8 August 2012
EMA/CHMP/66296/2012

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: FertiPro N.V. HSA-containing ART media

Ancillary medicinal substance: Human Albumin Solution

EMEA/H/D/2518

Applicant: DEKRA Certification

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

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# Administrative information

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|---|---|
| **Invented name of medical device:** | FertiPro N.V. HSA-containing ART media |
| **INN (or common name) of the ancillary medicinal substance:** | Human Albumin Solution |
| **Applicant for medical device CE certification:** | FertiPro N.V. |
| **Notified body:** | DEKRA Certification |
| **Applied intended purpose of the device:** | In vitro fertilisation |
| **Intended purpose of the ancillary medicinal substance in the device:** | Acts as carrier protein, binds irreversible to fatty acids, trace minerals, growth factors and steroids<br>Chelates potentially toxic divalent cations and heavy metals.<br>Acts as surfactant to inhibit non-specific binding of gametes and embryo to solid surfaces such as tissue culture ware. |
| **Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:** | Not applicable<br><br>25% w/v (250 g/L) |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The notified body DEKRA certification submitted to the European Medicines Agency (EMA) on 3 May 2011 an application for consultation on Human Albumin Solution as ancillary medicinal substance(s) used in a medical device FertiPro N.V. HSA-containing ART media in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Tomas Salmonson Co-Rapporteur: Ian Hudson

- The application was received by the EMA on 3 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first assessment report was circulated to all CHMP members on 12 August 2011. The Co-Rapporteur's first assessment report was circulated to all CHMP members on 12 August 2011.
- During the meeting on 22 September 2011, 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 27 September 2011.
- The applicant submitted the responses to the CHMP consolidated list of questions on 12 October 2011.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of questions to all CHMP members on 25 November 2011.
- During the CHMP meeting on 15 December 2011, 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 21 December 2011.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP members on 3 January 2012.
- During the meeting on 16-19 January 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the committee, issued a positive opinion for quality and safety including the clinical benefit/risk profile of Human Albumin Solution as ancillary medicinal substance(s) used in FertiPro N.V. HSA-containing ART media on 19 January 2012.

## *1.3. Manufacturers*

### Manufacturer of the active substance used as ancillary medicinal substance

Talecris Biotherapeutics Inc
8368 US 70 West Clayton
North Carolina, 27520
USA

An inspection of these manufacturing sites was carried out by the German inspectorate in Darmstadt. 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

Grifols Deutschland GmbH
Lyoner Strasse 15
60528 Frankfurt am Main
Germany

### Manufacturer of the medical device

FertiPro N.V.
Industriepark Noord 32
B-8730 Beernem
Belgium

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*

Several of the stability studies for respective solutions of FertiPro N.V. are still ongoing and the manufacturer of the medical device has stated that they intend to extend the shelf-life of several of the items to up to 18 months for some solutions. Since stability data is available for up to 14 months this is acceptable with regards to stability of albumin, provided that the specification limits are fulfilled at the extended shelf-life. No further data needs to be submitted to the EMA.

### *1.5. Recommended measures to the notified body*

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

| **Area**[1] | **Description** |
|---|---|
| Quality | The instructions for use (IFU) for FertiPro N.V. HSA-containing media should be brought into line with "Note for guidance on the warning on transmissible agents in summary of product characteristics and package leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03)" relevant for Albumin. The following should be reworded in the "Warnings and Precautions" section of the Instructions for use:<br><br>From:<br><br>~~"XXXXXX contains human serum albumin. Source materials from which this product was derived was found negative when tested for antibodies to HIV and HCV and non-reactive for HbsAg, HBV RNA, HCV RNA, HIV-1 RNA and syphilis.~~<br>~~No known test method can offer assurance that products derived from human blood will not transmit infectious agents."~~<br><br>To:<br><br>"Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of proven virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes."<br><br>*(DEKRA Certification noted that the update could be verified and accepted).* |

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

# 2. Scientific overview and discussion

### *2.1. General information*

FertiPro N.V. HSA-containing ART media are classified as medical devices according to the Commission Directives 93/42/EEC as amended. DEKRA Certification, is consulting the CHMP regarding the quality, safety and clinical benefit/risk profile of the albumin component of FertiPro N.V. HSA containing media.

FertiPro N.V. HSA-containing ART media consists of a set of 13 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. These media contain human albumin as an ancillary medicinal substance. As albumin source, FertiPro N.V. uses Human Albumin Solution (HSA) Low Aluminium (L/A) 25% also known as Plasbumin-25.

**About the ancillary medicinal substance**

The ancillary substance, Human Albumin Solution L/A 25% is manufactured by Talecris Biotherapeutics Inc, USA, 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).

Complete composition of Human Albumin Solution L/A 25%.

| Ingredient | Reference | Function |
|---|---|---|
| Protein[1] | EP | Active ingredient |
| Sodium caprylate | EP | Stabiliser |
| N-acetyl-DL-tryptophan | EP | Stabiliser |
| Sodium[2] | In-house | Tonicity |
| Water for injections | EP | Solvent |

**About the medical device**

FertiPro N.V. HSA-containing ART media consist of various compositions of physiological salts, nutritional and energy substances and buffer systems. To enhance specific properties, some media also contain cryoprotectants or antibiotics.

The Human Albumin Solution L/A 25% is incorporated in the media with the intended purpose of (1) acting as carrier protein, binding irreversible to fatty acids, trace minerals, growth factors and steroids, (2) chelating potentially toxic divalent cations and heavy metals and (3) acting as a surfactant to inhibit non-specific binding of gametes and embryo to solid surfaces such as tissue culture ware.

The amount of Human Albumin Solution L/A 25% is dependent on the type of medium and is ranging from 1.6% to 8% (v/v), corresponding with 3.94 g/l and 20 g/l human albumin respectively. There is no manipulation of the albumin before adding it to the medical device solution.

## *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 L/A 25% are described in the Talecris Plasma Master File (PMF) and are in accordance with current requirements. Full details of the collection and testing of plasma are provided in the PMF.

The Talecris PMF has been certified in the centralised PMF procedure. The PMF certificate (EMEA/H/PMF/000004/04) was provided together with an expert statement stating that the referred PMF is fully applicable for the manufacture of Human Albumin L/A 25%.

*Manufacture*

The drug substance is defined as the final sterile bulk before filling into the final container.

The manufacturing process is based on the Cohn-Oncley fractionation followed by further purification steps. The fractionation starts with pooling of plasma and ends with collection of fraction V paste. For further purification of the albumin, the dissolved fraction V is clarified. The albumin fraction is then precipitated, separated by centrifugation and dried with acetone.

The albumin powder is dissolved with water for injections. The solution is sterile filtered and may be stored prior to filling into final containers.

The description of the manufacturing process for the drug substance together with the validation data, have been presented. The composition and physicochemical properties of intermediate fractions have been extensively studied. In process controls and hold times have been adequately established. The removal of expected impurities and process related impurities have been demonstrated. Validation data for the process indicate that the process is adequately controlled and that the albumin produced is of acceptable quality.

*Specifications*

The drug substance specifications have been set. The methods have been adequately validated.

*Stability*

The results of stability studies for Albumin (Human) intermediates were within applicable acceptance criteria.

All data for the final sterile bulk (drug substance) met the established acceptance criteria.

The stability of the intermediates and final sterile bulk/drug substance has been satisfactorily demonstrated.

**Drug product**

The drug product for Human Albumin Solution L/A 25% is defined as the packaged final container.

Albumin L/A 25% is a clear, slightly viscous pale yellow, amber or green coloured liquid that is administered intravenously.

*Pharmaceutical development*

Most of the description of pharmaceutical development is based on literature data since the Cohn-Oncley process is a well established process. Standard stabilisers are added to limit the potential degradation of high temperature pasteurisation. The final formulation specifications are in compliance with current Ph. Eur. Human Albumin Solution.

The suitability of the container system has been demonstrated. The stoppers have been verified to meet the specifications of the current European Pharmacopoeia.

*Manufacturers*

GMP certificates issued by an EU Competent Authority were provided for the manufacturing sites/laboratories.

*Manufacture*

Production of the drug product from sterile albumin bulk consists in aseptic filling into the final sterile container, pasteurisation and incubation in the final container in accordance with the Ph. Eur. monograph for Human Albumin Solution. The product is filled in glass vials.

The manufacturing process has been acceptably described and satisfactory consistency in production has been demonstrated. The final albumin product is controlled in accordance with the Ph. Eur. monograph.

A list of in process controls has been provided.

The validation of the aseptic filling and stoppering is based on room certification, fill equipment validation, filling support equipment and sterile cycle validation and media fills. Validation of the sterilisation/depyrogenisation has demonstrated at least 3 log reduction in endotoxin load. The oversealing has also been validated and found acceptable by the manufacturer.

The pasteurisation step has been validated for the pasteurizers used in production.

*Specifications*

A set of release and shelf life specifications have been provided and are in accordance with compendial requirement.

A short description of the test methods and the test principles has been provided. Validation reports were provided for test methods which are not performed according to the Ph. Eur. methods.

*Container Closure System*

During the procedure the applicant clarified that 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.

*Stability*

Stability data provided supported that the final albumin drug product filled in glass vials is stored at 2°-25°C. The stability data demonstrates acceptable stability of the final albumin product. The container and stoppers have been verified in stability studies.

Annually, one lot of Albumin is placed into the stability program.

**Adventitious agents' safety**

**TSE and prion Safety**

With regard to the risk of transmission of transmissible spongiform encephalopathies (TSE) through the use of plasma-derivatives, the safety of the medicinal product is accomplished by the suitability of plasma donors, the use of low-risk raw materials and steps in the manufacturing process that have been shown to achieve TSE clearance.

The plasma is collected from healthy plasma donors in plasmapheresis centres as specified in Talecris PMF EMEA/H/PMF/000004/04, which is re assessed every year in a centralised procedure guaranteeing that the plasma used is of acceptable quality. Plasma is sourced using donors that fulfil the requirements of European legislation and guidance. No animal derived materials are used in the manufacture of Albumin. Both animal bioassay TSE infectivity assay and western-blotting were performed to monitor prion reduction. The studies are in compliance with the requirements of current guidelines (CPMP/BWP/CPMP/5136/03).

The ability of the manufacturing process to remove TSE infectivity has been demonstrated satisfactorily.

### Viral safety

With regard to the risk of transmission of viruses, the safety of the medicinal product is demonstrated by the sourcing of plasma from a centrally approved PMF and by steps in the manufacturing process that have been shown to achieve viral removal/inactivation.

Extensive studies have been conducted which demonstrate the ability of the albumin production process to inactivate/remove both enveloped and non-enveloped viruses, including robustness studies and validation of the scaled-down methods used. Full reports have been provided and the studies conducted are in compliance with current CHMP guidelines.

Enveloped viruses are satisfactorily removed/inactivated in the production process. Effective inactivation (>4log reduction) of BVDV, HIV-1 and PRV has been demonstrated. Additional reduction of HIV-1, PRV and BVDV was seen.

Regarding non-enveloped viruses, it was demonstrated that HAV (hepatitis A) can be inactivated by the pasteurisation step. Normally for albumin solution, substantial reduction of HAV is demonstrated in the Cohn fractionation of the process (i.e. 40% ethanol precipitation). The applicant has chosen not to validate this step in the virus studies. Since robust and effective inactivation has been demonstrated for the pasteurisation step and additional removal has been shown for one of the fractionation steps and for the depth filtration and taken into account that this is a product that has been licensed in some EU member states for over ten years and the excellent safety records of albumin solutions this is found acceptable. Validation studies showed reduction of parvovirus. Other steps in the process were also shown to contribute to reduction of parvovirus, for example the pasteurisation step.

The viral safety of the albumin drug product has been satisfactorily demonstrated.

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

### Qualitative and Quantitative particular of the constituents

FertiPro N.V. HSA-containing ART media are aqueous solutions of physiological salts to which nutritional / energy substances and buffer systems are added. To enhance specific properties, some media also contain cryoprotectants or antibiotics. All FertiPro N.V. HSA-containing ART media are supplemented with Human Albumin Solution L/A 25%. The amount of Human Albumin Solution L/A 25% is dependent on the type of medium and is ranging from 1.6% to 8% (v/v). The amounts are based on long term experience in the field. Human Albumin Solution L/A 25% is compatible with all other medium components, and remains stable until the end of shelf life. The exact medium compositions are outlined below.

### Description of method of manufacture

All media manufacture takes place in Fertipro N.V. manufacturing facilities in Belgium. The manufacturing facilities have been certified by the notified body (DEKRA).

The Human Albumin Solution N/A 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. Flowcharts have been provided for the manufacturing process and also a more detailed description of the sterilisation procedure.

**Control of starting materials**

Each new batch of Human Albumin Solution N/A 25% has to meet specific release criteria, which includes compliance to certificate of analysis and EU official batch release by OMCL laboratory.

The performance of the additional internal quality control tests is supported.

**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, it is acceptable that there are no specific in-process test for albumin.

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

Final control tests of the ancillary medicinal substance in the medical device consist of test of the albumin concentration and the albumin quality.

The final control tests and the proposed specifications are considered suitable for a qualitative and quantitative control of albumin in the medical device.

**Stability**

Stability data has been provided for all media of FertiPro N.V. HSA-containing ART media.

Data has been presented for several batches from start of stability till the end of shelf-life, demonstrating that albumin is stable in these solutions. Several of the stability studies are on-going and the manufacturer of the medical device has declared that they intend to extend the shelf-life provided that all specifications are fulfilled at the extended end of shelf-life (up to 18 months). Substantial amount of stability data (up to 14 months) has already been provided demonstrating that albumin is stable under the proposed storage conditions; this is acceptable with regards to stability of albumin, provided that the specification limits are fulfilled at the extended shelf-life.

## 2.2.2. Discussion and conclusion on chemical, pharmaceutical and biological aspects

The ancillary substance, Human Albumin Solution L/A 25%, is manufactured by a well established, validated process and the final product 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 Talecris PMF and are in accordance with current requirements.

The description of the 13 solutions or kits of solutions is acceptable. The manufacturing process has been described in detail. The final control tests for albumin and the proposed specifications are considered suitable for a qualitative and quantitative control of albumin in the medical devices. Stability data provided support the current shelf life. The manufacturer of the medical device has satisfactorily described the measures in place to ensure that the shelf-life of the albumin is synchronised with the shelf-life of the different solutions of FertiPro N.V.

The manufacturer of the device has described in detail the measures taken to minimise the risk with using albumin in FertiPro N.V. HSA containing media, including risks of transmitting virus and prions. This includes the use of Talecris PMF, which has been approved in the centralised PMF procedure and which undergoes yearly updates. Adequate testing at donation level, mini pool and manufacturing pools ensure a good quality and safety of the plasma.

This in combination with the reduction factors presented for the manufacturing process of Albumin (Human) 25%, Low Aluminium demonstrate that there is a sufficient safety margin with regards to virus transmission. The albumin complies with the Ph. Eur. monograph of Human Albumin Solution.

## *2.3. Non-clinical documentation*

### Pharmacodynamics

The role of albumin in cell culture media has been adequately reviewed by the Applicant. In conclusion, albumin:

- Acts as a chelator to toxic metal ions and metabolic wastes, binding to waste products from cell metabolism and potential contaminants introduced in the media
- Provides colloid osmotic regulation
- Inhibits lipid peroxidation (that can be damaging to sperm cells) by binding hydroperoxy fatty acids
- Acts as a carrier and source of essential molecules needed by the embryo
- Acts as a cryoprotecting macromolecule in cell culture media for cryopreservation of gametes and embryos (reducing physical damage due to freezing/ thawing).
- Has a buffering capacity for small ionic molecules, lipids, and growth promoting substances secreted by the embryo
- Facilitates gamete or embryo manipulation by preventing adsorption to surfaces such as plastic or glass recipients (standard IVF-laboratory equipment) through saturation of the potential binding sites
- Increases medium viscosity, which acts to stabilize cell membranes.

### Pharmacokinetics

Not applicable.

### Toxicity

The Core SPC for Human Albumin Solution (CPMP/PhVWP/BPWG/2231/99/Rev. 2) reviews a number of aspects relevant for toxicity for Human Albumin. Human albumin is a normal constituent of human plasma and acts like physiological albumin. Animal studies have revealed little relevance in single-dose studies; no signs of acute toxicity are observed and theses studies do not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity studies are impracticable, due to the development of antibodies to heterologous protein in animal models. Human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.

In addition, results from tests on cell culture media containing Human Albumin Solution do not indicate toxicity for gametes/embryos during shelf life. Results from these studies have been summarised in the Quality Part under the Stability reports.

**Local tolerance**

The route of exposure to the ancillary product is different from its conventional application. Human Albumin Solution L/A 25% is used to restore and maintain circulating blood volume when needed, and when the use of a colloid is appropriate. The solution needs to be injected intravenously with an infusion rate not exceeding 1-2 mL/minute. The route of exposure to Human Albumin Solution L/A 25% when incorporated in FertiPro N.V. HSA-containing media is different. Most of the media comes only in direct contact with human gametes / embryos.

Only two components come into direct contact with the mucosal membrane of the uterus during embryo transfer or intra-uterine injection of semen. Local tolerance potential for both media was evaluated according to EN ISO 10993-1 (MEDDEV guidance 2.1/3 rev 2, July 2001). Both media meet requirements of the ISO 10993-10 guidelines.

## 2.3.1. Discussion and conclusion on the non-clinical documentation

No risks for human safety have been detected for the proposed use of this product. The applicant has adequately described the pharmacodynamic applications of use of human serum albumin and for its incorporation as a medical device in FertiPro N.V. HSA-containing ART media.

A useful discussion of the pharmacokinetics of FertiPro N.V. HSA-containing ART media has been provided. With the exception of two media which are used during embryo transfer or intra-uterine injection of semen, FertiPro N.V. HSA-containing ART media are not intended to come into contact with the user or patient. Systemic exposure of the patient or user to human serum albumin is not envisaged and so no non-clinical concerns have been raised.

No concerns are raised for single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity or reproductive and developmental toxicity. For Human Albumin Solution L/A 25%, the route of exposure of the ancillary product is different from its conventional application. The route of exposure to Human Albumin Solution L/A 25% when incorporated in FertiPro N.V. HSA-containing media comes only in direct contact with human gametes / embryos. Only two media come into direct contact during embryo transfer or intra-uterine injection of semen, both of which have been examined for irritancy and sensitising potential in line with EN ISO 10993 guidelines. No irritancy or sensitisation concerns have been raised.

It is confirmed that DEKRA Certification B.V., The Netherlands is a Notified Body that appears on the NANDO website as NB 0344 and is designated to carry out conformity assessments of medical devices according to EU Directive 93/42/EEC, as amended. The Notified Body has submitted a report verifying the usefulness of human serum albumin as part of the medical device,

The use of Human Serum Albumin in IVF products is already well-established and some are already licensed and on the EU market. The currently proposed Human Serum Albumin is obtained from Talecris BioTherapeutics and uses an EMA-certified PMF.

There are no objections from a non-clinical point of view to acceptance of the currently proposed medical device, FertiPro N.V. HSA-containing media.

## *2.4. Clinical evaluation*

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

The Culture media is intended for use in assisted reproductive procedures which include gamete and embryo manipulation and is a protein supplement for culture medium. The HSA has an ancillary effect, with the purpose to assist the function of the medical device.

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. 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.

HSA is used as a protein supplement in the medical device, 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. The Applicant states that there are several arguments to support that the Culture media supplemented with HSA is beneficial when culturing human embryos and that its use has been shown to increase pregnancy outcome.

The media composition differs between the different solutions within the Culture media system, e.g. regarding amino acids, buffer system and antibiotics. The Applicant lists 13 different products that have as intended purposes media for culturing of gametes and embryos, preparation of gametes (sperms and oocytes) before IVF, freezing and thawing embryos, and others. All these products are supplemented with HSA at the production site. The particular composition has been based on the latest scientific research regarding reproductive physiology. HSA is supplemented to these media to exert the claimed functions stated above. From the review process and data submitted, the links between the scientific literature and composition of the media could be verified.

It is recognized by the applicant that the use of HSA has disadvantages by carrying some risk of disease transmission and contamination. 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 Culture media for assisted reproductive procedures 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. Compared to older versions of media, the current media have more optimized amino acid and vitamin compositions and the different solutions all have the same ionic backbone which gives similar pH and osmolality in the different media.

The safety and effect or usefulness of HSA-solution are assessed by review and evaluation of available published data for the Culture media for assisted reproductive procedures. Data from the studies have also been submitted. From the review reports and data submitted, the links between the scientific literature and the claimed attributes of HSA could be verified.

### 2.4.2. Clinical safety of the medical device

The major 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 risk for transmission of viral/prion related diseases is considered by the Applicant to be extremely remote due to the effective donor screening, selection

and a pasteurization procedure during the HSA manufacturing process and the small (<20µl) amount of HSA to which the patient is exposed during embryo transfer.

### 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 evidence provided by the medical device manufacturer, together sufficiently demonstrated the usefulness of HSA added to the ART media. Further, the Medical Device Manufacturer 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 further submissions from the manufacturer detailing a log reduction in viral particles during the manufacturing process. The clinical benefit-risk balance for this product is considered to be positive and the application could be approvable.

### 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 by both the medical device manufacturer and Notified Body on albumin's physiological roles and, in addition, the medical device manufacturer submitted published literature 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 Medical Device Manufacturer 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 is considered to be low but not non-existent. In this regard, the product labelling should contain information outlining these risks.

Overall the clinical benefit-risk balance for this product is considered to be positive and the application could be 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**

Satisfactory quality and safety has been demonstrated for the Albumin before incorporation into the medical device. Manufacture and control of the albumin has been adequately described. All questions raised have also been satisfactorily addressed.

With regards to albumin after incorporation, the question regarding the method validation for the MEA test has now been satisfactorily responded to and all issues have now been resolved.

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

## *2.6. Recommendation*

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality and safety including the benefit risk profile of Human Albumin Solution used as ancillary medicinal substance(s) in the FertiPro N.V. HSA-containing ART media was favourable and therefore granted a positive opinion in the consultation procedure.