26 April 2019
EMA/280752/2019
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Striascan

International non-proprietary name: ioflupane (123I)

Procedure No. EMEA/H/C/004745/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Administrative information

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| **Name of the medicinal product:** | Striascan |
| **Applicant:** | CIS BIO International<br>Route Nationale 306<br>Saclay BP 32<br>91192 Gif-Sur-Yvette<br>FRANCE |
| **Active substance:** | IOFLUPANE (123I) |
| **International non-proprietary name/Common name:** | ioflupane (123I) |
| **Pharmaco-therapeutic group (ATC Code):** | central nervous system, iodine (123I) compounds<br>(V09AB03) |
| **Therapeutic indication(s):** | This medicinal product is for diagnostic use only.<br>Striascan is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:<br>• In adult patients with clinically uncertain parkinsonian syndromes, for example those with early symptoms, in order to help differentiate essential tremor from parkinsonian syndromes related to idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Striascan is unable to discriminate between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy.<br>In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. Striascan is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia. |
| **Pharmaceutical form(s):** | Solution for injection |
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| **Strength(s):** | 74 MBq/ml |
| **Route(s) of administration:** | Intravenous use |
| **Packaging:** | vial (glass) |
| **Package size(s):** | 1 vial |

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# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant CIS BIO International submitted on 2 May 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Striascan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 January 2017.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union the basis of a complete dossier in accordance with Article 8(30) of Directive 2001/83/EC.

The applicant applied for the following indication:

This medicinal product is for diagnostic use only.

Striascan is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:

- In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. Striascan is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.
- In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. Striascan is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

**The legal basis for this application refers to:**

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and the reference medicinal product DaTSCAN instead of non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: DaTSCAN, 74 MBq/ml, solution for injection
- Marketing authorisation holder: GE Healthcare Limited
- Date of authorisation: (27-07-2000)
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number: EU/1/00/135/001 and EU/1/00/135/002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: DaTSCAN, 74 MBq/ml, solution for injection
- Marketing authorisation holder: GE Healthcare Limited
- Date of authorisation: (27-07-2000)

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/135/001 and EU/1/00/135/002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- N/A (this medicinal product is a parenteral preparation. Therefore a bioequivalence study is not applicable according to CPMP/EWP/QWP/1401/98 Rev.1)

### *Information on paediatric requirements*

Not applicable

### *Information relating to orphan market exclusivity*

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The applicant did not seek scientific advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra Co-Rapporteur: Simona Badoi

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| The application was received by the EMA on | 2 May 2018 |
| The procedure started on | 24 May 2018 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 14 August 2018 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 24 August 2018 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 20 September 2018 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 21 December 2018 |
| The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on | 4 February 2019 |

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| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 14 February 2019 |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | 28 February 2019 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 27 March 2019 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 10 April 2019 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Striascan on | 26 April 2019 |

# 2. Scientific discussion

## *2.1. Introduction*

This application for a marketing authorisation for Striascan solution for injection is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. The reference product is DaTSCAN, 74 MBq/ml, solution for injection (GE Healthcare Limited), authorised in EU since 27 July 2000 through the centralised procedure. For DaTSCAN two presentations were developed for single and total use i.e. 2.5 ml and 5 ml vials, providing 185 MBq per vial and 370 MBq per vial respectively, at the reference time (EU/1/00/135/001-002).

DaTSCAN is indicated for diagnostic use only. DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:

• In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

• In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. DaTSCAN is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

Ioflupane ($^{123}$I), the active ingredient of Striascan is a radioiodinated cocaine analogue. This cocaine analogue is a ligand with high affinity to dopamine transporter (DaT) located on the presynaptic nerve endings (axon terminals) in the striatum. The axon terminals are projections of the dopamine neurones in the substantia nigra. Therefore, binding of ioflupane ($^{123}$I) in the striatum is claimed to reflect the number of dopaminergic neurones in the substantia nigra. It has been developed as a dopamine transporter imaging agent for single photon emission computed tomography (SPECT). The technique is claimed to be sensitive enough to differentiate changes in the nigrostriatal dopaminergic system in patients with Parkinsonism and healthy controls.

Parkinson's disease is characterised by akinesia, rigidity and abnormal involuntary movements. True Parkinsonian syndrome includes conditions like multiple system atrophy (MSA) and progressive

supranuclear palsy (PSP), in addition to Parkinson's disease. This syndrome is characterised by the loss of dopaminergic cells and the resultant decrease in striatal dopamine. The prevalence in the community of Parkinson's disease, MSA and PSP are approximately 82%, 10% and 8% respectively. Essential tremor (ET) is often confused clinically with Parkinson's disease and related syndromes but is not associated with nigrostriatal degeneration. DaTSCAN is presented as a sterile 5% (v/v) ethanolic solution for intravenous injection and should be used without dilution. The recommended dose for adults and the elderly is 111-185 MBq. DaTSCAN is not recommended for use in children or adolescents, as data are not available for these age groups. Patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine. SPECT imaging should take place between three to six hours post injection.

Ioflupane ($^{123}$I) also binds to the serotonin transporter on 5-Hydroxytryptamin (5-HT) neurons but with approximately 10-fold lower binding affinity. There is no experience in types of tremor other than essential tremor.

The applicant is seeking all of the indications and dosing regimens for which DaTSCAN is registered in the EU.

The dosage form and route of administration is identical to DaTSCAN.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as solution for injection containing 74 MBq/mL of ioflupane ($^{123}$I) at reference time (0.07 to 0.13 µg/mL of ioflupane) as active substance.

Each 2.5 mL single dose vial contains 185 MBq ioflupane ($^{123}$I) (specific activity range 2.5 to 4.5 x 1014 Bq/mmol) at reference time.

Each 5 mL single dose vial contains 370 MBq ioflupane ($^{123}$I) (specific activity range 2.5 to 4.5 x 1014 Bq/mmol) at reference time.

Other ingredients are: acetic acid, glacial (E 260), sodium acetate, trihydrate (E 262), ethanol, anhydrous (E 1510), phosphoric acid, concentrated (E 338), and water for injections.

The product is available in amber glass vial sealed with a rubber closure and metal overseal, the vial is placed into a lead container for protective shielding and packed in a metal box as described in section 6.5 of the SmPC.

### 2.2.2. Active substance: Ioflupane ($^{123}$I)

***General information (Active substance)***

The chemical name of the active substance is [I-123] 8-Azabicyclo[3.2.1]octane-2-carboxylic acid, 8-(3-fluoropropyl)-3-(4-iodophenyl)-, methyl ester, (1R,2S,3S,5S) corresponding to the molecular formula $C_{18}H_{23}F^{123}INO_2$. It has a relative molecular mass of 427.285 g/mol and the following structure:

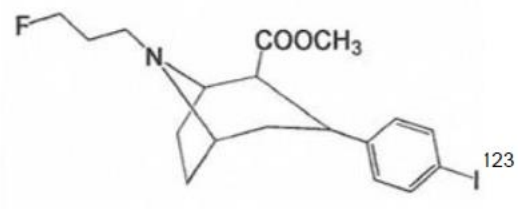

**Figure 1: Active substance structure**

As the final steps of the active substance manufacture involve a continuous process leading to the finished product, the final active substance is not isolated. Therefore, no formal structure elucidation of the final active substance has been performed.

As the final active substance is not isolated during the manufacturing process, no information regarding its general properties can be provided.

The active substance is soluble in water and ethanol. The carbon bearing the methyl ester function is a chiral centre. The product used is the enantiomer β form.

***Manufacture, characterisation and process controls (Active substance)***

The active substance is an iodinated cocaine analogue. The manufacturing process consists of preparing the labelled product by electrophilic radioiodination from a Sn-FP-CT precursor. The active substance is synthesised in 3 main stages:

1. Manufacture of precursor
2. Manufacture of intermediate (Sodium Iodide ($^{123}$I) solution (Na$^{123}$I))
3. Manufacture of final active substance (Ioflupane ($^{123}$I);

***1. Precursor:***

***General information (Precursor)***

The chemical name of the precursor Sn-FP-CT is 8-azabicyclo[3.2.1]octane-2-carboxylic acid, 8-(3-fluoropropyl)-3-[4-(trialkylstannyl)phenyl]-, methyl ester, (1R,2S,3S,5S)-. It has a relative molecular mass of 594.43 g/mol and the following structure**:**

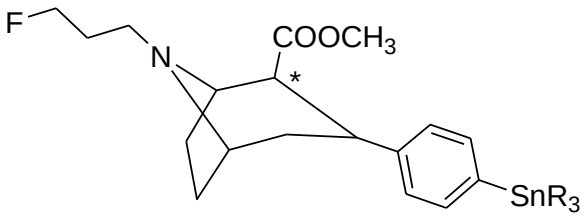


Figure 1: Precursor (Sn-FP-CT) structure

The chemical structure of Sn-FP-CT was elucidated by a combination of IR spectrometry, $^{1}$H-NMR, $^{13}$C-NMR, $^{119}$Sn-NMR, $^{19}$F-NMR, mass spectrometry.

The precursor is a colourless to yellowish droplets, soluble in ethanol, chloroform, acetone and acetonitrile, not soluble in water.

Sn-FP-CT exhibits stereoisomerism due to the presence of 1 chiral centre. The precursor used is the enantiomer β form.

***Manufacture, characterisation and process controls (Precursor)***

The precursor is synthesised in 5 main steps using well defined starting materials with acceptable specifications

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the precursor and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

***Specification (Precursor)***

The precursor specification includes tests for appearance (visual), Sn-FP-CT identification (IR, LC), residual solvents (GC), organic impurities content (LC), residues of catalysts or metal residues (atomic absorption spectrometry), microbiological quality (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and purity (LC).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of the precursor are provided. The results are within the specifications and consistent from batch to batch.

***Stability (Precursor)***

Stability data from 3 commercial scale batches of the precursor from the proposed manufacturer stored in the intended commercial package for up to 6 months under long term conditions (-20°C, 5°C) and for up to 6 months under accelerated conditions ( 25 °C / 60% RH) according to the ICH guidelines were provided. A stress study was conducted on one batch stored at 40$^{o}$C ± 2$^{o}$C/ 75 % ± 5% RH over a period of 5 days, for shipping condition.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

All the stability results reported comply with the specification. Moreover, the stability data collected for the accelerated storage conditions (25 °C / 60% RH) did not demonstrate any critical degradation. The result for shipping conditions confirms the overall stability of the precursor. The stability results indicate that the precursor manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 6 months stored at 5 °C ± 3$^{o}$C in the proposed container.

## 2. Intermediate: Sodium Iodide ($^{123}$I) solution (Na$^{123}$I)

### *General information (Intermediate)*

Sodium iodide ($^{123}$I) is supplied by several manufacturers and separated information is provided for each manufacturer.

The chemical name of sodium iodide is sodium iodide ($^{123}$I) corresponding to the molecular formula Na$^{123}$I. It has a relative molecular mass of 146 g/mol.

$^{123}$I isotope is identified by gamma spectrometry

The sodium iodide is supplied as a clear and colourless solution.

*S*odium iodide ($^{123}$I) has a non - chiral molecular structure and polymorphism has not been observed.

### *Manufacture, characterisation and process controls (Intermediate)*

Sodium iodide ($^{123}$I) is manufactured by several manufacturers.

All manufacturers prepare Iodine ($^{123}$I) by irradiation, with 30 MeV protons in a cyclotron, of the xenon ($^{124}$Xe) gas target .

Adequate in-process control is applied during the synthesis. The specifications and control methods for other intermediate products are not applicable in this case The characterisation of the intermediate (sodium iodide ($^{123}$I) solution) and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

### *Specification (Intermediate)*

The intermediate (sodium iodide ($^{123}$I) solution (Na$^{123}$I)) specification complies with Ph. Eur. 2314 (sodium iodide ($^{123}$I) solution for radiolabelling), current edition. It includes tests for appearance, identification (Ph. Eur.), alkalinity (Ph. Eur.), radionuclidic purity (Ph. Eur), radioactive concentration (Ph. Eur).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of the intermediate (sodium iodide ($^{123}$I) solution) are provided. The results are within the specifications and consistent from batch to batch.

### *Stability (Intermediate*)

Stability data from 3 commercial batches from the suppliers stored in the intended commercial package for up to 3 days in the production area at a temperature $\leqslant$ 25 °C are provided. The end of the production corresponds to the distribution of the solution in the flask at the end of the purification process.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

The stability results indicate that the intermediate manufactured by the proposed suppliers is sufficiently stable. The stability results demonstrate that the 3 suppliers for intermediate (sodium iodide ($^{123}$I) solution) have provided batches compliant with the specifications. When stored in the production area at

a temperature ≤ 25°C, the shelf-life is set from 29 to 54 hours after manufacturing depending the manufacturer.

**3. Final active substance (Ioflupane ($^{123}$I))**

The final active substance (Ioflupane ($^{123}$I)) is synthesised from a key starting material Sn-FP-CT via oxidative iododestannylation with sodium ($^{123}$I)-iodide.

This manufacturing process is continuous; thus, the final active substance is not isolated and is directly processed to finished product manufacture. Consequently, no control is performed on synthesis intermediates or on the final active substance and consequently, there is no specific active substance container. The active substance impurities are assessed in the finished product. For a radioactive active substance this approach is acceptable

***Specification (Active substance)***

The final active substance (Ioflupane-I-123) is manufactured through a continuous process leading to the finished product without isolation of the active substance. Therefore, the complete description of specification, analytical procedures, validation of analytical procedures, batch analysis and justification of specification are described for the finished product only. For radioactive active substance this approach is acceptable.

***Stability (Active substance)***

The final active substance (Ioflupane-I-123) is manufactured through a continuous process leading to the finished product without isolation of the active substance. Therefore, no data is presented on stability of the final active substance. For radioactive active substance this approach is acceptable.

## 2.2.3. Finished medicinal product

***Description of the product and Pharmaceutical development***

The finished product (Striascan) is a solution for injection containing $^{123}$I-ioflupane in acetic acid / acetate buffer (containing 5.0 % of ethanol) having a radioactive concentration of 74 MBq/mL at reference time.

Striascan is packaged in monodose vials. The minimum and maximum volumes dispensed per vial are respectively 2.5 mL and 5 mL. Considering that the radioactive concentration at reference date and time is 74 MBq/mL, the total activity per vial is respectively 185 MBq (2.5 mL vial) and 370 MBq (5 mL vial) at reference date and time.

Striascan is a generic medicinal product. The reference medicinal product is DaTSCAN 74 MBq/mL, solution for injection, authorised in the European Union on 27 July 2000.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The objective of the formulation development was to produce a generic product showing the same qualitative and quantitative composition in active substance and excipients as DaTSCAN and also with the same physicochemical characteristics in terms of radioactive concentration, specific activity at reference time and impurity profile. It was shown that the generic medicinal product is identical to the reference medicinal product with regards to: pharmaceutical form, nature and amount of the active substance, the specific activity at reference time , radioactivity, to ioflupane content, the radioactive concentration at reference time, 74 MBq/mL, the nature and amount of solvent, the nature of the buffer, the amount of acetate buffer (based on analytical results), the pH of the solution (based on analytical results), the impurity profile (based on analytical results), and the decay product (physical process inherent to

radioactivity). Therefore, no bioequivalence study is needed according to the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98Rev.1/ Corr**) for parenteral solutions.

The process initially developed led to the manufacture of a finished product complying to the specification of the reference medicinal product, with one impurity contained in the precursor. The current process has been upgraded to remove this impurity from the finished product.

Ioflupane is known to be sensitive to heat. Therefore, the process was adapted to include a sterilising filtration. The ioflupane ($^{123}$I) solution is dispensed in an aseptic environment after sterilising filtration process with relevant control of sterility and bubble point testing and subsequent filling of the product into pre-sterilized vials under EU grade A environment.

Extraction experiments have been performed by the applicant without any deviation from the protocol. Extractable analyses are currently on going and results will be provided through a Post Authorisation Measure procedure. From the study report a risk analysis on potential toxicity of extractables will be performed to define the leachable study protocol if applicable. The CHMP recommends implementing data on the leachable test, if applicable, when the results from extractable study will be available.

The primary packaging is amber glass vial sealed with a rubber closure and metal overseal. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The finished product manufacturing process consists of 3 main steps: dilution, sterilisation by filtration, dispensing and packaging. The process is considered to be a standard manufacturing process.

The major steps of the manufacturing process have been validated in three commercial scale batches by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

***Product specification***

The finished product specifications include appropriate tests for this kind of dosage form; appearance (visual examination), radionuclidic identification (gamma-ray spectrometry), ioflupane identification (LC), radionuclidic purity (gamma-ray spectrometry), pH, specific activity (LC), acetaldehyde (GC), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), radioactive concentration (Ionization chamber), radiochemical purity (LC), and ethanol content (GC).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

***Stability of the product***

Stability data from 3 commercial scale batches of finished product stored for up to 35 h for the 2.5 mL vial and up to 48 h for the 5.0 mL-vial, after manufacture under long term conditions (25 ºC ± 2°C) and under accelerated conditions (40 ºC ± 2°C) according to the ICH guidelines were provided. The batches of

medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are the same as for release. The analytical procedures used are stability indicating. All the stability results comply with the specifications.

Based on available stability data, the proposed shelf-life of EOS (end of synthesis) + 35h for the 2.5 mL presentation and EOS (end of synthesis)+ 48 h for the 5.0 mL presentation as stated in the SmPC (section 6.3) are acceptable.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

### 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a one minor unresolved quality issue having no impact on the benefit/risk ratio of the product.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

- To implement data on the leachable test, if applicable, when the results from extractable study will be available.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

### 2.3.2. Ecotoxicity/environmental risk assessment

At start of this procedure several ERA-related concerns were raised. Main issues were related to PEC calculation and lacking Kow data. PEC calculation was based on a refined $F_{pen}$ according to the sales

forecast of the product (DaTSCAN and STRIASCAN) in the 8 countries where the product will be registered or is already marketed (Spain, Italy, Germany, UK, France, The Netherlands, Belgium, Luxembourg). This was not considered acceptable. In accordance with the Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev. 1), prevalence data for the sought indication(s) (independent data bases or literature) which are not linked to consumption data, but to case numbers are needed for a correction of the market penetration factor. Later in the procedure the Applicant presented an updated PEC calculation as well as Kow literature data. The concerns related to PEC calculations were considered resolved, although, according to Question 6, Q&A on Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev.° 1.) the Applicant was asked to provide the study report of an experimentally determined n-octanol/ water partition coefficient (log Kow) for ioflupane (123I). The provided response was considered to be in agreement with Question 6, Q&A on Guideline on the environmental risk assessment of medicinal products for human use and the determined Log Dow was well below 4.5., thus allowing the CHMP to consider all of the concerns regarding ERA, resolved.

It was concluded that introduction of Striascan manufactured by CIS BIO International is considered unlikely to result in any significant increase in the combined sales volumes for all ioflupane (123I) containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

## 2.3.3. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of ioflupane are known. As ioflupane is a widely used, well-known active substance, the applicant has not conducted additional nonclinical pharmacodynamic, pharmacokinetics, toxicology, reproductive toxicology, genotoxicity or carcinogenicity studies. Overview based on literature review is, thus, appropriate.

Ioflupane has been used in neuro-imaging diagnostic of Parkinson's disease and the differential diagnosis of Parkinson's disease over other disorders presenting similar symptoms and to help distinguish between dementia with Lewy bodies and Alzheimer’s disease, since 2000 and has been approved by EMA as DaTSCAN solution for injection. The biowaiver has been requested since the proposed medicinal product has an identical qualitative and quantitative composition in the active substance available at the reference time compared to the approved reference medicinal product 74 MBq/mL of ioflupane (123I) and the same pharmaceutical form and route of administration as an aqueous solution for injection for intravenous use. Therefore, in this submission, the non-clinical information was based on the literature review and non-clinical data from DaTSCAN development.

The present nonclinical literature review does not bring any additional data that from the regulatory point of view would change the safety profile of ioflupane in its present clinical use.

Therefore, the CHMP agreed that no further non-clinical studies are required.

## 2.3.4. Conclusion on the non-clinical aspects

A non-clinical overview has been provided and was based on up-to-date and adequate scientific literature and environmental risk assessment. The CHMP is of the opinion that the applicant has justified the lack of non-clinical studies based on the literature review and the claim that Striascan is a generic of the reference product DaTSCAN.

The CHMP considered this application acceptable from non-clinical point of view.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

This is an application for solution for injection containing ioflupane (123I).

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of ioflupane (123I) based on published literature. The relevant SmPC sections are in line with the SmPC of the reference product.

No formal scientific advice by the CHMP has been requested for this medicinal product.

### *GCP*

The Applicant did not submit clinical trials in this application.

### *Exemption*

Striascan has been developed as a pharmaceutical equivalent of DaTSCAN solution for injection. Striascan is essentially similar to the approved reference product, DaTSCAN; it is qualitatively and quantitatively identical in composition to that of DaTSCAN. The active ingredient, dosage form, route of administration and strength of are identical to those of the reference medicinal product. Striascan is presented in packs of 1 vial containing 2.5 mL or 5 mL of solution, which is the same as registered presentations of reference product.

The biowaiver was requested by the Applicant.

According to the guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **): "Bioequivalence studies are generally not required if the test product is to be administered as aqueous intravenous solution containing the same active substance as the currently approved product".

As the route of administration is intravenous, the qualitative and quantitative composition in active substance is identical and no excipient interaction occurs with the drug substance, bioequivalence studies are not required.

Therefore for Striascan the essential similarity with the reference medicinal product was only based on pharmaceutical equivalence.

Striascan has the same qualitative and quantitative composition in active substance as the reference medicinal product DaTSCAN 74 MBq/mL solution for injection (GE Healthcare Limited) and the same pharmaceutical form and route of administration.

The excipients of the proposed drug product are identical to the reference product DaTSCAN, with the exception of phosphoric acid, that is presented in the composition of the claimed generic medicinal product Striascan and it is used in the elution solution of HPLC purification of the reaction mixture.

Data concerning the proportion between the radioactive and non-radioactive forms of ioflupane (ratio of "hot" - I-123 and "cold" - I-127 forms) confirms the similarity between both products.

Specification of the specific activity of ioflupane is 2.5 to 4.5x1014 Bq/mmol at the reference time for both Striascan and DaTSCAN. For the two products, the reference time is equally set at 28 hours and 35 hours from the end of the manufacturing process for the 2.5-mL single-dose vial and the 5-mL single-dose vial respectively.

Striascan composition is identical to that of DaTSCAN with regard to the nature and amount of the active substance, the specific activity, the radioactivity concentration, the nature and amount of solubiliser, with

only minor differences in excipient composition. These minor differences have no effect on biodistribution of the tracer.

Therefore, general biowaiver-criteria are fulfilled according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

## 2.4.2. Pharmacokinetics

No new pharmacokinetic studies were submitted. In view of the i.v. injection, 100% availability can be assumed. The physical half-life of $^{123}I$ is 13.2 hours.

No bioequivalence study was submitted and no study is required according to the Guideline on the Investigation of Bioequivalence biowaiver-criteria are fulfilled. The company has presented literature review in support of this application which was accepted by the CHMP.

According to literature data at 1 hour post-injection of 100 MBq ioflupane (123I), the total blood activity was on average 53% IA, and slowly decreased thereafter. The levels of radioactivity were highest in the lungs, liver and brain. The images showed rapid lung uptake and hepatobiliary excretion. The highest absorbed doses were in the urinary bladder wall and lungs. Brain uptake was approximately 7% of the injected activity, with 30% of this concentrated in the striatum (2.1% IA). The mean urinary excretion at 48 hours post-injection was 60% ± 9% and mean predicted fecal excretion was 14% ± 1%. Radiation dose estimates confirmed an effective dose of 0.024 mSv/MBq 10,75. The self-dose to the striatum was estimated to be 0.23 mGy/MBq.

Only one metabolite has been identified in human plasma, which was believed to be free carboxylic acid form of FP CIT formed by enzymatic hydrolysis of the methyl ester group.

## 2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

## 2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

## 2.4.5. Discussion on clinical aspects

No new pharmacokinetic and pharmacokinetic studies were submitted. A summary of the literature with regard to clinical data of Striascan and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Striascan is to be administered as an aqueous intravenous injection and contains the same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration as for the reference product. It has an identical qualitative and quantitative composition in terms of the active substance as its reference medicinal product and also contains the same excipients. As it is indicated for intravenous administration and in accordance to CPMP/EWP/QWP/1401/98 Rev.1, Appendix II, Parenteral solutions, bioequivalence can be concluded without the need for further studies. There are no differences in non-clinical or clinical effects that are expected. Safety profile is comparable to that of reference product.

## 2.4.6. Conclusions on clinical aspects

The CHMP is of the opinion that the applicant has justified the lack of clinical studies based on the claim that Striascan is a generic of the reference product DaTSCAN. As the product contains the same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration as for the reference product, the lack of bioequivalence studies is considered acceptable. The literature data and the publicly available information presented in the dossier are considered acceptable and sufficient for the assessment of clinical aspects of Striascan in the applied indications.

## *2.5. Risk management plan*

### *Safety concerns*

**Summary of safety concerns**

| | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | None |
| **Missing information** | Increased risk of radiation exposure in patients with renal and hepatic impairment |

### *Pharmacovigilance plan*

Not applicable

### *Risk minimisation measures*

**Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| **Safety concern** | **Risk minimisation measures** | **Pharmacovigilance activities** |
|---|---|---|
| Increased risk of radiation exposure in patients with renal and hepatic impairment | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4 and 5.2<br>PL section 2<br><br>This medicinal product is for use in hospitals or in designated nuclear medicine facilities only and should be handled by persons experienced in radioisotope diagnostic imaging.<br><br>Additional risk minimisation measures: None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>Not applicable<br><br>Additional pharmacovigilance activities: Not applicable |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

### *2.6. Product information*

### 2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## 3. Benefit-risk balance

This application concerns a generic version of ioflupane (123I) solution for injection. The reference product DaTSCAN is indicated for for diagnostic use only for detecting loss of functional dopaminergic neuron terminals in the striatum:

- In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.
- In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease.
  DaTSCAN is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A bioequivalence study was not submitted and this was considered acceptable as Striascan contains the same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration (parenteral) as for the reference product.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## 4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that

the benefit-risk balance of Striascan is favourable in the following indication:

This medicinal product is for diagnostic use only.

Striascan is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:

- In adult patients with clinically uncertain parkinsonian syndromes, for example those with early symptoms, in order to help differentiate essential tremor from parkinsonian syndromes related to idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Striascan is unable to discriminate between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy.
- In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. Striascan is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

## *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.*

Not applicable.