EU Risk Management Plan for STRIASCAN (Ioflupane (^{123}I))

RMP version to be assessed as part of this application:

RMP Version number: 2.0

Data lock point for this RMP: 18Dec2023

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Rationale for submitting an updated RMP: Renewal of the marketing authorisation assessment report.

Summary of significant changes in this RMP: Change of the safety concern "missing information"

Other RMP versions under evaluation: not applicable

RMP Version number: 2.0

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Details of the currently approved RMP:

Version number: 1.0

Approved with procedure: EMEA/H/C/005520

Date of approval (opinion date): 25/05/2023

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s and QPPV.

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Ioflupane (^{123}I)
Pharmacotherapeutic group(s) (ATC Code)	Diagnostic radiopharmaceutical central nervous system ATC code: V09AB03
Marketing Authorisation	CIS bio international BP 32 91192 Gif sur Yvette France
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Striascan
Marketing authorisation procedure	Centralised
Brief description of the product • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Chemical class This diagnostic medicinal product contains the active substance ioflupane (^{123}I) INN, (otherwise referred to as ^{123}I-FP-CIT or ^{123}I-β-CIT-FP) which is a radioiodinated cocaine analogue.
	Summary of mode of action Summary of mode of action: 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. Ioflupane (^{123}I) is a dopamine transporter imaging agent for single photon emission computed tomography (SPECT).
	Important information about its composition: Ioflupane is radiolabelled by (^{123}I).
Hyperlink to the Product Information	See summary of Products Characteristics in Module 1.3.1.

Indication(s) in the EEA	Current: Ioflupane (^{123}I) is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of 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. It is indicated in adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. Ioflupane (^{123}I) is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy and is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: A single dose of 110-185 MBq administered by intravenous route.
	Proposed: not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection Each ml of solution contains 74 MBq of ioflupane (^{123}I) at calibration time. One vial contains 1.5 to 5 mL of solution with a range activity of 110 – 185 MMq at calibration date
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable: Striascan is licensed under a generic status.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable: Striascan is licensed under a generic status.

Part II: Module SIII - Clinical trial exposure

Not applicable: Striascan is licensed under a generic status.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable: Striascan is licensed under a generic status.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable: Striascan is licensed under a generic status.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable: Striascan is licensed under a generic status.

Part II: Module SV - Post-authorisation experience

Not applicable: Striascan is licensed under a generic status.

SV.1 Post-authorisation exposure

Not applicable: Striascan is licensed under a generic status.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable: Striascan is licensed under a generic status.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised).

Risks	**Supportive information**
Injection site pain	**Sufficiently covered by guidance in product information** Section 4.2 (method of administration): To minimise the potential for pain at the injection site during administration, a slow intravenous injection (not less 15 to 20 seconds) via an arm vein is recommended. Section 4.8: Frequency Uncommon. Injection site pain (intensive pain following administration into small veins).
Drug ineffective, Drug-drug interaction, biodistribution alteration	**Sufficiently covered by guidance in product information** Section4.2: Image acquisition SPECT imaging should take place between three and six hours post-injection. Images should be acquired using a gamma camera fitted with a high-resolution collimator and calibrated using the 159 keV photopeak and a ± 10% energy window. Angular sampling should preferably be not less than 120 views over 360 degrees. For high resolution collimators the radius of rotation should be consistent and set as small as possible (typically 11-15 cm). Experimental studies with a striatal phantom, suggest that optimal images are obtained with matrix size and zoom factors selected to give a pixel size of 3.5-4.5 mm for those systems currently in use. A minimum of 500 k counts should be collected for optimal images. Normal images are characterised by two symmetrical crescent-shaped areas of equal intensity. Abnormal images are either asymmetric or symmetric with unequal intensity and/or loss of crescent. Section 4.5: Ioflupane binds to dopamine transporter. Medicines that bind to the dopamine transporter with high affinity may therefore interfere with Ioflupane diagnosis. These include amphetamine, benzatropine, bupropion, cocaine, mazindol, methylphenidate, phentermine and sertraline.
Potential uptake of (^{123}I) by the thyroid gland	**Sufficiently covered by guidance in product information** Section 4.2: Patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine, for example by oral administration of approximately 120 mg potassium iodide 1 to 4 hours prior to injection of Striascan (^{123}I) CIS bio international

Risks	Supportive information
Use in patients suffering from alcoholism, liver disease and epilepsy due to an excipient ethanol	**Risk seriousness:** No case reports of DaTSCAN concerning adverse reactions in patients suffering from alcoholism, liver disease and epilepsy due to an excipient ethanol have been identified by the Innovator. **Sufficiently covered by guidance in product information** Section 4.4: Specific warnings This medicinal product contains 39.5 g/L (5% volume) ethanol (alcohol), up to 197 mg per dose, equivalent to 5 mL beer or 2 mL wine. Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease or epilepsy. **Risk frequency:** Not known **Impact on the benefit/risk balance:** The benefit / risk balance of the product remains positive in the indication currently registered.
Use in pregnant and lactating women	**Risk seriousness:** Cumulatively, no case reports concerning adverse effects in pregnant and lactating women have been identified by the Innovator. **Sufficiently covered by guidance in product information** Section 4.3: Contraindication: Pregnancy Section 4.6: Animal reproductive toxicity studies have not been performed with this product. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Administration of 185 MBq of ioflupane (^{123}I) results in an absorbed dose to the uterus of 2.6 mGy. Breastfeeding It is not known whether ioflupane (^{123}I) is excreted in human milk. Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If administration is considered necessary, breast-feeding should be interrupted for 3 days and substituted by formula feeding. During this time, breast milk should be expressed at regular intervals and the expressed feeds should be discarded. **Risk frequency:** Use in pregnancy and lactating women is contraindicated. Therefore, the frequency is not known. **Impact on the benefit-risk balance:** Considering the target population and the absence of case reports, the risk of adverse effects in pregnant and lactating women is low. The benefit / risk balance of the product remains positive in the indication currently registered.

Risks	Supportive information
Hypersensitivity	**Risk seriousness:** Cumulatively, 19 case reports concerning hypersensitivity and potential manifestations has been received for DaTSCAN from all sources (both from postmarketing experience and clinical trials). Four (4) of the cases were serious and 15 were non-serious. Most frequently reported reactions were rash, hypersensitivity, erythema and pruritus. Information concerning outcome was provided in 17 of the 19 cases. In 15 cases the patient had recovered or were recovering at the time of reporting, while in 2 cases the patient had not recovered at the time of reporting. The outcome was unknown in 2 of the cases. **Sufficiently covered by guidance in product information** Section 4.8: No serious adverse reactions related to ioflupane have been reported. However, Hypersensitivity reactions have been reported with DatScan (Innovator) with a not known frequency. From the most recently available PSUR for DaTSCAN (innovator) five hypersensitivity reports were collected. These five reactions were all non-serious. Section 4.2: Prior to administration appropriate resuscitation equipment should be available. Section 4.3: Hypersensitivity to the active substance or to any of the excipients. Section4.4: If hypersensitivity reactions occur, the administration of the medicinal product must be discontinued immediately and, if necessary, intravenous treatment initiated. Resuscitative medicinal products and equipment (e.g. endotracheal tube and ventilator) have to be readily available. **Risk frequency:** The true incidence of hypersensitivity reaction in the general population cannot be estimated from the available data. The Innovator DaTSCAN has cumulatively reported 19 case reports (until DLP 27.07.2017) concerning hypersensitivity and potential manifestations. Compared with the estimated exposure of DaTSCAN, the number of case reports suggested a very low frequency. **Impact on the benefit-risk balance:** Hypersensitivity reactions to ioflupane (^{123}I) have been reported as non-serious. The benefit of ioflupane (^{123}I) in diagnostic use outweighs the risk of hypersensitivity.
Risk of cancer induction and hereditary defects further to exposure of ionising radiation	**Risk seriousness:** No case reports of DaTSCAN were identified concerning SOC Congenital, familial and genetic disorders or HLT Radiation injuries. Six cases reports were identified within SOC Neoplasms benign, malignant and unspecified (including cysts and polyps). One serious case from post-marketing experience concerning thyroid cancer, provided limited information and does therefore not contribute with new information about exposure to ionising radiation. The remaining 5 serious cases

Risks	Supportive information
	were reports from clinical trials, and all events were considered unrelated to the study drug, according to the reporting investigators. Ionizing radiation is linked with cancer induction and can lead to development of hereditary defects via radiation induces DNA-damage. The administration of radiopharmaceuticals creates risks for external radiation contamination from improper handling of the product and exposure to urine or other bodily excretions from a patient undergoing an imaging procedure. Safety measures have been implemented in sections 4.4, 4.8, of the SmPC in order to minimise this risk. **Sufficiently covered by guidance in product information** Section 4.4: For each patient, radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information. Section 4.8: Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 4.6 mSv when the maximal recommended activity of 185 MBq is administered these adverse events are expected to occur with a low probability. **Risk frequency:** Not known. **Impact on the risk-benefit balance of the product:** The benefit / risk balance of the product remains positive in the indication currently registered.
Risks	**Supportive information**
Increased risk of radiation exposure in patients with hepatic or renal impairment	**Risk seriousness**: No relevant case reports concerning adverse effects in patients with hepatic or renal impairment have been identified neither by the Innovator nor by CURIUM. An increased radiation is possible in patients with renal impairment because approximately 60 % of the injected radioactivity is excreted in the urine. Faecal excretion is calculated at approximately 14%. Section 4.2: Formal studies have not been carried out in patients with significant renal or hepatic impairment. No data are available (see section 4.4). Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. Section 4.4: Renal impairment / Hepatic impairment ; Formal studies have not been carried out in patients with significant renal or hepatic impairment. In the absence of data, Ioflupane (^{123}I) is not recommended in cases of moderate to severe renal or hepatic impairment. Careful consideration of the benefit risk ratio in these patients

Risks	Supportive information
	is required since an increased radiation exposure is possible. Patient preparation The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation. Risk frequency: None **Impact on the benefit-risk balance**: The benefit / risk balance of the product remains positive in the indication currently registered.

Known risks that do not impact the risk-benefit profile:

Risks	Supportive information
Appetite increase	Sufficiently covered by guidance in product information Section 4.8: Frequency Uncommon. Appetite increased.
Headache, Dizziness, Formication, Dysgeusia	Sufficiently covered by guidance in product information. Section 4.8: Frequency Common. Headache. Section 4.8: Frequency Common. Dizziness, Formication, Dysgeusia
Vertigo	Sufficiently covered by guidance in product information Section 4.8: Frequency Uncommon. Vertigo
Nausea, dry mouth, Vomiting	Sufficiently covered by guidance in product information Section 4.8: Frequency Uncommon. Vomiting (not known)
Erythema, pruritus, rash, urticaria, Hyperhidrosis	Sufficiently covered by guidance in product information Section 4.8: Frequency Not known
Blood pressure decreased	Sufficiently covered by guidance in product information Section 4.8: Frequency Not known
Injection site pain (intense pain or burning sensation following administration into small veins) Feeling hot	Sufficiently covered by guidance in product information Section 4.8: Frequency Uncommon Not known: Feeling hot

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk	**None**
Important potential Risk	**None**
Missing information	**None**

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The important potential risk of "Increased risk of radiation exposure in patients with hepatic or renal impairment" has been removed from the list of safety concerns.

Reason for removal to the list of safety concerns: known risk sufficiently covered by guidance in the product information.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

There is no important identified risk and no important potential risk.

SVII.3.2. Presentation of the missing information

There is no missing information.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The safety information in the proposed product information is aligned to the reference medicinal product.

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable: Routine pharmacovigilance activities as described in Part III.1 are sufficient.

V.2. Additional Risk Minimisation Measures

Not applicable: Routine pharmacovigilance activities as described in Part III.1 are sufficient to identify and characterise the risks of the product.

V.3 Summary of risk minimisation measures

Not applicable: Routine pharmacovigilance activities as described in Part III.1 are sufficient to identify and characterise the risks of the product.

Part VI: Summary of the risk management plan

Summary of risk management plan for Striascan (Ioflupane (^{123}I))

This is a summary of the risk management plan (RMP) for Striascan.

Striascan summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Striascan should be used.

This summary of the RMP for Striascan should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Striascan's RMP.

I. The medicine and what it is used for

Striascan is authorised for diagnostic use only.

It contains ioflupane (^{123}I) as the active substance and it is given by intravenous route of administration. It is used to help identify conditions in the brain. It belongs to a group of medicines called "radiopharmaceuticals", which contain a small amount of radioactivity. When a radiopharmaceutical is injected, it collects in a specific organ or area of the body for a short time and this small amount of radioactivity can be detected from outside the body using special cameras. An image, known as a scan, can be taken. This scan will show exactly where the radioactivity is inside the organ and the body. This can give the doctor valuable information about how that organ is working and help in deciding on possible treatment. In the case of Striascan, collection is observed in area of the brain. Changes in this area of the brain occur in Parkinsonism (including Parkinson's disease) and dementia with Lewy bodies.

(See SmpC for the full indication).

Further information about the evaluation of Striascan's benefits can be found in Striascan's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Striascan, together with measures to minimise such risks and the proposed studies for learning more about Striascan, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of Striascan is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Striascan are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Striascan. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation.

There are no studies which are conditions of the marketing authorisation or specific obligation of Striascan.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Striascan.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.