22 April 2021
EMA/323721/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Celsunax

International non-proprietary name: ioflupane (^{123}I)

Procedure No. EMEA/H/C/005135/0000

Note

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

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List of abbreviations

^{123}I	Iodine-123
5-HT	serotonin
β-CIT	123I-2β-carboxymethoxy-3β-(4-iodophenyl-nortropane)
β-CIT-FE	123I-2β-carboxymethoxy-3β-(4-iodophenyl)N—(2-fluoroethyl)-nortropane
β-CIT-FP	123I-2β-carboxymethoxy-3β-(4-iodophenyl)N—(2-fluoropropyl)-nortropane
DA	dopamine
DAT	dopamine transporter
DOSEai	maximum daily dose consumed per inhabitan
EOS	End of synthesis
ERA	Environmental Risk Assessment
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICP-MS	Inductively coupled plasma mass spectrometry
IP-β-CIT	isopropyl ester of β-CIT
IP-β-CIT-FE	isopropyl ester of β-CIT-FE
IP-β-CIT-FP	isopropyl ester of β-CIT-FP
IR	Infrared
FDOPA	6(18F)fluoro-L-3,4-dihydroxyphenylalanine
Fpen	(Market) Penetration Factor
GLP	Good Laboratory Practise
LoQ	List of Questions
MBq	Megabecquerel
NMR	Nuclear Magnetic Resonance
PEC	Predicted Environmental Concentration
PET	positron emission tomography
Ph. Eur.	European Pharmacopoeia
TLC	Thin layer chromatography
TTC	Toxicoloical Treshold Concentration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant applied for the following indication:

This medicinal product is for diagnostic use only.

Celsunax 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.
  Celsunax 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.
  Celsunax is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

The legal basis for this application refers to article 10(1), Generic of DaTSCAN, a Centrally Authorised Medicinal Product.

The application submitted is composed of administrative information, complete quality data.

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.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
31 May 2018	EMEA/H/SA/3820/1/2018/SME/I	*Minne Casteels, Mario Miguel Rosa*

The Scientific advice pertained to the following *clinical* aspects:

- *Need for in vivo bioequivalence studies.*

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: N/A

The application was received by the EMA on	1 July 2019
The procedure started on	18 July 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 October 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 October 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 October 2020
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 October 2020

The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 & 18 February 2021
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 & 13 April 2021
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 Celsunax on	22 April 2021

2. Scientific discussion

2.1. Problem statement

Ioflupane (^{123}I) (Celsunax) 74 MBq/ml solution for injection is a diagnostic radiopharmaceutical product, ATC code: V09AB03. It is a generic to the reference medicinal product DaTSCAN™ 74 MBq/mL solution for injection from GE Healthcare, which is approved since 2000 in the European Union according to Regulation (EC) 726/2004 under the marketing authorisation numbers EU/1/00/135/001 and EU/1/00/135/002.

Ioflupane is a cocaine analogue. Studies in animals have shown that ioflupane binds with high affinity to the presynaptic dopamine transporter and so radiolabelled ioflupane (^{123}I) can be used as a surrogate marker to examine the integrity of the dopaminergic nigrostriatal neurons. Ioflupane also binds to the serotonin transporter on 5-HT neurons but with lower (approximately 10-fold) binding affinity.

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 10^{14} 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 10^{14} Bq/mmol) at reference time.

Other ingredients are glacial acetic acid, sodium acetate trihydrate, ethanol (96 percent) and water for injections

The product is available in glass vial (Type I) with a rubber stopper and a flip cap as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of ioflupane (^{123}I) is methyl (1R,2S,3S,5S)- 3-(4-iodophenyl)- 8-(3-fluoropropyl)- 8-azabicyclo[3.2.1]octane- 2-carboxylate corresponding to the molecular formula $C_{18}H_{23}F_{123}INO_2$. It has a relative molecular mass of 427.29 g/mol and the following structure:

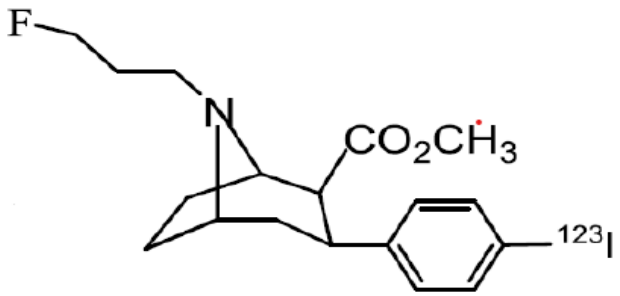

Figure 1: Active substance structure

As the active substance is not isolated during the manufacturing process, the cold analogue ioflupane (^{127}I) was used for structure elucidation. The chemical structure of ioflupane (^{127}I) was elucidated by a combination of ^{1}H NMR and ^{19}F NMR spectra.

The potential for isomerism is limited, as only highly purified chemical precursor (TMSCT-FP, purity of ≥ 95%) with four chiral centres (1R, 2S, 3S, 5S) is used in the manufacturing process. The weakness of the carbon-tin bond of the chemical precursor (TMSCT-FP) readily gives regiospecific radioiodination of the chemical precursor without changing the four-existing chiral centres (1R, 2S, 3S, 5S). Therefore, the destannylation method prevents formation of other isomers. The resulting active substance ioflupane (^{123}I) has four chiral centres (1R, 2S, 3S, 5S), just as for ioflupane (^{127}I).

Ioflupane (^{123}I) contains an atom of the photon emitting radionuclide ^{123}I. ^{123}I decays through electron capture (100%) to the nearly-stable isotope tellurium-123 (^{123}Te), through emission of electrons, X-ray and gamma radiation. The emitted gamma radiation has a predominant energy of 159 keV, which is primarily used for imaging purposes (Single Proton Emission Computer Tomography). Due to the short half-life of ioflupane (^{123}I), the physiochemical characteristics of its "cold" analogue ioflupane (^{127}I) are presented. The "cold" analogue only differs from the active substance in terms of lack of radioactivity and molecular weight due to replacement of the ^{123}I by the ^{127}I atom. The "cold" analogue is a white to off white solid soluble in water and chloroform.

Manufacture, characterisation and process controls (Active substance)

The manufacture of the active substance ioflupane (^{123}I) is a continuous process carried out in closed systems. As a consequence, it is not isolated. Ioflupane (^{123}I) is synthesised via oxidative iododestannylation of the chemical precursor trimethylstannyl-CTFP (TMSCT-FP) with the radionuclide ^{123}I. During the synthesis, the non-radioactive isotope ^{127}I is added, which reacts with TMSCT-FP to form ioflupane (^{127}I).

The active substance is synthesised in 3 main stages:

1. Manufacture of precursor (TBSCT-FP)
2. Manufacture of Sodium Iodide (^{123}I) solution (Na^{123}I)
3. Manufacture of final active substance (Ioflupane (^{123}I)

1. Precursor: TBSCT-FP

According to the Guideline on Radiopharmaceuticals, information on chemical precursors is presented in a separate section 3.2.S in Module 3.

General information (Precursor)

The chemical name of the precursor (TBSCT-FP) is *(1R,2S,3S,5S)-methyl-8-(3-fluoropropyl)-3-(4-(trimethylstannyl)phenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate* corresponding to the molecular formula $C_{21}H_{32}FNO_2Sn$. It has a relative molecular mass of 468.19 g/mol and the following structure:

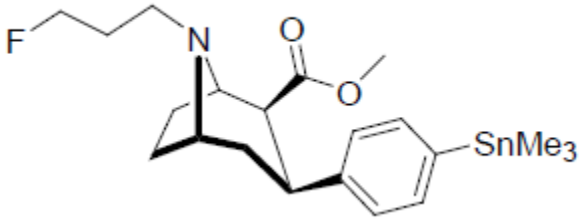

Figure 2: Precursor (TBSCT-FP*)* structure

The chemical structure of the precursor was elucidated by a combination of ^{1}H-NMR, ^{119}Sn-NMR, ^{13}C-NMR, IR, and HPLC.

TBSCT-FP (also known as SCTP- 09) is a colourless to yellowish oil soluble in organic solvents such as acetonitrile, dichloromethane and ethyl acetate, and slightly soluble in water.

TMSCT-FP is a stereoisomeric compound. Cocaine hydrochloride is used as structure providing starting material (chiral pool) of the synthesis. The stereochemistry of the bridgehead atoms in cocaine is fixed and controls further chemical conversions. The use of cocaine has the advantage, that the tropane structure is already part of the molecule and has not to be synthesized by a complicated diastereoselective synthesis.

Manufacture, characterisation and process controls (Precursor)

The precursor is synthesized in 8 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 active substance 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.

The active substance is packaged in clear glass vial and closed by a chlorobutyl sealing cone and screw caps which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification (Precursor)

The precursor specification includes tests for appearance (visual), identity (HPLC, ^{1}H-NMR, ^{119}Sn-NMR, IR), impurities (HPLC), residual solvents (GC), heavy metals (ICP-MS), assay (difference calculation), bioburden (Ph. Eur.), and bacterial endotoxins (Ph. Eur.)

The limits for related substances and total impurities were chosen according to current Ph. Eur. monograph number 2902 "Chemical precursors for pharmaceutical preparations".

The impurity A is the main "by-product" of synthesis and will be removed via flash chromatography during the synthesis. It could also arise as a cold analogue of certain radiopharmaceutical products in the manufacturing process. It has therefore to be limited to a very low level in order to achieve high radiospecific yield. The process validation data confirm this limit as acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, purity and assay testing has been presented.

Batch analysis data (7 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability (Precursor)

Stability data from 3 validation batches of the precursor from the proposed manufacturers stored in the intended commercial package for up to 24 months under long term conditions (−20°C ± 5°C) and 1 validation batch for up to 6 months under accelerated conditions (5°C ± 3°C and) according to the ICH guidelines were provided. Due to the high viscosity of the precursor, the vials were stored in upright position.

Stress stability testing was carried out in one validation batch at 30°C ± 2°C and 75% ± 5% RH for up 14 days to address the effects of short term excursions during handling and transportation. The aforementioned storage conditions should be sufficient to cover storage, shipment and subsequent use.

The following parameters were tested: appearance, purity, assay, and microbiology.

Under long term conditions, no decrease in quality was detected and the purity remained at about 100%. Under accelerated conditions, the results complied with the specification. At stress conditions, all tested parameters met the acceptance criteria.

The CHMP recommended to provide stability testing results for the precursor (TMSCT-FP) for last testing point 24 months (REC 001)

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months if the product is stored in a freezer in the proposed container.

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

During evaluation, the CHMP stated that information on ^{123}I provided in different sections was found too brief and inconclusive. Therefore, it was requested as Major Objection (MO) that the applicant should provide whole 3.2.S section dossier for ^{123}I describing in detail the quality of this material. Especially, the manufacturing process of the radionuclide precursor sodium iodide (^{123}I) solution for radiolabelling should be described in detail starting with the cyclotron production, the targeting, the irradiation conditions, the radionuclide intermediates (Cs-123 and Xe-123), the chemical intermediates (I-123 in higher oxidation states than [^{123}I]iodide), the transfer to the separation and purification process and ending with the dispensing process. The specification and quality control methods should be described and justified. Starting material should also comply with relevant Ph. Eur. requirements for solution for radiolabelling. This information was provided in a separate section Sodium iodide (^{123}I) solution (see below) by the applicant and it was considered satisfactory.

General information

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

Sodium Iodide is a clear and colourless solution with a half life of 13.2 hours

Sodium Iodide (^{123}I) bulk solution contains the active ingredient, ^{123}I, in the form of sodium iodide (Na^{123}I) in 0.02 M sodium hydroxide solution.

^{123}I decays with a half-life of 13.2 hours into ^{123}Te by electronic capture (no β^+ emission). There is an excited transition state involved, which is different from ^{123m}Te.

Manufacture, characterisation and process controls

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

The cyclotron principle is to accelerate charged particles inside an acceleration chamber under reduced pressure. These particles pass repeatedly through a high frequency electric field for acceleration and they are guided on a circular path by a magnetic field. The proton beam is extracted from the cyclotron and is guided into the transport channel of the beam leading to an irradiation casemate. The gas target includes a pressure vessel as target body with pressurized gas. It is made of an AlMgSi alloy, the inner walls are

chemically Ni-plated. During irradiation the target body is wate cooled. It is separated from the transport channel of the proton beam by a thin molybdenum window.

Before irradiation, xenon (^{124}Xe) enriched gas is stored in a cylinder placed in the irradiation casemate and it is transferred to the target body by cryogenic pumping. The xenon gas is enriched with ^{124}Xe up to more than 99.7%. Irradiation of xenon (^{124}Xe) enriched gas is performed under a suitable pressure with a proton beam characterized by an initial energy of (30 $\pm$ 1) MeV and with a current ≤120 μA for a minimum of about 3 hours.

^{123}I is produced as iodide. Radiochemical impurities consist of oxidized forms of iodine, mainly iodate ($^{123}IO_3$), and unspecified higher oxidation states of iodine. To avoid any oxidation of iodide (^{123}I) during production of the sodium iodide (^{123}I) bulk solution, all the reagents used are purged with helium.

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 active substance 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.

Sodium iodide is packaged in injection vial with rubber stopper and aluminium crimp cap which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

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. The intermediate specification includes tests for appearance (visual), pH (pH indicator strips), bacterial endotoxins (Ph. Eur.), identity (γ-spectrometry, TLC), radiochemical purity (TLC), radionuclidic purity (γ-spectrometry), and maximum specific activity.

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 (4 commercial scale batches) of the intermediate (sodium iodide (^{123I}) solution) are provided. The results are within the specifications and consistent from batch to batch.

Stability

Four sample batches were prepared and analysed for radiochemical and radionuclidic purity at time of manufacture and at t = 48 h.

As is expected, the radiochemical purity is not affected at all over time. If the process of purification, concentration and dispensing runs according to validated procedures, there is no transformation of ^{123}I-iodide into ^{123}I-iodate or into other higher oxidation states of iodine to be expected. Thus, radiochemical purity is not a determining factor in setting the shelf life.

The general picture in case of radionuclidic purity, however, is different. At first, short lived impurities will decay faster than ^{123}I, increasing radionuclidic purity. In the course of time, the longer-lived impurities take over while 1^{23}I decays further, decreasing radionuclidic purity.

From these considerations a shelf-life of between 40 and 60 hours post-calibration (65-85 hours post manufacturing) was accepted.

3. Active substance (Ioflupane (^{123}I))

The manufacture of the active substance ioflupane (^{123}I) is a continuous process carried out in closed systems. As a consequence, it is not isolated prior to the finished product manufacturing process. The manufacturing process is, therefore, described in detail in the finished product section.

Specification (Active Substance)

The 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 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 is a sterile clear colourless solution for injection containing the active substance ioflupane (^{123}I), with 2.5 ml and 5 ml in a 10 ml glass vial. Each ml of solution contains 74 MBq ioflupane (^{123}I) (specific activity range 2.5 to 4.5 x 1014 Bq/mmol) at reference time. Reference time is equal to 28 hours after the end of synthesis (EOS). This corresponds to 0.07 to 0.13 μg/ml ioflupane (^{123}I

Celsunax is a generic version of the centrally authorized medicinal product DaTSCAN™ 74 MBq/mL solution for injection which was approved in the European Union in 2000. Ioflupane (^{123}I) solution for injection is to be administered intravenously and indicated for the visualisation of dopaminergic transporters. The choice was based on activity levels compatible with both the quality control appropriate to the manufacturing process and occupation of transporter sites without producing any human pharmacological effect (1%).

The active substance ioflupane (^{123}I) is a cocaine analogue and is not isolated. Ioflupane (^{123}I) is formed from the chemical precursor trimethylstannyl-CTFP (TMSCT-FP) via oxidative iododestannylation with sodium (^{123}I)-iodide. The finished product also contains the non-radioactive analogue ioflupane (^{127}I). Each of the molecules TMSCT-FP chemical precursor, ioflupane (^{123}I) active substance and ioflupane (^{127}I) non-radioactive analogue) is present as a single stereoisomer (1R,2S,3S,5S). This isomer is chosen because of the known pharmacological activity of natural (1R)-cocaine and its derivatives.

The available stability data demonstrate the compatibility of the active substance with the excipients and the stability of the active substance in the formulation.

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 finished product has an identical qualitative and quantitative composition as the reference medicinal product. The non-radioactive analogue ioflupane (^{127}I) is also present, which derives from the reaction between sodium iodide (^{127}I) and the chemical precursor under the same manufacturing conditions. Sodium iodide (^{127}I) solution is used to rinse the nuclide vial containing sodium iodide (^{123}I) to obtain the targeted specific activity.

The quality target profile (QTTP) contains quality characteristics that are equivalent to the reference medicinal product.

There were not provided any data on comparability of the generic and the reference medicinal product. Therefore, the CHMP requested as Major Objection (MO) to provide information on comparability results that justify the critical quality attributes for the generic medicinal product. In particularly, comparison on the amount of Ioflupane (127I) and on the impurity profiles for both products should be discussed. The comparative impurity profile was determined between the proposed radiopharmaceutical product Ioflupane (^{123}I) solution for injection and the reference medicinal product using the HPLC method. In the study performed, identical impurity amounts are observed for reference medicinal product and the proposed radiopharmaceutical product. No differences in the levels of related substances have been observed. Based on the results obtained, it can be concluded that the generic medicinal product has the same impurity profile as that of the reference medicinal product. Therefore, there are no safety concerns regarding the impurities in the proposed radiopharmaceutical product.

The finished product is administered as intravenous injection. For injectable solutions, the following parameters are mandatory: suitable osmolality, tolerable pH, sterility, controlled level of bacterial endotoxins, and free of visible particles. Due to the small intravenous injection volume of each dose, osmolality is not considered and, therefore, not specified. The pH was thoroughly studied in the past and is known as a factor influencing the radiochemical purity, an acidic pH was found most favourable, which is similar to the pH value of the reference medicinal product. The pH is maintained by a buffer system formed by of acetic acid, glacial and sodium acetate trihydrate. Sterility and controlled level of bacterial endotoxins are assured by aseptic processing in controlled environment. Minimisation of particulate impurities is assured by manufacturing in a controlled environment.

Ethanol is used to solubilise the active substance. It also serves as radical scavenger for radical species formed by irradiation of aqueous solutions, thereby stabilising the radioligands. The concentration of ethanol 96 per cent in the finished product is identical to the percentage used in the reference product. A small percentage of ethanol is useful for the solubility of the ioflupane, which is lipophilic and only moderately soluble in water. Therefore, complete removal of ethanol by evaporation would significantly reduce the radiochemical purity. Stability studies showed that the finished product was stable in the formulation containing the chosen amount of ethanol 96 per cent.

The manufacturing process consists of the following steps: radiosynthesis of ioflupane (^{123}I), purification of ioflupane (^{123}I), formulation and dilution, and sterile filtration and aseptic dispensing.

The radiosynthesis and purification of ioflupane (^{123}I) are carried out in an automated synthesis module. The use of an automated synthesis module can potentially reduce operator radiation dose and operator assistance time and allows precise dosing of the components needed for the production of ^{123}I-ioflupane. Radiosynthesis and purification are completed after the start of the synthesis. The production process is

relatively fast and can thus cope with the short half-life of the radioisotope. The automated synthesis module runs through a computer program that opens and closes valves in the right time and order. Liquid is transported through the tubes by inert gas pressure. Addition and withdrawal of solutions occurs by syringe or cannula. The synthesis is performed automatically. Purification of the crude active substance ^{123}I-ioflupane is performed by semi-preparative reverse phase high performance liquid chromatography to reach acceptable purity of the finish product.

Concerning the sterilisation of the finished product, for the reference medicinal product DatSCAN measurements of radiochemical purity were made on vials of the product autoclaved at 121°C for at least 15 minutes. The results of these measurements proved unacceptable, with a fall in radiochemical purity of 20% being recorded, demonstrating that ^{123}I-ioflupane is a heat-unstable molecule. Due to non-feasibility of sterilisation of the finished product in its final container closure system, terminal heat sterilization has been replaced with a combination of aseptic filtration and aseptic processing following the EMA decision trees for selections of sterilisation methods.

To ensure sterility, the manufacturing process takes place in a controlled, classified area. The automated synthesis module is placed inside a lead-shielded hot cell equipped with a laminar flow to achieve a grade A clean room environment. Sterile radionuclide vials, bulk vials, product vials, filters (for venting or dispensing), cannula, syringes are single-used items that are pre-sterilised. Wherever possible, sterile starting materials are used. Otherwise, solutions are pre-filtered before use (e.g. diluent and formulation buffer). Peracetic acid, hydrogen peroxide, acetic acid and ethanol 96% are not presumed to support growth or survival of microorganisms and are therefore not sterile-filtered.

Following radiosynthesis the product is manufactured by aseptic assembly, i.e. sterile filtration (with relevant control of bioburden and bubble point testing), and subsequent filling of the product into pre-sterilised containers under EU grade A environment in a grade C room. As the qualitative and quantitative composition of the finished product is identical to that of the reference medicinal product, sterile filtration has been chosen as the method of sterilisation. Due to the lipophilic character of the finished product ^{123}I-ioflupane, it could stick onto the membrane during final sterile membrane filtration. To ensure optimal sterile filtration, a sterile nylon membrane is used and the finished product solution is manufactured to have a suitable ethanol concentration and pH. As in-process control, the filter integrity test (bubble-point test) is performed after filtration. The filter integrity is tested after sterile filtration of the product only. There is no filter integrity test performed before sterile filtration as all filter units have been tested for integrity by the manufacturer. For transportation they are individually packed, and the packaging is qualified by the manufacturer. Therefore, the risk of damage of the filter during transportation is very low. In addition, the filter needs to be wetted with water prior to integrity testing. This exposes the filter to the risk of contamination. To minimize this risk, the filter package is opened immediately before sterile filtration.

Validation of the filtration process for the finished product was performed with a non-radioactive ioflupane solution and the sterilizing grade filter elements as used during the manufacturing process. The following tests were addressed within the scope of this validation study: viability test, bacteria challenge test, chemical compatibility test, extraction procedure, and analysis for leachables. All the results were considered acceptable.

The primary packaging is a glass vial (Type I) with a rubber stopper and a flip cap. The material complies with Ph. Eur. and EC requirements. To show the integrity of the container closure system, the self-sealing

test and dye ingress test according to Ph. Eur. was performed. The results demonstrate the integrity of the container closure system.

Manufacture of the product and process controls

The manufacturing process consists of 4 main steps: radiosynthesis of ioflupane (^{123}I), purification through semi-preparative HPLC; formulation and dilution, and sterile filtration and dispensing. The process is considered to be a non-standard manufacturing process.

A "closed" filling technique of the vials is used by inserting the filling needle through the rubber closure of a closed vial, leading to a finished product with a pierced closure. Considering that the finished product (sterile aqueous buffered solution without a microbiological preservative) will be stored in a vial with two holes pierced in rubber closure for longer than one working day – the sterility of the finished product is not considered assured throughout its shelf-life. The container integrity of the sterile solution should be unharmed. The CHMP requested as Major Objection to use an "open" filling technique in a class A environment with a stoppering of the vials with the closure after the filling of the product solution in the open vial. The applicant provided justification that "closed filling" technique developed at manufacturing site is appropriate to consistently produce sterile medicinal products. Considering that the finished product manufactured with use of "closed" filling procedure (sterile aqueous buffered solution without a microbiological preservative) will be stored for longer than one working day in a vial with two holes pierced in rubber closure – the sterility of the finished product was still not considered assured throughout its shelf-life. Therefore, the CHMP again requested that "open" filling technique should be implemented, or in case that the "closed" filling technique (puncturing of the stopper) is still used that the shelf-life of the finished product should be reduced to not more than 24 hours after EOS (end of synthesis). The applicant agreed to reduce the shelf-life of the finished product to 24 hours after EOS.

Due to the nature of this finished product, no intermediates are formed during the manufacture. The control of the manufacturing process is assured by the automated synthesis module, including a number of controls (so called virtual switches).

For the process validation, at least 3 consecutive manufacturing runs were performed. Stability testing of the radiopharmaceutical product was performed for at least 3 of the manufactured batches. For those batches, the radiochemical stability of the radiopharmaceutical product was evaluated in addition to the routine quality control testing for batch release at the end of the shelf-life.

Sterility testing requires a complete radioactive decay of the radiopharmaceutical product sample, which is a very long time after process validation to perform. Therefore, 3 bioburden runs were performed parallel to process validation. These bioburden runs were performed without radioactivity while simulating the routine production runs as much as possible and facilitated rapid evaluation of the microbiological purity of the manufacturing process.

The validation has been successfully performed. Data from both the chemical and microbiological validation runs performed confirm the suitability and robustness of the synthesis module and the computer program for the production of ^{123}I-ioflupane solution for injection.

The in-process controls are adequate for this type of product.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: activity (ionization chamber and weighing), radioactivity concentration at ART (ionization chamber), radionuclide identity (gamma-ray-spectrometry, HPLC), pH (Tests trips), appearance of solution (visual inspection), specific activity at ART (ionization chamber, HPLC), radionuclidic purity (according to manufacturer's certificate of analysis), radiochemical purity (HPLC), ethanol content (GC), bacterial endotoxins (Ph. Eur.), and sterility (Ph. Eur.).

The applicant should assure a full release testing of the finished product without the use of analytical data deriving from the manufacturer of sodium iodide (^{123}I). Control of the radionuclidic purity is required on the final product as described by the Ph. Eur for radiopharmaceutical products. Therefore, the CHMP recommended to develop and implement its own analytical method to control of the radionuclidic purity in final finished product (REC 002).

Regarding the radionucledic purity, the acceptance criterion is set according to the Ph. Eur. Monograph "Sodium iodide (^{123}I) solution for radiolabelling".

As a Ph. Eur. monograph for this radiopharmaceutical does not exist, the limits of radiochemical purity are set based on the Ph. Eur. monograph for ^{123}I-containing radiopharmaceutical (Iobenguane (^{123}I) injection). The specification for radioactivity due to ^{123}I-IFP is set tighter than the limit (minimum 95%) mentioned in the ^{123}I-containing radiopharmaceutical product (Iobenguane (^{123}I) injection). The limit for end of shelf-life specification is lower as it is common practice for radiopharmaceuticals (e.g. labelled with ^{18}F). The specification for free ^{123}I-iodide corresponds to the limit mentioned in the ^{123}I-containing radiopharmaceutical (Iobenguane (^{123}I) injection). This limit was set based on comparability results with the reference medicinal product.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

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.

Stability of the product

Due to the short half-life of ^{123}I (13.2 hours), the radiopharmaceutical product ^{123}I-ioflupane is typically meant for immediate use and its administration to patients immediately follows the preparation and quality control operations. A stability study was performed with samples (10 mL) withdrawn from three radiopharmaceutical batches, transferred to primary packaging vials and sealed. Those vials were placed in

an upright position and stored at room temperature in a shielded area for 35 hours after the end of synthesis (EOS). Samples were tested for pH, appearance of the solution and radiochemical purity. The analytical procedures used are stability indicating.

A decrease in ^{123}I-IFP by 2-3% was observed in the three tested radiopharmaceutical product batches, which was probably due to radioactive decay of the radiopharmaceutical over time. This was accompanied by an increase of free ^{123}-I by 2% in the three tested radiopharmaceutical product batches. However, both parameters still met the specifications 35 hours after EOS. No unspecified radiochemical impurities were detected. The three tested radiopharmaceutical batches also met the specifications for the pH and appearance of solution 35 hours after EOS. Based on the available stability data, the proposed shelf-life of ^{123}I-ioflupane is 7 hours from the activity time stated on the label, which corresponds to 35 hours after the end of synthesis.

Due to changes in manufacturing process, quality control and product specifications, a new stability study was performed. This was to replace the initial stability data. Stability data from 3 commercial scale batches per dose strength (2.5 mL and 5.0 mL) of finished product stored for up to EOS + 35 h under long term conditions (5 ± 3°C) and for up to EOS + 35 h for the 2.5 ml vials and EOS + 48 h under accelerated conditions (25 ± 2°C / 60 ± 5% RH and 40ºC / 75% RH) 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. During stability storage the samples were placed in lead containers. For two batches the vials were stored in upright position. For one batch the vials were stored in inverted position. Each product vial was only used for one stability testing and was then discarded. Samples were tested for pH, appearance of the solution and radiochemical purity. The analytical procedures used are stability indicating.

For 2.5 mL strength, all parameters met the specifications 35 hours after EOS when stored at 5±3°C, 25±2°C / 60±5% RH, in upright position, and at 40± 2°C / 75 ± 5% RH in inverted position.

For 5 mL strength stored at 5±3°C, 25±2°C/60±5% RH in upright position and at 40± 2°C / 75 ± 5% RH in inverted position, all parameters met the specifications 48 hours after EOS.

As mentioned above the applicant choose to keep a "closed" filling technique of the vials, therefore the shelf-life of the finished product is reduced to 24 hours and the CHMP recommended to provide results of sterility testing for batches for the three finished product batches after the completion of stability study (after full radioactive decay). (REC 003)

Based on available stability data, the proposed shelf-life of 24 hours from the end of the synthesis (EOS) time stated on the label and storage conditions: do not store above 25°C, do not freeze and store in the original lead shielding 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, pharmaceutical and biological 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.

Several issues were requested as MOs during the evaluation, it was requested to provide information for ^{123}I describing in detail the quality of this material, to provide information on comparability testing results between the generic and reference medicinal products, and to justify the use an "open" filling technique for the vials. All these issues were resolved satisfactorily.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to provide stability testing results for TMSCT-FP for last testing point 24 months, to develop and implement its own analytical method to control of the radionuclidic purity in final finished product, and to provide results of sterility testing for batches for the three finished product batches after the completion of stability study (after full radioactivity decay). These points are put forward and agreed as recommendations for future quality development

At the time of the CHMP opinion, there were a number of minor unresolved quality issues 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. Recommendations 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 points for investigation:

1. to provide stability testing results for TMSCT-FP for last testing point 24 months (REC 001)
2. to develop and implement its own analytical method to control of the radionuclidic purity in final finished product (REC 002)
3. to provide results of sterility testing for batches for the three finished product batches after the completion of stability study (after full radioactivity decay) (REC 003)

2.3. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of ioflupane (^{123}I) are well known. As this is widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is appropriate.

2.3.1. Ecotoxicity/environmental risk assessment

The risk of an adverse environmental impact from use of ioflupane (^{123}I) was evaluated in the environmental risk assessment Phase 1. ERA expert calculated predicted environmental concentration (PECSURFACEWATER) of drug substance using the EMA guideline pre-screening equation.

PECsurfacewater = 0,00000000017µg/L

The lipophilicity of ioflupane has not been experimentally determined.

logKow (LogP) calculated values range from 3.7 to 4.24.

The applicant assumed that the proposed drug product ioflupane (^{123}I) solution for injection is unlikely to represent a risk for the environment, following its prescribed usage in patients.

The calculated PEC SURFACE WATER value is far below 0.01 µg/L and according to the guideline, the assessment of the potential risks to the environment for Ioflupane (^{123}I) drug product is terminated and there is no need to go to phase II (Environmental fate and effects analysis).

2.3.2. Discussion on non-clinical aspects

The applicant submitted relevant data on quality aspects that might have a potential impact on the toxicological profile of the Celsunax product. This data meets the requirements of Annex I, Part I and II, of the European Dir. 2001/83/EC for generic products.

No toxicological concern can be derived from the composition or the impurity profile of ioflupane (^{123}I). The impurity profile is comparable to the reference medicinal product DaTSCAN.

2.3.3. Conclusion on the non-clinical aspects

There are no objections to accept the non-clinical documentation of Celsunax solution for injection.

2.4. Clinical aspects

2.4.1. Introduction

The applicant requested scientific advice from EMA to clarify whether the guideline on the investigation of bioequivalence is valid for a generic radiopharmaceutical intended for diagnostic purposes (EMA/CHMP/SAWP/302444/2018; Procedure No.: EMEA/H/SA/3820/1/2018/SME/I).

Ioflupane (^{123}I), solution for injection has an identical qualitative and quantitative composition compared to the approved reference medicinal product DaTSCAN™. Since ioflupane (^{123}I) is a chemical entity, the CHMP considered ioflupane (^{123}I), solution for injection to fall within the scope of the guideline on the investigation of bioequivalence. The opinion of QWP and Radiopharmaceutical WP of the CHMP was also requested. It was agreed that both the reference product and the present product share identical "hot and cold" forms of ioflupane in the composition. If the ratio of "hot" and "cold" form is the same, the specific radioactivity should be the same and the effect is expected to be the same. No additional in vivo studies in view of potentially different in use and in vivo stability of the generic are requested.

Following the scientific advice given by the CHMP, the applicant did not conduct new non-clinical or clinical trials with the active substance ioflupane (^{123}I).

2.4.2. Pharmacokinetics

No bioequivalence study was submitted to support the application and no study is required according to the Guideline on the Investigation of Bioequivalence as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. The excipients of both products are qualitatively the same for both formulations. All excipients comply with Ph. Eur. Monographs.

2.4.3. Discussion on clinical aspects

The clinical overview of the clinical pharmacology, efficacy and safety has been provided and is adequate. Celsunax is to be administered as an aqueous solution for injection for intravenous use containing the same active substance in the same concentrations as the currently authorised originator product.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr** Appendix II) no bioequivalence studies are required for intravenously administered aqueous solutions if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

A 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 (^{123}I) and the same pharmaceutical form and route of administration as an aqueous solution for injection for intravenous use are applied for. The excipients of the proposed generic medicinal product are identical to the reference product DaTSCAN.

Celsunax is considered essentially similar to DaTSCAN (GE Healthcare Limited).

2.4.4. Conclusions on the clinical aspects

Celsunax is considered essentially similar to DaTSCAN (GE Healthcare Limited). There are no objections to the approval of Celsunax from a clinical point of view.

2.5. Risk Management Plan

Safety concerns

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

Pharmacovigilance plan

The PRAC and CHMP agreed that routine pharmacovigilance activities, including collection and reporting of adverse reactions, and signal detection are considered sufficient to monitor the safety of the medicinal product in the licensed indication. No additional pharmacovigilance activities are deemed necessary.

Risk minimisation measures

The PRAC and CHMP agreed that routine risk minimisation measures are considered sufficient. The safety information in the PI is aligned with the originator product.

Conclusion

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

2.6. Pharmacovigilance

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.

2.7. Product information

2.7.1. 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

3.1. Conclusions

The overall B/R of Celsunax is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Celsunax is favourable in the following indication:

This medicinal product is for diagnostic use only.

Celsunax 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.
Celsunax 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.
Celsunax 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.