Public Assessment Report

Decentralised Procedure

FINTRIPZOID 0.5 MG CAPSULES, HARD
FINTRIPZOID 1 MG CAPSULES, HARD
FINTRIPZOID 5 MG CAPSULES, HARD

(Tacrolimus)

Procedure No: UK/H/5134/001-3/DC

UK Licence No: PL 37248/0002-4

PERGAMUS PHARMA LIMITED
LAY SUMMARY

On 14 November 2012, Belgium, Bulgaria, Italy, Luxembourg, Romania, Slovenia and the UK agreed to grant Marketing Authorisations to Pergamus Pharma Limited for the medicinal products Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard (PL 37248/0002-4; UK/H/5134/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 28 December 2012. These are Prescription-Only Medicines (POM).

Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard belong to a group of medicines called immunosuppressants. Following your organ transplant (e.g. liver, kidney, heart), your body’s immune system will try to reject the new organ. Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard are used to control your body’s immune response, enabling your body to accept the transplanted organ.

Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard are often used in combination with other medicines that also suppress the immune system. You may also be given Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard for an ongoing rejection of your transplanted liver, kidney, heart or other organ or if any previous treatment you were taking was unable to control this immune response after your transplantation.

No new or unexpected safety concerns arose from these applications and it was judged that the benefits of taking Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard outweigh the risks; therefore Marketing Authorisations were granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Patient Information Leaflet</td>
<td>6</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>7</td>
</tr>
<tr>
<td>Module 5: Scientific discussion during initial procedure</td>
<td>16</td>
</tr>
<tr>
<td>I Introduction</td>
<td></td>
</tr>
<tr>
<td>II About the product</td>
<td></td>
</tr>
<tr>
<td>III Scientific Overview and discussion</td>
<td></td>
</tr>
<tr>
<td>III.1 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>III.2 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>III.3 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>IV Overall Conclusions and benefit-risk assessment</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>26</td>
</tr>
</tbody>
</table>
## Module 1

| Product Name          | Fintripzoid 0.5 mg Capsules, hard  
|                       | Fintripzoid 1 mg Capsules, hard  
|                       | Fintripzoid 5 mg Capsules, hard  
| Type of Application   | Generic, Article 10.1  
| Active Substances     | Tacrolimus (as monohydrate)  
| Form                  | Capsules, hard.  
| Strength              | 0.5 mg, 1 mg and 5 mg.  
| MA Holder             | Pergamus Pharma Limited  
|                       | Suite 23  
|                       | Park Royal House  
|                       | 23 Park Royal Road  
|                       | London  
|                       | NW10 7JH  
| Reference Member State (RMS) | UK  
| Concerned Member States (CMS) | Belgium, Bulgaria, Italy, Luxembourg, Romania, Slovenia  
| Procedure Number      | UK/H/5134/001-3/DC  

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling
The following text is the approved labelling text as agreed during the decentralised procedure. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton for blister

1. NAME OF THE MEDICINAL PRODUCT
Fintripzoid 0.5mg Capsules, hard
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each Fintripzoid 0.5mg hard capsule contains 0.5mg tacrolimus (as monohydrate)

3. LIST OF EXCIPIENTS
Contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS
Capsule, hard
20 capsules
30 capsules
50 capsules
60 capsules
90 capsules
100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION
For oral 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
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS
Store below 25°C. Store in the original package in order to protect from moisture and light.
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**

Pergamus Pharma Limited
Suite 23
Park Royal House
23 Park Royal Road
London
NW10 7JH

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 37248/0002

13. **BATCH NUMBER**

Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

fintripzoid 0.5 mg capsules, hard

Place dispensing label here (on back panel)
READ ENCLOSED LEAFLET (on flaps)
Illustration
Barcode – New Barcode
Carton reference number
Carton size
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Fnitripzoid 0.5mg hard capsules  
Tacrolimus

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Perganuus Pharma Limited  
(logo)

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Batch

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blister

1. NAME OF THE MEDICINAL PRODUCT

Fintripzoid 1mg Capsules, hard
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Fintripzoid 1mg hard capsule contains 1mg tacrolimus (as monohydrate)

3. LIST OF EXCIPIENTS

Contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard
20 capsules
30 capsules
50 capsules
60 capsules
90 capsules
100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral 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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Store in the original package in order to protect from moisture and light.
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

Pergamus Pharma Limited
Suite 23
Park Royal House
23 Park Royal Road
London
NW10 7JH

12. MARKETING AUTHORISATION NUMBER(S)

PL 37248/0003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

fintripzoid 1mg capsules, hard

Place dispensing label here (on back panel)
READ ENCLOSED LEAFLET (on flaps)
Illustration
Barcode – New Barcode
Carton reference number
Carton size
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

Blisters

1. **NAME OF THE MEDICINAL PRODUCT**

   Fintripzoid 1mg Capsules, hard
   Tacrolimus

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Pergamus Pharma Limited  
   (logo)

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Batch

5. **OTHER**
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**
Carton for blister

1. **NAME OF THE MEDICINAL PRODUCT**
   Fintripzoid 5mg hard capsules
   Tacrolimus

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   Each Fintripzoid 5mg hard capsule contains 5mg tacrolimus (as monohydrate)

3. **LIST OF EXCIPIENTS**
   Contains Lactose

4. **PHARMACEUTICAL FORM AND CONTENTS**
   Capsule, hard
   20 capsules
   30 capsules
   50 capsules
   60 capsules
   90 capsules
   100 capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   For oral 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**
   Keep out of the sight and reach of children.

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

8. **EXPIRY DATE**
   EXP

9. **SPECIAL STORAGE CONDITIONS**
Store below 25°C. Store in the original package in order to protect from moisture and light.

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

Pergamus Pharma Limited
Suite 23
Park Royal House
23 Park Royal Road
London
NW10 7JH

12. MARKETING AUTHORISATION NUMBER(S)

PL 37248/0004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

fintripzoid 5mg capsule, hard

Place dispensing label here (on back panel)
READ ENCLOSED LEAFLET (on flaps)
Illustration
Barcode – New Barcode
Carton reference number
Carton size
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister</td>
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</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>Fniprizoid 5mg Capsule, hard Tacrolimus</td>
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<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>Pergamus Pharma Limited (logo)</td>
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</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Batch</td>
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<tr>
<th>5. OTHER</th>
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Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard (PL 37248/0002-4; UK/H/5134/001-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Belgium, Bulgaria, Italy, Luxembourg, Romania and Slovenia as Concerned Member States (CMS). These products are prescription-only medicines (POM).

Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard are indicated for:
- prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
- allograft rejection resistant to treatment with other immunosuppressive medicinal products.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Prograf 0.5 mg, 1 mg and 5 mg Hard Capsules (Astellas Pharma Ltd), which were first authorised in the UK in 1994 (1 mg and 5 mg strength) and 1999 (0.5 mg strength only). The reference products have been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired. The reference products used in the bioequivalence studies were Prograf 0.5 mg Kapseln and Prograf 5mg Hartkapslen (Astellas Pharma GmbH) taken from the German market. It has been confirmed that these products are identical to the equivalent products in the UK (Prograf 0.5 mg and 5 mg Hard Capsules).

Tacrolimus is a calcineurin inhibitor. It is derived from the soil bacterium Streptomyces tsukubaensis and has a macrolide structure. Inhibition of calcineurin in T lymphocytes leads to calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of lymphokine genes. Tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T cell activation and T helper cell dependent B cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

Two bioequivalence studies (single dose) were submitted to support these applications, comparing the test products Fintripzoid 0.5 mg and 5 mg Capsules, hard (Pergamus Pharma Ltd) with the reference products Prograf 0.5 mg Kapseln and Prograf 5 mg Hartkapslen (Astellas Pharma GmbH).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 207) on 14 November 2012. After the subsequent national phase, the licences were granted in the UK on 28 December 2012.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Fintripzoid 0.5 mg Capsules, hard  
|                                                 | Fintripzoid 1 mg Capsules, hard  
|                                                 | Fintripzoid 5 mg Capsules, hard |
| Name(s) of the active substance(s) (INN)        | Tacrolimus (as monohydrate) |
| Pharmacotherapeutic classification (ATC code)   | Immunosuppressants, calcineurin inhibitors, (L04AD02) |
| Pharmaceutical form and strength(s)            | 0.5 mg, 1 mg and 5 mg capsules, hard. |
| Reference numbers for the Mutual Recognition Procedure | UK/H/5134/001-3/DC |
| Reference Member State                         | United Kingdom |
| Concerned Member State                         | Belgium, Bulgaria, Italy, Luxembourg, Romania and Slovenia. |
| Marketing Authorisation Number(s)              | PL 37248/0002-4 |
| Name and address of the authorisation holder   | Pergamus Pharma Limited  
|                                                 | Suite 23  
|                                                 | Park Royal House  
|                                                 | 23 Park Royal Road  
|                                                 | London  
|                                                 | NW10 7JH |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S. Active substance

INN: Tacrolimus
Chemical names: \([3S,4R,5S,8R,9E, 12S18R, 19R, 26aS)\)
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro- 5,19-
dihydroxy-3-[(1E)-2-[(IR,3R,4R) - 4 - hydroxy-3-methoxycyclohexyl]-
1 - methylethenyl]- 14,16-dimethoxy- 4,10,12,18 – tetramethyl-8-(2-
propenyl) -15,19-epoxy-3H-pyrido [2,1-c] [1,4]oxazacyclotricosine-
1,7,- 2O,21 (4H,23H) tetrone monohydrate.

17-allyl- 1,14-dihydroxy- 12-[2-(4-hydroxy-3 methoxycyclohexyl)-
methylvinyl]-23,25- dimethoxy- 13,19,21,27-tetramethyl- 11,28 – dioxa
-4- azatricyclo[22.3.1.0^4,9]octacos-18-ene- 2,3,10,16-tetraone
monohydrate.

\[
\text{Molecular formula: } C_{44}H_{69}NO_{12}H_2O \\
\text{Molecular mass: } 822.05 \text{ g/mol} \\
\text{Appearance: } \text{Tacrolimus is a white to off-white powder.} \\
\text{Solubility: } \text{Tacrolimus is soluble in acetone, chloroform, ethyl acetate and ethanol.} \\
\text{It is insoluble in water, acid buffer and degrades in alkali buffer.}
\]

\text{Tacrolimus is not the subject of a European Pharmacopoeia monograph.}

\text{Synthesis of the active substance from the designated starting materials has been adequately} \\
\text{described and appropriate in-process controls and intermediate specifications are applied.} \\
\text{Satisfactory specification tests are in place for all starting materials and reagents and these are} \\
\text{supported by relevant certificates of analysis.}

\text{An appropriate specification is provided for the active substance. Analytical methods have} \\
\text{been appropriately validated and are satisfactory for ensuring compliance with the relevant} \\
\text{specifications.}

\text{Appropriate proof-of-structure data have been supplied for the active substance. All potential} \\
\text{known impurities have been identified and characterised. Satisfactory Certificates of Analysis} \\
\text{have been provided for all working standards. Batch analysis data are provided and comply} \\
\text{with the proposed specification.}

\text{Suitable specifications have been provided for all packaging used. The primary packaging has} \\
\text{been shown to comply with current guidelines concerning contact with food.}
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**P. Medicinal Product**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, croscarmellose sodium, hypromellose E5, magnesium stearate and black printing ink (consisting of shellac, propylene glycol, black iron oxide and potassium hydroxide). In addition:

- The 0.5 mg strength also contains the capsule shell components gelatin, water, sodium lauryl sulphate, yellow iron oxide (E172) and titanium dioxide (E171).
- The 1 mg strength also contains the capsule shell components gelatin, water, sodium lauryl sulphate and titanium dioxide (E171).
- The 5 mg strength also contains the capsule shell components gelatin, water, sodium lauryl sulphate, red iron oxide (E172) and titanium dioxide (E171).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the colourings black, yellow and red iron oxide, which are controlled to suitable in-house specifications. The black, yellow and red iron oxide colourings are in compliance with current EU Directives concerning the use of colouring agents. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin and lactose monohydrate, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in line with current European guidelines concerning minimising the risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE). The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as those farmed to provide milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate stable, robust, hard capsules containing 0.5 mg, 1 mg or 5 mg tacrolimus (as monohydrate), which could be considered generic medicinal products of Prograf 0.5 mg, 1 mg and 5 mg Hard Capsules (Astellas Pharma Ltd).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.
**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

**Finished Product Specifications**
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
All strengths of the finished product are packaged in polyvinylchloride (PVC)/aluminium/oriented polyamide (OPA)/aluminium blister strips in pack sizes of 20, 30, 50, 60, 90 and 100 capsules.

It has been stated that not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups of the labelling to the relevant regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Store below 25°C. Store in the original package in order to protect from moisture and light.’

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) forms**
The MAA forms are satisfactory.

**Quality Overall Summary**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.
Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of tacrolimus are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Since Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following two bioequivalence studies:

STUDY 1
An open label, randomised, single-dose, two-period, two-sequence, two treatment, crossover study to compare the pharmacokinetics of the test product Fintripzoid 5 mg Capsules, hard (Pergamus Pharma Ltd) versus the reference product Prograf 5 mg Hartkapslen (Astellas Pharma GmbH) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 5 mg capsule administered with 240 ml of water after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 192 hours post dose. The washout period between treatment periods was at least 21 days.

The pharmacokinetic results for tacrolimus are presented below (log-transformed values; geometric least squares mean and 90 % confidence intervals):

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed) Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng / mL)</td>
<td>41.937</td>
<td>36.255</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h / mL)</td>
<td>330.645</td>
<td>331.335</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h / mL)</td>
<td>355.494</td>
<td>354.925</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours.
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity.
C<sub>max</sub> maximum plasma concentration.
STUDY 2
An open label, randomised, single-dose, two-period, two-sequence, two treatment, crossover study to compare the pharmacokinetics of the test product Fintripzoid 0.5 mg Capsules, hard (Pergamus Pharma Ltd) versus the reference product Prograf 0.5 mg Kapseln (Astellas Pharma GmbH) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 0.5 mg capsule administered with 240 ml of water after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 20 days.

The pharmacokinetic results for tacrolimus are presented below (log-transformed values; geometric least squares mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed)</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Least Squares Mean</td>
<td>Test Product-B</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg / mL)</td>
<td>4160.796</td>
<td>3730.274</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-72h&lt;/sub&gt; (pg.h / mL)</td>
<td>28108.315</td>
<td>28551.247</td>
</tr>
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The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for tacrolimus for both strengths (0.5 mg and 5 mg) are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). The Efficacy Working Party of the CHMP recommends that the bioequivalence acceptance criteria for tacrolimus should be [90-111 %] for AUC and [80-125 %] for C<sub>max</sub> (Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics EMA/618604/2008 Rev 2). Therefore the prospectively defined acceptance criteria are acceptable.

The data support the claim that the test products are bioequivalent to the reference products.

Since the 1 mg strength of the product meets the criteria for a biowaiver specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 0.5 mg and 5 mg strength can be extrapolated to the 1 mg strength.
Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the SmPCs and in line with current guidance. The labelling is in line with current guidance.

MAA Forms
The MAA forms are satisfactory.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan has been submitted for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Fintripzoid 0.5 mg, 1 mg and 5 mg Capsules, hard 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 applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of tacrolimus are well-known.

Efficacy
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Fintripzoid 0.5 mg and 5 mg Capsules, hard (Pergamus Pharma Ltd) and the respective reference products Prograf 0.5 mg Kapseln and Prograf 5 mg Hartkapslen (Astellas Pharma GmbH). As the 0.5 mg, 1 mg and 5 mg strengths of the product meet the biowaiver criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 0.5 mg and 5 mg strengths can be extrapolated to the 1 mg strength.

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of tacrolimus is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products and are in line with current guidance.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with tacrolimus is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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