling is deemed acceptable. The company regularly performs media fills to monitor the system of filling.

The pasteurisation step has been validated for the pasteurizers used in production. Heat penetration and heat distribution was also monitored. No deviations in temperature were observed during the pasteurisation runs.

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 equivalence to Ph. Eur methods. Validation reports were provided for test methods, which are not performed according to the Ph. Eur. methods or for which no compendia method exists.

The specifications are based on the requirements in the Ph. Eur. monograph for Human Albumin Solutions.

Container Closure system

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

Stability of the Product

The data presented from an ongoing stability study support the proposed shelf life of 3 years at 25°C for the drug product. Since real time data is available for up to 42 months for four batches, the absence of accelerated data is acceptable.

Facilities and Equipment

The applicant has provided description of facilities and equipment.

Adventitious Agents Safety Evaluation

Risk of contamination with animal or human TSE

Animal TSE

No materials of bovine or other TSE-susceptible animal species are used at production. Media Fills used for qualification comply with with Guideline EMEA/410/rev02.

Human TSE

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

The drug product, Albumin 25%, is produced from human plasma by the established Cold Ethanol Fractionation followed by pasteurisation according to Ph. Eur. Several 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..

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.

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.

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material for the drug substance was re-certified in December 2005 (EMEA/H/PMF/000004/04/AU/0002).

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.

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

Introduction

The GIII series are comprised of different solutions used for handling gametes and embryos during In Vitro Fertilisation (IVF) and contain a protein supplement for culture medium. This protein supplement is human serum albumin (HSA), 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 GIII series consists of several solutions or kits of solutions intended for use during the different stages of IVF, for preparation, cultivation and storage of gametes and embryos. The solutions are supplemented with HSA, either at the production site or by the user. There is no manipulation of the HSA before adding it to the medical device solution. The HSA used as ancillary medical substance is Human Albumin L/A 25% from Talecris. Human Albumin 25% L/A is manufactured according to the Ph Eur monograph Human Albumin Solutions.

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 protein in the form of serum albumin (of animal or human origins) or serum. In the clinical setting, there has been a substantial development of the technologies to optimise the conditions for preparing gametes and culturing embryos. One important part of this development, associated with improvements in the success rates for implantations and pregnancies in IVF programs, has been the development of tailored media solutions.

It has been described that under stringent culture conditions, in the presence of amino acids, embryos can be cultured to the blastocyst stage in the absence of protein. However, the inclusion of protein is thought to facilitate gamete and embryo manipulation in vitro by acting as a surfactant, while also conferring benefit to the embryo by its ability to chelate potential toxins. Finally, albumin is the most abundant protein in the female reproductive tract, and has been described in literature to maintain embryo physiology and metabolism in vitro compared to embryos cultured in the presence of a synthetic macromolecule polyvinyl alcohol.

With biological products, like serum and serum albumin, the risk of disease transmission and contamination is of crucial importance. The use of animal albumins in human ART is no longer accepted by most countries. Recombinant human albumin has not yet come to any important use on the IVF market due to the high costs of its production.

- Qualitative and quantitative particulars of the constituents

The quantitative composition of the GIII series is described for each solution in the dossier. In general, the different solutions consist of a buffer supplemented with dipeptide, different combinations of amino acids, electrolytes, carbohydrates, vitamins, antibiotics and HSA. The solutions are supplemented with HSA either at the production site or by the user as indicated in table below. Some solutions also contain ingredients such as cryoprotectants, polysaccharides (hyaluronan) and/or chelators (EDTA).

List of solutions included in the GIII series

Name of solution	**Use of solution**	**HSA supplementation by**
G-MOPS™	Medium for handling and manipulation of oocytes and embryos	User
G-MOPS™ PLUS	Same as above	Production site
G-1™ version 3	Medium for culture of embryos from the pronucleate stage to the day 2 or day 3 stage	User
G-1™ version 3 PLUS	Same as above	Production site
G-2™ version 3	Medium for culture of embryos from day 3 to the blastocysts stage	User
G-2™ version 3 PLUS	Same as above	Production site
G-SPERM™	Sperm separation medium	User
G-SPERM™ PLUS	Sperm separation medium	Production site
G-Freeze Kit Blast™	Blastocyst freezing medium	User
G-Thaw Kit Blast™	Blastocyst freezing medium	User
SpermRinse™	Spermatozoa preparation medium	Production site
Hyase™	Denudation of oocytes (removal of cumulus cells)	Production site
CCM™	Medium for culture of embryos from day 3 to the blastocysts stage and transfer	Production site
G-FERT™	Medium for preparation and handling of gametes and for in vitro	User

	fertilisation	
G-FERT™ PLUS	Same as above	Production site
G-PGD™	Embryo biopsy medium	User
G-OOCYTE™	Oocyte supporting medium	User
Gamete™	Gamete preparation medium	Production site
IVF™	For in vitro fertilisation, culture and transfer of embryos	Production site
FreezeKit 1™	Embryo freezing medium kit	Production site
ThawKit 1™	Embryo thawing medium	Production site

- Description of method of manufacture

The production of respective solutions is performed by adding the different ingredients to water for injection, mixing and adjusting pH before filtering into plastic container. The sterile filling is a standard procedure according to GMP regulations. For solutions where the HSA addition is performed at the production site, 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. There is no manipulation of the HSA before adding it to the medical device solution at the production site.

The manufacture of the 100 mg/ml HSA solution consists of addition of water for injections to the production vessel. Human Albumin Solution L/A 25% is then added under stirring and the HSA solutionTM 100 mg/ml (10%) is then filled on vials.

The medical devices are manufactured in a plant designed for production of sterile products. The different raw materials are weighed and mixed in a class C area, the filling operation takes place in a class A zone where the solutions are filled into sterile bottles. The final labelling and packing are performed in a class D area.

The production of the medical device is documented in a production record and kept for 10 years. The notified body has performed an audit at Vitrolife in January 2005. Vitrolife has a Quality Management System in conformity with ISO 13485: 1996. The certificates are provided with the dossier.

- Controls of starting materials

The Shelf Life Specification for Human Albumin 25%,is provided. The manufacturer of the device should be aware that each albumin batch to be used for manufacture of the device should be batch released by the competent authority.

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

Not applicable

- Control tests on finished product

The product specification, composition, filling size and shelf life of the different solutions and kit components are provided in the documentation.

- Stability

Stability data were also provided for all solutions/kits where HSA is added at the manufacturing site. The stability data indicates that the solutions are stable throughout the storage time. There are no quantified limits for the albumin stability and compatibility in the GIII Series.

Shelf life of the GIII solutions/kits

Name of solution	**Shelf-life**
G-MOPS™ PLUS	21 weeks
G-2™ version 3 PLUS	21 weeks

G-SPERM™ PLUS	21 weeks
SpermRinse™	26 weeks
Hyase™	6 months
CCM™	25 weeks
G-1™ version 3 PLUS	21 weeks
G-FERT™ PLUS	17 weeks
Gamete™	25 weeks
IVF™	25 weeks
FreezeKit 1™	25 weeks
ThawKit 1™	25 weeks

The proposed shelf life of the HSA solution 10%, which is added by the user, is 12 months at 2-8 °C. To support this shelf life claim a stability study with validation batches that are smaller than commercial batches and container and closure that are not the same as used for marketing were submitted.

From the results a shelf life of 12 month for HSA 10% at 2-8°C is acceptable. To complete the data, a stability study is planned. The design of the stability study for HSA-SolutionTM is acceptable.

- Viral Safety

The manufacturer of Albumin L/A 25% has demonstrated that sufficient measures have been taken to assure viral safety of the albumin for its normal use (I.V. infusion). There have not been any reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes when used for i.v. infusion. However, when medicinal products are produced from human plasma, it can never be totally excluded that non-enveloped viruses such as parvovirus B19 are still present in the final product. The intended use of the medical device GIII series, preparation and manipulation of gametes and embryos is very different from the normal use of albumin solutions. The fact that parvovirus B19 may harm the foetus and that the GIII series are used in the different steps during IVF treatment where the solutions containing HSA and therefore potential virus contamination will be in direct contact with gametes and embryo, calls for particular concern.

The relevant Guideline (CPMP/BWP/5180/03) does not require a risk assessment for albumin (therapeutic i.v. doses: ca. 20g) with respect to B19 because conventionally-fractionated and pasteurised albumin is considered generally safe with respect to parvovirus B19. The risk assessment on parvovirus B19 transmission by GIII series demonstrated that the virus reduction capacity of the manufacturing process is clearly higher than the potential max. parvovirus B19 genome concentration in the plasma pool:

The risk assessment provided confirms the safety margin of albumin L/A 25% as used in the IVF Media GIII series with respect to parvovirus B19.

- Toxicity

In terms of toxicology, the Applicant refers to data on biocompatibility only. Under toxicology subsections “Reproductive function”; “Embryo/Foetal and perinatal toxicity”; “Mutagenic Potential”; “Carcinogenic potential” the applicant refers to the publication *MEDDEV 2.1/3 rev. 2 July 2001’, point B.3, and in particular to the statement that “it is envisaged that, where well-known substances for established purposes are involved, all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to the literature, including standard textbooks, experience and other information generally available.”

The blood derivative human serum albumin is classified as a well-known substance, e.g. products were used already during the 2nd World war as a blood substitute. HSA has been used in IVF media for over 20 years and is currently being used in almost all IVF treatments performed worldwide. With reference

to this, and the fact that the product is used ex vivo, the applicant has not included information regarding reproductive function; embryo/foetal and perinatal toxicity; Mutagenic Potential; Carcinogenic potential.

The justification is considered acceptable, and the lack of studies addressing the above-mentioned areas, as well as general toxicity (single and repeat dose toxicity) is accepted. However, it should be pointed out that even if albumin may have been used for many years in IVF media, data supporting its safety in this context appear very limited. This is further discussed in the clinical assessment.

- Reproductive function

The applicant has not included any information regarding this section; the justification provided is discussed in section “Toxicity” (see above).

- Embryo/foetal and perinatal toxicity

The applicant has not included any information regarding this section; the justification provided is discussed in section “Toxicity” (see above).

- Mutagenic potential

The applicant has not included any information regarding this section; the justification provided is discussed in section “Toxicity” (see above).

- Carcinogenic potential

The applicant has not included any information regarding this section; the justification provided is discussed in section “Toxicity” (see above).

- Pharmacodynamics

The applicant makes reference to a limited number of published articles to support their view as follows:

Historically, embryo culture media have been supplemented with protein in the form of either serum albumin or serum. Under stringent culture conditions, including the presence of amino acids, embryos can be cultured to the blastocyst stage in the absence of protein. However, the inclusion of protein does facilitate gamete and embryo manipulation in vitro by acting as a surfactant, while also conferring benefit to the embryo by its ability to chelate potential toxins albumin is the most abundant protein in the female reproductive tract, and has been shown to maintain embryo physiology and metabolism in vitro compared to embryos cultured in the presence of a synthetic macromolecule polyvinyl alcohol.

This will be further commented in the sections “Discussion on Quality, safety and usefulness” and “Overall conclusions and recommendation”.

- Pharmacokinetics

The Applicant states that pharmacokinetics is not applicable for this application.

As the product is used ex-vivo, it is agreed that pharmacokinetic data are not necessary for the current application.

- Local tolerance

Studies of biocompatibility and biological safety were undertaken in 3 test systems: Iso vaginal irritation in the rabbit, iso sensitization in the guinea pig and cytotoxicity using the agarose overlay method. All studies were conducted in the conformance with Good Laboratory Practice, ISO 17025 and Guide for Care and use of Laboratory Animals when applicable.

Iso vaginal irritation in the rabbit, repeated exposure (G-1 version 3 supplemented with HSA-solution), macroscopic and microscopic evaluation (TI265-801, Lab no. 01T 1541800)

Three rabbits / group (HSA or control saline) received a 2 ml intravaginal treatment once daily for 5 days. Macro-, and microscopic evaluations were undertaken. It was concluded that under the test conditions, the test article was a minimal irritant to the vaginal mucosal tissue of the rabbit.

Iso sensitization study in the guinea pig, maximization method, chemical solution (G-1 version 3 supplemented with HSA-solution), clinical and dermal observations (TI261-306, Lab no. 01T 1541600)

The test solution was intradermally injected and occlusively patched to ten test animals, or five controls. Six days after the injection, a sodium lauryl sulphate suspension was massaged into the injection areas. The day after, remaining suspension was removed, and text or control solutions applied. At 14 days after the induction patch application, test or control solution was applied again for 24 h. Observations for dermal reactions were made 24, 48 and 72 h after challenge patch removal. There were no abnormal clinical observations. The dermal observations did not show any evidence of sensitization. Thus, under the test conditions, there was no indication of delayed dermal contact sensitization in the guinea pig model.

Cytotoxicity study using the agarose overlay method, liquid (G-1 version supplemented with HSA solution)- macroscopic and microscopic evaluation (V0015-120, Lab no. 01T 1584001)

Filter discs with test article or controls (negative and positive) were applied on agars surfaces overlying confluent monolayers of L-929 mouse fibroblast cells. After 24 h incubation, the cell culture was examined for signs of cytotoxicity, both macro-, and microscopically. There were no signs of cell lysis or toxicity due to the test article. Positive and negative controls showed expected effects. The test article met USP requirements, as the grade was < 2 (mild reactivity).

According to a summary table submitted, these experiments were performed on HSA solution as supplement to either G-1 version 3 (LOT 10149), G-2 version 3 (LOT 011116) or G-MOPS (LOT 011115). However, only the experiments with Lot 10149 were submitted.

CHMP considers that, as the concentration of HSA in these solutions is the same, and from the perspective of assessing the biocompatibility of HSA, the submitted data are considered sufficient. Based on the data for Lot 10149, there are no concerns regarding vaginal irritation, delayed dermal sensitization or cytotoxic effects.

- Clinical documentation

Overview of non-clinical and clinical studies performed with GIII series

A formal assessment of these studies with regard to the medical device is beyond the scope of the CHMP assessment report.

However, to some extent the results are considered to contribute to the evaluation of the safety and potential “usefulness” of the HSA component for its intended purpose. Therefore the available unpublished and published data for the GIII series are reviewed below.

Biocompatibility studies have been described in previous sections.

The applicant claimed safety and efficacy on the basis of results from two studies in which HSA-solution is used for the supplementation of GIII culture media:

* Embryo culture in a new sequential media containing hyaluronan yields better quality embryos and higher implantation rates. (Unpublished article submitted for publication)

A prospective randomized study was performed at the American Hospital of Istanbul, comparing the GIIITM series and the sequential media G1.2TM/G2.2TM. Embryo transfer performed on day 3 (400 cycles) and day 5 (73 cycles), as well as frozen thawed embryo transfers (188 cycles) were analyzed. The media were supplemented with HSA-solution according to the GIII-seriesTM Manual. The sequential media G1.2TM/G2.2TM included HSA. Treatment cycles were randomized on the day of documented fertilization to embryo culture in G1.2/G2.2 versus the GIII series media. Random allocation was according to alternating days of the week.

For day 3 transfers both the clinical pregnancy rate and the implantation rate were significantly increased when the GIII seriesTM was used. The clinical pregnancy rate was 37.8% with G1.2TM/G2.2TM and 50.3% with the GIII seriesTM and implantation rates were 14.4% and 25.7%, respectively.

For day 5 transfers the implantation rate was significantly increased. The implantation rate was 29% with G1.2TM/G2.2TM and 45.1% with the GIII seriesTM. In addition, there was a clear trend towards a higher pregnancy rate, 51.3% with G1.2TM/G2.2TM and 69.4% with the GIII-seriesTM. However, the increase was not significant due to fewer cycles analyzed in this group.

* GIII Series-TM Multi Centre Evaluation. Results from 800 embryo transfers. (Data on file, Vitrolife Sweden AB.)

Twenty-one IVF clinics in 15 countries entered the program between Q4, 2002 and Q2, 2003. GIII Series-TM products used were G-RinseTM, G-MOPSTM, G-SPERMTM, G-1TM version 3, G-2TM version 3 and HSA-SolutionTM. In a sub-study, G-MMTM was used as protein source.

In total 800 patients with a mean age of 33 years were included in the program. The clinical pregnancy rates per transfer were 48.3% (350/730) for day 2/3 transfer and 60.0% (42/70) for day 5/6 transfer. Implantation rates were 28.2% and 40.0%, respectively.

The applicant concludes that the safety and efficacy of HSA-solution are confirmed by the clinical study performed at the American Hospital in Istanbul, as the study showed high clinical pregnancy and implantation rates for GIII series-TM supplemented with HSA-solution; the multicentre evaluation demonstrates that clinics using GIII series media supplemented with HSA-solution can achieve high clinical pregnancy and implantation rates; based upon both studies the HSA-solution is claimed to be safe, effective and to fulfil its intended purpose.

In CHMP's view it is not possible to evaluate from the first study the effect or usefulness of HSA per se since it was added in both treatment arms. The fact that, in the second study, results appeared superior in the GIII-series arm may be due to other and new components of the solution, e.g. amino acids, ion concentration. These data also do not allow assessing the safety in a direct way since no safety parameters were included in the study.

Additional data submitted are represented below. However, CHMP considers these additional data are not directly informative regarding the usefulness or safety of HSA in GIII Series:

- Cleavage rate and embryo quality in GIII Series. Culture of 21 638 oocytes. (Data on file)

The GIII Series support high cleavage rates and are more than 70% of the human embryos were of good or excellent quality when analyzing the culture of 21 638 oocytes.

- Experience with GIII Series in a single embryo transfer program. (Data on file)

The GIII Series showed improved pregnancy and implantation rates (37.1% and 32.6%) compared to controls.

- Comparison of GIII Series-TM (Vitrolife AB) and Universal IVF (Medicult A/S) in a single embryo transfer (SET) programme. A prospective study using sibling oocytes. (Data on file)

The implantation rate was higher and more embryos were of high quality for the GIII Series (44.0% and 31%) compared with the Universal IVF group (37.5% and 21%).

- Optimizing of possible success in an IVF program. (10)

The GIII Series significantly increased the clinical pregnancy rate (25.3%) compared to the control groups (15.0% and 18.8%).

- Labelling

The applicant has enclosed the instructions for use.

Discussion on Quality, Safety and Usefulness

The GIII Series solution is intended for use in assisted reproductive procedures, which include gamete and embryo manipulation. The Human serum albumin (HSA) is included as an ancillary medicinal substance with the purpose to assist the function of the medical device.

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 PhEur 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.

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.

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material for the drug substance was re-certified in December 2005 (EMEA/H/PMF/000004/04/AU/0002).

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.

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

In general, the quality aspects of the incorporation of HSA as ancillary medicinal substance in GIII Series were sufficiently addressed. The manufacturing process is described and critical steps are performed under sterile conditions.

The intended use of the GIII series, preparation and manipulation of gametes and embryos, is very different from the normal use of albumin solutions. The manufacturer of Human Albumin L/A 25% has demonstrated that sufficient measures are taken to assure viral safety of the albumin for its normal use (I.V. infusion). There have not been any reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes when used for i.v. infusion. The fact that parvovirus B19 may harm the foetus and that the GIII series are used in the different steps

during IVF treatment where the solutions containing HSA and therefore potential virus contamination will be in direct contact with gametes and embryo, was address by a risk assessment during the ongoing consultation procedure. This risk assessment confirmed the safety margin of Human Albumin L/A 25% as used in the GIII series IVF media with respect to parvovirus B19.

In summary, the quality of Human Albumin L/A 25% in its context of use in the IVF Media GIII Series has been sufficiently shown.

Safety and usefulness

For the evaluation of the safety and usefulness available unpublished and published data for the GIII series were reviewed. The main data set corresponds to two studies in which HSA-solution is used for the supplementation of GIII culture media. In these studies, it is not possible to evaluate the usefulness of HSA per se since it was added in both experimental treatments, nor is it possible to assess the safety in a direct way since no safety parameters were included in these studies. Data from additional studies are not directly informative regarding the usefulness or safety of HSA in the GIII Series.

Regarding safety, the main drawbacks of using HSA in the media are the possible risks of transmitting viral/prion contaminations, and the lot to lot variability and presence of impurities due to different contamination levels of fatty acids and other small molecules. The use of recombinant human albumin would in this respect be advantageous but has not yet come to any important use on the IVF market due to the high costs of its production. The risk for transmission of viral/prion related diseases is considered to be extremely remote due to an effective donor screening for HIV and Hepatitis B+C, testing of plasma pools for viral markers before fractionation and effective virus reduction in the manufacturing process. Special concerns were raised concerning parvovirus B19 but data presented in the quality part has demonstrated a sufficient safety margin for Human Albumin L/A 25% as used in the GIII series IVF media with respect to parvovirus B19. The toxicity of HSA (known from other uses of HSA), i.e. allergic or anaphylactic reactions, are not deemed to be relevant in the in vitro procedures in question. Non-clinical biocompatibility tests did not reveal any safety concerns.

The GIII series solutions are intended to be used sequentially and have been developed to meet the changing need of the embryo during the in-vitro culture period and to minimize intracellular stress. HSA is used as a protein supplement to the GIII series media system, intended to serve a number of functions such as a surfactant preventing the embryo from sticking to dishes and pipettes, a chelating agent against potential toxins, a nutritive source for the embryo, a pH buffer and mediating capacitation of spermatozoa in vitro. Historically, embryo culture media as well as other types of media used in IVF procedures have been extensively supplemented with protein in the form of serum albumin, as the inclusion of protein in the media is generally believed to be important. Endogenous albumin is the most abundant protein in the female reproductive tract and is believed to be important in maintaining embryo physiology. The scientific rationale for the various functions has not been further supported by specific references.

3.4. Overall conclusions and recommendation

The scope of this assessment is to evaluate the quality, safety and usefulness of Human Albumin L/A 25% (HSA) in the medical device GIII solutions for IVF procedures in relation to the specific intended purpose of the device. It refers to the suitability of HSA to achieve its intended action, and whether the

potential inherent risks (aspects of safety) due to HSA are justified in relation to the benefit to be obtained within the intended purpose of the device.

Quality

The quality of Human Albumin L/A 25% before and after incorporation in the IVF Media GIII Series has been sufficiently demonstrated.

Investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process of the Human Albumin L/A 25%. The capacity and robustness of the manufacturing process of the Human Albumin L/A 25% 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. A risk assessment confirmed the safety margin of Human Albumin L/A 25% as used in the GIII series with respect to parvovirus B19.

Safety

Of crucial importance is the safety of HSA, pertaining mainly to the risk of virus and prion transfer from donors, and the special consideration of possible damage to the foetus due to early viral infection of the embryo with parvovirus B19. Data presented in the quality part has however demonstrated a sufficient safety margin for Human Albumin L/A 25% as used in the GIII series IVF media with respect to parvovirus B19 and other blood borne viruses.

Usefulness

The usefulness of HSA in differently composed GIII series solutions, for preparations of gametes and culture of embryos, can be supported theoretically for several reasons. Proteins added to media seem to be both necessary and useful for good performance. Serum from the particular woman (undergoing IVF) is considered as an unnatural component and environment for gametes and embryos since it contains a large variety of macromolecules that may exert untoward effects. Albumin is therefore regarded as a better choice of a single protein to be added and that can have beneficial effects.

The sparse documentation presented by the Applicant can not support, in a direct way, the various claimed beneficial functions, i.e. being a surfactant, a chelating agent against potential toxins, a nutritive source for the embryo, a pH buffer and a mediator of capacitation of spermatozoa, nor can the documentation directly support the usefulness of HSA in the various types of solutions when used for their specific purposes.

Nevertheless, on the basis of the theoretical considerations (from literature review series and historical data) and existing clinical practice with generally favourable results when using the GIII-solution containing HSA, the usefulness of HSA as an ancillary medicinal 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 GIII Series was favourable and therefore granted a positive opinion in the consultation procedure, provided that a measure is requested from the manufacturer of the albumin by the Notified Body, as outlined in section 2.2 of this report.