Public Assessment Report

Decentralised Procedure

IELMAG3 0.2 mg kit for radiopharmaceutical preparation

Mertiatide (mercaptoacetyltriglycine)

Procedure No: UK/H/5251/001/DC

UK Licence No: PL 35903/001

Imaging Equipment Limited
On 12 July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Imaging Equipment Limited for the medicinal product IELMAG3 0.2 mg kit for radiopharmaceutical preparation (PL 35903/0001; UK/H/5251/001/DC). This is a prescription-only medicine (POM) and is a radiopharmaceutical product for diagnostic use only. The product may be referred to as IELMAG3 in this report.

IELMAG3 is used to study the function and structure and blood flow of the kidneys as well as function of the urinary tract, by making an image of these organs. After the medicine is injected, it temporarily collects in certain parts of the body. This radiopharmaceutical substance contains a small amount of radioactivity, which can be detected from outside of the body by using special cameras. The nuclear medicine doctor will then take an image (scintigraphy) of the concerned organs which can give the doctor valuable information about the about the structure and the function of these organs. The use of IELMAG3 does involve exposure to small amounts of radioactivity; the doctor and the nuclear medicine doctor will have considered that the clinical benefit that will be obtained from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using IELMAG3 0.2 mg kit for radiopharmaceutical preparation outweigh the risks, and a Marketing Authorisation was granted.
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Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>IELMAG3 0.2mg kit for radiopharmaceutical preparation</th>
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<tr>
<td>Type of Application</td>
<td>Well-established use, Article 10a</td>
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<tr>
<td>Active Substance(s)</td>
<td>Mertiatide (mercaptoacetyltriglycine)</td>
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<td>Form</td>
<td>Kit for radiopharmaceutical preparation</td>
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<tr>
<td>Strength</td>
<td>0.2 mg</td>
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<tr>
<td>MA Holder</td>
<td>Imaging Equipment Limited</td>
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<tr>
<td></td>
<td>The Barn, Manor Farm, Church Lane</td>
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<td></td>
<td>Chilcompton, Radstock BA3 4HP, United Kingdom</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria, Bulgaria and Ireland</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/5251/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 13 June 2013</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) 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 Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
## Module 4
### Labelling

### IELMAG3 0.2 mg Kit for radiopharmaceutical preparation

**Meratide (mercaptoacetyltriglycine)**

<table>
<thead>
<tr>
<th>Vial (1): IELMAG3 0.2 mg - Powder -</th>
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<tbody>
<tr>
<td>5 vials: each with 0.2 mg meratide.</td>
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</table>

Content / vial: active substance: 0.2 mg mercaptoacetyltriglycine (meratide);
excipients: Stannous chloride dihydrate; Disodium (R,R)-tartrate dihydrate;
Sodium hydroxide; Hydrochloric acid

EXP: Lot:

<table>
<thead>
<tr>
<th>Vial (2): IELMAG3 - Solvent -</th>
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<tbody>
<tr>
<td>5 vials: each with 2.5 mL solvent for solution for injection.</td>
</tr>
</tbody>
</table>

Content / vial: Sodium monohydrogenphosphate dihydrate; Sodium dihydrogenphosphate dihydrate; Hydrochloric acid; Water for injections

EXP: Lot:

Intravenous injection after reconstitution and radiolabelling.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store in the original package in order to protect from light. Store in a refrigerator at 2 – 8°C. Store the radiolabelled preparation at 2 - 8 ℃. Dispose of any unused product or waste material in accordance with radioactive material regulations.

Imaging Equipment Limited, The Barn, Manor Farm, Church Lane, Chilcompton
RADSTOCK BA3 4HP, United Kingdom

Marketing authorisation number: PL 35903/0001

Available on medical prescription only.

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### Vial (1): IELMAG3 0.2 mg - Powder -

**0.2 mg Mercaptoacetyltriglycine (Meratide)**

Intravenous injection after reconstitution and radiolabelling. Read the package leaflet before use. Inject the radiolabelled preparation within 6 hours.

EXP: Lot:

MA number: PL 35903/0001
Imaging Equipment Ltd, RADSTOCK BA3 4EN, UK

### Vial (2): IELMAG3 - Solvent -

Intravenous injection after addition to lyophilisate in vial 1.
Read the package leaflet before use. Inject the radiolabelled preparation within 6 hours. 2.5 mL phosphate buffer solution.

EXP: Lot:

MA number: PL 35903/0001
Imaging Equipment Ltd, RADSTOCK BA3 4EN, UK
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 IELMAG3 0.2 mg kit for radiopharmaceutical preparation (PL 35903/0001; UK/H/5251/001/DC) could be approved. The product is a prescription-only medicine (POM) and is a radiopharmaceutical preparation.

This medicinal product is for diagnostic use only. This product is indicated for adults; for use in the paediatric population see section 4.2 of the Summary of Product Characteristics.

The kit contains two different vials:
- Vial (1) contains 0.2 mg of mertiatide (mercaptoacetyltraglycine) as active substance
- Vial (2) contains 2.5 ml phosphate buffer solution.

The kit provides all non-radioactive components required for the reconstitution of technetium-(99mTc) mertiatide [Tc-99m mercaptoacetyltraglycine (MAG3)] solution for injection; the radioisotope technetium-(99mTc) is not part of the kit. After reconstitution and labelling with sodium pertechnetate (99mTc) solution, the radiopharmaceutical product obtained, technetium-(99mTc) mertiatide, is used for the evaluation of nephrological and urological disorders, in particular for the study of function, morphology and perfusion of the kidneys and characterisation of urinary outflow.

No pharmacodynamic effect is known for technetium-(99mTc) mertiatide at the chemical doses envisaged.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Bulgaria and Ireland as Concerned Member States (CMS). The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Bibliographic literature has been submitted to support this application.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 13 June 2013. After a subsequent national phase, a licence was granted in the UK on 12 July 2013.
II. ABOUT THE PRODUCT

Name of the product in the Reference Member State | IELMAG3 0.2mg kit for radiopharmaceutical preparation
--- | ---
Name(s) of the active substance(s) (INN) | Mertiatide (mercaptoacetyltriglycine)
Pharmacotherapeutic classification (ATC code) | Diagnostic radiopharmaceuticals, renal imaging (ATC code: V09CA03)
Pharmaceutical form and strength(s) | Kit for radiopharmaceutical preparation; 0.2 mg
Reference number for the Decentralised Procedure | UK/H/5251/001/DC
Reference Member State (RMS) | United Kingdom
Concerned Member States (CMS) | Austria, Bulgaria and Ireland
Marketing Authorisation Number | PL 35903/0001
Name and address of the authorisation holder | Imaging Equipment Limited
 | The Barn, Manor Farm, Church Lane
 | Chilcompton, Radstock BA3 4HP, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Mertiatide  
Chemical Name: N-(mercaptoacetyl)glycylglycylglycine  
Molecular formula: C$_8$H$_{13}$N$_3$O$_5$S  
Structure:

\[
\text{M}_r: \quad 263.27 \text{ g/mol} \\
\text{Appearance:} \quad \text{White amorphous or crystalline powder} \\
\text{Solubility:} \quad \text{Soluble in water, ethanol, methanol/water (30/70), acetonitrile and 0.9\% NaCl at room temperature, easily soluble in aqueous alkaline solution and limited solubility in aqueous acid solution.}
\]

Mertiatide (mercaptoacetyltriglycine) is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for the starting material and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

**MEDICINAL PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients in:

- Vial (1), namely stannous chloride dihydrate, disodium (R,R)-tartrate dihydrate, sodium hydroxide and hydrochloric acid, and
- Vial (2), sodium monohydrogenphosphate dihydrate, sodium dihydrogenphosphate dihydrate, hydrochloric acid and Water for injections.

Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of disodium-(r,r)tartrate, which complies to a suitable in-house specification. Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specification.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable kit (consisting of one vial containing the active substance 0.2 mg and one vial containing phosphate buffer solution) for the radiopharmaceutical preparation of technetium-(99mTc) mertiatide (European Pharmacopoeia monograph compliant), following reconstitution and labelling with sodium pertechnetate (99mTc) solution.

Suitable pharmaceutical development data have been provided for this application.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

**Control of Finished Product**

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

**Container-Closure System**

The finished product is packaged in 10 mL glass vials closed with a butyl rubber stoppers and sealed with aluminium crimpcaps.

IELMAG3 0.2 mg kit for radiopharmaceutical preparation is supplied in packs containing five vials with powder (active substance: mertiatide) and five vials with 2.5 mL sterile phosphate buffer solution.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidance concerning materials in contact with foodstuff.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, shelf-lives of 15 months
for the product in Vial (1) and 24 months for the product in Vial (2) have been set, with the storage instructions ‘Store in a refrigerator (2° – 8 °C). Store in the original package in order to protect from light.’ The shelf life of the product after radiolabelling is 6 hours; the radiolabelled preparation should be stored at 2°-8°C.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application.

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

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 the leaflet contains.

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

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

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of the radiodiagnostic agent technetium-(99mTc) mertiatide [Tc-99m mercaptoacetyltriglycine (MAG3)] are well-known, no new non-clinical data have been submitted and none are required.

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

The MAH has provided adequate justification for non-submission of an Environmental Risk Assessment (ERA). As this is an application for a product containing an active ingredient of well-established use; no increase in environmental burden is anticipated.

The grant of a Marketing Authorisation is recommended.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for this type of application. The clinical pharmacology of technetium-(99mTc) mertiatide is well-known.

Efficacy
No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of technetium-(99mTc) mertiatide as a radiopharmaceutical (for diagnosing kidney and urinary tract disorders) for the evaluation of nephro-urological functions is well-established.
Safety
No new safety data were supplied or required for this bibliographic application. Safety is adequately reviewed in the clinical overview. The safety profile of technetium-(\textsuperscript{\textsubscript{99m}}Tc) mertiatide is well-known.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (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.

Suitable justification has been provided for non-submission of a Risk Management Plan for this product. The application concerns a product, for which the active ingredient that has been in use for many years, and has a well-established safety profile. Routine Pharmacovigilance activities in accordance with EU regulations will be undertaken whilst the product is authorised. As the safety profile of the drug is well-established, a Risk Minimisation Plan is not considered necessary.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of IELMAG3 0.2 mg kit for radiopharmaceutical preparation 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. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

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

The published literature supports the efficacy of this product in the proposed indication. The efficacy of technetium-\(^{99m}\)Tc mertiatide is well-known. The presented evidence for well-established use of the active substance is sufficient.

SAFETY
The safety profile of technetium-\(^{99m}\)Tc mertiatide is well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The approved SmPC is satisfactory. The PIL and labelling are satisfactory, and consistent with the approved SmPC.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Mertiatide is a well-known active substance. Extensive clinical experience with technetium-\(^{99m}\)Tc mertiatide is considered to have demonstrated the compound to be an effective and safe medicinal product for diagnostic use. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPs TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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