Public Assessment Report

UKPAR

Alphanate, powder for injection

(HUMAN COAGULATION FACTOR VIII, VON WILLEBRAND FACTOR HUMAN)

UK Licence No: PL 12930/0017

INSTITUTO GRIFOLS S.A.
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>3</td>
</tr>
<tr>
<td>Scientific Discussion</td>
<td>5</td>
</tr>
<tr>
<td>Steps Taken for Assessment</td>
<td>16</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>17</td>
</tr>
<tr>
<td>Patient Information Leaflet</td>
<td>18</td>
</tr>
<tr>
<td>Labelling</td>
<td>19</td>
</tr>
</tbody>
</table>
LAY SUMMARY

Alphanate powder for injection
(Human Coagulation Factor VIII, Von Willebrand Factor Human)

This is a summary of the Public Assessment Report (PAR) for Alphanate powder for injection (PL 12930/0017). It explains how Alphanate powder for injection (PL 12930/0017) was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Alphanate powder for injection.

For practical information about using Alphanate powder for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Alphanate 2000 IU and what is it used for?
Alphanate is a clotting factor containing approximately 2000 IU of human coagulation factor VIII and 2400 IU of human von Willebrand factor per vial. Please note that IU stands for international unit, a standard measure of activity.

Alphanate powder for injection is used for the treatment and prevention of bleeding in patients with haemophilia A (congenital factor VIII deficiency) and the treatment and prevention of bleeding (haemorrhage) or surgical bleeding in von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated. Alphanate powder for injection may be used in the management of acquired factor VIII deficiency.

Haemophilia is a sex-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of Factor VIII are increased, thereby enabling a temporary correction of the Factor deficiency and correction of the bleeding tendencies.

How does Alphanate powder for injection work?
When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient’s circulation. Activated Factor VIII (FVIII:C) acts as a cofactor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X. Activated Factor X converts prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

How is Alphanate powder for injection used?
Alphanate powder for injection must be reconstituted as described in the patient information leaflet (PIL). Alphanate must be given by intravenous route. The administration rate should be 3ml/min and never more than 10ml/min to avoid undesirable side effects. Alphanate powder for injection must be injected immediately after reconstitution.

The amount of Alphanate powder for injection to be administered depends on many factors, such as your weight, your clinical status and the type and severity of bleeding. Your doctor will calculate the dose, the frequency and the intervals of administration of Alphanate powder for injection in order to reach the necessary level of factor VIII or von Willebrand factor in your blood.

What benefits of Alphanate powder for injection have been shown in studies?
A pharmacokinetic study in non-bleeding subjects with von Willebrand Disease showed the subjects experienced a shortened mean skin bleeding time one hour post-infusion with Alphanate at 60 VWF:RCo IU/kg. This effect was transient, generally lasting less than 6 hours following
treatment. Infusion also led to a predictable increase in the size of von Willebrand factor multimers which persisted for at least 24 hours.

**What are the possible side effects of Alphanate powder for injection?**
On rare occasions the following side effects may be experienced after the administration of Alphanate powder for injection: itching, local reactions at the injection site; allergic reactions; fever; faster heart beat (tachycardia).
Occasionally an anaphylactic shock may occur. If you observe any of the following symptoms during the injection/perfusion, interrupt the injection/perfusion and contact your doctor immediately: tightness of the chest/feeling unwell; dizziness; slight hypotension (slight drop of blood pressure with dizziness when you are standing); nausea.

There is also a risk of allergic reactions to the components of the product.
First time users of Factor VIII may be affected by the formation of neutralising antibodies of factor VIII (inhibitors).

For a full list of possible side effects, see the package leaflet.

**Why was Alphanate powder for injection approved?**
The MHRA decided that the benefits of Alphanate powder for injection outweigh the risks and recommended its approval.

**What measures are being taken to ensure the safe and effective use of Alphanate powder for injection?**
Suitable safety information has been included in the summary of product characteristics and the package leaflet for Alphanate powder for injection, including the appropriate precautions to be followed by healthcare professionals and patients.
Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Alphanate powder for injection**
The marketing authorisation for Alphanate powder for injection was granted on 28th March 2017.
For more information about treatment with Alphanate powder for injection, read the package leaflet or contact your doctor or pharmacist.
This summary was last updated in May 2017.
The full PAR for Alphanate powder for injection follows this summary.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .................................................. Page 6
Pharmaceutical assessment ............................... Page 8
Non-clinical assessment .................................. Page 13
Clinical assessment ......................................... Page 14
Overall conclusions and risk assessment .......... Page 15
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Instituto Grifols S.A. a marketing authorisation for the medicinal product Alphanate powder for injection (PL 12930/0017). The product is a prescription-only medicine (POM) indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This product may be used in the management of acquired factor VIII deficiency. Alphanate powder for injection is also indicated in the prevention and treatment of haemorrhage or surgical bleeding in patients with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

This application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, as a line extension application. The currently approved presentations are Alphanate 250 IU, Alphanate 500 IU, Alphanate 1000 IU and Alphanate 1500 IU PL 12930/0015 which have been licensed to Instituto Grifols S.A. since 19th February 1985 (strengths 1000 IU & 1500 IU) and 9th June 2000 (strengths 250 IU & 500 IU).

Alphanate powder for injection contains human coagulation factor VIII and human von Willebrand factor which have different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient’s circulation. Activated Factor VIII acts as a cofactor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X. Activated Factor X converts prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of Factor VIII are increased, thereby enabling a temporary correction of the Factor deficiency and correction of the bleeding tendencies.

Administration of von Willebrand factor allows correction of the haemostatic abnormalities exhibited by patients who suffer from von Willebrand factor deficiency (von Willebrand’s disease) at two levels:

- Von Willebrand factor re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium and to the platelet membrane), providing primary haemostasis as shown by the shortening of the bleeding time.

- Von Willebrand factor produces delayed correction of the associated factor VIII deficiency. Administered intravenously von Willebrand factor binds to endogenous factor VIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation. Administration of a FVIII:C containing VWF preparation restores the FVIII:C level to normal immediately after the first infusion.

No non-clinical or clinical studies were conducted, which is acceptable given that reference is made to medicinal products which have been licensed for over 10 years. Alphanate powder for injection shares the same final formulation excipients and primary packaging container closure system as the authorised presentations and is reconstituted with 10 ml water for injections preloaded syringe PL 4447/0016 already in use for 1000 IU and 1500 IU. The manufacturing process and the formulation process of the drug substance are not subject to any change.
The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and release of the product.
QUALITY ASSESSMENT

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION
The last inspection for Grifols Biologicals Inc. (GBI) was satisfactory.

INTRODUCTION
Legal Basis
Alphanate has been authorised in United Kingdom since 10.12.2003.

Instituto Grifols S.A has submitted an application for a line extension of the license of Alphanate powder for injection PL 12930/0015 to introduce a 2000 IU/vial potency to the currently approved presentations (250 IU, 500 IU, 1000 IU and 1500 IU). According to the MAH, this higher potency offers a significant advantage to patients that require a high dose therapy.

Alphanate powder for injection shares the same final formulation excipients and primary packaging container closure system as the authorised presentations and is reconstituted with 10 ml water for injections preloaded syringe PL 4447/0016 already in use for 1000 IU and 1500 IU. For this reason no additional clinical and non-clinical data has been considered necessary to support the new strength of the product and module 4 and 5 and corresponding overviews and summaries are not provided.

No changes have been performed in the specifications of the product.

Use
- Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This product may be used in the management of acquired factor VIII deficiency.
- Prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD) when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

Scientific Advice
Not applicable.

Legal Status
- Subject to medical prescription
- Product on prescription which may be renewed

DRUG SUBSTANCE
As this procedure concerns only the addition of a new strength of 2000 IU for Alphanate powder for injection and given that no changes to the individual components and to the formulation is stated, no data on drug substance are included in dossier and no formal assessment is performed within this extension procedure. Alphanate powder for injection (2000 IU) is equivalent to the already authorised presentations except for FVIII potency which is adjusted in the final steps of production process.
For information on the drug substance and starting materials, please refer to case PL 12930/0015 and to the Grifols PMF (a PMF certificate and PMF AU evaluation report have been included in this submission).

GENERAL INFORMATION
Not applicable.
MANUFACTURE
Not applicable.

CHARACTERISATION
Not applicable.

CONTROL OF DRUG SUBSTANCE
Not applicable.

- Suitability of the BP/Ph Eur monograph (if applicable)
Pharmacopoeial Access to the Data
Comments to the Pharmacopoeial Secretariat

Not applicable.

REFERENCE STANDARDS OR MATERIALS
Not applicable

CONTAINER CLOSURE SYSTEM
Not applicable.

STABILITY
Not applicable.

DRUG PRODUCT

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Active biological component:
The active ingredient of Alphanate powder for injection is human coagulation factor VIII and human von Willebrand factor in combination. The solvent used to reconstitute the product is water for injections. Detailed information of the solvent is enclosed in the license (PL 4447/0016). The description and composition of Alphanate powder for injection is in line with the licensed Alphanate presentations. The information provided by the Company is adequate.

PHARMACEUTICAL DEVELOPMENT
The purification method for Alphanate powder for injection is identical to that of current Alphanate products. Although no major differences in molecular structure or protein functionality were expected in the Alphanate 2000 IU product, a series of tests were performed in order to confirm the integrity and functionality of FVIII and VWF.

Suitable information on the pharmaceutical development of the formulation for Alphanate 2000 is provided. This is acceptable.

MANUFACTURE
Antihaemophilic Factor/von Willebrand Factor Complex (Human), Alphanate (AHF) is manufactured from human plasma. The manufacturing process steps have been sufficiently described. A list of materials and reagents has been provided by the Company. The preparation of the solutions/buffers and reagents added to the product has been sufficiently described and a table listing the types of reagent solutions employed for pH adjustment has been submitted. This is acceptable.
Control of critical steps and intermediates
The Company has provided information on critical steps and intermediates, together with several SOPs.

Process Validation
The MAH has performed process validation to document the production and lyophilisation of three conformance lots of Alphanate 2000 IU. The validation data demonstrated that the manufacturing and lyophilisation of the higher potency assay consistently yields a product that meets the defined specifications. Additionally, all existing licensed final container results are within the specifications established for the 2000 IU presentation. This is satisfactory.

Sterility Validation
The data results of the final bulk and final container Alphanate 2000 IU show the absence of any bacteriostatic or fungistatic activity by the higher potency product. The Applicant has taken into account both aerobic and anaerobic bacteria (as well as fungi). Overall, the sterility test has been successfully validated for the final bulk and final container of Alphanate 2000.

CONTROL OF EXCIPIENTS
No new information on excipients is presented in the dossier of this line extension. Alphanate 2000 shares the same final formulation excipients as the authorised presentations.

CONTROL OF DRUG PRODUCT
A table with the specification limits for all Alphanate presentations, including the new 2000IU presentation, has been provided. The specification limits for the 2000IU presentation are identical in most cases to those of the other licensed presentations

Batch analysis
The batch analysis data demonstrates that the tested batches are consistent and remain within specification limits. This is acceptable.

REFERENCE STANDARDS OR MATERIALS
There is no new information regarding reference standards. The reference standards for all licensed presentations are the same. This is acceptable.

CONTAINER CLOSURE SYSTEM
Alphanate 2000 shares the same primary packaging container closure system as the authorized presentations. It is reconstituted with 10ml water for injections in a preloaded syringe already in use for 1000 IU and 1500 IU. This is acceptable.

STABILITY
Alphanate Antihaemophilic Factor/von Willebrand Factor Complex (Human), Alphanate 2000 IU/vial, is stable for least 36 months when stored at or below 30 °C. In addition to storage at or below 30 °C, stability data was obtained for accelerated stability at 40 °C. Overall, the data looks satisfactory.
The proposed shelf life applied for Alphanate 2000 IU is 36 months, the same as for the other presentations of the product. This is considered acceptable.

APPENDICES
FACILITIES AND EQUIPMENT
Not applicable.
ADVENTITIOUS AGENTS SAFETY EVALUATION
Not applicable.

NOVEL EXCIPIENTS
None.

REGIONAL INFORMATION

PROCESS VALIDATION SCHEME FOR THE DRUG PRODUCT
Not applicable.

MEDICAL DEVICE ISSUES
Not applicable.

TSE ISSUES
Not applicable.

ASSESSOR’S COMMENTS ON MODULE I
NAME AND APPEARANCE (IF APPLICABLE)
Alphanate Powder for Injection 2000 IU

SPC
Overall, the SPC complies with QRD recommendations. The 2000IU presentation has been added to the other presentations in the SPC, as applicable. Furthermore, a link to the Yellow card reporting scheme has been added and the following sentence has been introduced at the end of the SPC (section 6.6, Special precautions for disposal and other handling): ’It is important to use the infusion set provided with the medicine. If medical infusion systems are used, please check the compatibility of the system with the prefilled syringe. Adapters should be used when required to ensure proper administration of the product.’
The a.m. changes are considered acceptable. Overall, the SmPC is satisfactory.

PATIENT INFORMATION LEAFLET
The 2000IU presentation has been added to the PIL, as applicable. Also, a link to the Yellow card reporting scheme has been added and the following sentence has been introduced at the end of the PIL (Section: Instructions for use/handling): ’It is important to use the infusion set provided with the medicine. If medical infusion systems are used, please check the compatibility of the system with the prefilled syringe. Adapters should be used when required to ensure proper administration of the product.’
The a.m. changes are considered acceptable. Overall, the PIL is satisfactory.

LABEL
Labelling is acceptable.

APPLICATION FORM
The application form is acceptable.

ASSESSOR’S OVERALL CONCLUSIONS
Grifols provided a dossier containing relevant information on the quality of the proposed new strength of Alphanate Powder for Injection 2000 IU. Alphanate 2000 IU shares the same final formulation excipients and primary packaging container closure system as the authorised presentations and is reconstituted with 10 ml water for injections preloaded syringe PL 4447/0016 already in use for 1000 IU and 1500 IU. The manufacture and formulation of the
drug substance are not subject to any change. In general, the development of the product has been described adequately:

Specifications for the final product remain either the same as approved for the licensed strengths or they have been increased proportionally. The product specifications cover appropriate parameters for this dosage form. Batch analysis has been performed. The batch analysis results presented show that the finished products meet the specifications proposed.

Stability data from three commercial lots are available for up to 36 months real time. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 36 months for the drug product is considered acceptable.

The PI documentation provided for Module 1 appears adequate and in line with QRD recommendations.

Altogether, the application for Alphanate 2000 IU is approvable.

Date: 10.11.16
NON-CLINICAL ASSESSMENT

No new non-clinical data were submitted and none are required for this type of application.
CLINICAL ASSESSMENT

No new clinical data were submitted and none are required for this type of application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Alphanate powder for injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.

CLINICAL
No new clinical data were submitted and none are required for this type of application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for Alphanate powder for injection.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Alphanate powder for injection is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is therefore considered to be positive.
ALPHANATE POWDER FOR INJECTION

PL 12930/0017

**STEPS TAKEN FOR ASSESSMENT**

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Application on 28(^{\text{th}}) June 2016.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 17(^{\text{th}}) August 2016.</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested information relating to the dossier on 27(^{\text{th}}) January 2017.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests providing further information on the dossier on 21(^{\text{st}}) February 2017.</td>
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<td>5</td>
<td>The application was granted on 28(^{\text{th}}) March 2017.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the SmPCs for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the PILs for products granted Marketing Authorisations at a national level are available on the MHRA website.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton box containing vial with the lyophilisate product, pre-filled syringe with solvent and accessories

1. NAME OF THE MEDICINAL PRODUCT

ALPHANATE®

Human coagulation factor VIII and von Willebrand factor complex, Freeze dried, Ph. Eur.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

High Purity
Solvent Detergent and Heat Treated

The reconstituted product contains nominally 200 IU FVIII/ml, 240 IU VWF/ml; protein (0.3 - 1.0 g/100 ml), arginine, albumin and histidine, once reconstituted with 10 ml of Water for Injections Ph. Eur.

3. LIST OF EXCIPIENTS

The reconstituted product contains nominally 200 IU FVIII/ml, 240 IU VWF/ml; protein (0.3 - 1.0 g/100 ml), arginine, albumin and histidine, once reconstituted with 10 ml of Water for Injections Ph. Eur.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Vial, pre-filled syringe with solvent and accessories

Accessories supplied consist of:
- vial adaptor
- filter
- butterfly needle
- 2 alcohol swabs

2000 IU FVIII / 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C. Do not freeze. Protect from light.
Use immediately

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PL Holder:
Instituto Grifols, S.A.
08150 Pares del Vallès
Barcelona - SPAIN

Distributed by:
Grifols UK Ltd.
Byron House
Cambridge Business Park
Cambridge CB4 0WZ

12. MARKETING AUTHORISATION NUMBER(S)

PL 12930/0017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE PRIMARY PACKAGING</th>
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<tbody>
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<td>Vial label</td>
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1. **NAME OF THE MEDICINAL PRODUCT**

ALPHANATE®

Human coagulation factor VIII and von Willebrand factor complex, Freeze-Dried, Ph. Eur.

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

The reconstituted product contains nominally 200 IU FVIII/ml, 240 IU VWF/ml; protein (0.3 - 1.0 g/100 ml), arginine, albumin and histidine, once reconstituted with 10 ml of Water for Injections Ph. Eur.

3. **LIST OF EXCIPIENTS**

The reconstituted product contains nominally 200 IU FVIII/ml, 240 IU VWF/ml; protein (0.3 - 1.0 g/100 ml), arginine, albumin and histidine, once reconstituted with 10 ml of Water for Injections Ph. Eur.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder for injection

2000 IU FVIII / 10 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use.
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C. Do not freeze. Protect from light.
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<td>PL 12930/0017</td>
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<tr>
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</tr>
<tr>
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</tr>
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