Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Doc. Ref.: CMDh/220/2006, Rev3
October 2016

Type IB group of variations
FVAR

Gamunex 10%
Human normal immunoglobulin

DE/H/0473/IB/73/G

eCTD 0140

Marketing Autorisation Holder: Grifols

Date: 12.08.2022

Variation Procedure Start Date	16.06.2022
Day 20 Variation Assessment Report	06.07.2022
Day 27 Deadline for Comments by CMS	13.07.2022
Day 28 clock stop	14.07.2022
Re-Start	
New Day 0 and FVAR	12.08.2022
New Day 20	01.09.2022
New Day 27 Deadline for Comments by CMS	**08.09.2022**
New Day 30 EOP	11.09.2022

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Gamunex 10%
Name of the active substance (INN, common name):	immune globulin intravenous (human)
Pharmaco-therapeutic group (ATC code)	J06BA02
Pharmaceutical form(s) and strength(s)	solution for infusion, 10%, 100 mg/ml

Procedure number	DE/H/473/001/IB/073/G
Member States concerned	AT, BE, CY, CZ, DK, EL, FI, HU, IE, LU, NL, PL, PT, SE, UK, ES, IT, SK, NO

RMS contact person	Name: [redacted]
Names of the assessors	**Quality:** Dr. [redacted] **Statistics:** [redacted] **Nonclinical: n/a** **Clinical:** [redacted] **RMP:** [redacted]

Nature of change/s requested	**Measles indication in SmPC and PIL and new specification parameter**

Active Substance Master File (ASMF) Assessment Report/s	N/A

I. RECOMMENDATION

Based on the review of the documentation the RMS considers that the group of variations for Gamunex 10%, for the proposed adaption of SmPC and PIL to the revised version of the "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 rev. 6)" including measles pre-/post exposure prophylaxis and addition of minimum measles antibody potency specification, is approvable as satisfactory responses have been given to questions posed in Section V, see Section VI.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

This **Variation Procedure DE/H/473/IB/73/G** encompasses changes to the:

- adaption of SmPC and PIL to the revised version of the "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 rev. 6) including measles pre-/post exposure prophylaxis
- Addition of minimum measles antibody potency specification
- change of the product name in the Slovak Republic

Type IB, C.1.z: Change(s) in the SmPC, labelling or package leaflet of human medicinal products in order to adapt to a recommendation of a competent authority

Grifols wishes to adapt the Gamunex Product Information to the revised version of the "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) EMA/CHMP/BPWP/94038/2007 rev. 6)" that came into effect on 1 January 2022, by filing a type IB variation according to article 5 of Commission Regulation (EC) No 1234/2008. Please note that this also includes the optional indication "measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised". The complete SmPC and PIL have been revised accordingly. The labelling is not affected by this change.

As committed during the MRP renewal procedure R/02, this revision of the product information also covers changes to the SmPC requested by the [redacted]. The revision of the product information also includes some minor adjustments to the latest version of the QRD template (version 4.2, 04/2021). The Risk Management Plan, which has been amended.

Type IB, B.II.d.1: Change in the specification parameters and/or limits of the finished product
c)Addition of a new specification parameter to the specification with its corresponding test method

According to the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (Rev. 4) a minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard must be met and added to the product specification in order to claim the indication on measles pre-/post exposure prophylaxis.

Details on the new analytical method for determination of measles antibody potency and the corresponding validation data are presented in module 3.2.P.5.2 and 3.2.P.5.3, respectively.

Type IB, A.2: Change in the (invented) name of the medicinal product
b) for nationally authorised products

We take the opportunity to change the product name in the Slovak Republic from "Gamunex 10% 100 mg/ml infúzny roztok" to "Gamunex 100 mg/ml infúzny roztok" by deleting the suffix "10%" from the invented name. The rationale for this change is to allow us to develop combined packaging material for Czech Republic and Slovak Republic. Please note that despite this change is affecting Slovak Republic only, according to Q2.2. of the CMDh Q&A document for Variations (CMDh/132/2009, Rev.57) it is "necessary to submit variation applications to all CMS even if they are not concerned by the specific change (e.g. change in the address of the MAH in only one CMS)".

Assessors comment: The applicant changes the product name in the Slovak Republic. Therefore, the Slovakian colleague is kindly asked to indicate if the name change is acceptable for the Slovak Republic.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

3.2.P DRUG PRODUCT

[redacted]

[redacted]

3.2.P.5.2 Analytical Procedures

[redacted]

[redacted]

3.2.P.5.3 Validation of Analytical Procedures

[redacted]

according to IG_MA-001064 (ver. 1.0) which is a direct transfer of the GT' s procedure to IG' s laboratories.
The determination of the titer of neutralizing anti-measles antibodies by means of a seroneutralization test in IGIV-C 10% samples, is performed in GT according to CS- 000BF-034 (ver. 29.0) using the Biological Working Reference (BWR) lot CNC134 at 10% protein concentration as a standard. BWR lot CNC142 is used as an in-house control. Both BWRs have been standardized against CBER/FDA Reference Immune Globulin Serum for Polio and Measles lot 176 and a correction factor is obtained and reported in the respective certificates of analysis. The method of analysis IG_MA-001064 (ver. 1.0) describes the use of BWR lot CNC134 at 10% protein concentration as the standard. The IGIV 2° ST lot 070519 is used as control and has been standardized against 10% BWR lot CNC134 (IG_IEST-000827).

In the interest of evaluating and comparing the results obtained through each procedure, the titer of neutralizing anti-measles antibodies of a sample for 10 lots of IGIV-C 10% is determined by the following formula:

$$\text{Ratio} = \frac{\text{sample } TCID_{50}}{\text{reference } TCID_{50}} \text{ x CBER/FDA lot 176 correction factor}$$

[redacted]

TABLE 1

[redacted]

[redacted]

[redacted]






[redacted]

[redacted]

[redacted]

Assessors comment:

[redacted]

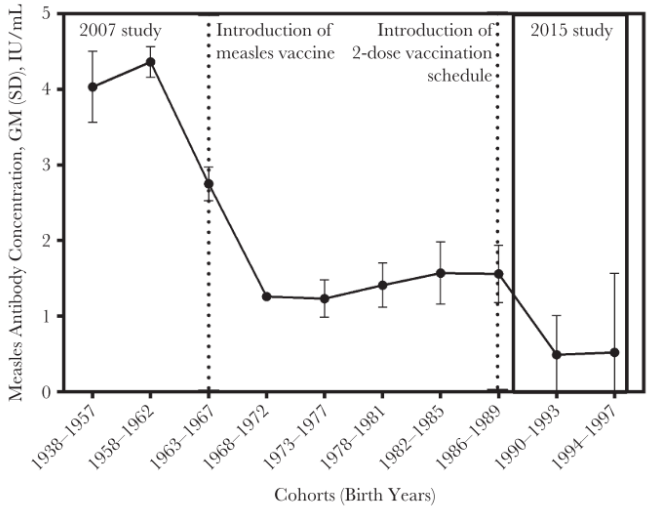
III.2 Non clinical aspects

N/A

III.3 Clinical aspects

Historical background:
The rationale to the changes in the CoreSPC for IVIG (EMA/CHMP/BPWP/94038/2007 Rev. 6; effective as of 01.01.2022) and the IVIG Guideline (EMA/CHMP/BPWP/94033/2007 rev. 4) to include the measles prophylaxis indication were four-fold:

1) The decline of anti-measles antibody titres in plasma donors since the introduction of measles vaccination combined with the fact that revaccination of plasma donors did not sustainably increase anti-measles antibody titres



Modrof et al The Journal of Infectious Diseases® 2017; 216:977–80 Measles Virus Neutralizing Antibodies in Intravenous Immunoglobulins: Is an Increase by Revaccination of Plasma Donors Possible?

2) The increase in measles clusters in Europe both pre-and at the beginning of the COVID pandemic From the Statement by the Measles & Rubella Initiative: American Red Cross, U.S. CDC, UNICEF, UN Foundation and WHO (14 April 2020):
As COVID-19 continues to spread globally, over 117 million children in 37 countries may miss out on receiving life-saving measles vaccine. Measles immunization campaigns in 24 countries have already been delayed; more will be postponed.

3) The US Pharmacopoeia requires anti-measles antibody titres in IVIG products to be above a certain threshold as part of the batch release criteria (0.36 x CBER176). The FDA provided dosing recommendations based on PK modelling (a 400 mg/kg dose of IVIG should provide patients with anti-measles antibody titers of at least 0.24 IU/ml for up to 2 weeks) and the WHO 3rd International Standard Reference serum the level of measles neutralizing antibody that corresponds with clinical protection is >0.12 IU/mL

4) The Eur Pharmacopoeia does **not** require anti-measles antibody titres in IVIG products as batch release criteria. Thus, it could not be guaranteed that batches released in the EU would have a sufficiently protective titre. In addition, different EU member states had up to 10x lower dosing recommendations than those proposed by the FDA.

To address these issues the IVIG coreSPC and IVIG GL were updated to include the following:

Core SPC

- Section 2.

<Minimum content anti-measles IgG is {x} IU/mL>

- Section 4.1.

<Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post exposure prophylaxis and active immunisation.>

- Section 4.2.

<Measles pre-/post exposure prophylaxis>

Post-exposure prophylaxis

If a susceptible patient has been exposed to measles, a dose of 0.4 g/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/mL of measles antibodies for at least 2 weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 0.4 g/kg possibly to be repeated once after 2 weeks may be necessary to maintain the serum level > 240 mIU/mL.

If a PID/SID patient has been exposed to measles and regularly receives IVIg infusions, it should be considered to administer an extra dose of IVIg as soon as possible and within 6 days of exposure. A dose of 0.4 g/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least 2 weeks.

Pre-exposure prophylaxis

If a PID/SID patient is at risk of future measles exposure and receives an IVIg maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to 0.53 g/kg. This should provide a serum level of >240 mIU/mL of measles antibodies for at least 22 days after infusion.

(The table in 4.2 was updated accordingly)

- Section 5.2.

[Measles pre-/post exposure prophylaxis] (see references)

No clinical studies have been performed in susceptible patients regarding Measles pre-/post exposure prophylaxis.

<Product name> meets the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard. The dosing is based on pharmacokinetic calculations, which take body weight, blood volume and half-life of immunoglobulins into consideration. These calculations predict a:

▪ Serum titre at 13.5 days = 270 mIU/mL (dose: 0.4 g/kg) This provides a safety margin more than double that of the WHO protective titre of 120 mIU/mL

▪ Serum titre at 22 days (t1/2) = 180 mIU/mL (dose: 0.4 g/kg)

▪ Serum titre at 22 days (t1/2) = 238.5 mIU/mL (dose: 0.53 g/kg –pre-exposure prophylaxis)

IVIG Guideline

- Section 5.3.4. (new products) Measles pre-/post-exposure prophylaxis

If the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard is met and added to the product specification, the indication “measles pre-/post exposure prophylaxis” as specified in the core SmPC could be added to the product information (FDA, 2018).

- Section 6.4 (changed products)

Should the indication “measles pre-/post-exposure prophylaxis” be sought, the requirements for anti-measles antibody titre threshold would be the same as for the parent product (see 5.3.4)

III.4 Product information

Module 1.3:
The company has submitted the Product Information for Gamunex according to Guideline on core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 6) and according to comments from the [redacted]
A clean and highlighted (track changes) version were provided in Module 1.3.
Another highlighted version which includes additional comments for justification of individual changes was provided as an attachment to the common eAF and also in the working documents (as word file).

Name of the human medicinal product in Slovakia: Gamunex

Assessor's comment:
The submitted SPC encompasses the coreSPC changes mentioned above regarding the new indication *Measles pre-/post exposure prophylaxis.* Furthermore, changes as requested by [redacted], QRD adaptions and some minor editorial changes have been implemented. The justifications for each change are acknowledged.

The PIL has been adapted accordingly.

The labelling is unchanged.

The documents are approvable.

III.5 Risk Management Plan

The Risk Management Plan, which has been amended with respect to the new measles indication.

Assessor's comment:
The RMP version 5.0 was updated to mirror the new indication *Measles pre-/post exposure prophylaxis* in line with the latest version of the IVIg core SmPC. In addition, information on clinical study and post-marketing data was updated with regard to the new data lock point (DLP, 31 May 2021).

The safety concerns remained unchanged.

For future RMP updates, the track change version submitted should be based on the most recent document approved. In this case, both changes leading the RMP version 4.1 and version 5.0 were included in the provided document.
Changes in the RMP are acceptable.

IV. OVERALL CONCLUSION

The requested changes to the SmPC, PIL and RMP are approvable and do not alter the overall benefit-risk profile of Gamunex.

V. REQUEST FOR SUPPLEMENTARY INFORMATION

V.1 Major objections

None

V.2 Other concerns

V.2.1 Quality aspects

[redacted]

< **V.2.1.2 Medicinal Product**>

N/A

<V.2.2 Non clinical aspects>

N/A

<V.2.3 Clinical efficacy>

N/A

<V.2.4 Clinical safety>

N/A

V.2.5 Product information

See also separate document with comments from [redacted]

Summary of Product Characteristics
Section 2
The [redacted] proposes that the statement regarding sodium content should be removed from section 2 as it is also included in section 4.4.

Package Leaflet and User Testing
Section 1
The [redacted] proposes the following revisions of the PL-text to increase readability and make the indication easier to understand (proposed deletions are highlighted by ~~strikethrough~~ and proposed additions are in ***bold Italics***):

Treatment of susceptible adults, children and adolescents (0-18 years) ***who have been exposed to measles or are at risk of measles exposure and*** in whom active vaccination against measles is not indicated or not advised ~~and who are at risk of future measles exposure or have been exposed to measles~~.

Section 2
The [redacted] questions the usefulness of including specific infusion rates in section 2 of the PL as the product is always administered by health care professionals. Inclusion of clinical information in the PL may impair readability. The applicant is asked to motivate or delete the inclusion of the infusion rates in section 2 of the PL.

V.2.6. Risk Management Plan

None.

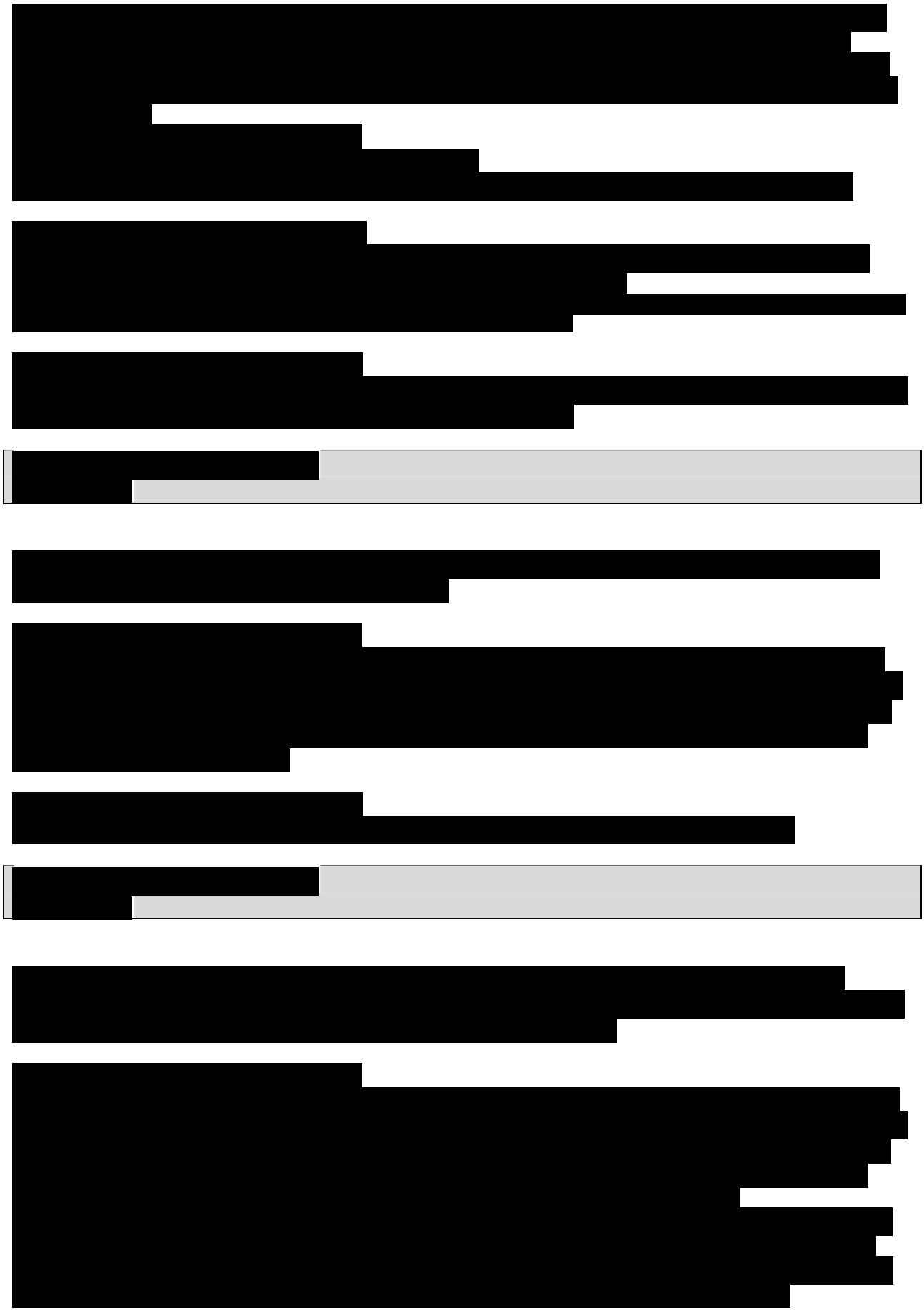
VI. EVALUATION OF RESPONSES

V.2 OTHER CONCERNS

V.2.1 QUALITY ASPECTS

1) The standard references used to determine the neutralizing antibodies against measles virus and the

[redacted]



[redacted]

[redacted]

V.2.5 Product information
See also separate document with comments from [redacted].

Summary of the Applicant´s Response:
Comments indicated by [redacted] in the Gamunex product information file (SmPC and PIL) have been considered, with the following exceptions/changes:

1. SmPC, section 2.2, Excipient(s) with known effect: Because of comments received from [redacted] the redundant paragraph on "Excipient(s) with known effect" was deleted. The information is still included in section 4.4.
2. SmPC, section 4.2, Posology: In contrast to the text of the core SmPC, the correct spelling of "body weight" is two words. Thus, this was not changed
3. SmPC, section 4.4, Sodium content: The wording of the information concerning sodium content in section 4.4 of the SmPC was not changed as it is in agreement with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) and the reading comprehension doesn't seem to be improved by the proposed wording.
4. SmPC, section 4.6, Breast-feeding: The sentence according to core SmPC is: "The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to breast-feeding mothers." It refers to the lack of studies in pregnancy but draws conclusions about the use of the medicinal product in breast-feeding mothers. To resolve this inconsistency, "human pregnancy" was replaced by "breast-feeding mothers" in the first part of the sentence.
5. SmPC, section 6.2: This paragraph is not verbatim according to the core SmPC, because compatibility studies were performed with Gamunex as described in section 6.6 of the Gamunex SmPC.

Assessment of the Applicant's response
Ad 1 Point solved
Ad 2 Agreed
Ad 3 Accepted
Ad 4 This is actually a more logical wording than the coreSPC and therefore is acceptable
Ad 5 Accepted

Summary of Product Characteristics
Section 2
The [redacted] proposes that the statement regarding sodium content should be removed from section 2 as it is also included in section 4.4.

Summary of the Applicant´s Response:
The statement on sodium content was removed from section 2 and kept in section 4.4.
The same change was requested by [redacted]

Assessment of the Applicant's response
Point solved

Package Leaflet and User Testing
Section 1
The MPA proposes the following revisions of the PL-text to increase readability and make the indication easier to understand (proposed deletions are highlighted by strikethrough and proposed additions are in ***bold Italics***):
Treatment of susceptible adults, children and adolescents (0-18 years) ***who have been exposed to measles or are at risk of measles exposure and*** in whom active vaccination against measles is not indicated or not ~~advised and who are at risk of future measles exposure or have been exposed to measles.~~

Summary of the Applicant´s Response:
Grifols agrees to the proposal of [redacted] and has changed the paragraph in the package leaflet accordingly.

Assessment of the Applicant's response
Accepted

Package Leaflet and User Testing
Section 2
The [redacted] questions the usefulness of including specific infusion rates in section 2 of the PL as the product is always administered by health care professionals. Inclusion of clinical information in the PL may impair readability. The applicant is asked to motivate or delete the inclusion of the infusion rates in section 2 of the PL.

Summary of the Applicant´s Response:
The information on specific infusion rates has been deleted from section 2 of the package leaflet to improve the readability for the patient. All necessary information on infusion rates can be found in the section intended for healthcare professionals at the end of the leaflet. Therefore, a new reference to that section was included in section 2 of the package leaflet.

Assessment of the Applicant's response
Point solved

Late comment from [redacted]:
SmPC, Section 2: Sodium
This sentence should be moved to section 4.4. Here, in section 2, excipient(s) with known effect should be stated qualitatively and quantitatively (see https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf)

Summary of the Applicant´s Response:
The statement on sodium content was removed from section 2 and kept in section 4.4.
The same change was requested by [redacted].
See links below for all SmPC revisions suggested in Section V.2.5
• 1.3.1 Annotated (highlighted) Product Information
• 1.3.1 Clean Product Information

Assessment of the Applicant's response
Point solved

Assessor's comment

All other changes in the SPC are acceptable.

ANNEX:
PROPOSED CHANGES TO THE <SmPC>, <PL>, <LABELLING>
ANNOTATED WITH THE RMS'S COMMENTS AFTER EACH SECTION