COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Monlutenca 40 GBq/mL radiopharmaceutical precursor, solution (Lutetium (^{177}Lu) chloride)

NL/H/5520/001/DC

Date: 6 February 2025

This module reflects the scientific discussion for the approval of Monlutenca 40 GBq/mL radiopharmaceutical precursor, solution. The procedure was finalised on 4 November 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

^{177}Lu	Lutetium (177Lu) chloride
ART	Activity reference time
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
N.C.A.	No-carrier added
PBT	Persistent, bioaccumulative and toxic substance
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
µg	microgram

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Monlutenca 40 GBq/mL radiopharmaceutical precursor, solution, from Monrol Europe SRL.

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted via a decentralised procedure pursuant to Article 10a of Directive 2001/83/EC, which concerns a well-established use (WEU) application. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Lutetium (^{177}Lu) chloride was first introduced to the European market as a radiopharmaceutical precursor more than ten years ago. It has been widely used for many years and has a recognised efficacy and an acceptable level of safety. Lutetium (^{177}Lu) chloride was previously authorised in the European Union via centralized procedures under the trade names Lumark (EMEA/H/C/002749 by I.D.B. Radiopharmacy B.V., since 2015) and EndolucinBeta (EMEA/H/C/003999 by ITM Medical Isotopes GmbH, since 2016). For Monlutenca, the MAH has submitted an adequate clinical overview. As Monlutenca is a radiopharmaceutical precursor, bridging between the proposed drug product and the products used in the literature is not applicable.

The concerned member states (CMS) involved in this procedure were Austria, Belgium and Germany. A repeat-use procedure (NL/H/5520/001/E/001) has been used to register the product in France, Italy, Portugal, Spain and Sweden.

Monlutenca is a radiopharmaceutical product and therefore should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation. The required precautions regarding these matters, have been included in the labelling, package leaflet and SmPC of the product. Monlutenca is a radiopharmaceutical precursor solution, which contains lutetium (^{177}Lu) chloride as drug substance. Monlutenca should not be administered directly to the patient. It is intended for *in vitro* radiolabelling of medicinal products which are subsequently administered by the approved route. This product is only to be used by specialists experienced with *in vitro* radiolabelling. For instructions on preparation of the medicinal product before administration, see section 12 (Instructions for preparation of radiopharmaceuticals) of the SmPC.

II. QUALITY ASPECTS

II.1 Introduction

Monlutenca 40 GBq/mL is a radiopharmaceutical precursor, solution. It is a clear colourless solution. 1 mL solution contains 40 GBq lutetium (^{177}Lu) chloride on activity reference time (ART), corresponding to 10 micrograms of lutetium (^{177}Lu) chloride. The minimal specific activity is 3000 GBq/mg lutetium (^{177}Lu) chloride at ART. The product is presented in 3, 10 and 20 mL vials:

- Each 3 mL vial contains an activity from 1 to 120 GBq, corresponding to 0.25-30 µg lutetium (^{177}Lu), at ART. The volume is 0.025-3 mL.
- Each 10 mL vial contains an activity from 1 to 200 GBq, corresponding to 0.25-50 µg lutetium (^{177}Lu), at ART. The volume is 0.025-5 mL.
- Each 20 mL vial contains an activity from 1 to 600 GBq, corresponding to 0.25-150 µg lutetium (^{177}Lu), at ART. The volume is 0.025-15 mL.

Lutetium (^{177}Lu) emits both medium-energy beta particles and imageable gamma photons and has a half-life of 6.6 days. The primary radiation emissions of lutetium are described in the SmPC.

The only excipient in this product is diluted hydrochloric acid.

The radiopharmaceutical precursor solution is packaged in:
Primary package:

- colourless glass 3 mL and 10 mL vials, closed with bromobutyl stoppers and aluminium over seals.
- colourless glass 3 mL, 10 mL, 20 mL vials closed with fluoropolymer coated bromobutyl stoppers and aluminium over seals.

The volume filled in the vials can vary in the ranges of 0.025-3 mL, 0.025-5 mL and 0.025-15 mL, respectively.

Secondary package - Lead shield.

II.2 Drug Substance

The active substance is lutetium (^{177}Lu) chloride, is an established active substance which is described in the European Pharmacopoeia (Ph.Eur.). The active substance is produced as solution in diluted hydrochloric acid and is not isolated in the production process, which is usual for a radionuclide. As the active substance is in dissolved form, before incorporation into the finished product which is also a solution, control of particle size and polymorphism is not considered necessary.

Manufacturing process

Lutetium (^{177}Lu) chloride radiopharmaceutical precursor solution formulation is manufactured in a continuous process starting with the irradiation of the starting material to the manufacturing of the finished product. The active substance is not isolated during the production process. The fully manufacturing process is described in section II.3 Medicinal Product of this PAR.

Quality control and stability of drug substance

The product is manufactured under a one way process and the drug substance is not isolated during the process. Therefore, control and specifications are only applicable for the target material and the finished medicinal product. These specifications are considered adequate to control the quality and meets the requirements of relevant guidelines for radiopharmaceuticals.

II.3 Medicinal Product

Pharmaceutical development

The aim of the pharmaceutical development was to develop a sterile finished product according to the Ph.Eur. for lutetium (^{177}Lu) solution for radiolabelling. The only excipient used is a 0.05 M hydrochloric acid solution. Influence of radioactivity on the excipient has not been discussed. This is not a problem as dilute hydrochloric acid is also used in the Ph. Eur. monograph lutetium (^{177}Lu) solution for radiolabelling with the same requirement for pH (i.e. 1.0 – 2.0). The choice of the excipient and manufacturing process, including the selection of the separation/purification and sterilisation methods are justified. The material of the container and closure system are commonly used for this type of products and compatibility of the radiolabelled product with the container and closure have been adequately discussed. Overall, the product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacturing process

Lutetium (^{177}Lu) is a radioisotope of the element lutetium, which is in the lanthanides group in the periodic table. Lutetium (^{177}Lu) chloride radiopharmaceutical precursor solution formulation is manufactured in a continuous process starting with the irradiation of the target material to the manufacturing of the finished product. Lutetium (^{177}Lu) is obtained by decay of ytterbium (^{177}Yb) produced by neutron bombardment of highly enriched (>99 %) ytterbium (^{176}Yb) (non-fission). This method produces no-carrier-added lutetium (^{177}Lu) indirectly. The nuclide (^{177}Lu) is a non-fission product. The active ingredient lutetium (^{177}Lu) chloride is not isolated during the manufacturing process; it is provided in an ampoule, as a solution containing ^{176}Yb and ^{177}Lu dissolved in hydrochloric acid solution. The manufacturing consists of the main steps of preparation of the target material, preparation of the ampoules (cleaning, filling with enriched target material and closing), irradiation of the ampoules in the nuclear reactor, ampoule crashing, dissolution of Yb/Lu containing bulk, target processing, separation/purification step, dispensing, sterilisation, outer labelling and packaging. The information submitted on impurities of the target material and finished product is deemed sufficient. Control of radionuclidic- and radiochemical impurities is in line with the Ph. Eur. monograph No. 2798 with additional in-house requirements for Ytterbium. Furthermore, a wide range of trace metal elements are monitored for chemical purity. Overall, the

manufacturing process has been described in sufficient detail. The most critical quality attributes of the target material and finish product are adequately controlled, this is considered acceptable.

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three production scale batches.

Control of excipients

Hydrochloric acid solution is the only excipient present in the finished product. The solution is prepared with HCl and water for injection, both comply with the Ph. Eur. These specifications are acceptable.

Microbiological attributes

The drug product is sterilised under the reference conditions of the Ph. Eur., endotoxins are also controlled through adequate tests and limits according to the Ph. Eur. The integrity of the closed vials was demonstrated using sterility test methods. The water for injection is in line with the Guideline on the quality of water for pharmaceutical EMA/CHMP/CVMP/QWP/496873/2018. The vials and the stoppers comply with the respectively Ph. Eur. monograph. The aluminium over seal is disposable and does not come into contact with the drug product.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, chloride identification, pH, identification (by gamma ray spectrometer, pH and TLC), radioactive concentration, radioactivity value, lutetium specific activity, radionuclidic purity, radiochemical purity, copper, iron, lead, zinc, ytterbium, sterility and bacterial endotoxin. Radioactivity value is valid at the calibration time, after which it decreases over time. Specific activity limit is used only for information, as it has no effect on product quality. The drug product specification is in line with the relevant European Pharmacopoeia monograph with additional in-house requirements for the radionuclidic purity of the target material (Ytterbium (^{176}Yb). Sterility test is performed after releasing, in line with the requirements of Ph.Eur. monograph. Limits in the specification for release and stability are identical, except for the parameter's radioactivity and specific activity. Overall, limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches (of the vial presentations 3, 10 and 20 mL each) from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three finished product batches, stored in the proposed package covering twelve days under long term conditions (25°C/ 60%RH) and three finished product batches, stored in the proposed package covering fifteen days under intermediate conditions (30°C/ 75%RH). The stability was tested in accordance with applicable European guidelines. All results comply. In-use stability data of the product have been submitted. Post stability studies at accelerated conditions (25°C/ 60%RH and 40°C/ 75% RH have been adequately performed, see section II.4 post-approval commitments. Based on the data submitted and considering the sterilisation method of the product, the shelf life is mainly determined by the half-life of ^{177}Lu. The following shelf life and labelled conditions are granted:

Shelf life: 'up to 15 days from the date of manufacture. From a microbiological point of view, unless the method of withdrawal from the vial or any insertion into the vial preclude the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.'

Special precautions for storage: 'Store in its original lead shield. Store in the original package in order to avoid unnecessary radiation exposure. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Monlutenca has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- A commitment of the MAH has been submitted stating that additional stability studies at 40°C (accelerated conditions) will be performed and restricted storage temperature will be applied if the finished product is not stable at accelerated conditions.

At the time this PAR was written, this commitment had been fulfilled and completed via variation procedures. The data submitted was found acceptable. The product information (SmPC, PL and labelling) has been updated accordingly.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The MAH submitted a literature review and has not provided additional studies and further studies are not required. Overview based on literature review is acceptable.

III.2 Pharmacology

The description of the non-clinical literature by the MAH is for ^{177}Lu salts, the relevance of these data will be limited when ^{177}Lu complexed with an appropriate carrier before clinical use. It will only reflect any potential effect of ^{177}Lu when it is released *in vivo*. However, the currently used radiopharmaceutical incorporating ^{177}Lu consist of stable complexes, minimising the release of ^{177}Lu, although this release will not be zero. ^{177}Lu is a radionuclide used for radiodiagnostic and radiotherapeutic purposes. It is not injected directly into patients as a No-carrier-added (NCA) solution but complexed with a carrier consisting of a chelating part (e.g. DOTA), a linker, and a target-binding structure (O'mara et al., 1969). ^{177}Lu will bind to Ca^{2+}-binding sites of receptors and potentially interferes with the function of these receptors when present at sufficiently high concentrations (EPA, 2018; Nesmerak, 2013; Pearce & White, 1981). Ca^{2+}-blocking effects are observed in several *in vitro* and *in vivo* experimental models, including paralysis and death (Bruce et al., 1963; Haley et al. 1962; Haley et al., 1964). However, such effects are only observed at concentrations/doses far exceeding the clinical dose.

III.3 Pharmacokinetics

^{177}Lu appears to be rapidly cleared from the blood and excreted by the kidneys and its gastrointestinal absorption is low (Durbin et al., 1956; EPA, 2018; Leggett et al., 2014; O'mara et al., 1969; Spode et al.,1958). In most preclinical studies, radioactivity administered by parenteral routes is largely absorbed by bone tissue remaining there for a long time, the half-life is several months to years (Dash et al., 2015; Durbin et al., 1956; Müller et al., 1978). Distribution to the liver and spleen can be substantial as well but is usually less than to the bone (Bahrami-Samani et al., 2012; Hakimi et al., 2015; Hashimoto et al., 2003; Hisada & Ando, 1973; Nakamura et al., 1997). This pharmacokinetic pattern does not apply to ^{177}Lu when chelated in stable fashion, where pharmacokinetics is determined by the carrier and usually it is excreted by kidneys and bone tissue and reticuloendothelial involvement is minimal (O'mara et al., 1969). There are no findings in literature regarding the excretion of ^{177}Lu in lactate milk. Due to its poor solubility at physiological pH, ^{177}Lu forms colloidal or hydroxide complexes, which may interfere with clearance (EPA, 2018; Evans, 1983; Nesmerak, 2013).

III.4 Toxicology

Single dose studies with non-radioactive lutetium chloride in animals have shown LD_{50} values in the range of 12.5 mg/kg when given intravenously to cats to 4.4 g/kg and when given orally to rats (Bruce, 1963; EPA, 2018; Haley et al., 1964; Haley, 1965). A limited qualitative description of toxic effects in animals was submitted. Considering that the clinical dose of ^{177}Lu (2-3 µg) that has been added to a carrier is far below the doses causing adverse effects in

animals, the toxic properties of lutetium after single dose administration in animals are of little relevance for its clinical use. Most relevant, is the recent publication by Kang et al., about five patients that have been accidently injected with ^{177}Lu chloride (7.4 GBq). The patients showed severe signs of radiotoxicity several days after the incident. Five weeks after the incident one patient died from mid brain haemorrhage related to disseminated intravascular coagulation (Kang et al., 2020). In repeated dose toxicity studies, no adverse effects were seen when non-radioactive lutetium (625 mg/kg) was given to rats for 90 days (Haley et al., 1964). Since ^{177}Lu is a radionuclide, it can be assumed it will cause DNA damage and subsequent mutations (EPA, 2018; Müller et al., 1983; Ritt et al., 2021). Studies in mice have shown that osteosarcoma can be induced, which is dose and time-dependent (Bruce et al., 1963; Müller et al., 1983). At the clinical dose applied, lutetium as an element does not confer a risk for reproductive or developmental toxicity. However, since lutetium (^{177}Lu) chloride is a radionuclide precursor carrying inherent radioactivity, any radiopharmaceutical prepared by ^{177}Lu will also emit radiation. Therefore, treatment with ^{177}Lu labelled agents are contraindicated in pregnancy or suspected pregnancy. Both genders should employ effective contraceptive measures to avoid pregnancy for a period up to 6 months after treatment (Haley et al., 1964; Wei et al., 2020).

III.5 Ecotoxicity/environmental risk assessment (ERA)

Monlutenca contains no-carrier-added preparation of lutetium (^{177}Lu) chloride, which exhibits very high radionuclidic purity. No detectable tracers of long-lived ^{177m}Lu ($t_{1/2}$= 160.44 days) are present in the preparation. As indicated in the SmPC, any lutetium (^{177}Lu) chloride should be handled in accordance with the relevant national legislation, minimising environmental exposure of any unused lutetium (^{177}Lu) chloride. Regarding excretion by the patient, the dosage of the product is very low (2-3 µg lutetium (^{177}Lu) chloride) and although no formal calculation of F_{PEN} has been provided, it is expected that the action limit value of 0.01 µg/L will not be exceeded. Based on this, ^{177}Lu is not considered a PBT (persistent, bioaccumulative and toxic substance) and it is not expected to pose a risk to the environment. Overall, Monlutenca is not considered a PBT but it should be used according to the precautions stated in the SmPC to minimise any potential risks to the environment. Furthermore, it is concluded that the clinical use of Lutenca will not pose an environmental risk.

III.6 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The proposed medicinal product is a radioactive precursor, which is only intended for *in vitro* labelling purposes and not for immediate use in patients. Therefore, no clinical studies could be performed by the MAH instead a clinical overview including numerous publications has been submitted for the justification of the proposed indications and posology. This is acceptable.

IV.1 Pharmacology

The MAH did not perform clinical pharmacology studies, which is acceptable. The pharmacokinetics and pharmacodynamics of lutetium will be dependent on the pharmacokinetics and pharmacodynamics of the medicinal product to be radiolabelled.

Since lutetium (^{177}Lu) chloride is a radionuclide precursor, no pharmacological study describing direct injection has been found. The maximum amount of ^{177}Lu administered to a patient in any radiopharmaceutical form is usually about 7.4 GBq and the amount of lutetium it contains is below 20 µg, this depending on the specific activity. The non-carrier added lutetium (^{177}Lu) chloride product mentioned in this report has a minimum specific activity of 3000 GBq/mg, containing 2-3 µg lutetium. Lutetium is not expected to be released from the radiopharmaceutical in the human body and circulate freely in the body. It has been shown by the HPLC analysis of blood and urine of patients injected with ^{177}Lu-labelled radiopharmaceuticals, that the labelled products were excreted intact without damaging the integrity (Kwekkeboom et al., 2001). Furthermore, based on the submitted preclinical studies, it can be concluded that even if such a small amount of free lutetium is released to the circulation, no pharmacological or toxic effects are expected (EPA 2018; Haley et al., 1964; Müller et al., 1978).

As requested, the MAH clarified their calculation of the maximum amount of lutetium per patient dose and explained what the maximum amount is.

IV.2 Clinical efficacy

The MAH evaluated the clinical efficacy of lutetium (^{177}Lu) chloride in combination with commonly used radiopharmaceuticals based on a bibliographic basis. Since lutetium (^{177}Lu) chloride is not directly administered to patients, this is acceptable. The clinical overview discussed the use of lutetium (^{177}Lu) chloride in patients with neuroendocrine tumors, patients with prostate cancer, patients with prostate and breast cancer who received treatment of pain due to bone metastases and patients who were treated with a radiopharmaceutical prepared with lutetium (^{177}Lu) chloride for neuroendocrine tumours. The MAH also referred to four studies published more than 10 years ago from which three studies were on ^{177}Lu-Peptide for neuroendocrine tumors (Garkavij et al., 2010; Hörsch et al., 2008; Kwekkeboom et al., 2001) and one study on the treatment of prostate cancer with ^{177}Lu-PSMA (Bander et al. 2005). It is also relevant to support the clinical efficacy that lutetium (^{177}Lu) chloride has been already

registered on the basis of a WEU application since 2015 (EU/1/15/1013). The MAH has adequately discussed the clinical efficacy of lutetium (^{177}Lu) chloride. No post-authorisation efficacy studies are required as the product itself has no indication and therefore no disease or target population is associated.

IV.3 Clinical safety

Because lutetium (^{177}Lu) chloride is not directly used in humans, the MAH discussed the safety based on radiopharmaceuticals that are prepared with lutetium chloride and are used in humans. This is considered acceptable, as the safety of lutetium (^{177}Lu) chloride mainly depends on the radiation the carrier molecule carries. The MAH discussed the use of lutetium ^{177}Lu chloride in patients with neuroendocrine tumours, prostate cancer and the use of ^{177}Lu in patients with bone metastases due to prostate or breast cancer. No new safety concerns were raised by the articles submitted. The adverse advents mentioned in the articles are already included in section 4.8 of the SmPC. Furthermore, the quantity of Lutenca required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use. As requested, the MAH clarified their calculation of the maximum amount of lutetium per patient dose and explained what the maximum amount is. The MAH also provided substantiation that this amount is safe for patients in case the lutetium completely disconnects from the carrier molecule. Although, the maximum dose could be higher than 7.4 GBq, even in case of a conservative approach of 10 GBq, the amount of lutetium would be 3.33 µg. Given the toxicity of lutetium, this would still be a safe dose.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Monlutenca. The summary of safety concerns is in line with the lutetium (Lu^{177}) chloride registered through centralised procedures, i.e. Lumark. At the time of approval, the most recent version of the RMP was version 0.2 dated (final sign off) 25 April 2022 and is as shown in Table 1.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Radiotoxicity, including occupational exposure and inadvertent exposure • Developmental Toxicity including reproductive toxicity • Myelosuppression • Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	• Medication Errors associated with preparation and procedures • Osteosarcoma • Radiation nephropathy • Hepatotoxicity
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this application, no new clinical studies were conducted. The MAH submitted data available from the literature on the pharmacology of Monlutenca. Risk management is adequately addressed. Based on the data, the necessary warnings and recommendations have been included in the SmPC of the medicinal product. Overall, this medicinal product can be used for the specified indications. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to EndolucinBeta (EMEA/H/C/003999) for content and to Montek (DK/H/1741/001/DC) for layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Monlutenca 40 GBq/mL radiopharmaceutical precursor, solution has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. The overall benefit-risk is considered approvable.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Monlutenca 40 GBq/mL with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 November 2022.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5520/001 /IB/001	Change in the specification parameters and/or limits of the finished product: - Addition of a new specification parameter to the specification with its corresponding test method.	No	07-02-2023	Approved	N.A.
NL/H/5520/001 /E/001	Repeat-use application to register the product in France, Italy, Portugal, Spain and Sweden.	No	01-10-2023	Approved	N.A.
NL/H/5520/001 /IA/003	Change in the specification parameters and/or limits of the finished product: Addition of a new specification parameter to the specification with its corresponding test method.	No	13-03-2024	Approved	N.A.
NL/H/5520/001 /II/002	Other variation: - Implementation of the updates for the product information (SmPC, PL and Labelling).	Yes	28-06-2024	Approved	N.A.
NL/H/5520/001 /IB/005	Change in the batch size (including batch size ranges) of the finished product: Up to 10-fold compared to the originally approved batch size.	No	21-08-2024	Approved	N.A.
NL/H/5520/001 /II/004	Change in immediate packaging of the finished product: - Change in type of container or addition of a new container. Sterile medicinal products and biological/ immunological medicinal products.	Yes	17-09-2024	Approved	N.A.