EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Human Albumin

Date: November 2024

Unit: Technical Assessment Unit

Assessment report

(Human Albumin Grifols)

Administrative information:

Invented name of the medicinal product:	Human Albumin Grifols
INN (or common name) of the active substance(s):	Human albumin
Marketing Authorization holder	Instituto Grifols, S.A., Can Guash 2. Pol. Ind. Levante, 08150 Parets del Valles, Barcelona spain-SPAIN
Applied Indication(s):	Human Albumin Grifols is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate. Human Albumin Grifols can be used for all age groups
Pharmaceutical form(s) and strength(s):	Solution for infusion, the following strengths will be registered: Human Albumin Grifols 2gm/10ml Human Albumin Grifols 10gm/50ml Human Albumin Grifols 20gm/100ml Human Albumin Grifols 5gm/100ml Human Albumin Grifols 12.5gm/250ml Human Albumin Grifols 25gm/50ml
Route of administration	intravenous

List of abbreviations

API active pharmaceutical ingredient
EU European union

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 2.1.2023 after providing all the required documents according to the Checklist for documents of new biological products registration file.
- Full CTD along with detailed SOPs were provided.

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1. General introduction about the product including brief description of the AI, its mode of action and indications

- the Albumin (Human) is a native albumin, which is a normal constituent of human Plasma.
- Human albumin active ingredient is obtained from human plasma following a fractionation process. From this purification process, the isolated active ingredient is not obtained but the final product is obtained directly. Albumin is a protein constituted by one peptide chain. It has a compact internal structure, firmly maintained by 17 disulfide bonds. It has 584 residues of amino acids, abundant in aspartic acid, glutamic acid and lysine which determine the polarity of the molecule, 6 residues of methionine and one residue of tryptophan.

About the product

- Human albumin is a little and asymmetric protein with an approximate molecular weight of 66300.

Albumin is a very soluble protein: solutions with 30% of albumin can be prepared.
This high solubility is surely related to the large number of ionizable groups that albumin contains. Since the number of carboxy groups is higher than the number of basic groups, the isoelectric point is lower than 7.
The ultraviolet absorption spectrum of albumin shows a maximum at 279 nm and a minimum at 225 nm..

2. **Quality aspects:**

2.1 Introduction

2.2 Drug Substance (Active ingredient)

- **General information**

- Recommended International Nonproprietary Name (INN): Human albumin Compendial name: Ph. Eur.: Human Albumin Solution USP: Albumin (Human) Chemical name(s): Not Applicable Other non-proprietary name(s): Not Applicable Chemical Abstracts Service (CAS) registry number: 9048-49-1Enoxaparin Sodium consists of a complex set of oligosaccharides that have not yet been completely characterized. The colour of concentrated albumin solutions can range from yellow to reddish brown. This coloration is due to the presence of coloured substances as bilirubin and hematin

Manufacture, process controls and characterization:

Manufacturer:

-Instituto Grifols, S.A. (IG), c/Can Guasch, 2, Pol. Ind. Levante, Parets del Vallès, 08150 Barcelona, Spain, is the responsible for the whole manufacturing process, i.e. from plasma starting material through to the labelling, packaging, quality control testing and batch release of the finished product.

-As an alternative manufacturer, fraction V starting material is processed from Source Plasma at Grifols Biologicals LLC. (GB), 5555 Valley Boulevard, Los Angeles, CA 90032 USA and transferred to Instituto Grifols, S.A. for further manufacture of HADP.

-The alternate secondary packaging site for the finished product is located at Grifols Worldwide Operations LTD. (GWWO), Grange Castle Business Park, Grange Castle, Clondalkin, Dublin 22, Ireland

Description of Manufacturing Process and Process Controls

- Human albumin is manufactured in three steps (purification, production and fractionation) starting from human albumin API.
- The description of each stage in manufacturing process of human albumin drug substance, flow chart, quantity of used material, operating parameter, in process control and the percentage yield had been submitted in the file
- The flow chart for each stage represent the in process control and typical yield ranges is also illustrated in the file.

Control of Materials

-Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

-All raw materials are sourced from qualified suppliers. Raw materials are received, identified, tested and released according to written Standard Operating Procedures (SOPs) as required by cGMP.

-Materials used in the manufacture of drug substance are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.

Controls of Critical Steps and Intermediates

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

Process Validation

-The human albumin active substance manufacturing process has been validated adequately.
- Tests results of critical quality attribute and results for critical parameter attribute in each stage of human albumin drug substance manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

Manufacturing Process Development.

- Instituto Grifols, S.A. conducted a development study of the production process for Human Albumin Grifols.
- **Characterization**

  Instituto Grifols, S.A. carried out a biochemical characterisation of Fraction V from GB compared with Fraction V obtained at Instituto Grifols,The results of the analyses performed do not show significant differences between the Fr V batches processed at GB and the Fr V batches processed at Instituto Grifols. Both fractions can be considered equivalent.
- **Specification**

The release specification for the active substance comprises tests for physical characters, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes.
The specification has been prepared in line with the requirements of requirements of European Pharmacopoeia monograph

- **Analytical Procedures**

  All analytical procedures either pharmacopeia or in house developed were described in the submitted MA file.
- **Batch analysis**

  Commercial batches representing process validation analyses data were submitted and their results comply with specification sheet and defined acceptance criteria.
- **Reference Standards or Materials**

  Information regarding the reference standards used is sufficient. With respect to method validation, sufficient validation data for methods have been provided.

Container closure system

- The packaging material in contact with the product consists of Type II glass vials/bottles and chlorobutyl stoppers which comply with the specifications of the European Pharmacopoeia
- **Stability of drug substance**

Active substance: -Double sterile bulk: ≤ 72 hours -Fr V paste: 2 years Approved Storage Conditions: Active substance: Double sterile bulk: at 25±2 ºC Fr V paste: ≤ -20ºC

2.3 Drug product:

-Description and Composition of the Drug Product:

Active biological component: Human Albumin Drug Product (HADP) is a sterile solution of human albumin obtained by fractionation according to a Cohn's based procedure with cold ethanol from pooled human plasma

- Pharmaceutical Development

Components of drug product

HADP is a sterile solution of albumin obtained according to the modified method of Cohn from a plasma pool. The product is pasteurised (60 ºC, 10 h). The excipients used are: sodium. chloride which acts as isotonic agent, sodium caprylate and sodium N-acetyltryptophanate which are added as stabilisers. Sodium caprylate is a good stabiliser against heat effects when used at adequate concentration. Human Albumin has been extensively characterized, showing a high degree of purity, and maintaining its functional properties.

- Formulation Development

The composition of the drug product was selected to match exactly the formulation of the reference products. No own formulation development was performed but followed the reference product formulation.

- Physicochemical and Biological Properties

Instituto Grifols, S.A. carried out characterization studies in order to observe different characteristics of HADP to know about it adequately.

- Manufacturing Process Development

Instituto Grifols, S.A. conducted a development study of the production process for Human Albumin Grifols.

- Microbiological Attributes

-API is controlled with Microbial limits to meet the EU requirement

- Compatibility

Not applicable

Manufacture of the drug product:

Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer:

-Instituto Grifols, S.A. (IG), c/Can Guasch, 2, Pol. Ind. Levante, Parets del Vallès, 08150 Barcelona, Spain, is the responsible for the whole manufacturing process, i.e. from plasma starting material through to the labelling, packaging, quality control testing and batch release of the finished product.

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- Control of critical steps and intermediates

The critical steps of the human albumin drug product manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- Process validation and / or evaluation

-A prospective Process validation data protocol is provided in the file includes Evaluation of results of product analysis for three commercial batches .

-The results of all production steps are valid .

-Media fill protocol for lyophilized hormone department is provided in the file and the results were satisfactory.

- **Product specification:**

-The specifications for human albumin are established based on the current EU monograph for human albumin

-The specifications include physical characters, general tests, tests for identity, tests for puri, activity, quantity, tests for contaminants.

- Justification of the drug product specifications at the release and during stability studies are provided.

- (Compendial excipients) Sodium chloride, sodium caprylate and sodium N-acetyl-DLtryptophan comply with the corresponding European Pharmacopoeia monographs. Certificates of analyses are provided.

-These components are controlled and tested to the standards appropriate for their intended use and function.

-no excipients of human or animal origin are used in the drug product production.

- **Reference Standards or Materials.**

Primary reference standards and In-house working reference material are used in performing the relaease and stability testing of human albumin.

- **Container closure system**

The packaging material in contact with the product consists of Type II glass vials/bottles and chlorobutyl stoppers which comply with the specifications of the European Pharmacopoeia

Stability of the drug product

Approved shelf life for Finished product: 3 years After first opening, the product should be used immediately. Approved storage conditions: Do not store above 30 ºC. Do not freeze. -Keep the bottle in the outer carton in order to protect from light. -Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipient

3. Non –clinical aspect and 4.<u>Clinical aspects</u>

Human Albumin Drug Product (HADP) (5%, 20% and 25%) (from Instituto Grifols, S.A.) was first authorized in Europe, in Spain, since 23 September 1968. In the USA it was authorized since August 1978 (HADP from Grifols Biologicals, LLC).

The proposed name for the registration of Human Albumin 5% and 20% (Manufactured by Instituto Grifols) in Egypt is Human Albumin Grifols 50 g/l and 200 g/l because the Human

Albumin manufactured by Grifols Biologicals (partner company in the USA) is registered in Egypt under Albutein trade name.

As the Albumin (Human) is a native albumin, which is a normal constituent of human plasma to be used at physiological levels and according to the EMEA guideline EMA/CHMP/BPWP/494462/2011 rev.3, there is no need for submission of new pre-clinical and clinical studies for evaluation as this product is already found in the market since September 1968

Benefit/risk conclusion

- **In conclusion the overall benefit/risk of human albumin is favourable in the following:**

restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate. Human Albumin Grifols can be used for all age groups

6. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.