8 August 2012
EMA/850703/2011

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: Culture media for Assisted Reproductive Procedures

(CooperSurgical Inc ART Media)

Ancillary medicinal substance: Human Albumin Solution

EMEA/H/D/2307

Applicant: British Standards Institution BSI Healthcare

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

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Table of contents

Administrative information

Invented name of medical device:	Culture media for Assisted Reproductive Procedures
INN (or common name) of the ancillary medicinal substance:	Human Albumin Solution 25%
Applicant for medical device CE certification:	CooperSurgical, Inc. for SAGE In-Vitro Fertilization 95 Corporate Drive Trumbull, CT 006611 USA
Notified body:	British Standards Institution BSI Healthcare Kitemark House Maylands Avenue Hemel Hempstead, Herts, HP2 4SQ
Applied intended purpose of the device:	Assisted reproductive techniques culture media
Intended purpose of the ancillary medicinal substance in the device:	Human serum albumin ancillary action prevents adsorption to the container of various amino acids, vitamins which may be present in trace quantities and acts as a carrier of these substances to support growth and maintenance of gametes and/or embryos. Scavenges embryotoxic components generated during embryo's metabolism *in vitro*.
Pharmaceutical form and strength of the ancillary medicinal substance:	Not applicable 25% w/v (250 g/L)

1. Background information on the procedure

1.1. Submission of the dossier

The notified body British Standards Institution BSI Healthcare submitted to the European Medicines Agency (EMA) on 1 March 2010 an application for consultation on Human Albumin Solution as ancillary medicinal substance used in a medical device Culture media for Assisted Reproductive Procedures, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Dr Hudson Co-Rapporteur: Dr Salmonson

- The application was received by the EMA on 1 March 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first assessment report was circulated to all CHMP members on 9 August 2010. The Co-Rapporteur's first assessment report was circulated to all CHMP members on 28 July 2010.
- During the meeting on 20-23 September 2010, the CHMP agreed on the consolidated list of questions to be sent to the applicant. The final consolidated list of questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated list of questions on 15 October 2010.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of questions to all CHMP members on 26 November 2010.
- During the CHMP meeting on 13-16 December 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated list of questions on 17 January 2011.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP members on 31 January 2011.
- During the meeting on 14-17 February 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the committee, issued a positive opinion for the quality and safety including the clinical benefit/risk profile of Human Albumin Solution 25% as ancillary medicinal substance used in the Culture media for Assisted Reproductive Procedures on 17 February 2011. General conditions are the use of the ancillary medicinal substance in the medical device.

1.3. Manufacturers

Manufacturers of the active substance used as ancillary medicinal substance

CSL Behring AG
Wankdorfstrasse 10
3000 Bern 22
Switzerland

An inspection of these manufacturing sites was carried out by SwissMedic, Switzerland. The findings of the inspection are in compliance with the Community Good Manufacturing Practice requirements.

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

Not applicable

Manufacturer of the medical device

CooperSurgical, Inc.
95 Corporate Drive
Trumbull CT 006611
USA

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

1.4. Remarks to the notified body

The manufacturer of Human Albumin Solution 25% has confirmed that only plasma pools that have been tested for B19V will be used in the manufacture of Human Albumin Solution 25% supplied for use in ART Media.

Both, the human albumin manufacturer and the medical device manufacturer committed that only Human Albumin Solution lots which are batch released by an official medicines control laboratory (OMCL) will be supplied and used for the manufacture of the ART media.

1.5. Recommended measures to the notified body

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

Area[1]	**Description**
Quality	As requested during the consultation procedure the medical device manufacturer will implement a release test for human albumin content for ART media.
Quality	The medical device manufacturer committed to inform the Notified Body of any out of specification results for human albumin in the

Area[1]	Description
	ongoing ART media stability studies.

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

2. Scientific overview and discussion

2.1. General information

The medical devices consist of a family of sterile, liquid culture media intended for application in human assisted reproductive techniques including in-vitro fertilization procedures. These media contain human albumin as an ancillary medicinal substance. Human albumin solution supplied by other manufacturers is used in other CE-marked medical devices including ART media similar to the products under consideration here.

About the ancillary medicinal substance

The ancillary substance, Human Albumin Solution 25% (HSA) is manufactured by CSL Behring AG, Switzerland employing a well established, validated process. The final product manufactured for marketing in the EU meets the requirements of the Ph.Eur.monograph 'Albumini humani solutio' (Ph Eur 2010:0255).

This ancillary substance is approved for marketing as a medicinal product in Italy and Denmark.

Composition of Human Albumin Solution 25%

NAMES OF INGREDIENTS	UNIT AND/OR PERCENTAGE FORMULA	FUNCTION	REFERENCE
Active ingredient Human albumin	Albumin 25% (250 g/L)	Active ingredient	Ph. Eur.
Other ingredients Sodium N-acetyl-tryptophanate		Stabilizer	Ph. Eur.
Sodium caprylate		Stabilizer	Ph. Eur./
Sodium chloride2)		Tonicity Agent	Ph. Eur., USP
Water for injections		Solvent	Ph. Eur., USP

About the medical device

CooperSurgical Inc ART Media are a range of media and supplements designed for use in assisted reproductive techniques (ART). The media products are used for the storage, manipulation, in-vitro culture and transfer of human gametes and embryos and are for in vitro use only.

The Human Albumin Solution 25% Solution provides the following functions when incorporated into the device(s):

a. Acts as a carrier protein, it reversibly binds fatty acids, trace minerals, cellular growth factors and steroids.

b. Chelates potentially toxic divalent cations and heavy metals

c. Acts as a surfactant to inhibit non-specific binding of gametes/embryos to solid surfaces such as tissue culture ware.

There are 14 solutions in the media range, each containing human serum albumin (HSA). The ART media are generally isotonic (excluding those products intended for cryopreservation of gametes or embryos), sterile liquid culture media solutions of physiological pH. They consist of various organic compounds, inorganic salts, amino acids, carbohydrates and proteins (HSA).

Items included in the medical device media for assisted reproductive procedures

Item No.	Ref Number	Product
1	ART-1005/1006	Quinn's® Sperm Wash
2	ART-1012	Quinn's® Sperm Wash without antibiotic
3	ART-1520	Quinn's Advantage® Protein Plus Fertilization (HTF) Medium
4	ART-1600	In Vitro Maturation kit
5	ART-2004/2016	PureCeption®, 4, 16 determination kits

6	ART-4005-A	PVP, 7% Ready to Use Solution
7	ART-8014	Quinn's Advantage® Embryo Freezing Kit
8	ART-8015	Quinn's Advantage ® Blastocyst Freezing Kit
9	ART-8016	Quinn's Advantage® Thawing kit
10	ART-8017	Oocyte Freezing Cryo Kit
11	ART-8018	Oocyte Thawing Kit
12	ART-8022	Quinn's Advantage® Sperm Freezing Medium Kit
13	ART-8025	Vitrification kit
14	ART-8030	Vitrification Warming Kit

2.2. Quality documentation

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

Drug substance

Starting Material

The selection and screening of donors for the plasma used to manufacture human albumin are described in the Plasma Master File (PMF) and are in accordance with current requirements. Full details of the collection and testing of plasma used to manufacture Human Albumin 25% are provided in the CSL Behring PMF which has been approved in the centralised PMF procedure. The PMF certificate including the evaluation report, the PMF package and expert statement has been provided.

Manufacture, Specification, Stability

No drug substance dossier sections have been submitted with this application. The applicant states, that the dossier has been compiled for a medicinal product, in which albumin is present as an excipient. Whilst Human Albumin Solution 25% is used in the medical device as an ancillary medicinal product, rather than as an excipient, sufficient data on the quality of the ancillary medicinal product have been provided in the submission and the responses to the lists of questions and outstanding issues to provide assurance that the manufacturing process consistently results in a product of acceptable quality.

Drug product

Composition

See chapter 2.1 – General Information

Pharmaceutical Development

The Human Albumin 25 % Solution is produced according to the well established Kistler-Nitschmann process (cold ethanol fractionation) followed by pasteurisation of final container in accordance with the Ph.Eur. monograph for human albumin. The stabilisers use are commonly used in human albumin solutions.

Manufacturer

Release of the Human Albumin 25 % Solution occurs at the manufacturing site. The medical device containing human albumin is imported into the EEA as a finished product. Each batch (and each plasma pool used) is released by an OMCL. Both, the human albumin manufacturer and the medical device manufacturer committed that only human albumin lots which are batch released by an OMCL will be supplied and used for the manufacture of the ART media.

Manufacture

Human Albumin Solution 25% is manufactured according to the Kistler-Nitschmann procedure. The original procedure has been adapted to remove precipitates by filtration instead of centrifugation, and to remove ethanol by diafiltration instead of lyophilisation.

The manufacturing process has been described in detail. A flow chart as well as batch formula and batch size has been documented. Information regarding in-process controls and limits and reprocessing have also been provided. Acceptable process validation documentation have been provided for this product to show that the process is consistent and reproducible. Criteria for reprocessing of the pasteurisation step are defined. The shelf life for the intermediate is justified by stability data.

As requested during the consultation procedure the applicant appropriately revised the section on drug product specifications to include specifications for Human Albumin Solution, which comply with the Ph.Eur. monograph. In addition, a description of the analytical procedures for final product testing was included.

Container closure system

The specifications for the primary container for Human Albumin Solution were provided.

Bottles and stoppers are cleaned (if applicable) and sterilized using suitable processes.

Stability

Stability data indicate that the human albumin is stable for 3 years when stored ≤ 25°C, protected from light.An alert limit is used at release to ensure that the aluminium specification is met throughout the shelf-life.

Adventitious agents' safety

TSE and prion safety

None of the ingredients is derived from ruminant material. Human plasma is used as raw material which poses a risk of transmitting Creutzfeldt - Jakob disease (CJD) and related neurodegenerative disorders including variant CJD (vCJD). The company has described measures taken with regards to sourcing of plasma to minimise this risk. A study has been conducted to investigate the TSE agent removal capacity of the manufacturing process. The conclusion is that for the albumin manufacturing process TSE agent reduction has been demonstrated suggesting an acceptable safety margin. The TSE risk associated with Human Albumin Solution is considered to be extremely low.

Virus safety

Four steps in the manufacturing process have been validated for virus inactivation/reduction capacity,. Relevant model viruses were included in these studies. The results demonstrate that the process is efficient in reducing enveloped virus. For non-enveloped virus such as hepatitis A (HAV) and B19V, it was demonstrated that two steps were capable of reducing HAV (or model virus for HAV). For B19V, it was demonstrated that a single step in the fractionation process and the pasteurization step had a reduction factor capacity. The supplier of Human Albumin Solution has confirmed that only plasma pools that have been tested for B19V will be used in the manufacture of Human Albumin Solution supplied for use in ART Media.

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

Qualitative and Quantitative particular of the constituents

The qualitative and quantitative composition of each of the medium listed in the table below has been provided. It is noted that raw materials, chemicals, amino acids, and carbohydrates used in the formulations meet USP or Ph Eur specifications, where available. Quantities used in these products vary with the specific product formulation and have been defined in the application. Human Albumin Solution is added to the media at the medical device manufacturing site at a range of concentrations:

Item	Ref Number	Name of Medical Device	Components
1	ART-1005 ART-1006	Quinn's® Sperm Wash Kit Quinn's® Sperm Wash, 100 mL	ART-1005-12 Quinn's® Sperm Wash, 12 x 12 mL NA
2	ART-1012	Quinn's® Sperm Wash Kit (without antibiotic)	ART-1012-12 Quinn's® Sperm Wash without antibiotic 12 x 12 mL

3	ART-1520	Quinn's Advantage® Protein Plus Fertilization (HTF) Medium, 1 x 20 mL	NA
4	ART-1600	In Vitro Maturation Kit	ART-1600-A Oocyte Washing Medium, 1 x 50 mL ART-1600-B Oocyte Maturation Medium, 1 x 20 mL ART-1600-C Embryo Maintenance Medium, 1 x 5 mL
5	ART-2004 ART-2016	PureCeption®, 4 determination Kit PureCeption®, 16 determination Kit	ART-2005-12 Sperm Washing Medium, 1 x 12mL ART-2040-12 PureCeption® 40% Upper Phase, 1 x 12mL ART-2080-12 PureCeption® 80% Upper Phase 1 x 12 mL
			ART-2005-12 Sperm Washing Medium, 4 x 12mL ART-2040-12 PureCeption® 40% Upper Phase, 4 x 12mL ART-2080-12 PureCeption® 80% Upper Phase 4 x 12 mL
6	ART-4005-A	PVP, 7% Ready to Use Solution Kit	ART-4005 PVP, 7% Ready to Use Solution, 6 x 0.5 mL
7	ART-8014	Quinn's Advantage® Embryo Freezing Kit	ART-8001-12 1.5M Propanediol 0.1M Sucrose Freezing Medium 2 x 12 mL ART-8003-12 1.5 M Propanediol Freezing Medium, 2 x 12 mL ART-8013-12 Cryokit Diluent 1 x 12 mL
8	ART-8015	Quinn's Advantage ® Blastocyst Freezing Kit	ART-8009-12 5% Glycerol Freezing Medium, 1 x 12 mL ART-8011-12 9% Glycerol, 0.2M Sucrose Freezing Medium, 1 x 12 mL ART-8013-12 Cryokit Diluent, 1 x 12 mL
9	ART-8016	Quinn's Advantage® Thawing Kit	ART-8005-12 0.5M Sucrose Thawing Medium, 1 x 12 mL ART-8007-12 0.2M Sucrose Thawing Medium, 1 x 12 mL ART-8013-12 Cryokit Diluent, 1 x 12 mL
10	ART-8017	CSC Freezing Medium Kit	ART-8017-A CSC Freezing Medium, 1 X 10 mL
11	ART-8018	CSC Thawing Medium Kit	ART-8018-A 0.5M Sucrose CSC Thawing Medium ART-8018-B 0.2M Sucrose CSC Thawing Medium ART-8018-C CSC Washing Medium with HEPES
12	ART-8022	Quinn's Advantage® Sperm Freezing Medium Kit	ART-8020-12 Quinn's Advantage® Sperm Freezing Medium 6 x 12 mL
13	ART-8025	Vitrification Kit	ART-8025-A Equilibration Solution, 1 x 2 mL ART-8025-B Vitrification Solution, 1 x 2 mL
14	ART-8030	Vitrification Warming Kit	ART-8030-A 1.0M Sucrose Warming Solution, 1 x 4 mL ART-8030-B 0.5M Sucrose Warming Solution, 1 x 2 mL ART-8030-C MOPS Solution, 1 x 6 mL

Description of method of manufacture

All media manufacturing takes place at a US registered medical device manufacturer that operates a Quality Assurance program which is considered ISO 13485-2003 compliant by the Notified Body (1/7/2009).

The Human Albumin Solution 25% is added to the media at the manufacturing site. The manufacturing process with regards to incorporation of the ancillary medicinal substance is comprised mainly of mixing, sterile filtration and aseptic filling. This has been sufficiently described. In addition, the medical device manufacturer described how the traceability of each batch of Human Albumin Solution 25% used in each batch of each medium is assured.

Control of starting materials

For the assessment of the ancillary substance as incorporated in the medical device, the specifications for the ancillary human blood derivative are of importance. These have been provided and comply with the relevant Ph Eur monograph.

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

As there is no alteration of the human albumin at the time of media formulation, there is no specific in-process test for this component. This is considered acceptable.

The in-process testing of each reproductive media formulation has been detailed These data are embedded within the batch record.

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

Release tests for ART media are listed. As requested during the consultation procedure the medical device manufacturer will implement stability and release testing for human albumin content of the ART media. The method has already been successfully validated for two media. An acceptance criterion of human albumin content will be applied to lot release. Given the functions of human albumin in the media, the proposed acceptance criterion is acceptable.

Stability

Stability data submitted to date are sufficient to support a 12 month shelf-life for the ART media.-The data provided indicate that the media are stable for all quality parameters, including albumin content, for 9 months when stored at 2-8^{o}C. Given the data provided previously for ART media containing human albumin from another supplier, and the commitment to inform the Notified Body of any out of specification results for human albumin in the ongoing stability studies, the medical device manufacturer's proposal for a 1 year shelf-life for ART media is acceptable with regard to the stability of the ancillary substance.

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

The ancillary substance, Human Albumin Solution 25%, is manufactured by a well established, validated process and the final product manufactured for marketing in the EU meets the requirements of the Ph.Eur.monograph 'Albumini humani solution' (Ph Eur 2010:0255). The selection and screening of donors for the plasma used to manufacture human albumin are described in the Plasma Master File and are in accordance with current requirements.

In general the description of all 14 medical devices is acceptable. The manufacturing process has been described in sufficient detail. As requested, the medical device manufacturer has agreed to introduce a control test for human albumin content to the specification for each medium. Stability data submitted to date are sufficient to support a 12 month shelf-life for the ART media including human albumin. The medical device manufacturer committed to inform the Notified Body of any out of specification results for human albumin in the ongoing ART media stability studies.

Concerning TSE and prion safety, the human albumin manufacturer has described measures taken with regards to sourcing of plasma to minimise this risk. In addition results from a study investigating the ability of manufacturing steps used in the production of albumin and immunoglobulin products by Kistler–Nitschmann process to remove TSE agents suggest an acceptable safety margin. The TSE risk associated with ancillary medicinal substance is considered to be extremely low.

A comprehensive package has been provided which presents the viral clearance studies carried out to support the viral safety of the albumin product. The manufacturer of Human Albumin Solution 25% has confirmed that only plasma pools that have been tested for B19V will be used in the manufacture of Human Albumin Solution 25% supplied for use in ART Media.

All issues regarding the chemical, pharmaceutical and biological aspects of the ancillary blood derivative as incorporated in the medical device have been resolved. Two measures to be addressed for medical device approval are recommended to the Notified Body (section 1.5).

2.3. Non-clinical documentation

Pharmacodynamics

The intended action of human serum albumin as the ancillary human blood derivative in-vitro fertilisation (IVF) is:

- To act as a carrier protein - it reversibly binds fatty acids, trace minerals, cellular growth factors and steroids.
- To chelate potentially toxic divalent cations and heavy metals
- To act as a surfactant to inhibit non-specific binding of gametes/embryos to solid surfaces such as tissue culture ware.

Pharmacokinetics

Not applicable.

Toxicity

No repeat-dose toxicity, genotoxicity, carcinogenicity or reproductive and developmental toxicity studies have been submitted and none are required as human serum albumin is a constituent of normal blood which is a well-known substance used in IVF media for over 20 years.

The Core SPC for Human Albumin Solution states the following:
"In animals, single dose toxicity testing is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.

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

Local tolerance

No information regarding local tolerance has been provided (see discussion on the non-clinical documentation below).

2.3.1. Discussion and conclusion on the non-clinical documentation

Human serum albumin is a constituent of normal blood which is a well-known substance used in IVF media for over 20 years. Historically, embryo and gamete media for culture, manipulation, and storage have been supplemented with protein in the form of either serum albumin or serum. The role of albumin in culture media includes colloid osmotic regulation, carrier of growth promoting substances, possible scavenger of toxins, and coating agent to prevent the attachment of gametes and embryos to laboratory ware.

The lack of pharmacokinetic studies is acceptable since the reproductive media solutions are not expected to cause any systemic exposure to the ancillary human blood derivative in the patient.

According to the Core SmPC for Human Albumin Solution (CPMP/BPWG/2231/99 Rev. 2), to date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.

The lack of investigation of local tolerance was further discussed during the consultation procedure. The manufacturer's argument that specification limits for osmolality, pH, endotoxin, together with the release requirement of >80% blastocyst formation, provide an appropriate justification of the lack of local tolerance studies has not been concurred by the CHMP. According to the ISO matrix, CooperSurgical IVF media are classified as surface devices in contact with intact mucosa during limited exposure. As such, biocompatibility would be required to be discussed in compliance with the EN ISO 10993 Standards, which require cytotoxicity, sensitisation and irritation testing. Blastocysts are not considered an appropriate test system for local tolerance as they are not suitable to assess sensitisation and irritation endpoints. However, the inclusion of albumin on its own did not raise a concern regarding local tolerance. During assessment the Notified Body confirmed that the sensitisation and irritation potential of the device is being investigated according to EN ISO 10993 Standards.

2.4. Clinical evaluation

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

The medical device manufacturer initially submitted a brief critical review, 11 publications and some sales data to demonstrate the usefulness of HSA as an ancillary medicinal substance to ART media. The Notified Body also submitted an assessment of usefulness, largely based on the medical device manufacturer's critical clinical review. These reviews outlined the physiological functions and physicochemical properties of albumin which would suggest some benefit in supplementing ART media with HSA. In addition, the manufacturer submitted a number of publications to specifically provide evidence for the role of albumin in sperm capacitation and fertilisation in animals.

However, the collection of publications submitted did not report any studies in humans where HSA was compared to another supplement (without any other change in formulation of the trial medium) or compared to placebo. This made it difficult to attribute any benefits seen with using HSA supplemented media specifically to its HSA content. Therefore, whilst some of the studies were large enough and of suitable design to demonstrate compatibility of HSA supplemented ART media with reasonable sperm motility, high fertilisation rates, normal blastocyst growth and embryo transfer and respectable clinical pregnancy and delivery rates, they did not on their own demonstrate usefulness of the HSA component of the media. The committee acknowledged that likelihood of performing or identifying studies comparing HSA to placebo (or no supplementation) may have been difficult, given the widespread and long-standing practice of serum albumin supplementation of ART media.

However, a small number of publications reporting animal studies comparing protein-free IVF culture media to similar media with added non-human, mammalian serum albumin or whole serum were also submitted. These studies demonstrated that supplementation of IVF media with serum albumin is useful and necessary for achieving the highest outcome rates for fertilisation and gamete and embryo development and maturation. Contrary to what is stated by the medical device manufacturer, these publications did not provide conclusive evidence that the addition of albumin to IVF media is essential for achieving successful IVF media related outcomes. Further, it should be noted that the submitted studies did not demonstrate the clinical effectiveness of serum albumin supplementation of IVF media, as asserted by both the manufacturer and the Notified Body.

The established practice of serum albumin (bovine or human) supplementation of ART media was only briefly discussed by both the medical device manufacturer and the Notified Body within their submissions. The CHMP acknowledged however, that the practice of albumin supplementation of ART media is widely accepted and routine.

Overall, the committee considered that usefulness was sufficiently demonstrated by:

- discussion of albumin's roles and properties
- established use of serum albumin supplementation of ART media
- evidence for compatibility of HSA supplemented media with expected outcome rates associated with ART

2.4.2. Clinical safety of the medical device

The human albumin 25% constituent of the medical device, supplied by, is currently licensed in Denmark and Italy, and strengths have been licensed through a number of mutual recognition procedures since 2004 and are now approved in 21 member states. The medical device manufacturer has confirmed that no modification of the finished albumin product occurs prior to its incorporation into the medical device.

The CHMP considered that the main drawback of supplementing the media with HSA is the possible risk of transmitting viral particles and prions. However, the medical device manufacturer considered the risk of such transmission to be remote due to effective donor screening and selection and the demonstrated reduction factors in viral particles during the HSA manufacturing process (see section 2.2.1 – Adventitious agents' safety). The manufacturer has also provided a worst-case risk assessment relating to the potential effects of parvovirus B19 being transmitted from Human Albumin Solution 25% to the embryo. Furthermore, the manufacturer has also included a warning statement on risk of transmissible infections in applicable IFUs, in line with the Note for Guidance on the warning on transmissible agents in SmPCs (CPMP/BPWG/BWP/561/03 [October 2003]). Currently, there are no cases of proven virus transmission with albumin manufactured to European Pharmacopoeia specifications by established processes.

HSA has been approved for use within EU member states and has been used clinically for a number of decades, such that its safety profile is now very well characterised. Taking into account the very low risk of viral transmission from HSA, the small amount of HSA which may be transferred to the patient during intrauterine insemination (IUI), the small amount to which gametes and embryos are exposed during ART procedures, and the tropism of B19V towards cells expressing the blood P antigen e.g. erythroid progenitor cells and erythroid cell lines, there are not considered to be any major safety concerns from the clinical perspective. Risks of allergic or anaphylactic reaction related to exposure to the media are also expected to be low.

In the literature provided by the medical device manufacturer no relevant safety data were presented and certainly no safety data from any comparisons of ART media with and without HSA were submitted or discussed. Indeed, it was apparent that in the studies reported there was no formal monitoring, collecting, reporting or analysing of adverse events. However, this was not considered a major concern given the well-characterised safety profile of human albumin and its historical use within ART media. The medical device manufacturer also addressed the question of safety with submission of a complaints analysis and a risk-management work up in accordance with ISO 14971 and MDD 93/42/EEC.

A discussion of safety based on the well-characterised profile of adverse events associated with HSA and its very low risk of transmissible infections as well as an assessment of safety of the device in its entirety was provided. These identified the most pertinent safety concerns related to the medical device: risk of bacterial contamination, risk of viral contamination and risk of local irritant effects. It should be noted that the CHMP did not agree that the local irritant effects of the device can be determined using murine blastocyst developmental testing. However, it is within the remit of the Notified Body to determine whether local tolerance testing of components of the device other than the ancillary medicinal substance has been adequately undertaken. During assessment the Notified Body confirmed that the sensitisation and irritation potential of the device is being investigated according to EN ISO 10993 Standards.

On balance the CHMP considered that the medical device manufacturer and Notified Body have jointly, sufficiently demonstrated the safety of the HSA incorporated into the ART medical device.

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

The discussions provided by both the medical device manufacturer and Notified Body on albumin's physiological roles and the established use of serum albumin supplementation of ART media, in addition to the literature provided by the medical device manufacturer, together sufficiently demonstrated the usefulness but not clinical effectiveness, of HSA added to the ART media. Further, the Notified Body has outlined the well-established safety profile of human albumin and has clearly detailed the risks of human albumin used within these media, particularly the risk of transmissible infections, which are considered to be low. This is supported by submissions from the human albumin manufacturer detailing TSE and virus reduction factors during the manufacturing process. In addition, a warning statement regarding the risk of transmissible infections in accordance with the Note for Guidance on the warning of transmissible agents in SmPCs has been included within all applicable IFUs.

The CHMP considered the risk benefit balance to be favourable.

2.4.4. Discussion and conclusion on the clinical evaluation

The established practice of serum albumin supplementation of ART media is well recognised and widely accepted and has been shown by the medical device manufacturer to be compatible with average or above average rates of embryo and blastocyst survival, blastocyst implantation, clinical pregnancy and live births in humans. Discussions were provided on albumin's physiological roles. In addition, published literature was submitted to demonstrate the usefulness of albumin supplementation of ART media. Taken together, the discussions, submitted literature and record of historical practice sufficiently demonstrated the usefulness of HSA added to the ART media.

The well-established safety profile of human albumin was outlined clearly detailing the risks of human albumin used within these media, particularly the risk of transmissible infections, which is considered

to be low but not non-existent. In this regard, a warning statement regarding risk of transmissible infections in accordance with the Note for Guidance on the warning of transmissible agents in SmPCs within all applicable IFUs has been included in the labelling.

Overall the benefit-risk balance for this product is considered to be positive and the application is approvable.

2.5. Overall conclusions

Overall conclusions on the quality and safety including the clinical benefit/risk profile of the ancillary medicinal substance in the context of its use in the medical device

As outlined above, it is considered that the quality, safety and usefulness of the ancillary medicinal substance, Human Albumin Solution 25%, in the context of its use in the medical device, Culture media for Assisted Reproductive Procedures, have been demonstrated.

All the issues raised during the consultation procedure have been satisfactorily resolved. Two measures to be addressed for medical device approval are recommended to the Notified Body (section 1.5).

2.6. Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality and safety including the benefit risk profile of Human Albumin Solution 25% used as ancillary medicinal substance in the Culture media for Assisted Reproductive Procedures was favourable and therefore granted a positive opinion in the consultation procedure.