Public Assessment Report

Decentralised Procedure

AZAFALK 50 MG FILM-COATED TABLETS
(Azathioprine)

Procedure No: UK/H/2846/004/DC

UK Licence No: PL 08637/0026

DR FALK PHARMA GMBH
This is a summary of the public assessment report (PAR) for Azafalk 50 mg Film-coated Tablets (PL 08637/0026). It explains how Azafalk 50 mg Film-coated Tablets 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 Azafalk 50 mg Film-coated Tablets.

For practical information about Azafalk 50 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What is Azafalk 50 mg Film-coated Tablets and what is it used for?

Azafalk 50 mg Film-coated Tablets is a ‘hybrid medicine’. This means that Azafalk 50 mg Film-coated Tablets is similar to a ‘reference medicine’ already authorised in the European Union (EU). Azafalk 50 mg Film-coated Tablets is considered to be a hybrid medicinal product to the reference product Imuran 50 mg Tablets.

Azafalk 50 mg Film-coated Tablets contains the active ingredient azathioprine. This medicine is prescribed to treat one of the following conditions:
- to help your body accept an organ transplant
- to control some diseases where your immune system is reacting against your own body.

Azafalk 50 mg Film-coated Tablets can be used alone or in combination with other medicines to treat the following conditions:
- severe rheumatoid arthritis
- severe inflammation of the gut (Crohn’s disease or ulcerative colitis)

Or to treat:
- some disease where your immune system is reacting against your own body (autoimmune diseases) including severe inflammatory diseases of the skin, liver, artery and some blood disorders

How is Azafalk 50 mg Film-coated Tablets used?

This medicine can only be obtained with a prescription. Azafalk 50 mg Film-coated Tablets should be taken during meals with a glass of liquid. The duration of treatment with this medicine is determined by the doctor. The usual first day dose for patients who have had a transplant is up to 5 mg/kg of body weight per day. The usual dose is then 1-4 mg/kg of body weight per day. For other conditions, the usual dose of this medicine is 1-3 mg/kg of body weight per day. Azafalk 50 mg Film-coated Tablets is not recommended for use in children below the age of 18 years.

How do Azafalk 50 mg Film-coated Tablets work?

Azafalk 50 mg Film-coated Tablets belong to a group of medicines called immunosuppressives. Immunosuppressive medicines work by reducing the strength of the immune system.
How has Azafalk 50 mg Film-coated Tablets been studied?

Azafalk 50 mg Film-coated Tablets is a hybrid medicine. Studies in patients have been limited to tests to determine that this medicine is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Azafalk 50 mg Film-coated Tablets?

Azafalk 50 mg Film-coated Tablets is a hybrid medicine and is bioequivalent to the reference medicine. Therefore, the benefits and risks are taken as being the same as those of the reference medicine.

Why is Azafalk 50 mg Film-coated Tablets approved?

It was concluded that, in accordance with EU requirements, Azafalk 50 mg Film-coated Tablets has been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the view was that, as for the reference medicine, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Azafalk 50 mg Film-coated Tablets?

A risk management plan has been developed to ensure that Azafalk 50 mg Film-coated Tablets is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Azafalk 50 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Azafalk 50 mg Film-coated Tablets

Austria, Germany, Lithuania, the Netherlands, Portugal, Slovenia and the United Kingdom agreed to grant a Marketing Authorisation for Azafalk 50 mg Film-coated Tablets at Day 187 of the procedure on 04 April 2014. A Marketing Authorisation was granted in the UK on 02 May 2014.

The full PAR for Azafalk 50 mg Film-coated Tablets follows this summary. For more information about treatment with Azafalk 50 mg Film-coated Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July-2014.
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Module 1
Information about initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Azafalk 50 mg Film-coated Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Hybrid Application, Article 10(3)</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Azathioprine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>50 mg</td>
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</table>
| **MA Holder** | Dr. Falk Pharma GmbH  
Leinenweberstr. 5  
79108 Freiburg  
Germany |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Austria, Germany, Lithuania, the Netherlands, Portugal, Slovenia |
| **Procedure Number** | UK/H/2846/004/DC |
| **Timetable** | Day 187– 04 April 2014 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPC) for products that have been 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 Patient Information Leaflet for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Azafalk® 50mg film-coated tablets
Azathioprine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dr. Falk Pharma GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Azafalk 50mg film-coated tablets
Azathioprine

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 50 mg azathioprine.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20, 30, 50, 60, 90 or 100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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 in the original package in order to protect from light.

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

Medicine should not be disposed of via wastewater or household waste.
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

12. **MARKETING AUTHORISATION NUMBER**

FL08637/0026

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRaille**

Carton: Azafalk 50 mg
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 application for Azafalk 50 mg Film-coated Tablets (PL 08637/0026; UK/H/2846/004/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), Austria, Germany, Lithuania, the Netherlands, Portugal and Slovenia as Concerned Member States (CMS).

This product can only be obtained with a prescription (legal classification POM).

This application was made under the Decentralised Procedure (DCP), according to Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of the reference product, Imuran Tablets (PL 39699/0005). Imuran Tablets was granted a Marketing Authorisation on 03 October 1986 to The Wellcome Foundation Limited (PL 00003/0226). Following a series of change of ownership procedures the Marketing Authorisation was transferred to the current Marketing Authorisation Holder, Aspen Pharma Trading Limited on 05 January 2012 (PL 39699/0005).

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and a methyl nitroimidazole moiety. Azathioprine has cytotoxic and immunosuppressive effects. Azathioprine is metabolised to mercaptopurine and then to thioinosinate which interferes with purine metabolism. The enzyme thiopurine S-methyltransferase (TPMT) deactivates 6-mercaptopurine. Genetic polymorphisms of TPMT can lead to excessive drug toxicity. The most common side-effects of azathioprine are myelosuppression and opportunistic infections in the immunocompromised.

Azafalk 50 mg Film-coated Tablets is indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression). It is also indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic kidney, liver, heart, lung, or pancreas transplants.

Azafalk 50 mg Film-coated Tablets is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and/or procedures which influence the immune response. Therapeutic effect may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.

Azafalk 50 mg Film-coated Tablets is indicated either alone or in combination with corticosteroids and/or other drugs and procedures in severe cases of the following diseases, in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids:

- severe active rheumatoid arthritis that cannot be kept under control by less toxic agents (disease modifying anti-rheumatic drugs, DMARDs)
- severe or moderately severe inflammatory intestinal disease (Crohn’s disease) or ulcerative colitis
- systemic lupus erythematosus
- dermatomyositis and polymyositis
- auto-immune chronic active hepatitis
- polyarteritis nodosa
- auto-immune haemolytic anaemia
- chronic refractory idiopathic thrombocytopenic purpura
No new non-clinical studies were conducted, which is acceptable given that this application was based on being a generic medicinal product of the reference product, which has been licensed for over 10 years.

With the exception of the bioequivalence study comparing the pharmacokinetics of this product with, Imurek 50 mg Tablet (Aspen Europe GmbH), no new clinical studies were conducted. This is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practise (GCP).

The reference product used in the bioequivalence study is Imurek 50 mg Tablets, licensed in Germany to GlaxoSmithKline GmbH. This product is considered to be pharmaceutically equivalent to the UK reference product Imuran 50 mg Tablets.

The RMS 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 batch release of this product.

The RMS and CMS countries considered that this application could be approved at Day 187 of the DCP on 04 April 2014. After a subsequent national phase, a licence was granted in the UK on 02 May 2014.
## ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Azafalk 50 mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other immunosuppressants (L04AX01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>50 mg film-coated tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/2846/004DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>UK</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Austria, Germany, Lithuania, the Netherlands, Portugal, Slovenia</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 08637/0026</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Dr. Falk Pharma GmbH</td>
</tr>
<tr>
<td></td>
<td>Leinenweberstr. 5</td>
</tr>
<tr>
<td></td>
<td>79108 Freiburg</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance – Azathioprine
rINN: Azathioprine
Chemical name: 6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)sulfanyl]-7H-purine.
Structure:

Molecular formula: C₉H₇N₇O₂S
Molecular weight: 277.3
Appearance: Pale yellow powder
Solubility: Practically insoluble in water and in ethanol (96 per cent). It is soluble in dilute solutions of alkali hydroxides and sparingly soluble in dilute mineral acids.

The active ingredient azathioprine is the subject of a European Pharmacopeia (Ph.Eur.) monograph. All aspects of the manufacture and control of the active substance azathioprine are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

All potential known impurities have been identified and characterised.

The container – closure system and retest period are satisfactory and comply with the details given on the EDQM Certificate of Suitability.

P. Medicinal Product
Other Ingredients
Other ingredients consist of the following pharmaceutical excipients:
The tablet core consists of:
Croscarmellose sodium, colloidal anhydrous silica, lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, starch, pregelatinised and povidone K25.

The tablet coating consists of:
Opadry II 85F19250 clear, which consists of macrogol 3350, polysorbate 80, poly(vinyl alcohol) and talc.

With the exception of Opadry II 85F19250 clear, all excipients used comply with their respective European Pharmacopoeia monographs. Opadry II 85F19250 clear complies with its in-house specifications. The components of Opadry II 85F19250 clear all comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients are of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used.
in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a hybrid medicinal product of the reference product Imuran 50 mg Tablets (Aspen Pharma Trading Limited).

Comparative physico-chemical data, including *in vitro* dissolution and impurity profiles have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

A satisfactory account of the pharmaceutical development has been provided.

The reference product used in the bioequivalence study is Imurek 50 mg Tablets, licensed in Germany to GlaxoSmithKline GmbH. This product is considered to be pharmaceutically equivalent to the UK reference product Imuran 50 mg Tablets.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of finished product. The results are satisfactory.

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

**Container-Closure System**
The finished product is packaged in aluminium/polyvinylchloride blister packs of 20, 30, 50, 60, 90 or 100 film-coated Tablets.

The Marketing Authorisation Holder has stated that they do not intend on marketing the product at present. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

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 foodstuffs.

**Stability of the product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years with the storage conditions “Store in the original package in order to protect from light”.

**Bioequivalence/bioavailability**
The reference product used in the bioequivalence study is Imurek 50 mg Tablets, licensed in Germany to GlaxoSmithKline GmbH. This product is considered to be pharmaceutically equivalent to the UK reference product Imuran 50 mg Tablets.
A bioequivalence study was performed to compare the pharmacokinetics of the test product Azathioprine Falk 50 mg Film-coated Tablets (Dr Falk Pharma GmbH) versus the reference product Imurek 50 mg Tablets (Aspen Europe GmbH).

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are acceptable from a pharmaceutical perspective.

A satisfactory bridging report to the user testing of Salofalk 1000mg gastro-resistant prolonged release granules, authorised to Dr Falk Pharma GmbH on 1 September 2003 (PL 08637/0008) has been provided. The results indicate that the PIL 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 they contain. It has also been agreed that the content of the PIL for this application will remain identical to the already approved and authorised PIL for Immunoprin 75 mg Film-coated Tablets (AT/H/0270/001/DC; PL 14510/0056).

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

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

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

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics and Pharmacodynamics
With the exception of the below study, no new pharmacodynamic or pharmacokinetic data have been submitted with this application and none are required.

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A single-dose, randomised, two-treatment, two-sequence, crossover study to compare the bioequivalence and pharmacokinetics of the test product Azathioprine Falk 50 mg film-coated tablets (Dr Falk Pharma GmbH) versus the reference product Imurek 50 mg tablets (Aspen Europe GmbH) in healthy non-smoking subjects in a fed state.
The study was of an appropriate design and was conducted to the principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products.

Subjects were dosed orally with either the test or reference product following at least a 10-hour fast. The drug was administered in the morning together with 200ml tap water and continental breakfast. Blood samples were taken pre-dose and up to 24 hours post dose. There was a washout period of at least 7 days between each treatment period.

Pharmacokinetic parameters were measured from the plasma and statistically analysed. The active metabolite for azathioprine, 6-mercaptopurine is also responsible for the effect of the medicinal product, therefore this was also measured.

A summary of the main pharmacokinetic results is presented in the table below:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Pharmacokinetic Parameter</th>
<th>Treatment A (Azafalk 50mg Tablets)</th>
<th>Treatment B (Imurek 50mg)</th>
<th>Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>$\text{AUC}_{0-t}$ (h*ng/mL)</td>
<td>12.54</td>
<td>12.68</td>
<td>98.93 (94.93; 103.08)</td>
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<tr>
<td></td>
<td>$\text{C}_{\text{max}}$ (ng/mL)</td>
<td>8.30</td>
<td>8.97</td>
<td>92.50 (82.70; 103.45)</td>
</tr>
<tr>
<td>6-mercaptopurine</td>
<td>$\text{AUC}_{0-t}$ (h*ng/mL)</td>
<td>17.04</td>
<td>18.39</td>
<td>92.68 (86.76; 98.99)</td>
</tr>
<tr>
<td></td>
<td>$\text{C}_{\text{max}}$ (ng/mL)</td>
<td>6.12</td>
<td>6.87</td>
<td>89.15 (77.03; 103.16)</td>
</tr>
</tbody>
</table>

LS: Least squares; CI: Confidence interval. Source: CSR AZT-8/BIO, Tables 11-3, 11-4

AUC0-t: area under the plasma concentration-time curve from time zero to t hours

Cmax: maximum plasma concentration

The 90% confidence interval of the test/reference ratio for the $\text{AUC}_{0-t}$, and $\text{C}_{\text{max}}$ was within the pre-defined limits of 80.00-125.00% as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion, bioequivalence has been demonstrated between the test and the reference product.

Efficacy
No new data on efficacy have been submitted and none are required for this type of application.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues arose during the bioequivalence study.

SmPC, PIL and Labels
The SmPC, PIL and labelling are acceptable from a clinical perspective.

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 risk management plan has been developed to ensure that Azafalk 50 mg Film-coated Tablets is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Azafalk 50 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

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

Conclusion
The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Azafalk 50 mg Film-coated Tablets 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 an application of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Azafalk 50 mg Film-coated Tablets product and its respective reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with azathioprine 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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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