13 October 2016
EMA/734748/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SomaKit TOC

International non-proprietary name: edotreotide

Procedure No. EMEA/H/C/004140/0000

Note

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

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List of abbreviations

^{68}Ga-DOTATATE	^{68}Ga-DOTA- Phe^{1}-Tyr^{3}-octreotide
^{68}Ga-DOTATOC	^{68}Ga-edotreotide or ^{68}Ga-DOTA-Phe^{1}-Tyr^{3}-octreotide ^{68}Ge Germanium-68
Acc	diagnostic accuracy
CT	computed tomography
CE	CT contrast enhanced computed tomography
CTV	clinical target volume
DOTATOC	edotreotide
DWI	diffusion-weighted imaging
EUS	endoscopic ultrasonography
FDG	^{18}F-fludeoxyglucose
FDOPA	6-fluoro-(^{18}F)-L-dihydroxyphenylalanine (or 6-fluoro-(^{18}F)-L-dopa) FSRT fractionated stereotactic radiotherapy
FWHM	full width half maximum
Gd-EOB-DTPA	gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid GEP
NET	gastroenteropancreatic neuroendocrine tumour
GTV	gross tumour volume
i.a.	intra-arterial
IMRT	intensity modulated radiation therapy
i.v.	intravenous
MDCT	multidetector computed tomography
mRNA	messenger ribonucleic acid
NET	neuroendocrine tumour
PET	positron emission tomography
PET/CT	positron emission tomography/computed tomography
p.i.	post injection
PRRT	peptide receptor radionuclide therapy
PTV	planning target volume
RECIST	Response Evaluation Criteria in Solid Tumours SB skull base

Se	sensitivity
Sp	specificity
SPECT	single photon emission computed tomography
SPECT/CT	single photon emission computed tomography/ computed tomography SRPET somatostatin positron emission tomography
SRS	somatostatin receptor scintigraphy
SST	somatostatin
SSTR(s)	somatostatin receptor(s)
sstr2	somatostatin receptor subtype 2
SUV	standardized uptake value
SUVmax	maximal standardized uptake value
SUVmean	mean standardized uptake value
SUV T/L	standardized uptake value tumour/liver
SUV T/S	standardized uptake value tumour/spleen
T/NTR	tumour/non-tumour (target/non-target) ratio
wbMRI	whole-body magnetic resonance imaging
VOI	volume of interest

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Advanced Accelerator Applications submitted on 8 October 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for SomaKit TOC, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 February 2015.

SomaKit TOC was designated as an orphan medicinal product EU/3/15/1450 on 19 March 2015 for Diagnosis of gastro-entero-pancreatic neuroendocrine tumours.

The applicant applied for the following indication: "This medicinal product is for diagnostic use only. After reconstitution and radiolabelling with 68-Gallium (^{68}Ga) chloride solution, the solution obtained is indicated in adults for the diagnosis and management of somatostatin receptor bearing gastroenteropancreatic neuroendocrine tumours (GEP-NET), including their localisation, characterisation, staging and restaging through positron emission tomography (PET). Gallium (^{68}Ga) edotreotide binds to somatostatin receptors. Tumours which do not bear somatostatin receptors will not be visualised."

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of SomaKit TOC as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 8 October 2015.
- The procedure started on 29 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 January 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 January 2016.
- During the meeting on 11 February 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 12 February 2016.
- During the meeting on 25 February 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 February 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 June 2016.
- During the PRAC meeting on 7 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 8 July 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2016.
- On 23 September 2016, the CHMP agreed via written procedure on a second List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 07 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 October 2016.
- During the meeting on 10 to 13 October 2016, 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 SomaKit TOC on 13 October 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Neuroendocrine tumours (NETs) are characterised by the expression of general markers (neuron specific enolase, chromogranin, synaptphysin) and are hormone secretion products. They represent a very heterogeneous group of neoplasms that can occur at in part of the body despite having a shared origin from neuroendocrine cells. They arise from the endocrine cells within glands (adrenal medulla, pituitary, parathyroid) or from endocrine islets in the thyroid, the pancreas, or the respiratory and gastrointestinal tract. Common types of NETs are located in the gastrointestinal tract or the pancreas and are collectively referred to as gastroenteropancreatic (GEP-) NETs. GEP-NETs constitute a heterogeneous group of tumours with their origin in neuroendocrine cells of the embryological gut (Öberg et al. 2012[1]).

2.1.2. Epidemiology

GEP-NETs are relatively rare but with an increasing incidence. The incidence of GEP-NET tumours was estimated at less than 12/million population in the southern European countries (Spain, Portugal, Greece, France, Italy), and between 12 and 24/million in the northern countries (Switzerland, Austria, UK, Scotland, Ireland, Finland, Sweden, Norway, Germany, and The Netherlands).

For NETs, Taal and Visser (2004)[2] reported on age-standardised incidence rates for carcinoids varying from 0.65 to 2.5 per 100,000 inhabitants. In eight European countries the age-standardised incidence of carcinoids is maximally 2.5 per 100,000 inhabitants (Taal and Visser 20042; Lepage 2004[3]; Lepage 2007[4]). However, carcinoids do not include islet cell tumours of the pancreas. Endocrine pancreatic tumours are uncommon tumours occurring in approximately 1 in 100,000 of the population (Bieligk 1995[5]; Öberg 2005[6]). Therefore, the incidence of GEP-NETs can be estimated at maximally 3.5/100,000 inhabitants.

Data on survival of patients with GEP-NETs in population-based studies is rarely reported. However, survival data published by Taal and Visser (Taal 2004), correlating extent of disease with the percentage of GEP-NET patients surviving at 5-years, gives 93% for local disease, 74% for regional disease and 19% for metastatic disease. It is likely that the rate of patients with distant metastases is underestimated (Lebtahi 1997[7]) as better imaging techniques have helped with the detection of GEP-NETs. Therefore the mean survival is estimated to be between 6 and 8 years.

[1] Öberg K, Knigge U, Kwekkeboom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
[2] Taal BG , Visser O (2004). Epidemiology of neuroendocrine tumours. Neuroendocrinology 80 Suppl 1:3-7
[3] Lepage C, Bouvier AM, Phelip JM, Hatem C, Vernet C, Faivre J (2004). Incidence and management of malignant digestive endocrine tumours in a well defined French population. Gut 53(4):549-553
[4] Lepage C, Rachet B, Coleman MP (2007). Survival from malignant digestive endocrine tumors in England and Wales: a population-based study. Gastroenterology 132(3):899-904
[5] Bieligk S , Jaffe BM (1995). Islet cell tumors of the pancreas. Surg Clin North Am 75(5):1025-1040
[6] Oberg K , Eriksson B (2005). Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 19(5):753-781
[7] Lebtahi R, Cadiot G, Sarda L, Daou D, Faraggi M, Petegnief Y, Mignon M, le Guludec D (1997). Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. J Nucl Med 38(6):853-858

For GEP-NETs, no specific prevalence data are available for Europe. Prevalence can be estimated by multiplying the incidence with the mean survival time since initial diagnosis (Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation, 26 March 2002, Doc ref. COMP/436/01). With the reported maximum incidences of midgut NETs and islet cell tumours of 3.5 (2.5 + 1) per 100,000 and a median survival of 6 to 8 years, the prevalence of GEP-NETs can be estimated at maximally 2.8 per 10,000 inhabitants in the Community.

2.1.3. Biologic features

The classification of NETs has evolved over the past two decades to reflect a separation in two current major categories according to the 2010 WHO nomenclature and classification of neuroendocrine neoplasms of the digestive system (Rindi et al. 2010[8]):

1) well-differentiated neuroendocrine tumours (NETs) traditionally referred to as “carcinoid and pancreatic neuroendocrine (islet cell) tumours”, and

2) poorly-differentiated neuroendocrine carcinomas (NECs) traditionally referred to as “small cell NECs and large cell NECs”.

Therefore, the term GEP-NETs refers to the 2010 WHO well-differentiated NETs located at the oesophagus, the oesophagogastric junction, stomach, ampullary region, small intestine, appendix, colon and rectum, and canal, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, and pancreas). NETs of unknown primary tumour site (also known as CUP-NETs) are mostly GEP-NETs.

A unique feature of well-differentiated GEP-NETs is their overexpression of somatostatin receptors (SSTR) on the tumour cells. Several types of tumours are known to significantly express SSTR. According to the EANM guideline, the following tumours have a high SSTRs expression (Virgolini 2010[9]):

- Functioning and non-functioning gastroenteropancreatic neuroendocrine tumours (GEP-NET), gastrinoma, insulinoma, glucagonoma, VIPoma, etc.),
- Sympathoadrenal system tumours (phaeochromocytoma, paraganglioma, neuroblastoma,ganglioneuroma)
- Medullary thyroid carcinoma
- Pituitary adenoma
- Medulloblastoma
- Merkel cell carcinoma
- Meningioma

Out of the five subtypes of human somatostatin receptors (sstrs) which have been identified, most abundant in GEP-NETs is sstr2, followed by equal amounts of sstr1 and sstr5, lower amounts of sstr3 and hardly any

[8] Rindi G, Arnold R, Bosman FT, Capella C, Klimstra DS, Klöppel G, et al. 2010 Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In WHO Classification of Tumours of the Digestive System, pp 13–14. Eds Bosman FT, Carneiro F, Hruban RH & Theise N. Lyon: IARC Press.

[9] Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, et al. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging (2010) 37:2004–2010.

sstr4 (Johnbeck et al. 2014[10], Maxwell et al. 2015[11]). Poorly-differentiated NECs hardly express somatostatin receptors.

2.1.4. Clinical presentation

The diagnosis of GEP-NETs is based upon: (1) clinical features, especially in functioning tumours, (2) levels, in blood and urine, of several peptides and amines produced by the tumour (biomarkers), (3) localization of the primary and/or metastatic lesions as determined by imaging studies, and (4) histopathologic confirmation from biopsy or surgical specimen, which represents the 'gold standard' for diagnosis and should be obtained whenever possible (Plöckinger et al. 2004[12]).

2.1.5. Management

Many different imaging techniques are used to localize GEP-NETs. Cross-sectional (anatomical) imaging modalities, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have been used to localize primary lesions and to stage the extent of the disease. In the European consensus guidelines it is acknowledged that somatostatin receptor scintigraphy (SRS) using Octreoscan is an important part of the diagnostic work-up of patients with GEP-NETs (Delle Fave et al. 2012[13], Ramage et al. 2012[14], Öberg et al. 2012). It can still be considered the molecular imaging technique of choice at diagnosis and follow-up in the majority of patients with well-differentiated GEP-NET (level of evidence 3, grade of recommendation A/B) (Toumpanakis et al. 2014[15]).

The currently approved imaging diagnostic agent based on SSTRs for visualizing GEP-NETs is Octreoscan, which is an octreotide (pentetreotide) radiolabelled with indium-111, and has been granted marketing authorization in many member states of the EU. It binds with a high affinity to sstr2, a much lower affinity to sstr5 and sstr3, and no affinity to sstr1 and sstr4. It has been for many years the radiopharmaceutical of first choice for the visualization of GEP-NETs.

Octreoscan emits gamma radiation and thus imaging is obtained by either planar gammacameras or single photon emission computed tomography (SPECT). The diagnostic sensitivity depends on the tumour type and receptor status since GEP-NETs are found to express somatostatin receptors in 80-100% of cases but insulinomas have a lower prevalence (50-70%) (Johnbeck et al. 2014, Toumpanakis et al. 2014). Somatostatin receptor scintigraphy (SRS) with Octreoscan has the additional advantage of instantaneous whole body scanning, which also allows detection of metastases outside the abdominal region. In addition to anatomical information, SRS offers functional information on levels of somatostatin-receptor expression; this can help in the selection of appropriate candidates with advanced disease for somatostatin-based therapies. Indeed, patients who are considered candidates for PRRT

[10] Johnbeck CB, Knigge U, Kjær A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. Future Oncol 2014 Nov;10(14):2259-77.
[11] Maxwell JE and Howe JF. Imaging in neuroendocrine tumors: an update for the clinician. Int J Endocr Oncol 2015; 2(2):159–168.
[12] Plöckinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW, Goede A, Cap- lin M, Oberg K, Reubi JC, Nilsson O, Delle Fave G, Ruszniewski P, Ahlman H, Wiedenmann B; European Neuroendocrine Tumor Society: Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumors. A consensus statement on behalf of the European Neuroendocrine Tumor Society (ENETS). Neuroendocrinology 2004;80:394–424.
[13] Delle Fave G, , Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, et al. ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology 2012;95(2):74-87.
[14] Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012 Jan;61(1):6-32.
[15] Toumpanakis C, Kim MK, Rinke A, Bergestuen DS, Thirlwell C, Khan MS, et al. Combination of cross-sectional and molecular imaging studies in the localization of gastroenteropancreatic neuroendocrine tumours. Neuroendocrinology 2014;99(2):63-74.

should first undergo SRS to confirm a vid tracer uptake by the tumor lesions (level of evidence 3, grade of recommendation A/B) (Toumpanakis et al. 2014).

There are limitations to SRS with Octreoscan which include: (1) reduced sensitivity in smaller (sub-centimetre) lesions and in lesions exhibiting low receptor density; (2) 2-day imaging protocol; (3) potential interference by co-administration of therapeutic somatostatin analogues and (4) imaging organs with higher physiologic uptake (eg, liver) (Ramage et al. 2012, Ambrosini et al. 2014[16]). Positive findings on SRS reflect increased density of SST receptors rather than malignant disease, and therefore uptake is not only specific for malignant tumours. The physiological distribution of the radiopharmaceutical in a variety of benign conditions (autoimmune diseases, granulomas, radiation pneumonitis, and bacterial infections) and non-NETs (lymphomas, melanomas, sarcomas, and breast cancer) could interfere with the interpretation of the images.

PET/CT (positron emission tomography/computer tomography), using different radiopharmaceuticals has been introduced for the diagnostic work-up of GEP-NETs in the last decade. Fluorodopa (^{18}F), showing an increase of intracellular transport and of decarboxylation of dihydroxyphenylalanine, is approved at the national level in the EU for the staging and detection in case of reasonable suspicion of recurrent or residual disease of GEP-NETs in adults and children, and for localization of insulinomas in children.

Three gallium (^{68}Ga)-labelled somatostatin analogs, with a high affinity to sst2 and variable affinity to other somatostatin receptors on the tumor cell surface, are also used in clinical practice: gallium (^{68}Ga)-DOTATOC, gallium (^{68}Ga)-DOTATATE and gallium (^{68}Ga)-DOTANOC[,17,18].

Gallium (^{68}Ga)-labelled somatostatin analogues for PET are currently used in clinical practice, although no formal randomized trials have been performed, and hence there are some guidelines for PET/CT tumour imaging procedures that have been recently published (Virgolini et al. 2010). PET imaging with gallium (^{68}Ga)-labelled somatostatin analogues has several advantages compared with indium (^{111}In) pentetreotide SRS including better spatial resolution, whole-body scanning in a short time, and the added value of fusion imaging using a PET/CT hybrid scanner. The gallium (^{68}Ga) isotope has the advantage of being produced from a generator, and thus can be used in hospital departments that do not have access to a cyclotron.

Gallium (^{68}Ga) edotreotide is a radiopharmaceutical product used for functional imaging with positron emission tomography (PET) when the increased expression of somatostatin receptor (SSTR) is a diagnostic target. The rationale for its use in the assessment of SSTR expressing tumours is based on its high affinity for those receptors.

About the product

SomaKit TOC is a novel radiopharmaceutical composed of edetreotide, a somatostatin analogue. It is a kit for radiopharmaceutical preparation to be radiolabelled with gallium (^{68}Ga) chloride obtained from a germanium (^{68}Ge)/gallium (^{68}Ga) generator. The solution obtained, known as gallium (^{68}Ga) edetreotide or gallium (^{68}Ga) edotreotide, is intended for the diagnostic work-up of GEP-NETs by PET. This solution has a half-life of 68 min. Gallium (^{68}Ga) edotreotide binds in vitro with a very high affinity to the most prevalent somatostatin

[16] Ambrosini V, Fanti S. 68Ga-DOTA-peptides in the diagnosis of NET. PET Clin 2014;9:37–42.
[17] Werner RA, Bluemel C, Allen-Auerbach MS, Higuchi T, Herrmann K. 68Gallium- and 90Yttrium-/177Lutetium: “theranostic twins” for diagnosis and treatment of NETs. Ann Nucl Med 2015;29:1-7.
[18] Santhanam P, Chandramahanti S, Kroiss A, Yu R, Ruszniewski P, Kumar R, et al. Nuclear imaging of neuroendocrine tumors with unknown primary: why, when and how? Eur J Nucl Med Mol Imaging (2015) 42:1144–1155.

receptor subtype 2 (sstr2), and to a lesser extent to subtypes 1 and 5. Pharmacotherapeutic group: Other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX09.

Gallium (^{68}Ga a) edotreotide binds to somatostatin receptors. In vitro, this radiopharmaceutical binds with high affinity mainly toSSTR2 but also, to a lesser extent, to SSTR5. In vivo, quantitative correlation was not assessed between gallium (^{68}Ga) edotreotide uptake in tumours and the overexpression of SSTR in histopathological samples neither in GEP-NET patients nor in normal organs. Moreover, the in vivo binding of gallium (^{68}Ga) edotreotide to other structures or receptors remains unknown.

SomaKit TOC 40 micrograms kit for radiopharmaceutical preparation contains:

- Powder for solution for injection: the vial contains a white lyophilised powder.
- Reaction buffer: the vial contains a clear, colourless solution.

For radiolabelling with gallium (^{68}Ga) chloride solution. Each vial of powder contains 40 micrograms of edotreotide. The radionuclide is not part of the kit. The vial of buffer contains approximately 32.5 mg of sodium. For the full list of excipients, see section 6.1 of the SmPC.

The following indication was proposed by the applicant:

"This medicinal product is for diagnostic use only.

After reconstitution and radiolabelling, the ^{68}Ga-edotreotide solution obtained is indicated for the diagnosis and management of somatostatin receptor bearing gastro-entero-pancreatic neuroendocrine tumours (GEP-NET) in adults, for the localisation, characterisation, staging and restaging through positron emission tomography (PET).

^{68}Ga-edotreotide binds to somatostatin receptors. Tumours which do not bear somatostatin receptors will not be visualised."

The final indication is as follows:

"This medicinal product is for diagnostic use only.

After radiolabelling with gallium (^{68}Ga) chloride solution, the solution of gallium (^{68}Ga) edotreotide obtained is indicated for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases.

The medicinal product should only be administered by trained healthcare professionals with technical expertise in using and handling nuclear medicine diagnostic agents and only in a designated nuclear medicine facility."

Posology

The recommended activity for an adult weighing 70 kg is 100 to 200 MBq, administered by direct slow intravenous injection.

The activity will be adapted to patient characteristics, the type of PET camera used and acquisition mode.

Type of Application and aspects on development

This is an application in accordance with article 10a of Directive 2001/83/EC as amended.

The submitted clinical documentation is being based on data available in published literature.

This is an application based on "well established medicinal use" according to Directive 2001/83/EC. Therefore, it is possible to replace results of pharmacological and toxicological tests or clinical trials by detailed references to published scientific literature (information available in the public domain). The applicant has demonstrated that edotreotide has a well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety, at least 10 years have passed since its first systematic and documented use as a medicinal product in the European Union and has been extensively used for the 10-year period through Europe.

The following criteria for the demonstration of such well-established were taken into account:

- The company provided data since the first use of the product in Europe in clinical practice and published studies. In published data more than 1,000 patients with NET tumours not only GEP-NET (800 in papers and more than 200 in abstracts), from different centres and investigation groups in various European countries mostly Germany and Austria, have received gallium (^{68}Ga) edetreotide since 2001 up to 2016. In France there is a name-patient used program for this radiopharmaceutical. Besides, the applicant mentioned a survey in 25 European centres showing that the number of exams since the first use of gallium (^{68}Ga) edetreotide in 2005 has been 23,739 in clinical practice (mostly in Italy and Germany).
- Several European clinical and procedural guidelines from leading scientific societies (ESMO, ENETS and EANM) acknowledge the value of gallium (^{68}Ga) edetreotide (or ^{68}Ga labelled somatostatin analogues) for some objectives in the diagnostic and management of GEP-NET (Virgolini et al., 2010, Oberg et al. 2012, Falconi et al. 2016, Niederle et al. 2016, Pape et al. 2016, Pavel et al. 2016 and Delle Fave et al. 2016). This would demonstrate the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.
- It can be considered that the scientific interest in the use of gallium (^{68}Ga) edotreotide for some particular diagnostic objective of GEP-NET through Europe is shown based on the published scientific literature. The company initially provided with 31 tabulated papers assessing the clinical efficacy of gallium (^{68}Ga) edotreotide in the diagnostic work-up of 970 patients with NET tumours (not only GEP-NETs) in Europe (except 1 paper from India with 7 patients), from different centers and investigation groups in various European countries mostly Germany and Austria, since 2001 up to 2016 covering a period that is longer than the last 10 years. No data from compassionate use program have been submitted although compassionate use was available in some Member States (e.g. France).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as kit for radiopharmaceutical preparation containing 40 micrograms of edotreotide as active substance. As all kits for radiopharmaceutical preparation, it is not intended for direct administration to the patient. Instead, it must be radiolabelled immediately before use with a gallium (^{68}Ga) chloride solution to generate a gallium (^{68}Ga) edotreotide injection, which is the product actually injected to

the patient. Gallium (^{68}Ga) chloride solution for radiolabelling is obtained from a ^{68}Ga generator and is not part of this medicinal product.

Other ingredients are:

Vial of powder (Vial 1): 1,10-phenanthroline, gentisic acid, and mannitol (E421)

Vial of buffer (Vial 2): formic acid, sodium hydroxide (E524), and water for injections

After radiolabelling, the solution obtained also contains, as excipient, hydrochloric acid from the generator eluate.

The product is available in:

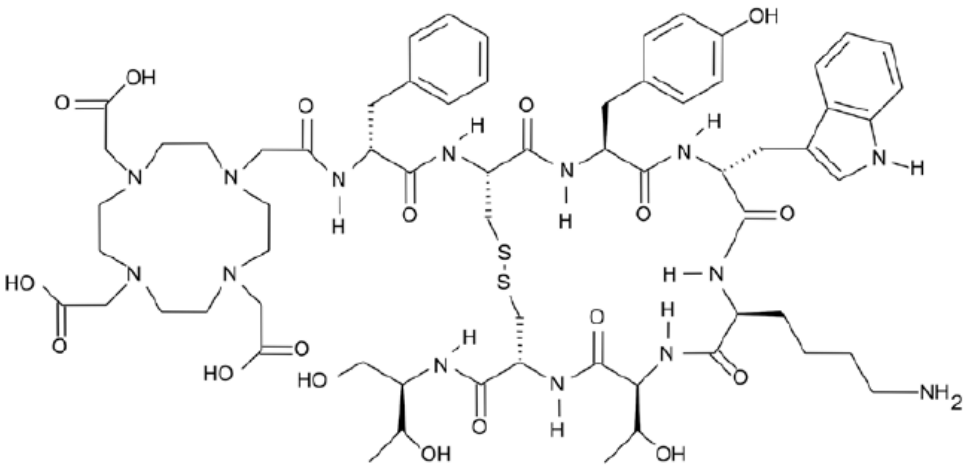
- One vial of powder for solution for injection: Type I glass vial closed with a chlorobutyl rubber stopper and a sealed with a flip-off cap.
- One vial of buffer: cyclic olefin polymer vial closed with a teflon stopper sealed with a flip-off cap. Each vial contains 1 ml of reaction buffer.

as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of edotreotide is 2-[4-[2-[[(2*R*)-1-[[(4*R*,7*S*,10*S*,13*R*,16*S*,19*R*)-10-(4- aminobutyl)-4-[[(2*R*,3*R*)-1,3-dihydroxybutan-2-yl]carbamoyl]- 7-[(1*R*)-1-hydroxyethyl]-16-[(4-hydroxyphenyl)methyl]-13-(1*H*-indol-3-ylmethyl)-6,9,12,15,18-pentaoxo-1,2-dithia- 5,8,11,14,17-pentazacycloicos-19-yl]amino]-1-oxo-3- phenylpropan-2-yl]amino]-2-oxoethyl]-7,10- bis(carboxymethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetic acid corresponding to the molecular formula $C_{65}H_{92}N_{14}O_{18}S_2$ $(CH_3COOH)n$. It has a relative molecular mass of 1,420.6 g/mol and the following structure:



(CH3COOH)n

Figure 1:Structure of edotreotide.

The structure of edotreotide was confirmed by suitable tests and they have been adequately described.

The active substance is a white to off white powder, freely soluble in water. Edotreotide is a peptide with 8 amino acids and with a covalently bound chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (also known as DOTA) . The molecule is cyclised through a disulfide formation of the SH groups of the cysteines. The counter ion of the molecule is acetate.

Edotreotide exhibits stereoisomerism due to the presence of few chiral centres. Enantiomeric purity is controlled.

Polymorphism is not relevant for the active substance since it is dissolved before being incorporated into finished product.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

One manufacturing site is proposed for the manufacture of the active substance. Edotreotide is produced by "classical" peptide synthesis. The process consists of 8 main steps using commercially available 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 manufacturer has investigated all possible sources for impurities (e.g. originating from starting materials, side products of the manufacturing process, formed during storage, etc.) that could be present in the chemical precursor. Potential and actual impurities were well discussed with regards to their origin and characterised. The characterisation of the active substance and its impurities are in accordance with the EU

guideline on chemistry of new active substances and in the light of the Ph. Eur. monograph on chemical precursors for radiopharmaceutical preparations (Ph. Eur. 2902).

Specification

The active substance specification includes tests for: appearance, identification (Sequencing (MS-MS), monoisotopic mass (mass spectrometry (MALDI-TOF)), amino acid analysis (GC), enantiomeric purity (GC), specific optical rotation (polarimeter), net peptide content (GC), peptide content (GC), assay (RP-HPLC), peptide purity (RP-HPLC), peptide related substances/impurities (RP-HPLC), residual solvents (GC), residual trifluoroacetic acid (GC), counter ion content (GC), water content (GC), microbial contamination / bioburden (Ph. Eur.), and bacterial endotoxins (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines except the HPLC method proposed for assay.

In this regard, the CHMP recommended completing the validation of the HPLC method proposed for the determination of edotreotide content (assay) and updating the ASMF accordingly, before the commercialisation of the finished product.

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

Stability

Stability data on two commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package under long term conditions at -20°C ± 5°C and under accelerated conditions at 25°C±2°C/60%± 5% RH according to the ICH guidelines were provided. The following parameters were tested*:* appearance, peptide purity, peptide related substances, monoisotopic mass, water content, counterion content (acetate), TFA, assay, bacterial endotoxins, and bioburden. The analytical methods used were stability indicating.

Results of the accelerated stability testing showed that the peptide purity remains constant. Hence it was concluded that a short term handling of the bulk material at room temperature does not have a negative impact on the quality of the precursor peptide. Data of the long term stability program confirm that the substance is stable over a maximum period of 12 months when stored at ≤ *-15*°C in the proposed container.

Additional supportive stability data from on one commercial scale batch in cryovials stored over 38 months at -20 °C +/- 5 °C were provided.

Photostability testing following the ICH guideline Q1B was performed on one batch. No change in the appearance was observed. Although the results of the peptide purity after light exposure are within the specification, it can be shown that the product DOTA-TOC is sensitive to light. As the bulk material is intended to be stored in freezers protected from light, an overexposure to light is not expected.

Additional stress testing was performed on one batch. Samples were exposed to acid, base, oxidizing, oxidizing and basic conditions, and dissolution in pure water.

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 when stored at ≤ -15°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The applicant developed the finished product as a sterile 2-vial kit which consists of:

- Vial 1: edotreotide, 40 µg, powder for solution for injection, to be reconstituted with a solution of gallium-68 chloride (^{68}GaCl) in HCl (eluted from a ^{68}Ge/^{68}Ga generator);
- Vial 2: Reaction buffer: to be added to the reconstituted Vial 1.

The applicant developed SomaKit TOC, 40 µg, as a kit for radiopharmaceutical preparation intended for use in a hospital radiopharmacy for the preparation of the radiolabelled imaging product ^{68}Ga-edotreotide solution for injection after reconstitution with gallium (^{68}Ga) chloride solution for radiolabelling. The physico-chemical properties of edotreotide have been considered when choosing the manufacturing process for Vial 1 in order to achieve the intended dosage form. The compatibility of the active substance with the excipients used in the finished product has been demonstrated by the stability studies.

The excipients chosen for the composition of Vial 1 are added to maintain stability of the active substance in the final formulation, to assure safety and efficacy of the finished product and also to obtain the required radiochemical purity of the ^{68}Ga edotreotide solution during the reconstitution procedure. 1,10-phenanthroline is a novel excipient, therefore a full toxicological evaluation and risk assessment have been done on the basis of studies published in the literature. As it is a novel excipient, appropriate data to support the quality and control of this excipient has been provided in line with the requirements of the *Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (Doc. Ref. EMEA/CHMP/QWP/396951/2006, 19 June 2007)*.

The formulation development of Vial 1 was performed with the aim of identifying the reaction mixture composition able to allow a simple labelling of the DOTA-peptide, based on direct reconstitution with the eluate from commercially available ^{68}Ge/^{68}Ga generators, without any processing of the eluate or any additional purification step.

The aim of the formulation development of the Vial 2 reaction buffer was to define a formulation that allows radiolabelling of edotreotide with high and reproducible complexation yields, by direct reconstitution with the eluate from the ^{68}Ge/^{68}Ga generator. This direct reconstitution approach makes the labelling process independent of automatic synthesis modules.

A justification of the designed manufacturing process for vial 1 has been presented. The choice of the sterilisation method has been adequately justified.

The buffer vial (Vial 2) is prepared using a standard manufacturing process for sterile products..

The primary packaging for Vial 1 is Type I glass vial closed with a chlorobutyl rubber stopper sealed with a flip-off cap and, for Vial 2 a cyclic olefin polymer vial closed with a teflon stopper sealed with a flip-off cap.

The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been appropriately validated for the intended use of the product.

Compatibility studies performed by the applicant following the same radiolabelling procedure as the one proposed for the end user in the hospital, demonstrated that the radiopharmaceutical kit provides a radiolabelled finished product within the required quality specification.

Manufacture of the product and process controls

The manufacturing process of Vial 1 consists of 6 main steps: bulk solution preparation, pre-filtration, sterilizing filtration, aseptic filling, lyophilisation and visual inspection, labelling and packaging. The process is considered to be a non-standard manufacturing process.

The acceptance criteria for in-process control tests have been well justified by the validation data of manufacturing process which was consistent from batch to batch and demonstrated that the process is well controlled within the selected limits. There are no intermediates involved in the manufacturing process of the finished products.

This non-standard manufacturing process has been validated on three consecutive production scale batches. The results are considered satisfactory.

The manufacturing process of Vial 2 consists of 7 main steps: bulk solution preparation, pre-filtration, aseptic filling, sealing and crimping, terminal steam sterilization, visual inspection and sampling and labelling and packaging

Major steps of the manufacturing process of vial 2 have been validated and it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

An overview of the reconstitution process for the preparation of the radiolabelled imaging product by the end user (hospital radiopharmacy) has also been provided. An explanation of the rationale of the procedure and the detailed description of the radiolabelling procedure is included in the SmPC.

Product specification

The finished product release specifications for vial 1 (lyophilisate powder) include appropriate tests for this kind of dosage form: appearance of the freeze dried cake, container closure integrity, uniformity of dosage units (Ph. Eur.), appearance of the reconstituted solution, reconstitution time, sub-visible particles (Ph. Eur.), residual moisture (Ph. Eur.), edotreotide identification (HPLC, MS), gentisic acid identification (HPLC), 1,10-phenanthroline identification (HPLC), edotreotide assay (HPLC), gentisic acid assay (HPLC), 1,10-phenanthroline assay (HPLC), related substances (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The finished product release specifications for vial 2 include appropriate tests for this kind of dosage form: appearance, sub-visible particles (Ph. Eur.), pH (Ph. Eur.), formic acid identification, formic acid quantification, sterility (Ph. Eur.), bacterial endotoxin (Ph. Eur.).

The finished product release specification for the radiolabeled product to be performed by the end user are: appearance, (Ph. Eur.), pH, radiochemical purity (HPLC, ITLC), % 68Ga edotreotide (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for three production scale batches of vial 1 and vial 2 confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

In case of vial 1, stability data of three commercial scale batches stored under long term conditions for up 12 months at 5 ºC and for up to 6 months under accelerated conditions at 25 ºC / 60% 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.

Samples were tested for appearance of the freeze dried cake, container closure integrity, appearance of the reconstituted solution, reconstitution time, sub-visible particles, residual moisture, edotreotide assay, gentisic acid assay, 1,10 phenanthroline assay, related substances, sterility, bacterial endotoxins, radiopharmaceutical purity: % free ^{68}Ga, ^{68}Ga- edotreotide and ^{68}Ga-colloidal species. The analytical procedures used are stability indicating.

During long term stability studies, the physical characteristics of the product maintained their quality over the tested period with no deterioration recorded when the finished product was stored at 5 ± 3°C. During the accelerated stability studies, all tested parameters were within the acceptance criteria of the shelf-life specification with good physical characteristics of the finished product over the studied period for the first two batches after 6 months of storage. In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on the study results the finished product should be kept in the original package in order to be protected from light.

For vial 2, stability data of three commercial scale batches stored under long term conditions for up 18 months at 5 ºC and for up to 6 months under accelerated conditions at 25 ºC / 60% 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.

Samples were tested for appearance, sub-visible particles, pH, formic acid quantification and sterility. The analytical procedures used are stability indicating.

During long term stability studies, the physico-chemical parameters for all batches of vial 2 reaction buffer were within the shelf-life specification at all testing points Vial 2 also showed good stability when stored at accelerated conditions. No deterioration in physico-chemical characteristics or out of specification results was observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed. Therefore it was concluded that the vial 2 reaction buffer is photostable.

An in-use stability study was also performed for the reconstituted radiolabelled finished product. The study was performed with two batches of vial 1 and two batches of vial 2. The preparation of the radiolabelled imaging product was performed according to the procedure used in the hospital by the end user as described

in the SmPC. The in-use stability study demonstrated that the radiolabelled imaging finished product is stable for the proposed in-use shelf-life of 4 hours when kept at room temperature.

Considering that both vial 1 and vial 2 will be stored in the same secondary packaging and the stability profile of vial 1 is more restrictive, the shelf life and storage conditions of vial 2 are adapted to those of vial 1. Based on available stability data, the proposed shelf-life of 12 months when stored in a refrigerator (2-8°C) and stored in the original package in order to be protected from light as stated in the SmPC (section 6.3) are acceptable. After radiolabelling the product should be used within 4 hours when stored below 25°C.

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 active substance is a peptide with 8 amino acids and a covalently bound chelator (DOTA). The finished product is a kit for radiopharmaceutical preparation. As all kits for radiopharmaceutical preparation, it is not intended for direct administration to the patient. Instead, it must be radiolabelled immediately before use with a gallium (^{68}Ga) chloride solution to generate a gallium (^{68}Ga) edotreotide injection, which is the product which is injected to the patient. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These will be addressed in the post-authorisation phase.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

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

- To complete the validation of the HPLC method proposed for the determination of edotreotide content (assay) and update the ASMF accordingly before the commercialisation of the finished product.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical sections of the dossier have been compiled from published literature. No new non-clinical data has been presented in this submission.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro binding studies in human cells (Reubi 2000[19], Deshmukh 2005)

Edotreotide and other somatostatin analogues affinity for somatostatin receptor was evaluated *in vitro* using cell lines transfected with the five human somatostatin receptor subtypes ($sstr_1$-$sstr_5$). Results are shown in Table 1. In this study it was shown that the affinity as IC50 of (^{68}Ga) edotreotide for $sstr_2$ (2.5 nM) is comparable with that of endogenous somatostatin SS-28 (2.7 nM) and other peptides, whereas IC50 for ^{111}In-DTPA^0-Octreotide (Octreoscan) was about 10-fold lower (22 nM). Binding affinity was higher when either edotreotide or DOTA^0-Tyr^3-Octreotate is labelled with gallium compared to the same peptides in the unlabelled form or labelled with yttrium, showing that the coordination geometry of the radiometal complex has a significant influence on affinity profiles.

Edotreotide or Ga-edotreotide did not show affinity for the human sst_1 and sst_4 receptors, while affinity for human sst_3 and sst_5 receptors was 30 to 250 times lower than the affinity for sst_2 receptor.

[19] Reubi, J. C., Schar, J. C., Waser, B., Wenger, S., Heppeler, A., Schmitt, J. S. and Macke, H. R. (2000). Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. European journal of nuclear medicine 27, 273-282.

Table 1: Affinity profiles of human sst1-5 receptors for somatostatin analogues (Reubi 2000 et al.)

	IC_{50} (nM) ± SEM				
Peptide	**hsst1**	**hsst2**	**hsst3**	**hsst4**	**hsst5**
Somatostatin-28 (SS-28)	5.2 ± 0.3	2.7 ± 0.3	7.7 ± 0.9	5.6 ± 0.4	4.0 ± 0.3
Octreotide	>10000	2.0 ± 0.7	187 ± 55	>1000	22 ± 6
$DTPA^0$-Octreotide	>10000	12 ± 2	376 ± 84	>1000	299 ± 50
In-$DTPA^0$-Octreotide	>10000	22 ± 3.6	182 ± 13	>1000	237 ± 52
Edotreotide	>10000	14 ± 2.6	880 ± 324	>1000	393 ± 84
Y-edotreotide	>10000	11 ± 1.7	389 ± 135	>10000	114 ± 29
Ga-edotreotide	>10000	2.5 ± 0.5	613 ± 140	>1000	73 ± 21
$DTPA^0$-Tyr^3-Octreotate	>10000	3.9 ± 1	>10000	>1000	>1000
In-$DTPA^0$-Tyr^3-Octreotate	>10000	1.3 ± 0.2	>10000	433 ± 16	>1000
$DOTA^0$-Tyr^3-Octreotate	>10000	1.5 ± 0.4	>1000	453 ± 176	547 ± 160
Y-$DOTA^0$-Tyr^3-Octreotate	>10000	1.6 ± 0.4	>1000	523 ± 239	187 ± 50
Ga-$DOTA^0$-Tyr^3-Octreotate	>10000	0.2 ± 0.04	>1000	300 ± 140	377 ± 18

In vitro binding and internalization studies in mouse tumour cells (Hofland 1995[20], de Jong 1998b[21])

The affinity of ^{125}I-Tyr^3-octreotide was assessed using murine AtT20 pituitary tumour cell membrane preparations as a source of $sstr_2$. Binding of ^{125}I-Tyr^3-octreotide was temperature dependent and inhibited by pertussis toxin. In table 2.1.2 it is shown the amount of several unlabelled octreotide derivatives required to displace the binding of ^{125}I-Tyr^3-octreotide to mouse AtT20 pituitary cell membranes.

Table 2: IC50 values of unlabelled competitor peptides to mouse AtT20 pituitary cell membranes (radioligand was 125I-Tyr3-octreotide) (de Jong 1998b)

Unlabelled peptide	**IC_{50} (nM)***
$DTPA^0$-Octreotide	3
$DTPA^0$-Tyr^3-Octreotide	3.2
$DTPA^0$-D-Tyr^1-Octreotide	6.3
$DTPA^0$-Tyr^3-Octreotate	3.6
Edotreotide ($DOTA^0$-Tyr^3-Octreotide)	0.6

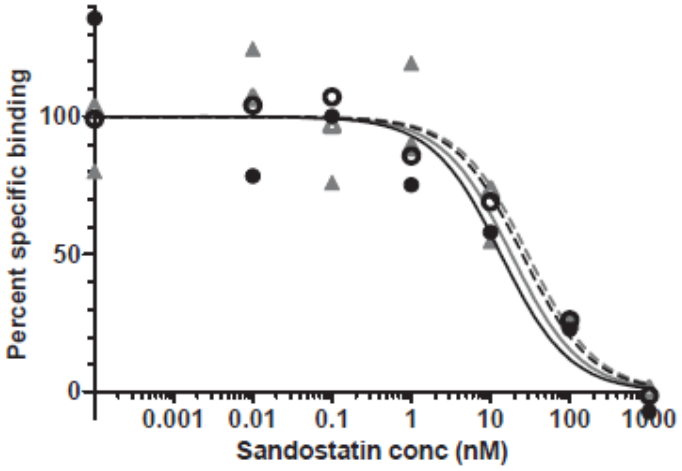
[20] Hofland, L. J., van Koetsveld, P. M., Waaijers, M., Zuyderwijk, J., Breeman, W. A. and Lamberts, S. W. (1995). Internalization of the radioiodinated somatostatin analog [125I-Tyr3]octreotide by mouse and human pituitary tumor cells: increase by unlabeled octreotide. Endocrinology 136, 3698-706.

[21] de Jong, M., Breeman, W. A., Bakker, W. H., Kooij, P. P., Bernard, B. F., Hofland, L. J., Visser, T. J., Srinivasan, A., Schmidt, M. A., Erion, J. L. et al. (1998b). Comparison of (111)In-labeled somatostatin analogues for tumor scintigraphy and radionuclide therapy. Cancer research 58, 437-441.

In vitro binding study in monkey brain (Velikyan 2012[22])

The $sstr_2$ binding affinity of ^{68}Ga-labelled edotreotide and DOTA^0-Tyr^3-octreotate was investigated in an *in vitro* autoradiography binding assay with Rhesus monkey brain frozen sections. The specificity of the binding to SSTR expressing tissue was confirmed by blocking experiments using excess of octreotide. All ligands visualized the cerebral cortex in the monkey brain, with much lower binding in the central structures, white matter or cerebellum. The nonspecific binding, as determined by the addition of a high concentration octreotide, was very low. In this study both compounds showed a very high selectivity in binding the $sstr_2$ subtype receptor (Figure 2). The individual IC50 values for edotreotide were 18.3 and 29.5 nM respectively for monkey 1 and 2.

Figure 2: Competition curves of octreotide (Sandostatin) versus (^{68}Ga) edotreotide (grey symbols and lines) and (^{68}Ga) DOTA0-Tyr3-Octreotate (black symbols and lines) in the cerebral cortex of two monkeys. Open symbols/dotted lines: monkey n. 1; filled symbols/c



In vivo pharmacology

In vivo pharmacology studies in mice and rats (de Jong 2001[23], de Jong 2005[24], Muzio 2015[25], Norenberg 2006[26], Stolz 1998[27])

[22] Velikyan, I., Xu, H., Nair, M. and Hall, H. (2012). Robust labeling and comparative preclinical characterization of DOTA-TOC and DOTA-TATE. Nuclear Medicine & Biology 39, 628-39.

[23] de Jong, M., Breeman, W. A., Bernard, B. F., Bakker, W. H., Schaar, M., van Gameren, A., Bugaj, J. E., Erion, J., Schmidt, M., Srinivasan, A. et al. (2001). [177Lu-DOTA(0),Tyr3] octreotate for somatostatin receptor-targeted radionuclide therapy. International journal of cancer. Journal international du cancer 92, 628-633.

[24] de Jong, M., Breeman, W. A., Valkema, R., Bernard, B. F. and Krenning, E. P. (2005). Combination radionuclide therapy using 177Lu- and 90Y-labeled somatostatin analogs. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 46 Suppl 1, 13S-17S.

[25] Muzio, V., Castaldi, E., Arena, F. and Fugazza, L. (2015). 68GaDOTATOC lyophilized ready-to-use kit for PET imaging in pancreatic cancer murine model. Abstract. New advances in animal models and preclinical imaging for translational research in cancerology workshop. La Pointe de Pen Bron, France, September 30th- October 3rd, 2015.

[26] Norenberg, J. P., Krenning, B. J., Konings, I. R., Kusewitt, D. F., Nayak, T. K., Anderson, T. L., de Jong, M., Garmestani, K., Brechbiel, M. W. and Kvols, L. K. (2006). 213Bi-[DOTA0, Tyr3]octreotide peptide receptor radionuclide therapy of pancreatic tumors in a preclinical animal model. Clinical cancer research : an official journal of the American Association for Cancer Research 12, 897-903.

[27] Stolz, B., Weckbecker, G., Smith-Jones, P. M., Albert, R., Raulf, F. and Bruns, C. (1998). The somatostatin receptor-targeted radiotherapeutic [90Y-DOTA-DPhe1, Tyr3]octreotide (90Y-SMT 487) eradicates experimental rat pancreatic CA 20948 tumours. European journal of nuclear medicine 25, 668-674.

A number of *in vivo* pharmacology studies in mice and rats using edotreotide labelled with different radionuclides (^{68}Ga, ^{111}In, ^{90}Y, ^{177}Lu) indicate that edotreotide is taken up by $sstr_2$-expressing tumour tissues, as well as by high $sstr_2$-expressing tissues or organs.

Biodistribution study of (^{68}Ga) edotreotide in mice (Muzio 2015)

Female nude mice bearing AR42J rat pancreatic tumour were administered with 0.3 mCi of the radiolabelled (^{68}Ga) edotreotide for biodistribution and PET analysis. Tumour uptake was confirmed at all time points analyzed. Tumour to kidney ratio was 0.36-0.42 for all time points, whereas tumour to blood ratio was 2.46, 5.61, 13.19 and 25.70 at 30 min, 1 h, 2 h and 4 h, respectively. The specificity of the uptake of edotreotide was confirmed by PET scan performed 45 minutes after an IV injection of unlabelled somatostatin analogue, showing a significant decrease in the uptake of (^{68}Ga)-edotreotide.

Therapeutic effect of (^{90}Y) edotreotide in $sstr_2$-expressing tumours (Stolz 1998)

A study was conducted to evaluate the therapeutic effect of (^{90}Y) edotreotide in Lewis rats bearing the somatostatin receptor-positive rat pancreatic tumour CA20948. *In vivo*, (^{90}Y) edotreotide distributed rapidly to the sst_2 expressing CA20948 rat pancreatic tumour, with a tumour-to-blood ratio of 49.15 at 24 h post injection. A single IV administration of 10 mCi/kg resulted in a complete remission of the tumours in five out of seven animals. No regrowth of the tumours occurred 8 months post injection. Control animals that were treated with 30 mg/kg of unlabelled edotreotide had to be sacrificed 10 days post injection due to excessive growth or necrotic areas on the tumour surface. Upon re-inoculation of tumour cells into those rats that had shown complete remission, the tumours disappeared after 3–4 weeks of moderate growth without any further treatment.

^{177}Lu-edotreotide for somatostatin receptor-targeted radionuclide therapy (de Jong 2001)

In this study it was shown that the cure rate depends on tumour size, with (^{177}Lu) edotreotide resulting in 40% cure of small rat pancreatic tumours (CA20948) after a single IV administration of 277.5 MBq and 60% cure after 2 repeated doses. In addition, a 100% cure rate was achieved in the groups of rats bearing small (<1 cm^2) CA20948 tumors after 2 doses of 277.5 MBq or after a single dose of 555 MBq.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been submitted (see non-clinical discussion).

Safety pharmacology programme

No studies on the safety pharmacology of (^{68}Ga) edotreotide were submitted (see non-clinical discussion).

Pharmacodynamic drug interactions

No studies on the pharmacodynamic drug interactions were submitted (see non-clinical discussion).

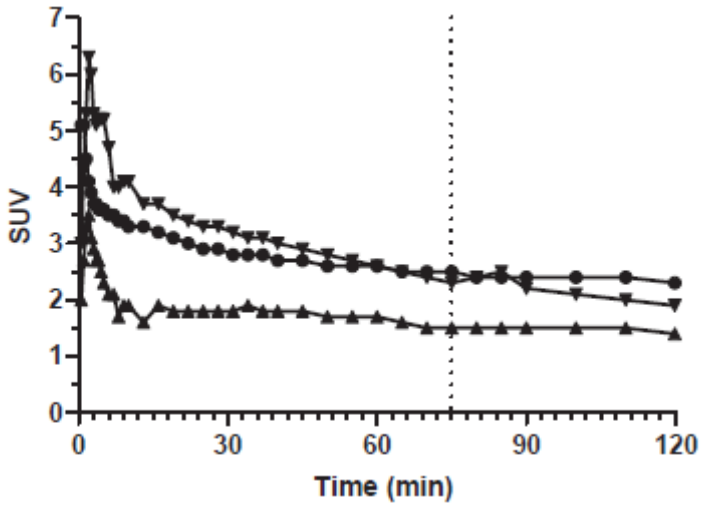
2.3.3. Pharmacokinetics

Edotreotide biodistribution has been studied in normal rats and rodent tumour models (CA20948 and AR42J) using both therapeutic and diagnostic radionuclides.

Biodistribution of (^{68}Ga) edotreotide and (^{68}Ga) DOTA^{0}-Tyr^{3}-octreotate in healthy rats (Velikyan 2012)

Dynamic PET scanning was performed after IV administration as a bolus of 8.96±1.0 MBq/animal of (^{68}Ga) edotreotide and (^{68}Ga) DOTA^{0}-Tyr^{3}-octreotate in male Sprague Dawley rats. Both somatostatin analogues showed a rapid uptake in the kidneys and outflow of activity in the first 15 minutes (Figure 3).

Figure 3: PET time activity curves for kidneys after administration of (^{68}Ga) edotreotide and (^{68}Ga) DOTA0-Tyr3-octreotate to rats. Triangles represent uptake in kidneys of (^{68}Ga) edotreotide (n=2), and circles of (^{68}Ga) DOTA0-Tyr3-octreotate (n=1). Vertical dotted line is at 75 min, the time chosen for the organ distribution study.

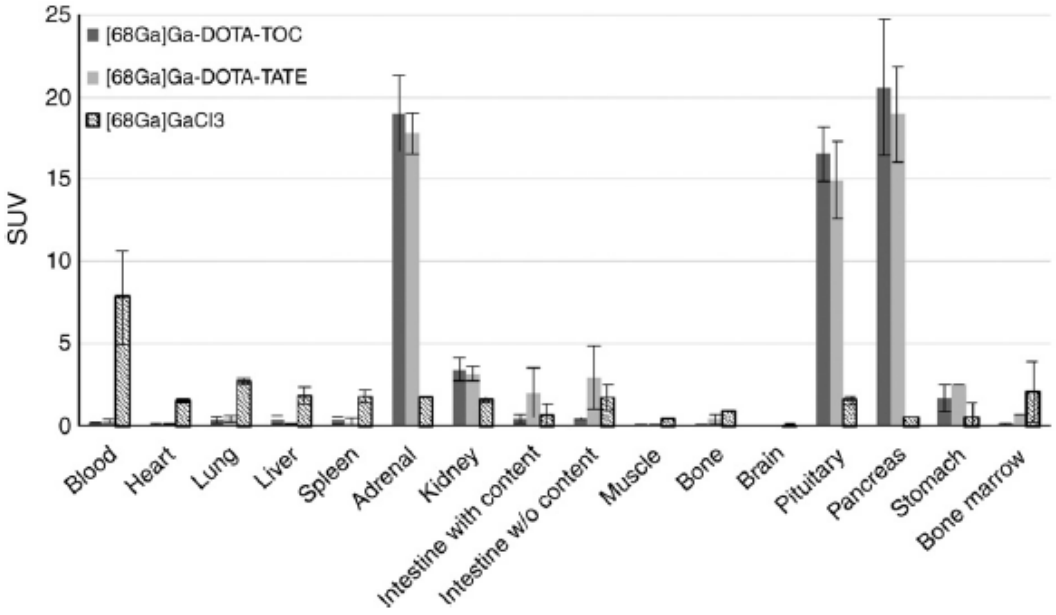


A second group of animals was also used for analysis of organ biodistribution. The time for sacrifice for this study was chosen to be 75 min because in the time activity curves for the uptake in the kidneys steady state was not obtained until over 1 h. Smaller organs like the adrenals and pancreas expressing sstrs physiologically showed high uptake of both tracers in the organ distribution studies, but could not be distinguished in the PET images due to the high uptake in kidneys and urinary bladder in the case of adrenals. Figure 4 shows the SUV (standardized uptake values) calculated for individual organs.

The average radioactivity concentration in blood was low, showing fast clearance from blood circulation. Organs without physiological expression of sstrs (heart, lung, liver, spleen, intestine, bone, muscle) had low uptake of somatostatin analogues.

The organ distribution of radioactivity in the form of buffered and formulated $^{68}GaCl_3$ was also studied in order to evaluate the possible contribution of free ^{68}Ga. The uptake of the radioactivity was the highest in the blood and evenly distributed in most of the organs. The accumulation of $^{68}GaCl_3$ in the heart, lung, liver and spleen was considerably higher as compared to that of peptide tracers.

Figure 4: Organ distribution of ^{68}GaCl3 (n=4), (^{68}Ga) edotreotide (n=3) and (^{68}Ga) DOTA0-Tyr3-octreotate (n=3) in healthy male Sprague–Dawley rats. Data presented as an average SUV and standard deviation



Biodistribution of (^{213}Bi) edotreotide in healthy rats (Norenberg 2006)

Biodistribution of edotreotide labelled with the α-emitter ^{213}Bi was assessed in rats. The biodistribution data showed receptor specificity to somatostatin receptor–expressing tissues when a blocking dose of edotreotide was coadministered with the (^{213}Bi) edotreotide. The somatostatin receptor–positive organs, pancreas, adrenals, stomach, and pituitary showed significantly decreased uptake of (^{213}Bi) edotreotide following a blocking dose of edotreotide. No significant difference was seen in the receptor-negative organs: blood, liver, spleen, muscle, bone, kidneys, testis, and blood.

Biodistribution of (^{68}Ga) edotreotide in AR42J tumour-bearing mice (Muzio 2015)

Female nude mice were inoculated with AR42J rat pancreatic tumour cells. AR42J tumour model has exclusive expression of the sst_2 receptor subtype and there is a high degree of sequence homology between human and rat $sstr_2$. Results are shown in Table 3 and Table 4.

Table 3: Biodistribution of ^{68}Ga-edotreotide in AR42J tumour bearing mice expressed as %ID/organ

	% ID/organ			
	30min	1h	2h	4h
Blood	0.681 ± 0.336	0.276 ± 0.051	0.094 ± 0.048	0.028 ± 0.016
Bladder	0.077 ± 0.038	0.103 ± 0.119	0.015 ± 0.010	0.080 ± 0.154
Kidneys (x2)	3.350 ± 0.491	3.339 ± 1.150	3.007 ± 1.694	2.691 ± 1.705
Adrenals	0.011 ± 0.001	0.008 ± 0.002	0.004 ± 0.001	0.004 ± 0.003
Spleen	0.073 ± 0.027	0.049 ± 0.018	0.027 ± 0.008	0.028 ± 0.032
Heart	0.081 ± 0.010	0.041 ± 0.010	0.017 ± 0.004	0.014 ± 0.013
Lungs (x2)	0.426 ± 0.213	0.235 ± 0.121	0.274 ± 0.351	0.148 ± 0.215
Thyroid	0.032 ± 0.011	0.016 ± 0.003	0.006 ± 0.002	0.004 ± 0.002
Pancreas	0.316 ± 0.124	0.176 ± 0.028	0.136 ± 0.027	0.102 ± 0.108
Stomach	1.01 ± 1.5947	0.107 ± 0.043	0.113 ± 0.059	0.092 ± 0.104
Small bowel	0.500 ± 0.581	0.111 ± 0.017	0.103 ± 0.050	0.049 ± 0.036
Large bowel	0.439 ± 0.386	0.134 ± 0.034	0.060 ± 0.008	0.051 ± 0.041
Tumor	1.268 ± 0.320	1.286 ± 1.053	1.137 ± 0.739	0.674 ± 0.396
Bone	0.119 ± 0.151	0.022 ± 0.014	0.014 ± 0.003	0.014 ± 0.011
Muscle	0.111 ± 0.134	0.038 ± 0.023	0.007 ± 0.003	0.007 ± 0.008
Tail	3.571 ± 1.484	3.091 ± 2.085	0.399 ± 0.176	0.520 ± 0.632
Liver	1.271 ± 0.797	0.650 ± 0.126	0.563 ± 0.123	0.366 ± 0.162
Head	2.292 ± 1.036	1.353 ± 0.377	0.588 ± 0.153	0.604 ± 0.451

Table 4: Biodistribution of ^{68}Ga-edotreotide in AR42J tumour bearing mice expressed as %ID/gram of organ or tissue

	%ID/gram			
	30min	1h	2h	4h
Blood	1.60 ± 0.57	0.63 ± 0.19	0.25 ± 0.08	0.11 ± 0.06
Bladder	4.18 ± 0.90	5.09 ± 4.99	0.73 ± 0.48	0.15 ± 0.02
Kidneys (x2)	9.75 ± 3.19	9.69 ± 2.57	7.79 ± 3.07	7.25 ± 3.05
Adrenals	0.78 ± 0.30	0.49 ± 0.22	0.28 ± 0.05	0.19 ± 0.10
Spleen	0.54 ± 0.13	0.35 ± 0.13	0.21 ± 0.07	0.24 ± 0.28
Heart	0.65 ± 0.19	0.30 ± 0.07	0.12 ± 0.03	0.09 ± 0.07
Lungs (x2)	2.02 ± 0.81	1.19 ± 0.52	0.48 ± 0.37	0.86 ± 1.27
Thyroid	1.18 ± 0.64	0.46 ± 0.14	0.18 ± 0.04	0.14 ± 0.13
Pancreas	1.08 ± 0.03	0.83 ± 0.15	0.56 ± 0.08	0.44 ± 0.34
Stomach	1.16 ± 0.51	0.77 ± 0.15	0.59 ± 0.11	0.48 ± 0.48
Small bowel	0.64 ± 0.07	0.38 ± 0.07	0.30 ± 0.10	0.18 ± 0.13
Large bowel	0.88 ± 0.21	0.53 ± 0.13	0.27 ± 0.03	0.32 ± 0.26
Tumor	3.93 ± 0.54	3.52 ± 1.46	3.32 ± 1.40	2.86 ± 2.11
Bone	0.63 ± 0.20	0.36 ± 0.17	0.20 ± 0.06	0.16 ± 0.11
Muscle	0.39 ± 0.17	0.23 ± 0.11	0.07 ± 0.02	0.06 ± 0.06
Tail	5.15 ± 0.62	5.42 ± 2.87	0.59 ± 0.19	0.82 ± 0.94
Liver	0.77 ± 0.23	0.52 ± 0.12	0.45 ± 0.08	0.31 ± 0.09
Head	0.89 ± 0.26	0.42 ± 0.10	0.19 ± 0.05	0.19 ± 0.12

Biodistribution of (^{68}Ga) edotreotide in CA20948 tumour-bearing rats (Breeman 2005[28])

A (^{68}Ga) edotreotide biodistribution in CA20948 tumour bearing rats showed a rapid and high uptake of the product in $sstr_2$-positive tissues, such as pancreas, adrenals, pituitary and CA20948 tumour. Results are shown in Table 5 .

[28] Breeman, W. A., de Jong, M., de Blois, E., Bernard, B. F., Konijnenberg, M. and Krenning, E. P. (2005). Radiolabelling DOTA-peptides with 68Ga. European journal of nuclear medicine and molecular imaging 32, 478-485.

Table 5: Tissue distribution of (^{68}Ga) edotreotide at 1h and 4h in tumour bearing rats (Breeman 2005)

Tissue	%ID/g ± SD (n=3)	
	1h	4h
Stomach	NA	NA
Spleen	0.13 ± 0.02	0.14 ± 0.01
Lungs	NA	NA
Muscle	0.01 ± 0.00	0.01 ± 0.00
Femur	0.14 ± 0.03	0.16 ± 0.03
Sternum	0.04 ± 0.01	0.01 ± 0.00
Pancreas	6.88 ± 0.45	6.00 ± 1.06
Pituitary	2.30 ± 0.49	1.47 ± 0.21
Tumour (CA20948)	2.90 ± 0.69	2.53 ± 0.97

NA: not applicable.

Biodistribution of ^{67}Ga-, ^{90}Y- and ^{111}In-labelled edotreotide in AR42J tumour-bearing mice and comparison with Octreoscan (Froidevaux 2002[29])

Edotreotide labelled with ^{90}Y, ^{111}In or ^{67}Ga was administered to tumour-bearing nude mice (AR42J rat pancreatic cell line) and its biodistribution was compared to that of (^{111}In) DTPA^0-octreotide (Octreoscan) 4 hours after injection. Labelled edotreotide showed a more favourable biodistribution compared to (^{111}In) octreotide, with higher tumour uptake, faster blood clearance and lower kidney retention, as well as higher uptake in sstr$_2$-positive tissues such as adrenals, pancreas and tumour.

Biodistribution of (^{111}In) edotreotide in AR42J tumour-bearing rats (Lin 2006[30])

Biodistribution and tumour uptake ratio after IV administration of (^{111}In) DTPA^0-octreotide and (^{111}In) edotreotide were compared in Lewis male rats bearing the AR42J rat pancreatic tumour. At 4 hours after administration of 3.7 MBq of the radiolabelled product, the highest radioactivity was observed in tumour and kidney for both radiolabelled analogues, with a higher activity in animals treated with (^{111}In) edotreotide (see Table 6).

[29] Froidevaux, S., Heppeler, A., Eberle, A. N., Meier, A. M., Hausler, M., Beglinger, C., Behe, M., Powell, P. and Macke, H. R. (2000). Preclinical comparison in AR4-2J tumor-bearing mice of four radiolabeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-somatostatin analogs for tumor diagnosis and internal radiotherapy. Endocrinology 141, 3304-12.

[30] Lin, Y. C., Hung, G. U., Luo, T. Y., Chen, C. H., Hsia, C. C., Hen, S. L., Ho, Y. J. and Lin, W. Y. (2006). A comparison of biodistribution between 111In-DTPA octreotide and 111In-DOTATOC in rats bearing pancreatic tumors. J Vet Med Sci 68, 367-71.

Table 6: Tissue biodistribution in rats bearing the AR42J tumour at 4 h after (^{111}In) DTPA0-octreotide (DTPAOC) or (^{111}In) edotreotide (DOTATOC) administration (Lin 2006)

	Biodistribution (%ID/g or ml)	
Organ Tissue	In-111 DTPAOC	In-111 DOTATOC
Tumor*	2.039 ± 0.876	6.934 ± 2.788
Blood	0.043 ± 0.003	0.048 ± 0.012
Muscle*	0.010 ± 0.005	0.027 ± 0.008
Liver	0.378 ± 0.103	0.465 ± 0.101
Spleen	0.574 ± 0.273	0.571 ± 0.058
Lung*	0.144 ± 0.018	0.316 ± 0.102
Small intestine	0.311 ± 0.061	0.212 ± 0.017
Bone*	0.019 ± 0.007	0.198 ± 0.075
Kidney*	3.345 ± 0.642	6.875 ± 1.357

Note: n=6. mean ± standard deviation (SD): * $p<0.05$

Excretion

(^{68}Ga) DOTA conjugated peptides are known to be excreted almost entirely through the kidneys (European Association of Nuclear Medicine EANM guideline: Virgolini 2010). Biodistribution studies in CA20948 tumour bearing animals treated with (^{90}Y) edotreotide (de Jong 1997[31]) showed that >80% of the injected radioactivity is excreted within 24 hours in the urine, of which 95.6±3.4% is still non-metabolized (^{90}Y) edotreotide.

2.3.4. Toxicology

Single dose toxicity

A single dose toxicity study was conducted in male and female Sprague Dawley rats in order to investigate the acute toxicity of the unlabelled edotreotide formulation.

Table 7: Single dose toxicity

Species / Strain	Method of Admin.	Doses (mg/kg)	Gender and No. per group	Observed Maximum Non-Lethal Dose (mg/kg)	Noteworthy Findings	Study No. or Reference
Sprague Dawley SD rats	i.v.	2	5M+5F	2	No significant changes compared to the control group were noted in terms of clinical signs, body weight, hematology, coagulation, clinical chemistry, urinalysis,	(Venturella et al., 2015)

[31] de Jong, M., Bakker, W. H., Krenning, E. P., Breeman, W. A., van der Pluijm, M. E., Bernard, B. F., Visser, T. J., Jermann, E., Behe, M., Powell, P. et al. (1997). Yttrium-90 and indium-111 labelling, receptor binding and biodistribution of [DOTA0,d-Phe1,Tyr3]octreotide, a promising somatostatin analogue for radionuclide therapy. European journal of nuclear medicine 24, 368-71.

					organ weight and macroscopic/microscopic observations, showing that a single i.v. administration of edotreotide at 2 mg/kg was well tolerated. This dose, corresponding to a 500-fold higher dose than the intended maximum human dose, is considered to be safe.	
CA20984 tumour-bearing Lewis rats	i.v.	0.014*# 0.010*## 0.012*## 0.014*##	4M 3M 3M 4M	NA	No differences in creatinine clearance were reported between the group receiving unlabelled edotreotide and ^{213}Bi-labelled edotreotide. Interstitial nephritis score was recorded for each cohort and was always minimal, if any. The cohort receiving the unlabelled edotreotide reported absolutely no kidney lesions. No other signs of toxicity were reported.	(Norenberg et al., 2006)

*calculated on an average weight of 250 g per rat; # Unlabelled edotreotide; ## 213Bi-labelled edotreotide

Repeat dose toxicity

Repeat dose toxicity studies with (^{68}Ga) edotreotide were not submitted (see non-clinical discussion).

Genotoxicity

Genotoxicity studies with (^{68}Ga) edotreotide were not submitted.

Genotoxicity studies with DOTA0-Tyr3-octreotate, a well-known somatostatin analogue belonging to the same chemical class as edotreotide, are available from the literature and indicate that the unlabelled peptide has no influence in the induction of cytogenetic damage, using an *in vitro* micronucleous assay with human peripheral lymphocites (Suzuki 2007).

Genotoxicity test on the novel excipient 1,10-phenanthroline

In published *in vitro* genotoxicity tests, 1,10-phenanthroline has been shown to be non-mutagenic in bacterial reverse mutation assay conducted in *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537), with and without metabolic activation. However, in a mouse lymphoma assay a positive result was observed suggesting that 1,10-phenanthroline is a potential mammalian cell mutagen. The lowest effective dose was calculated to be 0.75 µg/mL (4.2 µM) without metabolic activation and 25 µg/mL (139 µM) with

metabolic activation. Results were negative up to 25 µg/mL (2.77 µM) without metabolic activation and 20 µg/mL (111 µM) with metabolic activation (Whittaker 2001[32]).

Carcinogenicity

Carcinogenicity studies with (^{68}Ga) edotreotide were not submitted (see non-clinical discussion).

Reproduction Toxicity

No reproduction toxicity studies were submitted (see non-clinical discussion).

Toxicokinetic data

No toxicokinetics studies were submitted (see non-clinical discussion).

Local Tolerance

A GLP local tolerance study with an edotreotide formulation mimicking the composition of the final (^{68}Ga) edotreotide preparation to be administered in humans was performed in rabbits (Venturella 2015[33]).

Table 8: Local tolerance study in rabbits

Species/ Strain	Method of Admin.	Doses (mg/kg)*	Gender and no. per group	Noteworthy Findings	Study No. or Reference
New Zealand White Specific Pathogen Free (SPF) rabbits	i.v.	0.0034	6F	A single intravenous administration of edotreotide formulation (with same concentration and pH as the one foreseen in humans) induced mild to moderate perivascular region inflammation without relevant differences between animals receiving the test item or placebo. The observed effects are most likely ascribable to the acidic pH of the injected solutions (which is a common feature to this kind of diagnostic products).	(Venturella et al., 2015)

*Each animal was treated with test item or placebo in the right ear (the left ear was always treated with saline, as negative control)

[32] Whittaker, P., Seifried, H. E., San, R. H., Clarke, J. J. and Dunkel, V. C. (2001). Genotoxicity of iron chelators in L5178Y mouse lymphoma cells. Environ Mol Mutagen 38, 347-56.

[33] Venturella, S., Di Manno, P., Manno, R. A., Orlandi, F. and Chicco, D. (2015). Evaluation of acute intravenous toxicity in rats and local tolerance in rabbits of a formulation for the preparation of 68Ga-DOTATOC (68Ga-Edotreotide or 68Ga-DOTA0-Tyr3-Octreotide). Abstract. European Pharma Congress. Valencia, Spain, August 25th-27th, 2015.

Other toxicity studies

Reproductive and developmental toxicity

Studies to evaluate reproductive toxicity of (^{68}Ga) edotreotide were not submitted (see non-clinical discussion).

General toxicity of novel excipient 1,10-phenanthroline

The drug product contains 1,10-phenanthroline, a novel excipient. A toxicological evaluation and risk assessment of 1,10-phenanthroline was performed by the Applicant on the basis of studies published in the literature. The threshold of toxicological concern (TCC) approach was also applied (Kroes 2005[34]).

Acute toxicity studies in mice showed that 1,10-phenanthroline doses up to 300 mg/kg (corresponding to a human equivalent dose HED of 24 mg/kg, 260000 times higher than the foreseen human IV dose) administered by intraperitoneal route induced no mortality at 24, 72 or 168 hours post dose, while a dose of 450 mg/kg induced 100% mortality at 24 hours (McCann 2012[35]). No behavioural or body weight changes or changes in aspartate aminotransferase or alanine aminotransferase levels were noted in treated animals. In addition, no effects were observed after daily treatment of mice with 1,10-phenanthroline for 5 consecutive days by IP route at 45 mg/kg (corresponding to an HED of 3.7 mg/kg, 40000 times the foreseen human IV dose).

The Permitted Daily Exposure (PDE) estimated for 1,10-phenathroline was evaluated based on the results of a reproductive toxicity study reported in literature, performed on pregnant CF-1 albino mice, after intraperitoneal administration (Chang et al., 1977). In this study the Lowest Observed Effect Level (LOAEL) was 30 mg/kg/day. For a more conservative estimation of the PDE, all adjustment factors suggested by the guideline to account for various uncertainties and to allow the extrapolation to a reliable no-effect level, were set at their maximum level:

PDE = (30 mg/kg/day x 50 kg)/(12 x 10 x 10 x 10 x 10) = 12.5 µg/day

The value calculated, 12.5 µg/day, is highly conservative and represents the dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. This dose is more than 2-fold higher than the maximum 1,10-phenanthroline amount that will be administered in patients as a single dose.

The PDE was also estimated based on a repeated dose toxicity study in mice reported in literature (McCann et al.,2012), in which the NOEL was found to be 45 mg/kg/day. Also in this case, all adjustment factors were set at their maximum level and the PDE value was calculated as follows, in line with the Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA/CHMP/CVMP/SWP/169430/2012) and ICH guideline Q3C(R5):

PDE = (NOEL x Weight Adjustment) / (F1 x F2 x F3 x F4 x F5)

Where:

PDE = Permitted Daily Exposure

[34] Kroes, R., Kleiner, J. and Renwick, A. (2005). The threshold of toxicological concern concept in risk assessment. Toxicol Sci 86, 226-30.

[35] McCann, M., Santos, A. L. S., da Silva, B. A., Romanos, M. T. V., Pyrrho, A. S., M., D., Kavanagh, K., Fichtner, I. and Kellett, A. (2012). In vitro and in vivo studies into the biological activities of 1,10-phenanthroline, 1,10-phenanthroline-5,6-dione and its copper(II) and silver(I) complexes. Toxicol. Res. 1, 47-54.

NOEL = No Observed Effect Level

F1 = factor (values between 2 and 12) to account for extrapolation between species

F2 = factor of 10 to account for variability between individuals

F3 = factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4- weeks

F4 = factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity

F5 = variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

Using the NOEL observed in the repeated dose toxicity study (45 mg/kg) and setting all adjustment factors at their maximum level for a more conservative estimation of the PDE:

PDE = (45 mg/kg/day x 50 kg)/(12 x 10 x 10 x 10 x 10) = 18.7 µg/day

2.3.5. Ecotoxicity/environmental risk assessment

The applicant provided an experimental LogKow value of -2.93 ± 0.37 that is well below the cut-off of 4.5, limit by the EMA guideline. The value was based on the published data for ^{68}Ga-edotreotide.

Additionally, following the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (Doc. Ref. EMEA/CHMP/SWP/4447/00 corr 1*, 01 June 2006), the environmental risk assessment of medicinal products containing natural substances, including peptides (i.e. edotreotide) can be waived, as they do not pose significant impact on the environment.

Fpen = 0,00028 → PECSURFACE WATER is 0.0000056 µg/L.

Table 9: Summary of main study results

Substance (INN/Invented Name): edotreotide			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0002	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			No?

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

2.3.6. Discussion on non-clinical aspects

The applicant submitted published literature to present non-clinical data for edotreotide. *In vitro* and *in vitro* studies showed that edotreotide and other somatostatin analogues bind to the sst2 receptor, commonly over-expressed in GEP-NETs. In all studies, edotreotide is specifically taken up by sstr2 expressing tissues and organs, such as tumour tissue, pancreas and adrenals.

Regarding pharmacokinetics, biodistribution data of edotreotide in normal rats and rodent tumour models using both therapeutic and diagnostic radionuclides was submitted. In all studies, edotreotide is specifically taken up by sstr2 expressing tissues and organs, such as tumour tissue, pancreas and adrenals. Edotreotide, is rapidly taken up by the kidneys and fast clearance from blood circulation is observed. In addition, a study was conducted with the commercial formulation of SomaKit TOC in mice inoculated with AR42J pancreatic tumour cells. In this study, dosimetry data show high uptake in kidney (renal elimination) and tumour.

According to the literature, excretion appears to be mainly via the kidney, with relatively fast elimination kinetics and is excreted mostly as the intact parent compound.

The applicant submitted published data results from two single toxicity studies. No major findings were reported. Non-clinical data did not reveal any special hazard for gallium (^{68}Ga) edotreotide in humans.

The toxicity studies conducted with labelled or unlabelled edotreotide showed only minimal interstitial nephritis in animals treated with (213Bi) edotreotide. Radiation-induced nephritis is a known adverse effect of radiolabelled somatostatin analogues (Rolleman 2010). The study by Venturella 2015 is a GLP study conducted with unlabelled edotreotide formulation, including all the excipients and with the final pH of 3.5±0.3, at a dose about 500 times higher than the planned (^{68}Ga) edotreotide human dose. No signs of toxicity or treatment-related changes were observed.

No repeat dose toxicity studies are considered necessary because repeated (^{68}Ga) edotreotide administration for patient monitoring is unlikely to occur and the doses used in clinical practice are expected to be low and separated in time.

No studies on fertility, embryology, mutagenicity or long-term carcinogenicity have been conducted or were identified in the literature on (^{68}Ga) edotreotide. Carcinogenicity studies are not considered necessary. This is acceptable, considering the favourable safety profile of the compound, the clinical experience and that (^{68}Ga) edotreotide will be given as a single low dose for diagnostic purposes only.

Published data to evaluate reproductive toxicity of (^{68}Ga) edotreotide have not been submitted. It is not known if the compound could cause foetal toxicity when administered to pregnant women, or if it could have any effect on reproductive capacity. Moreover, the risk of the radiation exposure in pregnancy should be taken into consideration. Therefore, (^{68}Ga) edotreotide administration in pregnant women should be avoided, unless the potential benefit justifies the risk (see SmPC section 4.6).

Safety pharmacology studies conducted with somatostatin analogue DOTATATE showed no treatment-related effects in central nervous system, cardiovascular or respiratory system.

Local tolerance assessment resulted in mild to moderate inflammation signs in the perivascular region of some animals which can be attributed to the acidic pH of the solution.

Although no genotoxicity data are available for edotreotide, other somatostatin analogues (DOTA0-Tyr3-octreotate, lanreotide) have not shown evidence of genotoxicity. The justification of the Applicant for the lack of carcinogenicity and reprotoxicity studies is accepted.

The Applicant has conducted a risk assessment of the novel excipient 1,10-phenanthroline. The amount of 1,10-phenanthroline in each clinical dose is 5 µg/dose. Literature data (McCann 2012) has shown a lack of toxicity at doses (HED) much higher than the doses expected to be administered in patients (260000 times higher than the human dose in the single dose study or 40000 in the 5-day repeated dose study). In addition the Applicant has calculated the PDE of 1,10-phenanthroline assuming that the highest dose with no mortality of the literature data (McCann 2012) is the NOEL. The PDE value obtained with these data is 18.7 µg/day, which would be a dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. The value is higher than the 1,10-phenanthroline dose expected in patients treated with SomaKit TOC (5 µg), which will be administered only once or few times during a lifetime.

Regarding the novel excipient (1,10-phenanthroline), during the toxicity study conducted with the kit formulation of SomaKitTOC including 1,10-phenanthroline at a dose 400 fold higher than the human dose, no toxicity signs were observed. Genotoxicity studies on 1,10-phenanthroline available in the literature show negative results in bacterial mutation assay (Ames test), while in a mouse lymphoma assay an indication of possible genotoxicity was obtained at concentrations 750 times higher than the maximum 1,10-phenanthroline blood concentration achievable in patients. However, even taking as reference the highest limits for genotoxic and carcinogenic impurities, the risk related to the trace amounts of 1,10-phenanthroline in SomaKit TOC formulation is considered negligible at the dose to be administered in patients: the exposure

to 1,10-phenanthroline (5 µg/dose) is 24 fold lower than the acceptable daily intake for a genotoxic impurity (120 µg/day for exposures <1 month). However, with the low amounts administered to patients, the risk of 1,10-phenanthroline is negligible even if it were genotoxic. Therefore, considering the absence of findings in the studies conducted with the kit formulation of SomaKit TOC including 1,10-phenanthroline and the estimated PDE value, the risk of 1,10-phenanthroline is negligible at the dose expected in patients treated with SomaKit TOC.

Since the obtained value for Fpen is well below 0.01 µg/L threshold considered by the guideline for environmental testing, it is considered that edotrotide is unlikely to represent any relevant risk for the environment. Moreover, as endotrotide is a peptide, it is considered to unlikely result in a significant risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of edotreotide have been well characterized in the literature. The non-clinical aspects are considered to be appropriately addressed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Not applicable as no clinical studies have been submitted with SomaKit TOC.

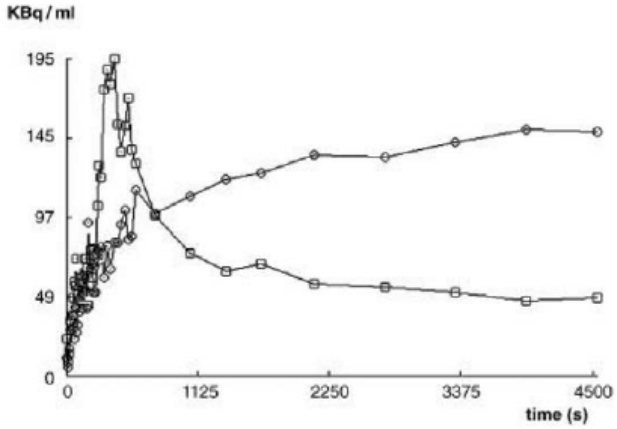
2.4.2. Pharmacokinetics

The PK assessment is based on published studies.

Biodistribution

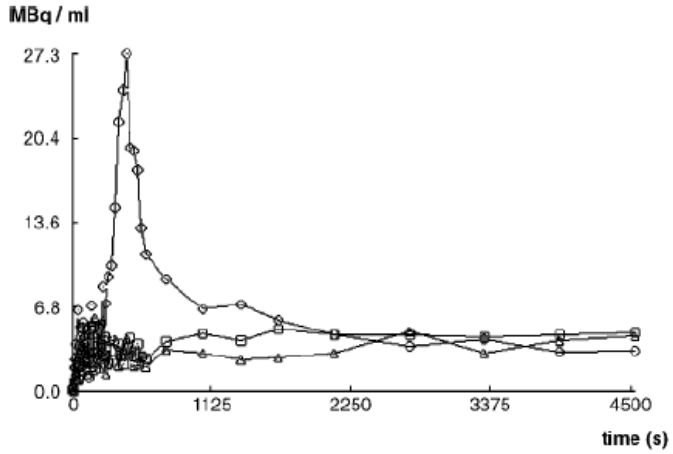
After intravenous injection, ^{68}Ga-edotreotide is rapidly cleared from the blood following bi-exponential arterial elimination of activity with two half-lives (2.0±0.3 min and 48±7 min). Please see figures below.

Figure 5: Time activity curves of ^{68}Ga-edotreotide over the tumour and kidney



Time-activity curves, measured over tumour (o) and over the right kidney (□), reveal very fast renal elimination of the tracer, whereas the tumour accumulated ^{68}Ga-edotreotide up to 75 min after the injection, with 90% of the peak uptake at 38 min (patient 1) (Hofmann 2001[36])

Figure 6: Time activity curves of ^{68}Ga-edotreotide over the kidney, liver and lumbar spine



Typical time-activity curves (patient 4) using ^{68}Ga-edotreotide measured over kidney (O), liver (□) and the lumbar spine (Δ). There is rapid renal elimination with similarly low retention in all three regions as early as 38 min p.i. (Hofmann 2001).

No radioactive metabolites were detected within 4 hours in serum. Maximal tumour activity accumulation was reached 70 ± 20 min post injection and similar time courses of local SUVs were observed in the spleen. The time-activity curves obtained from the renal parenchyma showed an initial peak followed by a rapid decrease. Between 10 and 15 min p.i. the activity concentration was of the same order of magnitude as that observed in the liver. The ratio of the SUVs of kidney to spleen ranged from 0.13 to 0.5 at times >90 min p.i. The activity concentration of the bone marrow was at least 1 order of magnitude lower than that of the tumours. In all patients, thyroid and pineal gland, both adrenal glands were clearly delineated with positive contrast.

[36] Hofmann M, Maecke H, B, Weckesser E, Sch, Oei L, Schumacher J, Henze M, Heppeler A, Meyer J, Knapp H (2001). Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 28(12):1751-1757

Activity levels in these organs remained almost constant after 90 min p.i., SUVs of these organs did not exceed a value of 2.5.

The organ with the highest ^{68}Ga-edotreotide uptake is the spleen (mean SUV2: 21.8 ± 2.2, N=3), followed by the kidneys (mean SUV2: 11.9 ± 3.1, N=3). The uptake in the liver, the pituitary, the thyroid gland and both adrenal gland is lower mean (SUV2 in liver=6.1 ± 1.4, in pituitary gland=1.4 ± 0.6). The highest SUVs were found at a plateau between 45 and 90 minutes with a maximum (mean SUV 38.1) 60 minutes post-injection (Hofmann 2001, Kowalski 2003 and Boy 2011). The liver metastases of another patient did not show an increase of the SUVs during the whole examination (120 minutes).

In the study of Boy et al., for each organ, SUVmax values demonstrated low within-patient variability with coefficients of variation between 25 and 48% (Boy 2011). Two of the 19 target regions, the uptake of which was measured on PET/CT, revealed significant gender differences: in the thyroid gland, SUVmax of male subjects exceeded that of female subjects by about 50% (female = 3.7 ± 1.6, male = 5.5 ± 2.4, $p<0.001$) and in the pancreatic head by about 25%, respectively (female = 5.5 ± 1.9, male = 6.9 ± 2.2, $p<0.001$). The SUVmax data were evaluated within a strict time window of 30–90 min post injection. The regional SUVmax values were comparable to those of the whole population with slightly different variation coefficients (e.g. in the subgroup, the uncinate process SUVmax was significantly different from that of all other pancreatic tissues including pancreas tail region). Moreover, in this subgroup, gender differences appeared to be limited to the thyroid (female = 3.7 ± 1.6 range = 1.1 – 7.6, male = 5.4 ± 2.6 range = 2.6 – 14.3, $p<0.001$), underlying thyroid pathology not being ruled out.

Overall, in the study of Boy et al. the ^{68}Ga-edotreotide SUVmax has been shown to be an age-independent and predominantly gender-independent parameter of normal adult human tissues (Boy 2011). ^{68}Ga-edotreotide uptake showed a correlation with in vitro SSTR2 but not with SSTR5 expression. Concordantly with the results of Boy et al. in 2011, there is a correlation between ^{68}Ga-edotreotide uptake on PET quantified by calculation of standardised uptake values (SUV) and expression of SSTR2 proven by immunohistochemistry (Miederer 2009[37], Müssig 2010[38]).

The frequent physiological uptake of ^{68}Ga-edotreotide by the pancreas uncinate process, which may be caused by an accumulation of pancreatic polypeptide-containing cells expressing SSTR, was confirmed by Jacobsson et al.[39]. As a consequence for image interpretation, if there is a normal finding on concomitant diagnostic CT, this uptake should be regarded as physiological (Al-Ibraheem 2011[40], Jacobsson 2012[41]). Kroiss et al. proposed a cut-off SUV of 17.1 to distinguish physiologic ^{68}Ga-edotreotide uptake by uncinate process from tumour (Kroiss 2013[42]).

[37] Miederer M, Seidl S, Buck A, Scheidhauer K, Wester HJ, Schwaiger M, Perren A (2009). Correlation of immunohistopathological expression of somatostatin receptor 2 with standardised uptake values in 68Ga-DOTATOC PET/CT. Eur J Nucl Med Mol Imaging 36(1):48-52

[38] Müssig K, Oksüz MO, Dudziak K, Ueberberg B, Wehrmann M, Horger M, Schulz S, Häring HU, Pfannenberg C, Bares R, Gallwitz B, Petersenn S (2010). Association of somatostatin receptor 2 immunohistochemical expression with [111In]-DTPA octreotide scintigraphy and [68Ga]-DOTATOC PET/CT in neuroendocrine tumors. Horm Metab Res 42(8):599-606

[39] Jacobsson H, Larsson P, Jonsson C, Jussing E, Gryb (2012). Normal uptake of 68Ga-DOTA-TOC by the pancreas uncinate process mimicking malignancy at somatostatin receptor PET. Clin Nucl Med 37(4):362-365

[40] Al-Ibraheem A, Bundschuh RA, Notni J, Buck A, Winter A, Wester HJ, Schwaiger M, Scheidhauer K (2011). Focal uptake of 68Ga-DOTATOC in the pancreas: pathological or physiological correlate in patients with neuroendocrine tumours? Eur J Nucl Med Mol Imaging 38(11):2005-2013

[41] Jacobsson H, Larsson P, Jonsson C, Jussing E, Gryb (2012). Normal uptake of 68Ga-DOTA-TOC by the pancreas uncinate process mimicking malignancy at somatostatin receptor PET. Clin Nucl Med 37(4):362-365

[42] Kroiss A, Putzer D, Decristoforo C, Uprimny C, Warwitz B, Nilica B, Gabriel M, Kendler D, Waitz D, Widmann G, Virgolini IJ (2013). 68Ga-DOTA-TOC uptake in neuroendocrine tumour and healthy tissue: differentiation of physiological uptake and pathological processes in PET/CT. Eur J Nucl Med Mol Imaging 40(4):514-523

The highest uptake was measured of the pancreas and the lowest in a patient with a medullary thyroid carcinoma (MEN-2). The analysis shows that k1 had the greatest impact on the global SUV, followed by Vb and k3. It was concluded that ^{68}Ga-edotreotide uptake in NET is mainly dependent on k1 (receptor binding) and Vb (fractional blood volume) with low cellular externalisation (k4).

Table 10: Evaluation of the pharmacokinetics of ^{68}Ga-edetreotide in patients with metastatic neuroendocrine tumours scheduled for ^{90}Y-edotreotide therapy (Koukouraki 2006a[43])

Variable[a]	Mean	Minimum	Maximum
k_1	0.512	0.045	0.999
k_2	0.468	0.020	0.999
k_3	0.128	0.005	0.751
k_4	0.027	0.000	0.164
V_b	0.154	0.01	0.411
FD	1.335	1.10	1.448
SUV	8.730	0.877	28.07

[a] The unit for k1-k4 is l/min. SUV and FD do not have units and are relative measures. FD is an absolute value (range, 0-2)

In Velikyan et al.[44], the net uptake rate (Ki) was calculated both using nonlinear regression of an irreversible 2-tissue-compartment model and using the Patlak method, which is a linearization of this model, for 3 most active lesions per patient. After intravenous administration, the ^{68}Ga-edotreotide was rapidly cleared from the blood. The radioactivity in the blood decreased to less than 4.7% of the peak level ^{68}Ga-edotreotide, within 45 min of the dynamic acquisition and to 2.0% at 195 min after administration. After 50 min, the accumulation of ^{68}Ga-edotreotide in all organs reached a plateau. The tumour accumulation for each patient was represented by the lesion with the highest radioactivity uptake. ^{68}Ga-edotreotide tumour uptake in all patients except one continually increased over time.

Dosimetry

The administration of 100-200 MBq of ^{68}Ga-edotreotide leads approximately to a total effective dose of 2.0-4.0 mSv for men and 2.3-4.6 mSv for women (Sandström 2013[45], Hartmann 2009[46]).

The critical organ receiving the highest absorbed dose from ^{68}Ga-edotreotide is the urinary bladder wall, spleen and kidney (0.119±0.058 mGy/MBq, 0.108±0.065 mGy/MBq and 0.082±0.020 mGy/MBq respectively) (Sandström 2013). Twofold higher absorbed doses by spleen any kidney has been observed by Hartmann et al. (Hartmann 2009): spleen 0.24 mGy/MBq, kidney 0.22 mGy/MBq, using a scanning protocol with sparser sampling requiring extrapolation over a larger fraction of the total decay of the tracer than in the study of Sandström et al. (Sandström 2013) (Table 11, Table 12, Table 13).

[43] Koukouraki S, Strauss LG, Georgoulias V, Schuhmacher J, Haberkorn U, Karkavitsas N, Dimitrakopoulou-Strauss A (2006a). Evaluation of the pharmacokinetics of 68Ga-DOTATOC in patients with metastatic neuroendocrine tumours scheduled for 90Y-DOTATOC therapy. Eur J Nucl Med Mol Imaging 33(4):460-466

[44] Velikyan I, Sundin A, S, Lubberink M, Sandstr, Garske-Rom, Lundqvist H, Granberg D, Eriksson B (2014). Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga-DOTATATE: net uptake rate for accurate quantification. J Nucl Med 55(2):204-210

[45] Sandström M, Velikyan I, Garske-Rom, S, Eriksson B, Granberg D, Lundqvist H, Sundin A, Lubberink M (2013). Comparative biodistribution and radiation dosimetry of 68Ga-DOTATOC and 68Ga-DOTATATE in patients with neuroendocrine tumors. J Nucl Med 54(10):1755-1759

[46] Hartmann H, Z, Freudenberg R, Oehme L, Andreeff M, Wunderlich G, Eisenhofer G, Kotzerke J (2009). [Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations]. Nuklearmedizin 48(5):201-207

Table 11: Residence times of ^{68}Ga-edotreotide [h] (n=9). LLI=lower large intestine; SI=small intestine; ULI= upper large intestine

Site	^{68}Ga-edotreotide
Kidney	0.048 ± 0.011
Liver	0.128 ± 0.041
Spleen	0.038 ± 0.023
Adrenal gland	0.003 ± 0.001
Lungs	0.006 ± 0.002
Urinary bladder contents	0.086 ± 0.052
Bone marrow	0.038 ± 0.016

Site	^{68}Ga-edotreotide
Heart contents	0.014 ± 0.005
Small intestine contents	0.018 ± 0.008
Upper large intestine contents	0.007 ± 0.003
Lower large intestine contents	0.001 ± 0.000
Remainder of body	1.149 ± 0.079

LLI = lower large intestine; SI= small intestine; ULI = upper large intestine (Sandström 2013).

Table 12: Summary of dosimetry of ^{68}Ga-edotreotide

Radiopharmaceutical	Whole body mean effective dose [mSv/MBq]	Absorbed doses by critical organs		
		Kidney [mGy/MBq]	Liver [mGy/MBq]	Spleen [mGy/MBq]
^{68}Ga-edotreotide (Hartmann 2009)	0.023 mSv/MBq (2.3-4.6mSv for 100-200 MBq)	0.22	0.074	0.24

Table 13: Dosimetry of ^{68}Ga-edotreotide per organs in male and female patients

Organ	Organ dose [mSv/MBq] according to Patient model	
	male	female
Adrenals	7,3E-02	8,4E-02
Brain	7,2E-03	9,5E-03
Breast	7,6E-03	9,8E-03
Urinary bladder wall	1,4E-02	1,7E-02
Intestinal wall (LLI)	9,4E-03	1,3E-02
Small intestine	1,0E-02	1,3E-02
Gastric wall	1,1E-02	1,4E-02
Intestinal wall(ULI)	1,0E-02	1,3E-02
Heart wall	9,9E-03	1,3E-02
Kidneys	2,1E-01	2,5E-01
Liver	6,8E-02	8,2E-02
Lung	9,2E-03	1,2E-02
Muscles	8,7E-03	1,1E-02
Ovaries	-	1,2E-02
Pancreas	1,5E-02	1,8E-02
Red marrow	1,2E-02	1,4E-02
Osteogenic cells	1,5E-02	2,0E-02
Skin	7,3E-03	9,4E-03
Spleen	2,5E-01	2,1E-01
Testes	8,0E-03	-
Thymus	8,3E-03	9,9E-03
Thyroid gland	7,9E-03	8,4E-02
Bladder wall	6,0E-02	1,3E-02
Uterus	1,0E-02	1,5E-02
Whole body	1,2E-02	8,4E-02
Effective Dosis	2,2E-02	2,5E-02

In the same study the urine was collected and 15.6% (SD 9.2) of ^{68}Ga-edotreotide was excreted into the urine during the first 4 h after injection. The Ki based on Patlak analysis correlated well with Ki based on compartment modelling. The relation between SUV and Ki was not linear; instead, SUVs no longer increased for Ki values larger than 0.2 mL/cm3/min.

Gallium-68 decays with a half-life of 68 min to stable zinc-68, 89% through positron emission with a mean energy of 836 keV followed by photonic annihilation radiations of 511 keV (178%), 10% through orbital electron capture (X-ray or Auger emissions), and 3% through 13 gamma transitions from 5 excited levels.

The dosimetry of gallium (^{68}Ga) edotreotide wascalculated by Sandstromet al.(2013),using OLINDA/EXM 1.1 software (Table 14).

Table 14: Dosimetry of radiolabeled drug ^{68}Ga-edotreotide

Absorbeddoseinselectedorgans	***mGy/MBq***
Organs	***Mean***
Adrenals	*0.077*
Brain	*0.010*
Breasts	*0.010*
Gallbladderwall	*0.015*
Lowerlargeintestinewall	*0.015*
Smallintestine	*0.023*
Stomachwall	*0.013*
Upperlargeintestinewall	*0.020*
Heartwall	*0.020*
Kidneys	*0.082*
Liver	*0.041*
Lungs	*0.007*
Muscle	*0.012*
Ovaries	*0.015*
Pancreas	*0.015*
Redmarrow	*0.016*
Osteogeniccells	*0.021*
Skin	*0.010*
Spleen	*0.108*
Testes	*0.011*
Thymus	*0.011*
Thyroid	*0.011*
Urinarybladderwall	*0.119*
Uterus	*0.015*
Totalbody	*0.014*
Effectivedose mSv/MBq	*0.021*

The effective dose resulting from the administration of an activity of 200 MBq to an adult weighing 70 kg is about 4.2 mSv.

For an administered activity of 200 MBq the typical radiation dose to the critical organs, which are the urinary bladder wall, the spleen, the kidneys and the adrenals, are about 24, 22, 16 and 15 mGy, respectively.

Elimination

After intravenous injection, ^{68}Ga-edotreotide is rapidly cleared from the blood following bi-exponential arterial elimination of activity with two half-lives (2.0±0.3 min and 48±7 min). The radioactivity in the blood decreased to less than 4.7% of the peak level ^{68}Ga-edotreotide, within 45 min of the dynamic acquisition and to 2.0% at 195 min after administration.

The majority of somatostatin analogue peptides are excreted as intact compound via the renal system. Approximately 16% of ^{68}Ga-edotreotide activity is removed from the body in the urine within 2 to 4 hours (Sandström 2013, Velikyan 2014).

Although gender differences were evident within the thyroid and the pancreatic head, the organ ^{68}Ga-edotreotide uptake has been shown to be age-independent and gender-independent parameter of normal adult human tissues.

Organ with the highest gallium (^{68}Ga) edotreotide uptake is the spleen, followed by the kidneys. The uptake in the liver, the pituitary, the thyroid gland and both adrenal gland is lower. Fifty minutes after intravenous administration of gallium (^{68}Ga) edotreotide, its accumulation in all organs shows plateauing.
Approximately 16% of ^{68}Ga-edotreotide activity is removed from the body in the urine during the first 4 hours. No degradation products of the radiopeptide were found in the serum within 4 hours after intravenous injection of gallium (^{68}Ga) edotreotide.

Metabolism

The metabolism of gallium (^{68}Ga) edotreotide was studied in 2001 by Hofmann et al. (Hofmann 2001[47]). In humans treated IV with (^{68}Ga) edotreotide, no radioactive metabolites were detected in serum 4 hours after administration. These results are in line with urine excretion data obtained in non-clinical biodistribution studies (de Jong 1997[48]), showing that >80% of the injected radiolabelled edotreotide is excreted within 24 hours in the urine, mostly as intact compound (see section 3.5).

Special populations

The applicant did not submit studies in special populations (see clinical pharmacology discussion).

Pharmacokinetic interaction studies

The applicant did not submit pharmacokinetic interaction studies (see clinical pharmacology discussion).

Pharmacokinetics using human biomaterials

The applicant did not submit pharmacokinetics studies using human biomaterials (see clinical pharmacology discussion).

2.4.3. Pharmacodynamics

Gallium (^{68}Ga) edotreotide is radiopharmaceutical composed of edotreotide, a somatostatin analogue, designed for PET imaging of somatostatin receptors in GEP-NET patients.

Mechanism of action

The company has provided with published data showing *in vitro* the affinity profile to human sstr of gallium (^{68}Ga) edotreotide, Octreoscan and some other somatostatin radiotracers. The profile resulted to be similar

[47] Hofmann M, Maecke H, B, Weckesser E, Sch, Oei L, Schumacher J, Henze M, Heppeler A, Meyer J, Knapp H (2001). Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 28(12):1751-1757

[48] de Jong, M., Bakker, W. H., Krenning, E. P., Breeman, W. A., van der Pluijm, M. E., Bernard, B. F., Visser, T. J., Jermann, E., Behe, M., Powell, P. et al. (1997). Yttrium-90 and indium-111 labelling, receptor binding and biodistribution of [DOTA0,d-Phe1,Tyr3]octreotide, a promising somatostatin analogue for radionuclide therapy. European journal of nuclear medicine 24, 368-71.

for gallium (^{68}Ga) DOTATOC and Octreoscan, mostly to sstr2 and sstr5; however, the affinity of the former was nine-fold higher in sstr2 and three-fold higher in sstr5 (Table 15).

The somatostatin agonist gallium (^{68}Ga) edotreotide is aDOTA-conjugated analogue of somatostatin with high affinity to somatostatin receptor subtype2 (SSTR2). In normal human tissues, gallium (^{68}Ga) edotreotide uptake on PET imaging is related to the expression of SSTR2 exclusively at the level of mRNA (Boy et al 2011[49]).

Table 15: Affinity profiles IC50±SEM (half maximal inhibitory concentration ± standard error of the mean) in nmol/L(number of experiments between parentheses) (Reubi2000)

Ligand/SST-subtype	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin-28	5.2±0.3(19)	2.7±0.3(19)	7.7±0.9(15)	5.6±0.4(19)	4.0±0.3(19)
^{111}In-pentetreotide	>10,000(6)	22±3,6(5)	182±13(5)	>1,000(5)	237±52(5)
^{68}Ga-DOTATATE	>10,000(3)	0.2±0.04(3)	>1,000(3)	300±140(3)	377±18(3)
gallium (68Ga) edotreotide	>10,000(6)	2.5±0.5(7)	613±140(7)	>1,000(6)	73±21(6)

No *in vivo* binding target(s) of gallium (^{68}Ga) edotreotide either in normal subjects or in targeted patients were submitted.

Primary and Secondary pharmacology

The uptake and distribution of gallium (^{68}Ga) edotreotide has been analyzed in patients with GEP-NETs in the study of Velikyan et al. 2010[50] aimed to evaluate the impact of peptide mass on the quantitative values of binding of gallium (^{68}Ga) edotreotide and on the image contrast. Six patients with GEP-NET underwent three sequential PET/CT examinations with gallium (^{68}Ga) edotreotide during the same day applied a3-h interval between the examinations (injected radioactivity:15–80 MBq; injected edotreotide: 1.54±0.58 µg and 4.95±0.7 µg, respectively, for the first and second/third administration). Prior to the second and third injections, 50 µg and 250 or 500 µg of octreotide were injected. The specific activity for the first injection was 35 ± 15 MBq/nmol, for the second injection was 0.93±0.07MBq/nmol and for the third injection was 0.25 MBq/nmol (250 µg of octreotide) and 0.14±0.03 MBq/nmol (500 µg of octreotide). A static whole-body 2D PET/CT image was obtained at 10 min postinjection of the radiopharmaceutical.

The authors conclude that the gallium (^{68}Ga) edotreotide uptake and image contrast in both tumours and normal organs depends on the total amount of administered peptide (both labelled and unlabelled). The pattern of the tumoural uptake for the three sequential tracer administrations was qualitatively similar in-between patients except for one patient. However, uptake increased versus baseline in almost all tumours or remained constant in the 50-µg pretreated scan, and thereafter decreased with the higher doses. An expected individual variability in tumour tracer accumulation was found, indicating significant differences in sst receptor density expression. There was that a large variation was also found in normal tissues. One

[49] Boy C, Heusner TA, Poeppel TD, Redmann-Bischofs A, Unger N, Jentzen W, Brandau W, Mann K, Antoch G, Bockisch A, Petersenn S (2011). 68Ga-DOTATOC PET/CT and somatostatin receptor (sst1-sst5) expression in normal human tissue: correlation of sst2 mRNA and SUVmax. Eur J Nucl Med Mol Imaging 38(7):1224-1236

[50] Velikyan I, Sundin A, Eriksson B, Lundqvist H, S, Bergstr, L (2010). In vivo binding of [68Ga]-DOTATOC to somatostatin receptors in neuroendocrine tumours--impact of peptide mass. Nucl Med Biol 37(3):265-275

explanation might be that apparent healthy tissues also contained varying amounts of micrometastases not seen in the PET images.

The lesion-to-liver ratio increased in four of five patients in which liver values were available from the baseline to the 50-µg pretreated scan. The average increase was 42% (range:13–108%) and the uptake increased in the metastases but decreased in the liver and spleen. The baseline lesion-to-liver ratio increased in four of five patients with the higher doses (average: 88%; range:1–223%).

The authors discuss that at the dose of 50 µg a blocking effect does not occurred in tumour but in normal tissues; so did for the higher amounts of the peptide both in the tumour tissue and in normal tissues (liver and spleen). They acknowledge that since the span of the peptide amount is rather wide, one cannot exclude the possibility that a better tumour-to-background contrast can be achieved at lower octreotide amounts.

The previous splenectomy should be considered as a relevant factor when reporting the outcome of SSTR targeted diagnostics and therapies since it leads to higher gallium (^{68}Ga) edotreotide uptake in tumour lesions, adrenal and kidney tissue(Kratochwil 2013[51]). These authors studied 22 pancreatic NET patients (eleven patients with and eleven patients without splenectomy). Imaging was started 60±10 minutes after I.V. injection of 116 to 164 MBq of ^{68}Ga– edotreotide.

[51] Kratochwil C, Mavriopoulou E, Rath D, Afshar-Oromieh A, Apostolopoulos D, Haufe S, Mier W, Haberkorn U, Giesel FL (2013). Comparison of 68Ga-DOTATOC biodistribution in patients with and without spleenectomy. Q J Nucl Med Mol Imaging 59(1):116-120

Table 16: Comparison of biodistribution of gallium (^{68}Ga) edotreotide in patients with and without splenectomy

Inter-individual comparison (matched pairs)		With spleen		Spleenectomy	
		Mean	St. Dev.	Mean	St. Dev.
Pituitary gland		4.08	1.79	4.92	1.93
Thyroid		2.56	1.33	2.66	0.94
Adrenal gland left		7.18	3.33	9.73	3.46
Adrenal gland right		7.32	3.03	11.19	5.72
Left and right adrenal glands		7.2	3.11	10.5	4.57
Left kidney		8.13	4.26	8.62	2.17
Right kidney		8.11	4.16	9.79	2.18
Left and right kidney		8.1	4.10	9.2	2.21
Liver parenchyma	Left lobe	5.74	1.60	6.20	2.12
	Upper right lobe	5.74	1.62	6.31	1.96
	Lowest right lobe	5.73	1.58	6.14	1.95
	mean	5.74	1.55	6.22	1.95
Liver metastasis	1	19.17	6.05	37.67	16.31
	2	21.08	10.94	30.70	10.11
	3	17.36	7.10	30.37	12.53
	mean	19.21	8.23	32.82	13.00

The absence of relevant in vivo saturation SSTR2 was proven in tumour lesions. Inversely, in normal tissue (liver, spleen) a limited SSTR2 capacity was confirmed (Velikyan2010, Ezziddin 2012[52], Giesel 2013[53], Sabet2013[54]).

- ***Pharmacodynamic interactions with other medicinal products or substances***

No *in vivo* pharmacodynamics drug-drug interaction studies performed with a number of drugs belonging to classes that may be frequently used by the intended population have been provided.

Given the lack of interaction studies, the recommendation to perform imaging with gallium (^{68}Ga) edotreotide at the end of therapeutic interval with unlabelled somatostatin analogues seems to be an acceptable compromise.

The following wording of section 4.5 of SmPC is included in the SmPC:

[52] Ezziddin S, Lohmar J, Yong-Hing CJ, Sabet A, Ahmadzadehfar H, Kukuk G, Biersack HJ, Guhlke S, Reichmann K (2012). Does the pretherapeutic tumor SUV in 68Ga DOTATOC PET predict the absorbed dose of 177Lu octreotate? Clin Nucl Med 37(6):e141--e147

[53] Giesel FL, Stefanova M, Schwartz LH, Afshar-Oromieh A, Eisenhut M, Haberkorn U, Kratochwil C (2013). Impact of peptide receptor radionuclide therapy on the 68Ga-DOTATOC-PET/CT uptake in normal tissue. Q J Nucl Med Mol Imaging 57(2):171-176

[54] Sabet A, Ezziddin K, Pape UF, Ahmadzadehfar H, Mayer K, P, Guhlke S, Biersack HJ, Ezziddin S (2013). Long-term hematotoxicity after peptide receptor radionuclide therapy with 177Lu-octreotate. J Nucl Med 54(11):1857-1861

Somatostatin and its analogues are probably competing to bind to the same somatostatin receptors. Therefore, when treating patients with somatostatin analogues, it is preferable to perform imaging with gallium (^{68}Ga) edotreotide the day(s) preceding the next administration of a somatostatin analogue.

A long-term exposure to endogenous hypercortisolism may down-regulate somatostatin receptor expression and negatively influence the results of somatostatin receptor imaging with gallium (^{68}Ga) edotreotide. In patients with Cushing syndrome, the normalisation of hypercortisolism should be considered before performing PET with SomaKit TOC.

2.4.4. Discussion on clinical pharmacology

The PK assessment is based on published studies published in scientific journals.

After intravenous injection, gallium (^{68}Ga) edotreotide is rapidly cleared from the blood following bi-exponential elimination of activity with half-lives of 2.0 ± 0.3 min and 48 ± 7 min respectively. The radioactivity in the blood decreased to less than 4.7% of the peak level gallium (^{68}Ga) edotreotide, within 45 min of the dynamic acquisition and to 2.0% at 195 min after administration. The organ with the highest physiological uptake of gallium (^{68}Ga) edotreotide is the spleen, followed by the kidneys. The uptake in the liver and in the pituitary, thyroid and adrenal glands is lower. High physiological uptake of gallium (^{68}Ga) edotreotide by the pancreas uncinate process can also be observed. About 50 minutes after intravenous administration, gallium (^{68}Ga) edotreotide accumulation shows plateauing in all organs.

The organ uptake has been shown to be age-independent in normal adult human tissues and also predominantly gender-independent (except for the thyroid and head of pancreas).

No radioactive metabolites were detected in serum within 4 hours after intravenous injection of gallium (^{68}Ga) edotreotide.

Approximately 16% of gallium (^{68}Ga) edotreotide activity is removed from the body in the urine within 2 to 4 hours. The peptide is excreted via kidneys as intact compound.

Given that the elimination rate is substantially slower than the physical half-life of ^{68}Ga (68 min), the biological half-life will have little impact on the effective half-life of the product which then would be expected to be somewhat less than 68 minutes.

Somatostatin and its analogues may compete to bind to the same somatostatin receptors. The company's recommendation to withdraw unlabelled somatostatin analogues therapy prior to gallium (^{68}Ga) edotreotide scan has been justified.

There is no data presented on renal and hepatic impairment. The pharmacokinetics in patients with renal or hepatic impairment has not been characterized. The safety and efficacy of gallium (^{68}Ga) edotreotide have not been studied in patients with renal or hepatic impairment (see section 4.2 and 5.2 of the SmPC). Severe renal or hepatic impairment might theoretically lead to increased bioavailability of gallium (^{68}Ga) edotreotide, however, no data on eventual impact on diagnostic performance are available. This question will be implemented into risk management plan for SomaKit TOC as "missing information" in the RMP and will be a subject of post-marketing pharmacovigilance activities.

For the elderly population, no special dosage regimen for elderly patients is required.

For information on the use in paediatric population, see section 4.2 of the SmPC.

At the chemical concentrations used for diagnostic examinations, gallium (^{68}Ga) edotreotide does not appear to have any clinically relevant pharmacodynamic effect.

Edotreotide is a somatostatin analogue. Somatostatin is a neurotransmitter in the central nervous system, but also a hormone which binds to cells of neuroendocrine origin and inhibits the release of growth hormone, insulin, glucagon, and gastrin. There is no data if the intravenous administration of edotreotide produces variation of serum gastrin and serum glucagon levels.

Interpretation of gallium (^{68}Ga) edotreotide images and limitations of use.

PET images with gallium (^{68}Ga) edotreotide reflect the presence of somatostatin receptors in the tissues.

The organs with high physiological uptake of gallium (^{68}Ga) edotreotide include spleen, kidneys, liver, pituitary gland, thyroid gland and adrenals. High physiological uptake of gallium (^{68}Ga) edotreotide by the pancreas uncinate process can also be observed. PET findings interpretation errors have been included as an important potential risk.

In GEP-NET, a more intense gallium (^{68}Ga) edotreotide uptake than normal background is a consistent finding. However, lesions of GEP-NET not expressing sufficient density of somatostatin receptors cannot be visualised with gallium (^{68}Ga) edotreotide. PET images with gallium (^{68}Ga) edotreotide should be interpreted visually, and semi-quantitative measurement of gallium (^{68}Ga) edotreotide uptake should not be used for clinical interpretation of images.

Data supporting efficacy of gallium (^{68}Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited (see section 5.1).

The applicant recommends normalising hypercortisolism in patients with ectopic Cushing's syndrome before performing PET with gallium (^{68}Ga) edotreotide based on the results of Davi et al. 2015[55] showing that long-term exposure to hypercortisolism may downregulate SSTR expression and negatively influence the results of gallium (^{68}Ga) edotreotide scan. Hypercortisolism is common for ectopic Cushing's syndrome (caused by tumors that secrete ACTH outside the pituitary or adrenal glands) and for other causes of Cushing's syndrome (such as oversecretion of ACTH by the pituitary gland, a tumor of the adrenal gland, or long-term administration of corticosteroid drugs commonly used to treat conditions such as rheumatoid arthritis and asthma). In case of Cushing syndrome, a long-term exposure to endogenous hypercortisolism may down regulate somatostatin receptor expression and negatively influence the results of somatostatin receptor imaging with gallium (^{68}Ga) edotreotide. Thus, in patients with GEP-NET and Cushing syndrome, normalisation of hypercortisolism should be suggested before performing PET with gallium (^{68}Ga) edotreotide.

An increased uptake of gallium (^{68}Ga) edotreotide is not specific for GEP-NET. Positive results require evaluating the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. As an example, an increase in somatostatin receptor density can also occur in the following pathological conditions: subacute inflammations (areas of lymphocyte concentrations), thyroid diseases (e.g. thyroid autonomy and Hashimoto's disease), tumours of the pituitary gland, neoplasms of the lungs (small-cell carcinoma), meningiomas, mammary carcinomas, lympho-proliferative disease (e.g. Hodgkin's disease and non-Hodgkin lymphomas) and tumours arising from tissue embryologically derived

[55] Davi' MV, Salgarello M, Francia G (2015). Positive (68)Ga-DOTATOC-PET/CT after cortisol level control during ketoconazole treatment in a patient with liver metastases from a pancreatic neuroendocrine tumor and ectopic Cushing syndrome. Endocrine 49(2):566-567

from the neural crest (e.g. paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas).

Splenectomy should also be considered as a relevant factor when reporting the outcome of somatostatin receptor targeted diagnostics.

No studies on PK intereaction or using human biomaterials were performed. This is acceptable as no specific interactions are foreseen with of medicines or biomaterials.

Concomitant use of somatostatin analogues

The Octreoscan SmpC and the EANM guideline in force for gallium (^{68}Ga) labelled somatostatin analogues recommends temporal withdrawal of unlabelled octreotide treatment based on empirical grounds. In the study of Velikyan et al. 2010 in GEP-NETs gallium (^{68}Ga) edotreotide scan preceded of administration of 50µg of unlabelled octreotide had better tumour-to-background contrast than baseline scan and 250-µg or 500-µgpretreated scan. It is preferable to perform imaging with gallium (^{68}Ga) edotreotide the day(s) before the next administration of somatostatin analogue. See section 4.5 of the SmPC.

The company has discussed potential *in vivo* pharmacodynamic drug-drug interactions with a number of drugs, apart from somatostatin analogues and glucocorticoids, belonging to classes that may be frequently used by the intended population. According to "Neuroendocrine gastro-entero-pancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" (Oberg et al. 2012), in addition to SST analogues, the following treatments may be also recommended in GEP-NET patients:

- interferon alpha
- mTOR-inhibitor (everolimus)
- tyrosine kinase inhibitors, sunitinib and pazopanib,
- streptozotocin and 5-fluorouracil (5-FU)/doxorubicin with objective temozolomide-based chemotherapy
- cisplatinum/etoposide
- temozolomide alone or in combination with capecitabine ± bevacizumab 5-FU i.v. or capecitabine orally combined with oxaliplatin or irinotecan
- Somatostatin analogue based Peptide Receptor Radionuclide Therapy (PRRT)

For these medicines, except in the case of PRRT, no data supporting eventual in vivo drug-drug interaction with gallium (^{68}Ga) edotreotide are available. Previous PRRT does not negatively influence the efficacy of gallium (^{68}Ga) edotreotide (Velikyan 2010, Giesel 2013, Sabet 2013).

2.4.5. Conclusions on clinical pharmacology

At the chemical concentrations used for diagnostic examinations, gallium (^{68}Ga) edotreotide does not appear to have any clinically relevant pharmacodynamic effect. The clinical pharmacology is considered well characterised in the literature. The clinical pharmacology aspects are considered to be appropriately addressed.

2.5. Clinical efficacy

2.5.1. Dose response studies

This posology was based on available experience from previously published studies with ^{68}Ga-edotreotide and supported by procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE (Virgolini 2010).

The reported image acquisition times in individual studies are provided in Table 17 in chronological order.

Table 17: Activities of gallium (^{68}Ga) edotreotide administered to GEP-NET patients as reported in the head to head comparative studies

Reference	^{68}Ga-edotreotide Imaging Technique activity administered	^{68}Ga-edotreotide Image acquisition time post-injection
Hofmann et al., 2001	PET 80-250 MBq	0-84 min (dynamic) 90-180 min (static)
Kowalski et al., 2003[56]	PET (164-198 MBq)	0-120 min (dynamic) 45, 60, 140 min (static)
Buchmann et al., 2007[57]	PET 100-228 MBq	45 min
Schreiter et al., 2014[70]	PET/CT 66-200 MBq	60 min
Lee et al. 2015[58]	1.60 MBq/Kg of body weight	1 hour
Van Binnebeek et al., 2015[59]	PET/CT 185 MBq	30 min

ND: not described, SD: standard deviation
**Range (mean±SD)*

The time window for ^{68}Ga imaging acquisition is relatively short, which is in line with the radio-nucleide's half-life of 68 min. After administration, there is a rapid accumulation of activity in tumours (80% within 30 min), followed by a rapid renal clearance, which together with low activity concentration in tissues with low or no expression of somatostatin receptor (SSTR) contributes to the fast tumour contrast enhancement obtained with gallium (^{68}Ga) edotreotide (Hofmann et al. 2001).

The proposed activity for gallium (^{68}Ga) edotreotide in SomaKit TOC (100 to 200 MBq for an average 70-kg adult) is consistent with the published evidence and also follows the currently available EANM guidelines.

[56] Kowalski J, Henze M, Schuhmacher J, M, Hofmann M, Haberkorn U (2003). Evaluation of positron emission tomography imaging using [68Ga]-DOTA-D Phe(1)-Tyr(3)-Octreotide in comparison to [111In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. Mol Imaging Biol 5(1):42-48

[57] Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Sch, Schilling T, Haufe S, Herrmann T, Haberkorn U (2007). Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 34(10):1617-1626

[58] Lee, I., J. C. Paeng, S. J. Lee, C. S. Shin, J. Y. Jang, G. J. Cheon, D. S. Lee, J. K. Chung, and K. W. Kang. 2015. 'Comparison of Diagnostic Sensitivity and Quantitative Indices Between (68)Ga-DOTATOC PET/CT and (111)In-Pentetreotide SPECT/CT in Neuroendocrine Tumors: a Preliminary Report', Nucl Med Mol Imaging, 49: 284-90.

[59] Van Binnebeek S, Vanbilloen B, Baete K, Terwinghe C, Koole M, Mottaghy FM, Clement PM, Mortelmans L, Bogaerts K, Haustermans K, Nackaerts K, Van Cutsem E, Verslype C, Verbruggen A, Deroose CM (2015). Comparison of diagnostic accuracy of (111)In-pentetreotide SPECT and (68)Ga-DOTATOC PET/CT: A lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours. Eur Radiol

This, based on published clinical experience suggests image acquisition in the range of 40 to 90 min for best results.

2.5.2. Main studies

The following tables summarise the efficacy results from the published literature to support the clinical efficacy of gallium (^{68}Ga) edotreotide in the current application.

Table 18: Summary of literature references

Reference	Nb of patients/ (Pathology)/ Age; Gender	^{68}Ga-edotreotide Imaging Technique/activity administered/Acquisition time p.i.	Comparator	Comparator imaging technique	Standard of truth	Performance ^{68}Ga-edotreotide	Performance comparator	Conclusion
(Hofmann et al. 2001)	8 (6 abdominal NET, 2 lung NET) 48-71 y; 6F, 2M	PET 80-250 MBq Immediately, until 180 min	^{111}In-octreotide	Planar, SPECT	Morphologic imaging	Patient based detection rate: 8/8=100% Site based detection rate: 40/40=100% >30% additional lesions to 111In-octreotide SPECT were detected by 68Ga-edotreotide	Patient based detection rate: 8/8=100% Site based detection rate: 34/40=85%	68Ga-edotreotide PET results in high T/NT contrast within a period of 30–40 min p.i. Specific advantages are low kidney accumulation and visualisation of small organs with physiological SST receptors. T/NTR are higher than those achieved with 111In-octreotide. This allows for the detection of very small lesions, which may become of decisive importance when SSTR PET is used in clinical routine
(Kowalski et al. 2003)	4 (NET) 46-55 y; 2F, 2M	PET 164-198 MBq Immediately, until 120 or 45, 60, 140 min	111In-DTPAOC	Planar, SPECT	Histology, biology, imaging	**Patient based detection rate:** 4/4=100% (photopenic liver metastases in 1 patient)	**Patient based detection rate:** 2/4=50%	68Ga-edotreotide is a promising PET tracer for imaging NET and their metastases. In comparison to the 111In-DTPAOC it seems to be superior especially in detecting small tumours or tumours bearing only a low density of SSTRs. It offers excellent imaging properties and very high T/NTR.
(Koukouraki, Strauss, Georgoulias, Schuhmacher, et al. 2006)	22 (9 GEP, 4 CUP NET, 2 lung, 2 thymus, 5 other)	PET 150-230 MBq Immediately, until 55-60 min			Histology, biopsy	**Patient based detection rate:** 21/22=95.5% **Lesion based detection rate:** 72/74=97.3%		68Ga-edotreotide uptake in NETs is mainly dependent on k1(receptor binding) and Vb (fractional blood volume). Pharmacokinetic data analysis can help to

	32-73 y; ND							separate blood background activity (Vb) from the receptor binding (k1).
(Koukouraki, Strauss, Georgoulias, Eisenhut, et al. 2006) [43]	15 (6 GEP NET, 3 CUP NET, 1 MEN-1, 3thoracic carcinoids, 1 PGL, 1 MTC) 36-60 y; ND	PET 150-230 MBq Immediately, until 55-60 min	FDG (^{18}F)	PET	Histology, follow-up, imaging	**Patient based detection rate:** 15/15=100% **Lesion based detection rate:** 58/63=92%	**Patient based detection rate:** 11/15=73.3% **Lesion based detection rate:** 43/63=68.2%	68Ga-edotreotide is a promising tool for evaluation of the SSTR2 expression NETs. The combination of FDG and 68Ga-edotreotide dynamic PET studies provides different information regarding the biological properties of lesions in patients with metastatic NETs
(Buchmann et al. 2007)	27 scheduled to receive DOTATOC radionuclide therapy (15 GEP, 8 CUP, 1 lung, 3 other, after primary treatment) 27-75 y; 14F, 13M	PET 100-228 MBq 45 min	111In-DTPAOC	SPECT	Histology, imaging	**Region based detection rate** 81 regions were positive In 52 regions concordant results of 68Ga-edotreotide and of 111In-DTPAOC **Lesion based detection rate** Discrepant findings of 68Ga-edotreotide and 111In-DTPAOC with SOT: 18/31 18/18=100% of discrepant lesions were correctly classified >279 lesions in 81 regions were identified **Impact rate** 1/27=4%	**Region based detection rate** 54 regions were positive In 52 regions concordant results of 68Ga-edotreotide and of 111In-DTPAOC **Lesion based detection rate** Discrepant findings of 68Ga-edotreotide and 111In-DTPAOC with SOT: 18/31 0/18=0% of discrepant lesions were correctly classified >157 lesions in 54 regions were identified **Impact rate**	68Ga-edotreotide PET is superior to 111In-DTPAOCSPECT in the detection of NET manifestations in the lung and skeleton and similar for the detection of NET manifestations in the liver and brain. 68Ga-edotreotide PET is advantageous in guiding the clinical management.

							0/27=0%	
(Gabriel et al. 2007)	84 28-79 y; 36F, 48M 13/84 suspected NET	PET 150 MBq 20, 60, 100 min	99mTc-HYNIC-TOC 111In-edotreotide	SPECT	Histology, follow-up, imaging	**Patient based** **Se** 4/5=80% **Sp** 8/9=89%	**Patient based** SPECT **Se** 2/5=40% **Sp** 8/9=89% CT **Se** 3/5=60% **Sp 8/9=89%**	68Ga-edotreotide PET shows a significantly higher detection rate compared with conventional SSTR scintigraphy and diagnostic CT with clinical impact in a considerable number of patients.
	36/84 initial staging	PET	99mTc-HYNIC-TOC 111In-edotreotide	SPECT	Histology, follow-up, imaging	**Patient based** **Se** 32/33=97% **Sp** ¾=75%	**Patient based** SPECT **Se** 14/33=42% **Sp** 3/22=14% CT **Se** 16/33=48% **Sp 3/5=16%**	
	35/84 Follow-up	PET	99mTc-HYNIC-TOC 111In-edotreotide	SPECT	Histology, follow-up, imaging	**Patient based** **Se** 33/34=97% **Sp** 1/1=100% **Overall patient based** **Se** 69/71=97% **Sp** 12/13=92% **Overall lesion based detection rate** 375 lesions **Additional diagnostic information to CT:** 18/84=21.4% **Additional diagnostic information to SPECT:** 12/84=14.3%	**Patient based** SPECT **Se** 21/34=62% **Sp** 1/1=100% CT **Se** 22/32=69% **Sp 1/3=33%** **Overall patient based** SPECT **Se** 37/71=52% **Sp** 12/13=92% CT **Se** 41/67=61% **Sp** 12/17=71% **Overall lesion**	

						Additional diagnostic information to SPECT or CT: 21/84=25%	**based detection rate** SPECT: 302 lesions CT: 295 lesions	
(Gabriel et al. 2009)[60]	46 (Advanced NET prior PRRT) 34-84 y; 17F, 29M	PET 100-150 MBq 90-100 min	CT	CT	RECIST criteria	**Patient based detection of progressive disease** Se 5/9=56% **Correct result in case of discordant finding with CT** 10/14=71%	**Patient based detection of progressive disease** Se 4/9=44% **Correct result in case of discordant finding with 68Ga-edotreotide** 4/14=29%	68Ga-edotreotide PET shows no advantage over conventional anatomic imaging for assessing response to therapy when all CT information obtained during follow-up is compared. Only the development of new metastases during therapy was detected earlier in some cases when whole-body PET was used. SUV analysis of individual lesions is of no additional value in predicting individual responses to therapy.
(Kumar et al. 2009)[61]	7 Characterisation of bronchial mass as NET 5F, 2M 14-64y	74-111MBq 45-60 min	FDG (^{18}F)	PET/CT	Histology	typical bronchial NET had high 68Ga-edotreotide uptake (SUVmax 23,5-58) atypical bronchial NET (SUVmax 68Ga-edotreotide 0.9-4.4.	typical bronchial NET had mild FDG (SUVmax 3,1-6,8), atypical bronchial NET SUVmax FDG 4.4-11)	This initial experience with the combined use of FDG and 68Ga-edotreotide PET-CT reveals different uptake patterns in various bronchial tumours.
(Putzer et al. 2009)	51 (bone metastases from NET) 34-84 y; 17F, 29M	PET 100-150 MBq 90-100 min	CT	CT	Imaging, Follow-up	**Patient based** **Se** 37/38=97% **Sp** 12/13=92%	**Patient based** **Se** 22/38=58% **Sp** 13/13=100%	68Ga-edotreotide PET is a reliable, method for the early detection of bone metastases in patients with NET. CT and conventional bone scintigraphy are less accurate than 68Ga-edotreotide PET in the

[60] Gabriel, M., A. Oberauer, G. Dobrozemsky, C. Decristoforo, D. Putzer, D. Kendler, C. Uprimny, P. Kovacs, R. Bale, and I. J. Virgolini. 2009. '68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy', J Nucl Med, 50: 1427-34.

[61] Kumar, A., T. Jindal, R. Dutta, and R. Kumar. 2009. 'Functional imaging in differentiating bronchial masses: an initial experience with a combination of (18)F-FDG PET-CT scan and (68)Ga DOTA-TOC PET-CT scan', Ann Nucl Med, 23: 745-51.

								primary staging or restaging of NET.
(Putzer et al. 2010)	15 (NET prior PRRT) 18-68 y; 10F, 5M	PET 150MBq 60-90 min	FDOPA (^{18}F)	PET	Imaging, Follow-up	**Patient based** **Se** 7/11=64% **Sp** 2/4=50% **Lesion based detection rate** 208 lesions detected 68Ga-edotreotide detected more lesions than FDOPA in 6 patients	**Patient based** **Se** 7/11=64% **Sp** 2/4=50% **Lesion based detection rate** 86 lesions detected FDOPA detected more lesions than 68Ga-edotreotide in 4 patients	68Ga-edotreotide and FDOPAPET are useful tools in the detection and staging of NET lesions. 68Ga-edotreotide may have a stronger impact in NET patients as it does not only offer diagnostic information, but is decisive for further treatment management.
(Frilling et al. 2010)	52 (49 GEP, 1 CUP NET, 2 lung) 24-76 y; 27F, 25M	PET/CT 120-250 MBq 60 min	CT, MRI	CT, MRI	Impact	**Patient based detection rate:** 52/52=100% **Se for primary of CUP NET** 3/4=75% -In 22/33=67% pts with liver metastases, SRPET identified additional lesions. -In 7/15=47% pts scheduled for liver transplantation distant lesions were confirmed **Overall impact** 31/52=59.6%	**Patient based detection rate:** 52/52=100% **Se for primary of CUP NET:** 0/4=0% **Overall impact** 0/52=0%	68Ga-edotreotide PET/CT proved clearly superior to CT and/or MRI for detection and staging of NET. More important, 68Ga-edotreotide PET/CT impacted our treatment decision in more than every second patient.
(Ruf et al. 2010)	66 (known or suspected NET, 47 confirmed GEP NET, 3 other NET) 29-79y 35F, 31M	PET/CT 100-120 MBq 60 min	CE CT	CE CT	Histology, imaging, follow-up	**Patient based detection rate** 50/50=100% **Lesion based detection rate** 181 lesions 28 lesions were positive with 68Ga-edotreotide alone **Impact** 24/64=38%	**Patient based detection rate** 50/50=100% **Lesion based detection rate** 181 lesions 31 lesions were positive with CT alone	68Ga-edotreotide PET/CT influences therapeutic management in about one third of patients examined. CT and PET are comparably sensitive, deliver complementary information and equally contribute to therapeutic decision making. Thus, despite the merits of the

								PET modality, the CT component must not be neglected and an optimized multiphase CT protocol is recommended.
(Versari et al. 2010)	19 (13 GEP, 6 other) 21-80 y; ND	PET/CT 1.5-2 MBq/kg 60 min	EUS, MDCT	EUS 19/19, MDCT 16/19	Histology (2 lesions), cytology (23 lesions), imaging, follow-up	**Patient based** **Se** 12/13=92% **Sp** 5/6=83% **Lesion based** **Se** 20/23=87% (10/11=91% for lesions <2cm)	**Patient based** EUS **Se** 13/13=100% **Sp** 6/6=100% MDCT **Se** 10/11=91% **Sp** 5/5=100% **Lesion based** EUS **Se** 22/23=96% (10/11=91% for lesions <2cm) MDCT **Se** 13/18=72% (5/10=50% lesions <2cm)	68Ga-edotreotide PET, EUS, and MDCT seem to have comparable accuracy in diagnosis of duodenopancreatic NET and their combination may allow an optimal preoperative diagnosis.
(Jindal et al. 2011)[62]	20 (Lung NET) 16-53 y; 9F, 11M	PET/CT 74-111 MBq 40-60 min	FDG (^{18}F)	PET/CT	Histology	**Overall lesion based detection rate** 19/20=95% Typical NET 13/13=100% Atypical NET 6/7=86%	**Overall lesion based detection rate** 14/20=70% Typical NET 7/13=54% Atypical NET 7/7=100%	Typical NETs had a lower uptake of FDG compared with the atypical NETs. Typical NETs showed higher uptake of 68Ga-edotreotide compared with the atypical NETs.
(Kumar et al. 2011)[63]	7 (pancreatic tumour) 14-46 y; 5F, 2M	PET/CT 132-222 MBq 30-45 min	CE CT, FDG (^{18}F)	CE CT, PET/CT	Histology, MRI, follow-up	**Patient based detection rate of primary tumour:** 20/20=100%	**Patient based detection rate of primary tumour:** CE CT 17/20=85% FDG PET/CT 2/8=25%	68Ga-edotreotide PET-CT is a very useful imaging investigation for diagnosing and staging pancreatic NET.

[62] Jindal, T., A. Kumar, B. Venkitaraman, M. Meena, R. Kumar, A. Malhotra, and R. Dutta. 2011. 'Evaluation of the role of [18F]FDG-PET/CT and [68Ga]DOTATOC-PET/CT in differentiating typical and atypical pulmonary carcinoids', Cancer Imaging, 11: 70-5.

[63] Kumar R, Sharma P, Garg P, Karunanithi S, Naswa N, Sharma R, Thulkar S, Lata S, Malhotra A (2011). Role of (68)Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours. Eur Radiol 21(11):2408-2416

(Ruf et al. 2011)[64]	51 (33 GEP, 4 lung, 14 unknown primary) 31-79 y; 26F, 25M	PET/CT 100-120 MBq 60 min	Triple-phase CE CT	triple-phase CE CT	Histology, follow-up, imaging	**Patient based** Se 32/39=82% Sp 8/12=67% **Lesion based** **Se** 258/354=72.8% **Sp** 152/156=97.4% **Impact** 24/64=38%	**Patient based** **Se** 33/39=84.6% **Sp** 6/12=50% **Lesion based** **Se** 273/354=77.1% **Sp** 133/156=85.3%	No CT phase can be omitted in NET imaging, and the triple-phase protocol continues to be strongly recommended also for PET/CT.
(Froeling et al. 2012) [65]	21 28 examinations in 21 patients (19 MEN1, 2 MEN2) 16-78 y; 10F, 11M	PET/CT ND ND	CE PET/CT	CE PET/CT	Histology, follow-up, imaging	**Lesion based overall** **Se** 55/60=91.7% **Sp** 29/31=93.5 non CE PET/CT **Se** 22/23=95.5% **Sp** 19/21=90.5% CE PET/CT **Se** 33/37=89.2% **Sp** 10/10=100% **Impact** 10/21=47.6%	**Lesion based overall** **Se** 26/60=43% **Sp** 19/31=61.3% non CE CT **Se** 5/23=21.7% **Sp** 10/10=100% CE CT **Se** 21/31=56.8% **Sp** 10/10=100%	68Ga-edotreotide PET/CT allows a high detection rate of NET lesions in the context of MEN-1syndrome as well as influence therapeutic management in nearly up to half of the patients. GA-68 DOTATOCPET/CT should include a CE-CT to improve MEN-associated NET lesion detection.
(Mayerhoefer et al. 2012) [66]	55 (11 search for primary, 9 staging, 35 restaging) 33F, 22M 37-80y	PET/CT 150 MBq 90 min	PET/CE CT	PET/CE CT	Histology, imaging, follow-up	**PET/CT** **Patient based** **Junior team** **Se** 33/33=100% **Sp** 17/22=77.3% **Senior team** **Se** 32/53=97% **Sp** 18/22=81.8% **Lesion based** **Junior team** **Se** 233/261=89.3% **Sp** 2194/2214=99.1% **Senior team** **Se** 240//261=92% **Sp** 2196/2214=99.2%	**PET/CE CT** **Patient based** **Junior team** **Se** 33/33=100% **Sp** 20/22**=**90.9% **Senior team** 33/33=100% **Sp** 21/22**=**95.5% **Lesion based** **Junior team** **Se** 241/261=92.3% **Sp** 2200/2214=99.4% **Senior team** **Se**	Intravenous. Contrast medium only moderately, albeit significantly, improves the sensitivity of 68Ga-edotreotide PET/CT for the detection of abdominal NETs, and hardly affects specificity. Thus, while contrast enhancement is justified to achieve maximum sensitivity, unenhanced images may be sufficient for routine PET/CT in NET patients.

[64] Ruf J, Schiefer J, Furth C, Kosiek O, Kropf S, Heuck F, Denecke T, Pavel M, Pascher A, Wiedenmann B, Amthauer H (2011). 68Ga-DOTATOC PET/CT of neuroendocrine tumors: spotlight on the CT phases of a triple-phase protocol. J Nucl Med 52(5):697-704

[65] Froeling V, Elgeti F, Maurer MH, Scheurig-Muenkler C, Beck A, Kroencke TJ, Pape UF, Hamm B, Brenner W, Schreiter NF (2012). Impact of Ga-68 DOTATOC PET/CT on the diagnosis and treatment of patients with multiple endocrine neoplasia. Ann Nucl Med 26(9):738-743

[66] Mayerhoefer, M. E., M. Schuetz, S. Magnaldi, M. Weber, S. Trattnig, and G. Karanikas. 2012. 'Are contrast media required for (68)Ga-DOTATOC PET/CT in patients with neuroendocrine tumours of the abdomen?', Eur Radiol, 22: 938-46.

							257/261=98.5% **Sp** 2202//2214=99.5%	
(Schraml et al. 2013)	51 (metastatic NET) Mean 57 y; 25F, 26M	PET/CT 150 MBq 30 min	WB MRI	WB MRI	Histology, follow-up, imaging	**Patient based** **Se** 40/41=98% **Sp** 10/10=100% **Acc** 50/51=98% **Lesion based detection rate** 381/593=64% 22 lesions were detected by PET alone **Impact** 30/51=59%	**Patient based** **CT** **Se** 37/41=90% **Sp** 9/10=90% **Acc** 46/51=90% **WB MRI** **Se** 40/41=98% **Sp** 9/10=90% **Acc** 49/51=96% **Lesion based detection rate** CT 482/593=92% WB MRI 540/593=91% 11 lesions were detected by CT alone 47 lesions were detected by WB MRI alone	PET/CT and WB MRI showed comparable overall lesion-based detection rates for metastatic involvement in NET but significantly differed in organ-based detection rates with superiority of PET/CT for lymph node and pulmonary lesions and of WB MRI for liver and bone metastases. Patient-based analysis revealed superiority of PET/CT for NET staging. Individual treatment strategies benefit from complementary information from PET/CT and MRI.
(Beiderwellen et al. 2013)[67]	8 (metastatic GEP NET) 25-74 y; 4F, 4M	PET/CT	PET/MRI	PET/MRI	Histology, imaging	**Patient based** PET/CT **Se** 4/5=80% Overall Se for 68Ga-edotreotide regardless the acquisition technique: 5/5=100%	**Patient based** PET/MRI **Se** 5/5=100%	Study demonstrates the potential of 68Ga-edotreotide PET/MRI in patients with GEPNET, with special advantages in the characterization of abdominal lesions yet certain weaknesses inherent to MRI, such as lung metastases and sclerotic bone lesions.

[67] Beiderwellen KJ, Poeppel TD, Hartung-Knemeyer V, Buchbender C, Kuehl H, Bockisch A, Lauenstein TC (2013). Simultaneous 68Ga-DOTATOC PET/MRI in patients with gastroenteropancreatic neuroendocrine tumors: initial results. Invest Radiol 48(5):273-279

(Froeling et al. 2014) [68]	38 pancreatic NET	PET/CT	multiphase CE CT	multiphase CE CT		Patient based detection rate 41/49=83.7%	Patient based detection rate arterial phase: 59.2% p=0.017	Patients with pancreatic NETs should undergo 68Ga-edotreotide PET/CT with at least as arterial and venous phase CT scan. SUV max and SIV max T/liver ratios provide additional information but do not reliably separate pancreatic NET from normal uptake inuncinated process.
(Schreiter, Bartels, et al. 2014) [69]	52 (33 CUP NET, 19 clinically suspected NET) 34F, 18M 13-83y (in 20/52 patients 111In-pentetreotide SPECT/CT was performed as well)	PET/CT 66-200 MBq 60 min	111In-pentetreotide (in 20 patients)	SPECT/CT	Histology, follow-up	**Overall localisation of site of primary NET** 17/52=32.7% CUP NET 15/33=45.5% Clinically suspected NET 2/19=10.5% **In 15 patients in whom 111In-pentetreotide SPECT/CT was performed Localisation of site of primary NET** 9/20=45%	**Localisation of site of primary** 2/20=10%	68Ga-edotreotide PET/CT is preferable to 111In-pentetreotide SPECT/CT when searching for primary NETs in patients with CUPNET but should be used with caution in patients with clinically suspected NET

[68] Froeling V, R, Collettini F, Rothe J, Hamm B, Brenner W, Schreiter N (2014). Detection of pancreatic neuroendocrine tumors (PNET) using semi-quantitative [^{68}Ga]DOTATOC PET in combination with multiphase contrast-enhanced CT. Q J Nucl Med Mol Imaging 58(3):310-318

[69] Schreiter, N. F., A. M. Bartels, V. Froeling, I. Steffen, U. F. Pape, A. Beck, B. Hamm, W. Brenner, and R. Rottgen. 2014. 'Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET: Evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA octreotide SPECT/CT', Radiol Oncol, 48: 339-47.

(Schreiter, Maurer, et al. 2014) [70]	Among 320 68Ga-edotreotide PET/CTs: 25 40 lesions of intestinal NET 13F, 12M	PET/CT 100-120 MBq 45-60 min	multiphase CE CT	multiphase CE CT	histology (28 lesions) and/or follow-up for a mean of 22.9 months	**Lesion based detection rate** (37 TP 3FP) 37/37=100%	**Lesion based detection rate** arterial phase: 3TP in conjunction with PET 8TP venous phase 3TP in conjunction with PET 11TP arterial scan performed significantly better than venous scan p<0.001	The arterial phase of multiphase 68Ga-edotreotide PET/CT might improve the localisation of intestinal NETs and, thereby, improve the overall diagnostic accuracy of this modality in the assessment of intestinal NETs by adding information about lesion perfusion not available when only venous CT is performed.
(Venkitaraman et al. 2014) [71]	34 (Lung NET) 28-45 y; ND	PET/CT 74-111 MBq 45-60 min	FDG (^{18}F)	PET/CT	Histology	**Patient based - overall** **Se** 25/26=96% **Sp** 6/6=100% Typical NET 21/21=100% Atypical NET 4/8=80%	**Patient based-overall** **Se** 18/26=69% **Sp** 1/9=11% Typical NET 13/21=62% Atypical NET 5/5=100%	68Ga-edotreotide PET/CT is a useful imaging investigation for the evaluation of pulmonary NETs FDGPET/CT suffers from low sensitivity and specificity in differentiating the pulmonary NETs from other tumours.
(Kratochwil et al. 2015)	30 (60 liver metastases of NET)	PET/CT 100-200 MBq 60 min	RECIST	Morphological imaging		SUVmax responding lesions 18.00 ± 3.59 tumour/spleen ratio 1.20 ± 0.37 tumour/liver ratio 3.15 ± 0.53 SUVmax non responding lesions 33.55 ± 4.62 p < 0.05 tumour/spleen ratio 1.90 ± 0.45, p < 0.05 tumour/liver ratio 4.97 ± 0.62, p < 0.05		To select patients for PRRT SUVmax cut-off of >16.4 from 68Ga-edotreotide PET/CT.AT/L ratio>2.2 might present a scanner-independent criterion that enables the translation of our results to other institutions. However, the robustness of this arbitrary unit still needs to be evaluated with different PET scanners.

[70] Schreiter NF, Maurer M, Pape UF, Hamm B, Brenner W, Froeling V (2014). Detection of neuroendocrine tumours in the small intestines using contrast-enhanced multiphase Ga-68 DOTATOC PET/CT: the potential role of arterial hyperperfusion. Radiol Oncol 48(2):120-126

[71] Venkitaraman, B., S. Karunanithi, A. Kumar, G. C. Khilnani, and R. Kumar. 2014. 'Role of ^{68}Ga-DOTATOC PET/CT in initial evaluation of patients with suspected bronchopulmonary carcinoid', Eur J Nucl Med Mol Imaging, 41: 856-64.

(Flechsig et al. 2015) [72]	16 Liver metastases of GEP NET 9F, 7M Mean 60y	PET/CE-CT 84-196 MBq 40-50min	MRI	non-contrast MRI CE MRI using Gd-EOB-DTPA	-	**Lesion based detection rate** 103/103=100%	**Lesion based detection rate** 103/103=100% Quantitative ROI-analysis demonstrated improved contrast ratio (CR) for DWI compared to all other non-contrast MR-sequences ($p<0.001$) CE-MRI presented with higher CR-values compared to 68Ga-edotreotide PET/CE-CT ($p<0.001$).	Anatomic imaging using non CE MRI with fl2D- and fl3D-sequences in combination with the molecular imaging modality 68Ga-edotreotide PET is optimal for the assessment of liver lesions in GEP-NET-patients. Even though CE-MRI was superior to non-contrast MRI, non-contrast MRI is sufficient to detect and quantify liver metastases in daily routine, especially in combination with DW-Imaging.
(Nakamoto et al. 2015) [73]	46 14 CUP NET, 7 localisation of recurrent NET because of high hormone levels, 25 localisation of NET because of high hormone	PET/CT 130 MBq 60 min			Histology, follow-up	**Impact on diagnostic thinking** Localisation of primary in CUP NET 8/14=57% detecting metastasis or recurrence after surgery for NET because of their high hormone levels 6/7=86% Detecting suspected NETs because of high hormone levels with no history of		68Ga-edotreotide was useful for detecting NETs, especially when recurrence or metastases were suspected because of high hormone levels after surgery for a NET. It is unlikely, however, that additional information can be acquired in patients with no history of NET simply based on high hormone levels.

[72] Flechsig, P., C. M. Zechmann, J. Schreiweis, C. Kratochwil, D. Rath, L. H. Schwartz, H. P. Schlemmer, H. U. Kauczor, U. Haberkorn, and F. L. Giesel. 2015. 'Qualitative and quantitative image analysis of CT and MR imaging in patients with neuroendocrine liver metastases in comparison to (68)Ga-DOTATOC PET', Eur J Radiol, 84: 1593-600.

[73] Nakamoto, Y., K. Sano, T. Ishimori, M. Ueda, T. Temma, H. Saji, and K. Togashi. 2015. 'Additional information gained by positron emission tomography with (68)Ga-DOTATOC for suspected unknown primary or recurrent neuroendocrine tumors', Ann Nucl Med, 29: 512-8.

	levels 34F, 12M 27-80y					histopathologically proven NET 1/25=4% **Overall:** 14/46=33%		
(Van Binnebeek et al. 2015)	53 Metastatic NET scheduled to PRRT 30F, 23M 31–80 y	PET/CT 185 MBq 30 min	111In-pentetreotide	SPECT	Follow-up	**Lesion based detection rate prior PRRT** 1098/1099=99.9% p<0.0001 68Ga-edotreotide was positive alone in 439/1098=40% lesions in 42/53=79% patients **Impact** 7/53=13%	**Lesion based detection rate prior PRRT** 660/1099=60% 111In-pentetreotide was positive alone in 1/1099=0.09% lesions in 1/53=2% patients	68Ga-edotreotide is superior to 111In-pentetreotide- scintigraphy SPECT for the detection of NET metastases, detecting a significantly higher number of tumoral lesions, especially in the skeleton and the liver. 68Ga-edotreotide PET is the nuclear medicine imaging method of choice for accurate depiction of NET tumour burden.
(Prasad et al. 2016) [74]	7/13 4F, 3M 17-72y	PET/CT 110 MBq 60 min	CE CT	CE CT	Histology, follow-up	**Patient based detection rate** 6/7=86%	**Patient based detection rate** 6/7=86%	SRPET can play a significant role in the detection and management of patients with pancreatogenic hypoglycaemia.
(Sanger and Freesmeyer 2016)	27 NET with liver metastases	PET/CT + Early dynamic PET/CT 125.3-142.5 MBq	CE CT	CE CT		- Early dynamic PET/CT proved comparable with ceCT in readily identifying hypervascular lesions, irrespective of the receptor status. - Early dynamic PET/CT also readily identified non-hypervascular, receptor-positive lesions. Positive image contrasts were		The high image contrast of hypervascular NET metastases in early arterial phases PET/CT can become a useful alternative in patients with contraindications to CECT. The high density of SSTR did not seem to interfere with the detection of the leion´shy

[74] Prasad, V., A. Sainz-Esteban, R. Arsenic, U. Plockinger, T. Denecke, U. F. Pape, A. Pascher, P. Kuhnen, M. Pavel, and O. Blankenstein. 2016. 'Role of Ga somatostatin receptor PET/CT in the detection of endogenous hyperinsulinaemic focus: an explorative study', Eur J Nucl Med Mol Imaging.

						obtained for hypervascular, receptor-positive lesion - early negative contrasts were obtained for nonhypervascular, receptor-negative lesions.		
(Lee et al. 2015)	13 NET	PET/CT	111In.pentetreotide	SPECT/CT		**Lesion based detection rate** 35/35=100% TNR 99.9 ± 84.3 p<0.001 r=0.692,	**Lesion based detection rate** 19/35=54% TNR 71.1 ± 114.9	68Ga-edotreotide PET/CT has a higher diagnostic sensitivity than 111In-pentetreotide scans with SPECT/CT. The TNR on PET/CT is higher than that of SPECT/CT, which also suggests the higher sensitivity of PET/CT. 111In-pentetreotide SPECT/CT should be used carefully if it is used instead of 68Ga-edotreotide PET/CT.
Overall	Resultsof977 examinationsin 970patients wereanalysed	Mean activity Administered 126-191MBq Range 80-250MBq Activity per body weight (onestudy) 1,5-2MBq/kg Mean acquisition time 56-77 min post injection				**Pooled patient Based detection rate/sensitivity 518/550=94%** **Pooled impact rate** **In patients Referred for Localisation and Staging of known Or suspected NET 109/234=47%** **In patients Scheduled to PRRT 8/80=10%**		

Se=sensitivity, Sp=Specificity, PD=progressive disease

Diagnostic and technical Performance of ^{68}Ga-edotreotide

1. Detection of the primary NET in case of proven NET metastasis or rising levels of a relevant Biochemical Tumour Marker

In the study of Gabriel et al. 2007[75], a group of patients was referred for detection of unknown primary tumour in the presence of clinical or biochemical suspicion of neuroendocrine malignancy, the patient-based sensitivity and specificity were the best with gallium (^{68}Ga) edotreotide (4/5=80% and 8/9=89%). The sensitivity and specificity was 2/5=40% and 8/9=89% with SPECT and 3/5=60% and 8/9=89% with CT. One false positive result consisting in increased tracer uptake was observed both on PET and SPECT in pancreatic head. Two false negative results were observed with SPECT and one with CT in case of small metastatic liver lesions which were positive with gallium (^{68}Ga) edotreotide.

In 3 of 4 patients with unknown primary tumour site of the series of Frilling et al. 2010 (Frilling 2010)[76], gallium (^{68}Ga) edotreotide PET/CT visualised the primary tumour region (jejunum, ileum, and pancreas, respectively) not identified on CT and/or MRI.

One head-to-head comparative paper of gallium (^{68}Ga) edotreotide and Octreoscan is that of Schreiter et al. 2014. In a total of 123 included patients with either CUP-NET or clinically suspected primary NET, the direct comparison of diagnostic performance of images with both radiopharmaceuticals was possible in 20 patients. The standard of truth included histopathology or clinical verification based on follow-up examinations. The detection rate of primary tumour was 2/20=10% for indium (^{111}In) pentetreotide and 9/20=45% for gallium (^{68}Ga) edotreotide. Imaging with gallium (^{68}Ga) edotreotide PET/CT was able to identify the primary tumour in 7/15=47% patients who had negative findings according to indium (^{111}In) pentetreotide SPECT/CT performed at the first examination. In two patients with a primary tumour detected by indium (^{111}In) pentetreotide SPECT/CT, the gallium (^{68}Ga) edotreotide confirmed the result. When indium (^{111}In) pentetreotide SPECT/CT was performed at the second examination after gallium (^{68}Ga) edotreotide PET/CT with negative findings (n=3), the procedure did not provide additional diagnostic information.

2. Ga-edotreotide and characterisation, staging and restaging of primary and metastatic GEP NET: Comparison of diagnostic performance with somatostatin receptor scintigraphy (SRS) with indium (^{111}In) pentetreotide or with 99mTc-HYNIC-[D-Phe^{1},Tyr^{3}]-Octreotide

The technical performance was made with indium (^{111}In) pentetreotide, the radiopharmaceutical which has been registered in the indications which are claimed for gallium (^{68}Ga) edotreotide and marketed as Octreoscan or with 99mTc-HYNIC-[D-Phe1,Tyr3]-Octreotide which is marketed as 99mTc-Tektrotyd.

The pharmacological properties of OctreoScan compared to newer analogues are different and further compounded by its radionuclide, ^{111}In, which provides relatively poor quality images in SPECT and planar scans (Baum 2012[77]). The spatial resolution of tumour targeted In-111-labelled peptides is poor because of the non-optimal energy of the emitted γ-rays. The low spatial resolution contributes to equivocal diagnosis of

[75] Gabriel, M., C. Decristoforo, D. Kendler, G. Dobrozemsky, D. Heute, C. Uprimny, P. Kovacs, E. Von Guggenberg, R. Bale, and I. J. Virgolini. 2007. '^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT', J Nucl Med, 48: 508-18.

[76] Frilling, A., G. C. Sotiropoulos, A. Radtke, M. Malago, A. Bockisch, H. Kuehl, J. Li, and C. E. Broelsch. 2010. 'The impact of 68Ga-DOTATOC positron emission tomography/computed tomography on the multimodal management of patients with neuroendocrine tumors', Ann Surg, 252: 850-6.

[77] Baum RP, Kulkarni HR, Carreras C (2012). Peptides and receptors in image-guided therapy: theranostics for neuroendocrine neoplasms. Semin Nucl Med 42(3):190-207

suspected lesions (Srirajaskanthan 2010)[78]. In the European consensus guidelines it is acknowledged that somatostatin receptor scintigraphy (SRS) using Octreoscan is an important part of the diagnostic work-up of patients with GEP-NETs (Delle Fave et al. 2012, Ramage et al. 2012, Öberg et al. 2012). It can still be considered the molecular imaging technique of choice at diagnosis and follow-up in the majority of patients with well-differentiated GEP-NET (level of evidence 3, grade of recommendation A/B) (Toumpanakis et al. 2014).

No literature data addressing the intra-individual comparison of gallium (^{68}Ga) edotreotide and 99mTc-Tektrotyd was submitted.

In comparison with scintigraphic imaging of SSTR (SRS), planar and/or SPECT which is performed with indium (^{111}In) pentetreotide, PET imaging of SSR (SRPET) which is used for gallium (^{68}Ga) edotreotide imaging has a two- (Gregory 2006)[79] to three-fold higher spatial resolution (3 to 6 mm vs. 10 to 15 mm). PET/CT facilitates quantification of tracer uptake and biodistribution administered by either using compartmental analysis for research applications or more simple parameters in routine (standardised uptake value or SUV); a similar approach is not possible with SPECT.

The first data on diagnostic performance of gallium (^{68}Ga) edotreotide compared to indium (^{111}In) pentetreotide were published by Hofmann et al. 2001, for detecting tumours expressing SSTRs and their metastases in 8 patients with histologically proven bronchial (n=2) or midgut (n=6) NETs. Of 40 lesions predefined by CT and/or MRI, gallium (^{68}Ga) edotreotide PET identified 40/40=100%, whereas indium (^{111}In) pentetreotide planar and SPECT imaging identified only 34/40=85%. T/NTR ranged from >3:1 for hepatic lesions (indium (^{111}In) pentetreotide=1.5) to 100 for CNS lesions (indium (^{111}In) pentetreotide=10). With gallium (^{68}Ga) edotreotide, more than 30% additional lesions were detected as compared with indium (^{111}In) pentetreotide imaging.

Gabriel et al. 2007 compared diagnostic performance of gallium (^{68}Ga) edotreotide and that of 99mTc-labeled hydrazinonicotinyl-Tyr3-octreotide (99mTc-HYNIC-TOC) and ^{111}In-edotreotide for staging 36 patients with proven or suspected NET. A composite standard of truth (SOT) was used: conventional imaging (CT or MRI) in case of concordant findings and histology and/or clinical follow-up >6 months in case of discordant findings of PET and SPECT with results of conventional imaging. On a per-patient base, the sensitivity and specificity were the best with gallium (^{68}Ga) edotreotide, 32/33=97% and 3/ 4=75% respectively. For SPECT (99mTc-HYNIC-TOC and ^{111}In-edotreotide) the sensitivity and specificity were 14/33=42% and 3/22=14% and similarly for CT 16/33=48% and 3/5=16%, respectively.

This series of Gabriel et al. also included 35 patients referred for restaging after primary treatment of NET (Gabriel 2007). The patient-based sensitivity and specificity was the best with gallium (^{68}Ga) edotreotide (33/34=97% and 1/1=100%). The sensitivity and specificity was 21/34=62% and 1/1=100% with SPECT and 22/32=69% and 1/3=33% with CT. One false negative result was observed with gallium (^{68}Ga) edotreotide in patient with small liver metastases. On the other hand, small liver metastases and small lymph nodes were missed by SPECT and CT the most frequently, but visible with gallium (^{68}Ga) edotreotide.

Buchmann et al. 2007 compared the value of gallium (^{68}Ga) edotreotide PET and indium (^{111}In) pentetreotide SPECT in 27 patients with GEP-NET (59%) or GEP-NETs of unknown primary (30%) and 3 non GEP-NET. Gallium (^{68}Ga) edotreotide PET and indium (^{111}In) pentetreotide SPECT were performed using standard techniques; treatment was not applied in between. A composite standard of truth was used. Findings were

[78] Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J (2010). The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. J Nucl Med 51(6):875-882

[79] Gregory R, Partridge M, Flower M, others (2006). Performance evaluation of the Philips "Gemini" PET/CT system. Nuclear Science, IEEE Transactions on 53(1):93-101

compared by a region-by-region analysis and verified with histopathology, CT and MRI within 21 days. SOT was obtained before therapy was initiated, whenever clinically and ethically justifiable. In several organs, metastases were multifocal and particularly confluent, limiting a lesion-based analysis. gallium (^{68}Ga) edotreotide PET imaged more lesions than indium (^{111}In) pentetreotide SPECT. On gallium (^{68}Ga) edotreotide PET, >279 lesions were positive (absolute numbers cannot be given owing to confluence of lesions). Lesions were most frequently seen in the liver (n>152), the skeleton (n>80) and lymph nodes (n>28). The mean SUV of all positive lesions ranged from 0.7 to 29.3 and the maximum SUV ranged from 0.9 to 34.4. In three lesions, the mean SUV was ≤1.1 (brain 0.7, skeleton 0.9, lung 1.1).

On indium (^{111}In) pentetreotide SPECT, a total of >157 lesions were positive. Lesions were most frequently seen in the liver (n>105), skeleton (n>20) and lymph nodes (n>21). The ratio between pathological positive lesions and the contralateral area was within a range from 1.8 to 7.3. The number of positive lesions on SPECT images acquired 4 and 24 h after injection did not differ significantly. A total of 52/81= 64% regions were interpreted as concordantly positive on gallium (^{68}Ga) edotreotide PET and indium (^{111}In) pentetreotide SPECT and 31/81=38% regions were interpreted as discordant. Among 18 discrepant sites with SOT, all were positive with gallium (^{68}Ga) edotreotide and negative with indium (^{111}In) pentetreotide ($p<0.001$). In a single patient (1/27=3.7%), gallium (^{68}Ga) edotreotide PET imaged widespread infiltration in 7 abdominal and pelvic lymph nodes, whilst indium (^{111}In) pentetreotide SPECT was positive in a single node. In this case, surgical intervention was extended owing to the PET findings. All 7 gallium (^{68}Ga) edotreotide - and the single indium (^{111}In) pentetreotide- positive nodes were positive at histopathology. No impact on patient management was observed with indium (^{111}In) pentetreotide. In this study gallium (^{68}Ga) edotreotide PET identified significantly more lesions of NET than indium (^{111}In) pentetreotide.

Van Binnebeek et al. 2015 compared the diagnostic accuracy of indium (^{111}In) pentetreotide and gallium (^{68}Ga) edotreotide in patients with metastatic NET scheduled for PRRT [GEP-NET (n=39), unknown origin (n=6) and non-GEP-NETs (n=8)]. In 53 patients, gallium (^{68}Ga) edotreotide detected 1098/1099=99.9% lesions (range: 1-105; median: 15) and indium (^{111}In) pentetreotide detected 660/1099=60% lesions (range: 0-73, median: 9)($p<0.0001$). 439/1098=40% lesions in 42/53=79% patients were detected by gallium (^{68}Ga) edotreotide alone. Inversely, indium (^{111}In) pentetreotide was positive alone in 1/53 patients. The organ-by-organ analysis showed that the gallium (^{68}Ga) edotreotide -positive-alone lesions were most frequently visualized in liver and skeleton. It was concluded that gallium (^{68}Ga) edotreotide PET/CT is superior for the detection of NET-metastases compared to indium (^{111}In) pentetreotide.

In the prospective study of Lee et al. in 13 GEP-NET patients (3 of them with suspected but not confirmed disease), a total of 35 positive lesions (i.e. positive means that lesion exhibited non-physiological increased uptake that was not discernible from the background) were detected in 10 patients on either Octreoscan SPECT/CT or Gallium (^{68}Ga) edotreotide PET/CT. Three patients did not exhibit any positive lesions on either imaging method. Gallium (^{68}Ga) edotreotide detected 35/35 (100%) vs 19/35=54% for Octreoscan SPECT/CT.

In the prospective study of Kowalski et al.2003 in 4 patients with GEP-NET, Gallium (^{68}Ga) edotreotide showed better patient-based detection rate (4/4=100%) than Octreoscan (2/4=50%). In one of these patients both radiopharmaceuticals showed multicentrical small bowel carcinoid in the lower abdomen, but at least seven small tracer accumulations were found in the left lower abdomen only in Gallium (^{68}Ga) edotreotide PET.

3. Comparison of diagnostic performance with Bone Scintigraphy

Putzer et al. compared the diagnostic value of CT with that of gallium (^{68}Ga) edotreotide in the detection of bone metastases in 51 patients with histologically proven NET after treatment (Putzer et al. 2009)[80]. ^{18}F-fluoride PET or 99mTc-dicarboxypropane diphosphonate bone scintigraphy or other imaging methods (FDG PET, MRI) or clinical follow-up served as the reference standard. Gallium (^{68}Ga) edotreotide PET results were true-negative for 12 patients, false-positive for one, and false- negative for another, resulting in a sensitivity of 37/38=97% and a specificity of 12/13=92%. The sensitivity of CT for detection of bone metastases was 22/38=58% and specificity 13/13=100%. Gallium (^{68}Ga) edotreotide PET detected bone metastases at a significantly higher rate than did CT (P<0.001). Furthermore, conventional bone scintigraphy confirmed the results of SRPET but did not reveal additional tumours in any patients.

4. Comparison of diagnostic performance with other PET tracers

FDOPA, an amino acid analogue, has been registered since 2006 for the detection of some NET using PET/CT. Putzer et al performed a comparative study of gallium (^{68}Ga) edotreotide and FDOPA PET and CT in 15 patients with various NET (Putzer et al 2010)[81]. Images were compared on a patient-basis as well as on a lesion-basis. Contrast-enhanced CT and histological follow-up served as the standard of truth. Furthermore, imaging results were matched with tumour marker levels and quantitative tracer uptake by the NET lesions. Both gallium (^{68}Ga) edotreotide and FDOPA PET reached sensitivity of 64% and a specificity of 100% on a patient-based analysis. Gallium (^{68}Ga) edotreotide and FDOPA PET showed equal findings in 7 out of 15 patients and differences in 8 patients. Gallium (^{68}Ga) edotreotide revealed more metastases than FDOPA PET in 6 patients, while FDOPA PET detected more metastases than gallium (68Ga) edotreotide in 4 patients. With gallium (^{68}Ga) edotreotide PET, 208 malignant lesions were detected, with FDOPA 86 lesions were found, and only 124 with CT.

Koukouraki et al. 2006 compared by means of dynamic PET in 15 patients with 63 lesions of confirmed metastatic NETs the uptake of gallium (^{68}Ga) edotreotide and of FDG, a marker of tumour glucose uptake and metabolism also suited for PET imaging. Histology of the primary tumours was confirmed in surgical specimens. Histology of the metastases was confirmed (depending on the location) in 11 out of 15 patients by needle biopsy. For lesions that were not easily reachable, the diagnosis was based on computed tomography (CT) and/or MRI follow-up findings and on clinical follow-up data. Enhanced FDG uptake was observed in 43/63=68.3% lesions. gallium (^{68}Ga) edotreotide showed pathologically enhanced uptake in all evaluated patients and in 58/63=92% lesions; 6 lesions were missed by gallium (^{68}Ga) edotreotide: 1 in a patient with metastatic NET of unknown primary, 3 in a patient with metastatic medullary thyroid carcinoma, 1 in a patient with a metastatic lung NET and 1 in a patient with a paraganglioma. Discordant results for FDG and gallium (^{68}Ga) edotreotide were observed in 6/15 patients. Global SUV was defined as the SUV measured in the last frame (55–60 min p.i.) of the dynamic series, for each tracer. The median global SUV uptake was 7.9 for gallium (^{68}Ga) edotreotide and 4.6 for FDG. The authors concluded that the combination of FDG and gallium (^{68}Ga) edotreotide dynamic PET studies provides different information regarding the biological properties of lesions in patients with metastatic NETs in whom ^{90}Y-edotreotide therapy is planned. Only patients with enhanced gallium (^{68}Ga) edotreotide uptake (SUV >5.0) were referred to ^{90}Y-edotreotide therapy in this study.

[80] Putzer D, Gabriel M, Henninger B, Kendler D, Uprimny C, Dobrozemsky G, Decristoforo C, Bale RJ, Jaschke W, Virgolini IJ (2009). Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. J Nucl Med 50(8):1214-1221

[81] Putzer D, Gabriel M, Kendler D, Henninger B, Knoflach M, Kroiss A, Vonguggenberg E, Warwitz B, Virgolini IJ (2010). Comparison of (68)Ga-DOTA-Tyr(3)-octreotide and (18)F-fluoro-L-dihydroxyphenylalanine positron emission tomography in neuroendocrine tumor patients. Q J Nucl Med Mol Imaging 54(1):68-75

There were no significant differences between patients with positive gallium (^{68}Ga) edotreotide and those with positive FDG in regards to therapeutic choice and it was concluded that the association of gallium (^{68}Ga) edotreotide and FDG slightly increases detection rate of pancreatic NET over gallium (^{68}Ga) edotreotide PET/CT alone. However, the combined dual tracers (FDG and gallium (^{68}Ga) edotreotide PET/CT) did not influence the therapeutic strategy.

5. Comparison of Diagnostic Performance between gallium (^{68}Ga) edotreotide PET/CT and anatomic imaging and the potential role of PET with contrast enhanced CT

In a series of 20 patients with proven (n=3) or suspected primary pancreatic NET (n=17), gallium (^{68}Ga) edotreotide correctly identified the primary or characterised the lesion as pancreatic NET in 20/20=100% cases using as standard of truth biopsy and histopathology for primary tumour (Kumar 2011). The detection rate of CE CT for primary tumour was 15/20=75%. Two false positive results were observed with CE CT. In 3 patients CE CT failed to show primary tumour. Distant metastases were correctly identified by gallium (^{68}Ga) edotreotide in all patients (sensitivity 13/13=100%), whereas CE CT identified only 7/13=57.1% of patients with distant metastases. In 4 patients, CE CT missed infracentimetric liver metastases, and in 5 patients infracentimetric non-enhancing lymph nodes. In 8 patients the FDG PET/CT was performed as well and its detection rate of primary tumour was 2/8=25%.

Versari et al. 2010[82] compared the value of endoscopic ultrasonography (EUS), multidetector CT (MDCT) and gallium (^{68}Ga) edotreotide PET/CT to detect and characterise the primary tumour in patients suspected to have primary duodenopancreatic NET. Nineteen consecutive patients underwent both gallium (^{68}Ga) edotreotide PET/CT and EUS, 16 patients underwent MDCT as well. Twenty-three NET were confirmed by cytology or histology in 13/19 patients. EUS correctly identified 13/13=100%, gallium (^{68}Ga) edotreotide PET/CT 12/13=92%, and MDCT 10/11=91% of duodenopancreatic NET patients. On a lesion base, EUS correctly identified 22/23=96%, gallium (^{68}Ga) edotreotide PET/CT 20/23=87% and MDCT 13/18=72% lesions (P=0.08 EUS vs. CT). Both on a patient and on a lesion base, specificity was 4/6=67% for EUS, 5/6=83% for gallium (^{68}Ga) edotreotide PET/CT and 4/5=80% for MDCT. The authors concluded that EUS, gallium (^{68}Ga a) edotreotide and MDCT had comparable accuracy in diagnosis of local duodenopancreatic NET and proposed their combination for optimal preoperative diagnosis.

Schraml et al. 2003[83] performed gallium (^{68}Ga) edotreotide PET/CT and whole-body magnetic resonance imaging (wbMRI) in 51 patients with histologically proven NET and suspicion of metastatic spread within a mean interval of 2.4 days (range 0-28 days). The CT protocol comprised multiphase CE CT imaging. The MRI protocol consisted of standard sequences before and after intravenous contrast administration at 1.5 T. Each modality (PET, CT, PET/CT, wbMRI) was evaluated independently by two experienced readers, with a consensus decision based on correlation of all imaging data. Histologic and surgical findings and clinical follow-up was established as the standard of truth. In 41/51=80% patients, 593 metastatic NET lesions were detected (lung 54, liver 266, bone 131, lymph node 99, other 43). One hundred and twenty PET-negative lesions were detected by CT or MRI. Of all 593 lesions detected, PET identified 381/593=64% true-positive lesions, CT 482/593=81%, PET/CT 545/593=92% and wbMRI 540/593=91%. Comparison of lesion-based detection rates between PET/CT and wbMRI revealed significantly higher sensitivity of PET/CT for metastatic lymph nodes (100% vs. 73%; p<0.0001) and pulmonary lesions (100% vs. 87%; p<0.0233), whereas

[82] Versari A, Camellini L, Carlinfante G, Frasoldati A, Nicoli F, Grassi E, Gallo C, Giunta FP, Fraternali A, Salvo D, Asti M, Azzolini F, Iori V, Sassatelli R (2010). Ga-68 DOTATOC PET, endoscopic ultrasonography, and multidetector CT in the diagnosis of duodenopancreatic neuroendocrine tumors: a single-centre retrospective study. Clin Nucl Med 35(5):321-328

[83] Schraml, C., N. F. Schwenzer, O. Sperling, P. Aschoff, M. P. Lichy, M. Muller, C. Brendle, M. K. Werner, C. D. Claussen, and C. Pfannenberg. 2013. 'Staging of neuroendocrine tumours: comparison of [(6)(8)Ga]DOTATOC multiphase PET/CT and whole-body MRI', Cancer Imaging, 13: 63-72.

wbMRI had significantly higher detection rates for liver (99% vs. 92%; p<0.0001) and bone lesions (96% vs. 82%; p<0.0001). Of all 593 lesions, 22 were found only in PET, 11 only in CT and 47 only in wbMRI. The patient-based overall assessment of the metastatic status of the patient showed comparable sensitivity of PET/CT and MRI with slightly higher accuracy of PET/CT. Patient-based analysis of metastatic organ involvement revealed significantly higher accuracy of PET/CT for bone and lymph node metastases (51/51=100% vs. 45/51=88%; p=0.0412 and 50/51=98% vs. 40/51=78%; p=0.0044) and for the overall comparison (251/253=99% vs. 227/253=89%; p<0.0001).

Froeling et al. 2012 analysed the diagnostic performance of gallium (^{68}Ga) edotreotide in patients with multiple endocrine neoplasia (MEN) proven by histology, biology or anatomic imaging. Twenty-eight gallium (^{68}Ga) edotreotide PET/CTs were performed in 21 MEN patients. Nineteen patients suffered from MEN-1, one from MEN-2a and one from MEN-2b syndrome. The examination was performed at restaging in 24 patients or at initial staging in 4 patients. Results of gallium (^{68}Ga) edotreotide were compared with composite standard of truth consisting of histopathologic examination and/or clinical follow-up data or the following imaging modalities such as CT, MRI, ultrasound, or further PET/CT. One hundred sixty-eight lesions were counted by 28 gallium (^{68}Ga) edotreotide PET/CT scans in 21 patients. Lesions appearing in consecutive PET/CT examinations were rated in the first examination only to avoid cluster effects from lesions counted repeatedly resulting in 127 lesions by only counting once. For 18 lesions, the standard of truth could not be obtained (10/18=55.6% were enlarged adrenal glands). A total of 109 lesions could be included in analysis: 78 lesions were MEN-associated lesions (in gastrointestinal tract, lymph nodes, lung, bones, pancreas, liver and parathyroid gland) and 31 non-MEN-associated lesions. The majority of 19 patients had a MEN-1 syndrome with a total of 91 MEN-associated lesions. 60 lesions were NET lesions and 31 lesions were benign MEN-associated lesions. In 16 cases, the gallium (^{68}Ga) edotreotide PET/CT was performed including a contrast enhanced (CE) CT. In this group 47 lesions (37 malignant, 10 benign) were confirmed. In conclusion, gallium (^{68}Ga) edotreotide PET/CT allows a high detection rate of NET lesions in the context of MEN-1 syndrome as well as influence therapeutic management in nearly up to half of the patients. Gallium (^{68}Ga) edotreotide PET/ CT should include a CE-CT to improve MEN-associated NET lesion detection.

The question whether or not PET/ CE CT may improve the diagnostic performance of PET/CT was also addressed by Mayerhoefer et al. 2012. In 55 patients with known or suspected NET, the ^{68}Ga-PET/ CE CT was performed. Images were interpreted by senior and junior team and results were compared to the composite standard of truth consisting out of histology, clinical follow-up and results of imaging examinations. Patient based sensitivities and specificities were for “unenhanced junior team” 33/33=100% and 17/22=77%, for “unenhanced senior team” 32/33=97% and 18/22=81.8%, for “CE-junior team” 33/33=100% and 20/22=90.9% and for “CE senior team” 33/33=100% and 21/22=95.5%. Overall, the contrast media application increased the sensitivity of gallium (^{68}Ga) edotreotide PET/CT to only moderate degree and in most cases unenhanced PET/CT was sufficient for detection of abdominal NETs and their metastases.

The same question was also addressed by Ruf et al. 2011[84] who analysed the value of the triple-phase (early arterial, portal-venous inflow, and venous) CE CT in comparison to gallium (^{68}Ga) edotreotide PET gallium (^{68}Ga) edotreotide PET/CT with triple-phase CE CT was performed in 51 patients with known or suspected NET and two readers assessed the data of PET and each of the 3 CT phases for NET lesions independently and a consensus of readings was reached. Only lesions within the abdominal field were evaluated since triple-phase CE CT cannot be performed as a whole body examination. Clinical and imaging follow-up,

[84] Ruf J, Schiefer J, Furth C, Kosiek O, Kropf S, Heuck F, Denecke T, Pavel M, Pascher A, Wiedenmann B, Amthauer H (2011). 68Ga-DOTATOC PET/CT of neuroendocrine tumors: spotlight on the CT phases of a triple-phase protocol. J Nucl Med 52(5):697-704

histopathology (if available), and the decision of an interdisciplinary truth-panel served as a composite standard of truth. NET was confirmed in 39/51 patients. The patient-based sensitivity, specificity and accuracy for PET and triple-phase CT were 82%, 67%, 96% and 84.6%, 50%, 76.6% respectively. Of 510 abdominal lesions observed, 354 were classified as malignant; lesion-based sensitivity was 77.1% for combined triple phase CT, 53.4% for arterial CT, 66.1% for portal-venous CT, 66.9% for venous CT, and 72.8% for PET. The respective specificities were 85.3%, 92.9%, 92.3%, 89.7%, and 97.4%. Although arterial CT was found to be inferior to PET, portal-venous CT, and venous CT ($P<0.001$), the differences between the other scans were not significant. Detection was exclusively by PET for 16.1% of lesions, by triple-phase CT for 20.3%, by arterial CT for 0.5%, by portal-venous CT for 3.9%, and by venous CT for 3.9%. Regarding inter-observer reliability, the kappa-value was 0.768 for PET, 0.391 for triple-phase CT, 0.577 for arterial CT, 0.583 for portal-venous CE CT, and 0.482 for venous CE CT. In summary, similar patient based sensitivities were observed for PET and triple-phase CE CT; The reproducibility of gallium (^{68}Ga) edotreotide PET was higher than that of triple-phase CT. Ruf et al. concluded that gallium (^{68}Ga) edotreotide PET/CT in NET patients should be performed as PET/ triple-phase CE CT.

6. Gallium (^{68}Ga) edotreotide and Predicting and Monitoring of Therapeutic Response in NET

The gallium (^{68}Ga) edotreotide uptake by NET lesions measured by SUV on PET may be helpful to predict the absorbed dose during PRRT as proposed by Ezziddin et al. 2012. Data of 21 patients with 61 evaluable tumour lesions undergoing both pretherapeutic gallium (^{68}Ga) edotreotide PET/CT and PRRT with ^{177}Lu-octreotate (6.08-8.86 GBq; intratherapeutic tumour dosimetry with serial whole-body scans; 1, 2, and 4 days post injection) were analysed. SUVs were compared with the tumour-absorbed doses per injected activity (D/A0) of the subsequent first treatment cycle. The correlation of SUV and D/A0 was $r = 0.72$ (SUVmean) and $r=0.71$ (SUVmax), both $P<0.001$. Pancreatic origin and hepatic localisation were associated with higher D/A0 and chromogranin-A level. Ki-67 index had no influence on SUV or D/A0. High-SUV lesions (SUVmean >15; SUVmax >25) resulted in high D/A0 (>10 Gy/GBq) in 66.7% to 70.8% and low D/A0 (<5 Gy/GBq) in only 8.3% to 12.5% on subsequent PRRT. The mentioned low D/A0 range, on the other hand, was achieved by all lesions with SUVmean <7 or SUVmax <9. In summary, SRPET may predict tumour absorbed doses on PRRT. The ability to indicate insufficient target irradiation by a low SUV could aid in selection of appropriate candidates for PRRT.

Two years later, Kratochwil et al. 2015 published their results on quantitative analysis of gallium (^{68}Ga) edotreotide uptake by liver metastases of NET as a predictor of therapeutic response to PRRT. In this study, gallium (^{68}Ga) edotreotide PET/CT was performed in 30 NET patients with 60 liver metastases at baseline and after PRRT. SUVmax of all hepatic lesions, of normal liver and spleen were measured and tumour to spleen ratio (T/S ratio), and tumour to liver ratio (T/L ratio) were calculated. Based on morphological criteria, after three cycles of PRRT, the lesions were divided into two groups: responding to PRRT ($n = 40$) and non- responding to PRRT ($n = 20$). Statistically significant differences were observed in the mean SUVmax for non-responding vs. responding lesions at baseline (18.00 ± 3.59 vs. 33.55 ± 4.62, $p < 0.05$) and for the mean T/S ratio (1.20 ± 0.37 vs. 1.90 ± 0.45, $p < 0.05$) and the mean T/L ratio (3.15 ± 0.53 vs. 4.97 ± 0.62, $p < 0.05$). Using the receiver operating characteristic curves, SUVmax was found a better metric than both T/L ratio and T/S ratio (area under the curve (AUC) of SUVmax 0.87; T/L ratio 0.78; T/S ratio 0.73) as a stratification criterion. Using a threshold value of >16.4 for SUVmax, the sensitivity and specificity in predicting responding lesions were 95 and 60%, respectively. In conclusion, with gallium (^{68}Ga) edotreotide PET/CT the SUVmax cut-off of >16.4 was proposed as a selection criteria of patients indicated to PRRT. A T/L ratio >2.2 might present a scanner- independent criterion that enables the translation of these results to other institutions; however this approach still needs to be evaluated with different PET cameras.

Similarly as in the case of other anticancer treatment, an accurate method is needed also in case of PRRT. In the study of Gabriel et al. (Gabriel 2007), early evaluation of therapeutic response to PRRT was compared using gallium (^{68}Ga) edotreotide, or CT or MRI using the Response Evaluation Criteria in Solid Tumours (RECIST). Furthermore, on gallium (^{68}Ga) edotreotide PET, the standardised uptake values (SUVs) were calculated and compared with treatment outcome. Data of 46 patients with advanced NETs were analysed before and after 2–7 cycles of PRRT. Long-acting somatostatin analogues were not applied for at least 6 weeks preceding the follow up gallium (^{68}Ga) edotreotide imaging. Gallium (^{68}Ga) edotreotide PET images were visually interpreted by 2 nuclear medicine physicians. For comparison, multislice helical CT scans and 1.5-T MRI scans were obtained. Repeated CT evaluation and other imaging modalities were used as the SOT. According to the SOT, gallium (^{68}Ga) edotreotide PET and CT showed a concordant result in 32/46=70% of patients. In the remaining 14/46=30% of patients, discrepancies were observed, with a final outcome of progressive disease in 9 patients and remission in 5 patients. Gallium (^{68}Ga) edotreotide PET was correct in 10/46=21.7% patients, including 5/9=56% of patients with progressive disease. In these patients, metastatic spread was detected with the follow-up whole-body PET but was missed when concomitant CT was used. On the other hand, CT confirmed small pulmonary metastases not detected on gallium (^{68}Ga) edotreotide in 1 patient and progressive liver disease not detected on gallium (^{68}Ga) edotreotide in 3 patients. In summary, gallium (^{68}Ga) edotreotide PET showed no advantage over conventional anatomic imaging for assessing response to therapy when all CT information obtained during follow-up is compared. However, in addition to conventional imaging, gallium (^{68}Ga) edotreotide whole-body PET can be helpful as an early predictor of progressive disease by detecting new metastases that developed during therapy.

In the study of Kroiss et al. (Kroiss 2013), a decrease in SUVmax more than 3 months after PRRT was found both in organs with physiological uptake (thyroid, lungs, spleen, adrenal glands, gluteal region, blood pool, uncinate process) and in pathological distribution of ^{68}Ga-edotreotide. However, a significant change in SUVmax after PRRT was only found in NET patients with liver metastases ($p<0.02$) in contrast to those with bone metastases ($p<0.1$) and those with NET of the pancreas ($p<0.3$).

The variation of gallium (^{68}Ga) edotreotide uptake by liver metastases of GEP NET after PRRT was analysed by Luboldt et al. 2010[85]. The aim of their study was to propose standardised method of therapy monitoring of hepatic metastases from GEP NET during the course of PRRT. In 21 consecutive patients with non-resectable hepatic metastases of GEP NET, chromogranin A (CgA) and gallium (^{68}Ga) edotreotide PET/CT were compared before and after the last PRRT. On gallium (^{68}Ga) edotreotide PET/CT, the SUVmax of normal liver and hepatic metastases was calculated. In addition, the volumes of hepatic metastases (volume of interest [VOI]) were measured using four cut-offs to separate normal liver tissue from metastases (SUVmax of the normal liver plus 10% [$VOI_{liver}+10\%$], 20% [$VOI_{liver}+20\%$], 30% [$VOI_{liver}+30\%$] and SUV=10 [VOI_{10SUV}]). The SUVmax of the normal liver was below 10 (7.2± 1.3) in all patients and without significant changes. Overall therapy changes (Δ) per patient (mean [95% CI]) were statistically significant with $p<0.01$ for Δ CgA -43 (-69 to -17), Δ SUVmax -22 (-29 to -14), and Δ VOI_{10SUV} -53 (-68 to -8)% and significant with $p<0.05$ for Δ $VOI_{liver+10\%}$ -29 (-55 to -3)%, Δ $VOI_{liver+20\%}$ -32 (-62 to - 2) and Δ $VOI_{liver+30\%}$ -37 (-66 to -8). Correlations were found only between Δ CgA and Δ VOI_{10SUV} ($r=0.595$; $p<0.01$), Δ SUVmax and Δ VOI_{10SUV} (0.629, $p<0.01$), and SUVmax and Δ SUVmax ($r=-0.446$; $p<0.05$).

[85] Luboldt W, Hartmann H, Wiedemann B, Z, Luboldt HJ (2010a). Gastroenteropancreatic neuroendocrine tumors: standardizing therapy monitoring with 68Ga-DOTATOC PET/CT using the example of somatostatin receptor radionuclide therapy. Mol Imaging 9(6):351-358

In this study, gallium (^{68}Ga) edotreotide PET/CT allowed volumetric therapy monitoring via an SUV- based cut-off separating hepatic metastases from normal liver tissue (SUV=10 recommended).

Analysis performed across trials - Meta-analysis

Introduction

Positron emission tomography with integrated CT (PET/CT) using the somatostatin analog, ^{68}Ga - edotreotide, is still investigational, but reports in the peer-reviewed literature suggest that it is significantly superior to the current approved somatostatin receptor imaging "gold standard" of ^{111}In- DTPA-octreotide (also called indium (^{111}In) pentetreotide). If ^{68}Ga - edotreotide PET/CT is at least equivalent (non-inferior) to ^{111}In-DTPA-octreotide imaging in the peer-reviewed literature in terms of safety and efficacy, then these results would support use of ^{68}Ga - edotreotide as a PET/CT imaging agent for patients with somatostatin receptor expressing tumours due to less radiation exposure arising from of ^{68}Ga-edotreotide PET/CT, and its significantly shorter required time between radiotracer injection to scan completion compared to ^{111}In-octreotide imaging.

Rationale

The systematic review and meta-analysis was performed to assess the published relevant information related to the safety, test performance and impact on disease management of PET/CT imaging with ^{68}Ga - edotreotide.

Objectives

To perform a systematic review and, if sufficient data are available, a meta-analysis to estimate the safety and diagnostic and staging accuracy of ^{68}Ga - edotreotide PET/CT for the common somatostatin receptor expressing tumours of pulmonary or gastroenteropancreatic (GEP) neuroendocrine tumours (NET), compared to the "gold standard" of ^{111}In-octreotide imaging.

Methods

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the publication of systematic reviews and meta-analyses (Moher 2009[86]). Study selection and the systematic review definition of objectives with clinical relevance followed the Population, Intervention, Comparison, Outcome, and Study Type (PICOS) method.

Eligibility criteria

Inclusion criteria

In order to be included in this analysis, a study had to comply with the following inclusion criteria:

1. Study design and quality:
    a. All study designs such as randomized, not randomized, blinded, open-label,

[86] D Moher, A Liberati, J Tetzlaff, DG Altman Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 151 (4), 264-269

prospective and retrospective, etc.;
   b. Published from 01 January 1999 until 17 July 2015;
   c. Studying ^{68}Ga - edotreotide PET/CT imaging performance, including but not limited to studies which used ^{111}In-DTPA-Octreotide SPECT as a direct comparator;
   d. Reported enough data to draft an imaging performance 2x2 contingency table;
   e. Used histology, conventional imaging, clinical information or a combination of these as the standard of truth for tumour assessment.
2. Patient population:
   a. Primary data in humans;
   b. All ages;
   c. All genders;
   d. Suffering from pulmonary or GEP NETs, complying with the following criteria:
   Embryonic site of origin (Pinchot 2008; Gustafsson 2008)
   (1) Foregut: (a) Broncho-pulmonary, also known as "pulmonary" NETs, (b) Stomach, (c) Pancreas, (d) Duodenum to the ligament of Treitz
   (2) Midgut (entire small intestinal tract distal to the ligament of Treitz, including the appendix and right hemi-colon to the distal transverse colon);
   (3) Hindgut (including rectum);
   (4) Publications reporting patients with metastatic disease from an unknown primary NET or in patients where studied imaging modalities were used to search for an unknown primary NET. In these cases it was assumed that the primary tumour was from the pulmonary or GEP groups since these two groups comprise about 90% of NETs.

Exclusion criteria

Any study that complied with at least one of the following exclusion criteria was not included in the analysis:
1. Publications which were either systematic reviews or case reviews;
2. Study population limited to 10 or less patients;
3. The study population included mainly other cancers without any possibility of extracting the data concerning pulmonary and GEP NETs;
4. Publications only about tumours from other sites of origin than GEP or pulmonary NETs
5. (e.g. ovary or nasopharynx NETs), because they are extremely rare, and are often reported either as a single case or a short case series, precluding meaningful statistical analysis;
6. Study including other imaging agents without any possibility for extracting the data only related to ^{68}Ga-edotreotide;
7. The ^{68}Ga - edotreotide imaging modality was not PET;
8. Publications with study populations included in multiple publications. Publications were excluded so that the population under study contributed only once to the meta-analysis. Authors were contacted if necessary to determine the uniqueness of a study population or when data were incomplete. Duplicate populations, in whole or in part, were excluded. When individual patients could not be determined, then the most recent publication was chosen for inclusion.

Endpoints analysed

All studies included in the meta-analysis were to be analyzed. The main analyses of the primary efficacy endpoint, secondary efficacy endpoint, and safety endpoint were to be performed on the Full Analysis Set.

No adjustment was applied for multiple testing.

All efficacy variables were listed by study. Data were summarized by imaging agent, with N, missing data, mean, median, standard deviation (SD), first and third quartiles, minimum and maximum summarized for continuous efficacy variables, and count and percentage used to summarize categorical efficacy variables. Overall test performance was estimated in a pooled fashion using forest plots and HSROCs.

To test the pooling assumptions, study heterogeneity was quantitatively measured by Cochran Q and I2 statistics and assessed graphically by forest plots and an unadjusted HSROC. A chi-square test was applied to determine if random effects were present. If not stated otherwise, all tests were two-tailed at the 5% significance level.

Sensitivity was defined as the percentage of patients found to be positive with the imaging procedure among the number of patients positive with the standard of truth:

Sensitivity %= (true positive [TP]/disease positive [DP])*100

Specificity was defined as the percentage of patients found to be negative with the imaging procedure among the number of patients negative with the standard of truth:

Specificity % = (true negative [TN]/disease negative [DN])*100

The non-inferiority of ^{68}Ga - edotreotide imaging performance compared to ^{111}In-DTPA- Octreotide imaging performance was to be tested as follow:

- The degree of study-to-study heterogeneity was measured by Cochran Q and I2 statistics and was visually assessed in forest plots.
- Study specific test performances with 95% CIs were displayed in forest plots.
- A 95% CI for the unadjusted overall sensitivity and specificity was reported.

However, this non-inferiority analysis was not conducted due to the small number of eligible studies identified from the systematic review. Therefore only ^{68}Ga - edotreotide imaging performance pooled estimates were calculated using an unadjusted random effect model (DerSimonian Laird method), which incorporates variation among studies (DerSimonian et al. 1986[87]). The CIs of overall sensitivity and specificity were calculated using the Wilson's exact method to compute the exact CIs for the binomial proportion. In addition, the diagnostic odds ratios were combined by the method of Rutter and Gatsonis to estimate the overall diagnostic odd ratio and hence to determine the best-fitting HSROC curve and the 95% confidence region for the overall odds ratio. The calculation of the HSROC was performed using the SAS-macro METADAS and displayed in Review Manager V5.3.

Information sources

Medline, EMBASE and Cochrane Reviews electronics databases were searched from 01 January 1999 through 17 July 2015 without language restrictions: literature was included if the article was in English or English abstract translation was available for non-English articles.

Search strategy

Article search criteria included all expression of pulmonary or GEP NETs, including "pulmonary", "lung", "bronchial", "bronchus", "carcinoid", "neuroendocrine", "gastroenteropancreat*", "stomach", pancreas", "kidney", "gut", etc. Separately any of the common expressions of edotreotide, octreotide, pentetreotide, somatostatin or somatostatin- derived receptors were included in the literature search. In addition,

[87] Rebecca DerSimonian, Nan Laird. Meta-analysis in clinical trials. Controlled Clinical Trials Volume 7, Issue 3, September 1986, Pages 177-188

bibliographies from meta-analyses and literature reviews were examined individually and papers of interest included in the final list of abstracts for review.

In studies with incomplete information, direct communication with the corresponding author was sought and is reported, and the studies were included in the analysis if the additional information via correspondence allowed inclusion. Studies with overlapping patient populations were limited to the single paper with the most relevant population or use of the most recent imaging technology as reported by the corresponding author or senior author of both manuscripts. Analysis was on a "per-patient" basis (i.e. diagnosis, staging and/or other impact on management) since, in patients with multiple lesions (primary tumour and metastases), it is not possible to confirm separately each of multiple lesions with biopsy/histology. An endpoint of cancer or benign diagnosis was also established and included as part of data extraction. Definitions of gold standard whether by pathology, imaging, or combination were abstracted.

Data analysis

Data synthesis

Abstracts were collected by the statistician and reviewed independently by clinical research reviewers. After abstract review, if the reviewers considered that full data extraction should be conducted, then a complete text review of the article was conducted and data extraction conducted independently by the reviewers. After complete article review and data extraction, the reviewers determined which studies to include in the final systematic review by consensus.

All analyses were performed with SAS V9.2. In addition, other tools could have been used to explore the data and create graphs, as necessary.

A descriptive summary of the design and quality of the studies included in the meta-analysis was provided.

In addition, study quality was assessed, summarized and presented according to the modified QUADAS. Publication bias was graphically charted by funnel plot and quantitatively measured by Deek's Asymmetry Test (Deeks 2005).

A meta-analysis model was to be estimated if more than 10 studies were found through the systematic review. However, no direct comparative studies to ^{111}In-DTPA-Octreotide were identified from the systematic review so it was not possible to conduct this analysis.

Assessment of the quality of the data

Study quality was assessed according to prospective criteria using a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) set of 14 questions (see below) (Whiting 2003; Fontela 2009). These questions addressed the technical quality of the index test, the technical quality of the reference test, the independence and accuracy of the test interpretation, and the sample size and population representation. Additional quality questions specifically measured possible mis-classification bias arising from pre-selection bias, incomplete diagnosis, or diagnosis driven by scan results. A quality score was created by adding the number of QUADAS criteria with which the study complied. The maximum possible score was 14.

Missing data

When published data were incomplete, the authors were contacted to make every possible effort to obtain additional information relevant to this meta-analysis. For the main analysis of the primary endpoint, missing data were not replaced, and only complete cases were analyzed.

Results

- Sensitivity Analyses

Results vary substantially for sensitivity and specificity between studies. Grubbs' test for outliers (Grubbs FE. Procedures for detecting outlying observations in samples. Technometrics. 1969; 11(1):1-21.) were applied to identify statistical significant outliers in the data. As a sensitivity analysis, the pooled estimates were performed excluding the identified outliers.

The objectives were to perform a systematic review and, if sufficient data were available, to conduct a meta-analysis to assess the safety and diagnostic and staging accuracy of gallium (^{68}Ga) edotreotide PET/CT for the common somatostatin receptor expressing tumours of pulmonary or GEP NETs, compared to the 'gold standard' of ^{111}In-DTPA-Octreotide imaging.

A summary of the efficacy results for the studies included in the meta-analysis is provided in the table below.

Table 19: Efficacy results for gallium (^{68}Ga) edotreotide

Study	Cancer / Benign	Sensitivity (%)	Specificity (%)	Treatment Management
Non-comparative studies				
Jindal 2010	20/0	95.0 TP 19 - FN 1	Not applicable	In one patient ^{68}Ga-edotreotide PET/CT facilitated the detection of additional lesions which were not identified in the conventional CT.
Mayerhofer 2012	33/22	97.0 TP 32 - FN 1	81.8 TN 18 - FP 4	One patient was a false-negative using unenhanced ^{68}Ga-edotreotide PET/CT but no patients were false-negative using contrast-enhanced ^{68}Ga-edotreotide PET/CT.
Koukouraki 2006a	22/0	100 TP 22 - FN 2	Not applicable	Impact on treatment not evaluated.
Studies comparing ^{68}Ga -edotreotide to conventional imaging (CT, MRI, ultrasound)				
Frilling 2010	52/0	100 TP 52 - FN 0	Not applicable	^{68}Ga-edotreotide PET/CT altered the treatment decision based on CT and/or MRI alone for 31 out of 52 patients (59.6%).
Versari 2010	13/6	92.3 TP 12 - FN 1	83.3 TN 5 - FP 1	On a lesion basis, ^{68}Ga-edotreotide PET detected 15% more lesions that multi-detector CT.
Ruf 2011	39/12	82.1 TP 32 - FN 7	66.7 TN 8 – FP 4	Impact on treatment not evaluated.
Kumar 2011	20/0	100 TP 20 - FN 0	Not applicable	Impact on treatment not evaluated.

Schraml 2013	41/10	97.6 TP 40 - FN 1	Not applicable	The imaging results influenced the treatment decision in 30 patients (59%).
Studies comparing ^{68}Ga-edotreotide to other radiopharmaceuticals				
Gabriel 2007	71/13	97.2 TP 69 - FN 2	92.3 TN 12 - FP 1	In 18 patients (21.4%), ^{68}Ga-edotreotide provided further clinically relevant information compared to diagnostic CT alone, including 9 patients with unknown bone metastases. The primary tumor was identified in 5 patients who had escaped detection by CT.
Putzer 2009	38/13	97.4 TP 37 - FN 1	92.3 TN 12 - FP 1	One patient was a false negative and another was a false positive.
Putzer 2010	11/4	63.6 TP 7 - FN 4	50.0 TN 2 - FP 2	Impact on treatment not evaluated.
Venkitaraman 2014	26/6	96.2 TP 25 - FN 1	100 TN 6 - FP 0	Impact on treatment not evaluated.

TP = true positive; FN = false negative; TN = true negative; FP = false positive

Overall, the pooled estimated sensitivity and specificity among the studies based upon a random effects model for gallium (^{68}Ga) edotreotide was 95% (95% confidence interval [CI]: 90% - 98%) and 84% (95% CI: 74% - 93%), respectively (see tables below).

Table 20: Summary of sensitivity

Study	Sensitivity	95% CI
Jindal 2010	0.95	0.76 - 0.99
Mayerhofer 2012	0.97	0.85 - 0.99
Koukouraki 2006b	1.00	0.85 - 1.00
Frilling 2010	1.00	0.93 - 1.00
Versari 2010	0.92	0.67 - 0.99
Ruf 2011	0.82	0.67 - 0.92
Kumar 2011	1.00	0.84 - 1.00
Schraml 2013	0.97	0.87 - 0.99
Gabriel 2007	0.97	0.90 - 0.99
Putzer 2009	0.97	0.87 - 1.00
Putzer 2010	0.64	0.35 - 0.85
Venkitaraman 2014	0.96	0.81 - 0.99
Pooled	**0.95**	**0.90 – 0.98**

Heterogeneity chi-squared = 26.1 (d.f. = 11) p = 0.006. Inconsistency (I-square) = 57.8%
No. studies = 12
0.5 was added to all cells of the studies with zero

Table 21: Summary of specificity

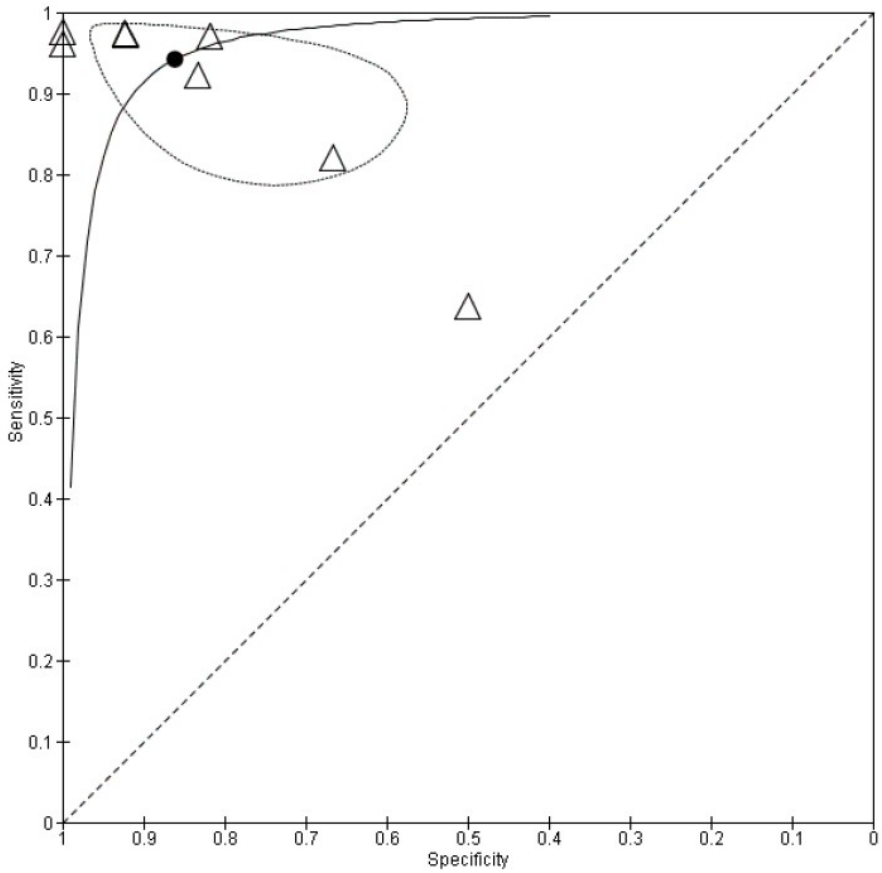
Study	Specificity	95% CI
Mayerhoefer 2012	0.82	0.61 - 0.93
Versari 2010	0.83	0.44 - 0.97
Ruf 2011	0.67	0.39 - 0.86
Schraml 2013	1.00	0.72 - 1.00
Gabriel 2007	0.92	0.67 - 0.99
Putzer 2009	0.92	0.67 - 0.99
Putzer 2010	0.50	0.15 - 0.85
Venkitaraman 2014	1.00	0.61 - 1.00
Pooled	**0.84**	**0.74 - 0.93**

Heterogeneity chi-squared = 10.6 (d.f. = 7) p = 0.16. Inconsistency (I-square) = 33.8%

No. studies = 8; 0.5 was added to all cells of the studies with zero

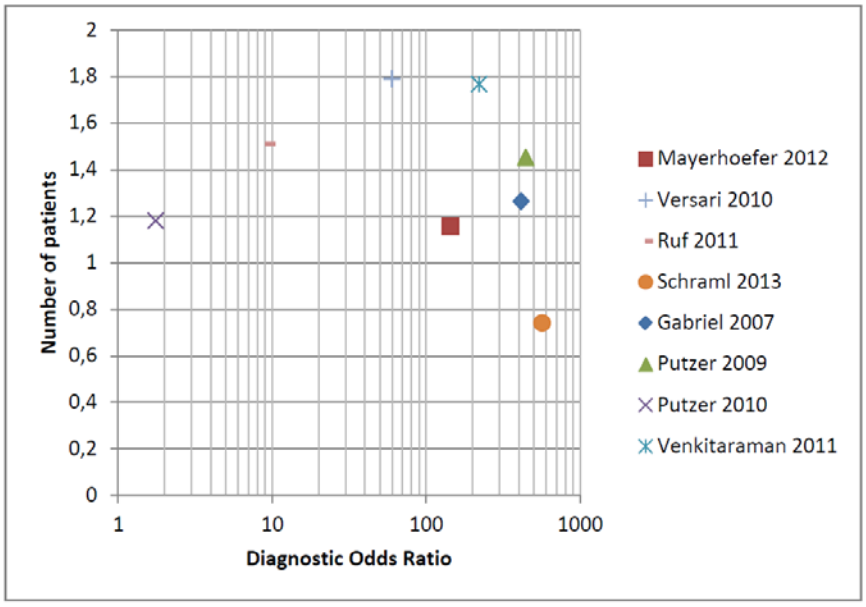
The results of the HSROC curve and the 95% confidence region of the summary point for ^{68}Ga - edotreotide are shown in Figure 1. The curve is towards the true positive side of the graph indicating the accuracy of the imaging method, which was confirmed by the fact that the area under the curve (AUC) is close to 1 (0.985).

Figure 7: HSROC Curve for ^{68}Ga- edotreotide with 95% Confidence Region



Based on the package insert from OctreoScan (2011), the sensitivity rate for ^{111}In-DTPA-Octreotide scintigraphy is 86% and for CT/MRI the rate is 68%. The specificity rate for ^{111}In-DTPA-Octreotide scintigraphy is 50%, and the rate for CT/MRI was 12%. Overall, including all tumour types with or without the presence of somatostatin receptors, the rate of FP was 0.6% and the rate of FN was 20.5%. Thus it can be seen that the sensitivity and specificity rates for ^{68}Ga - edotreotide were similar to or better than the ones observed for ^{111}In-DTPA-Octreotide scintigraphy (sensitivity 93% versus 86%; specificity and 89% versus 50%, respectively).

Figure 8: Deek's Funnel Plot of Publication Bias



The Funnel plot (Figure 2) suggests that the results from Putzer 2010 are an outlier. The Grubbs' test (G=2.81; critical value=2.51) confirmed this finding. As a sensitivity analysis, the pooled estimates of sensitivity and specificity were therefore calculated without the data of this publication. The results are shown in Table 4 and Table 5. The pooled estimates changed only marginally (sensitivity from 0.95 to 0.96; specificity from 0.84 to 0.86) but the inconsistency dropped for sensitivity from 57.8% to 39.3% and for specificity from 38.8% to 20.4%.

Table 22: Pooled Summary of Sensitivity

Study	No. of studies	Sensitivity	95% CI	Inconsistency (I-square)
Pooled sensitivity all studies	12	0.95	0.90 – 0.98	57.8
Pooled sensitivity excluding Putzer 2010	11	0.96	0.92 – 0.98	39.3

Table 23: Pooled Summary of Specificity

Study	No. of studies	Specificity	95% CI	Inconsistency (I-square)
Pooled specificity all studies	7	0.84	0.74 - 0.93	38.8
Pooled specificity excluding Putzer 2010	6	0.86	0.76 - 0.94	20.4

In this systematic review, no studies were identified that directly compared gallium (^{68}Ga) edotreotide to ^{111}In-DTPA-Octreotide imaging. However, a comparison of the published data on gallium (^{68}Ga a) edotreotide with the information from the Octreoscan package insert showed that the imaging performance was similar or higher than the one reported with ^{111}In-DTPA-Octreotide, with sensitivity of 93% versus 86% and specificity of 89% versus 50%, respectively. This supports the use of gallium (^{68}Ga)

edotreotide as a PET/CT imaging agent for patients with somatostatin receptor expressing NETs. Other advantages for the use of gallium (^{68}Ga) edotreotide PET/CT imaging over ^{111}In-DTPA-Octreotide imaging include; (1) less radiation exposure; (2) significantly faster acquisition and imaging procedure (same-day); and (3) lower radiation exposure.

Analysis performed across trials - pooled analyses

Table 24: Pooled summary of literature references

Reference	Nb of patients/ (Pathology)/ Age; Gender	^{68}Ga-edotreotide Imaging Technique/activity administered/Acquisition time p.i.	Comparator	Comparator imaging technique	Standard of truth	Performance ^{68}Ga-edotreotide	Performance comparator
Overall	Results of 977 examinations in 970 patients were analysed	**Mean activity administered 126-191MBq** **Range 80-250 MBq** **Activity per body weight (one study) 1,5-2 MBq/kg** **Mean acquisition time 56-77 min post injection**				**Pooled patient based detection rate/sensitivity** 518/550=94% **Polled impact rate** **In patients referred for localisation and staging of known or suspected NET** 109/234=47% **In patients scheduled to PRRT** 8/80=10%	

Clinical studies in special populations

No studies on the use of gallium (^{68}Ga) edotreotide in the elderly, paediatric population or in patients with renal or hepatic impairment were submitted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No clinical development programme has been conducted by the applicant to support this application for marketing authorisation. This is acceptable as this application is under Article 10(a) of Directive 2001/83/EC, "well established medicinal use". The submitted clinical documentation is being based on data available in published literature. The applicant has presented data from the literature since the first documented use of gallium (^{68}Ga) edotreotide in Europe in 2001 to 2016, including 970 patients in total, to support the indications in the diagnostic work-up GEP-NET tumours. The applicant has shown that gallium (^{68}Ga) edotreotide is being regularly used in the diagnostic work-up of patients with NET tumours for at least 10 years in the European Union. In addition, the degree of scientific interest in the use of gallium (^{68}Ga) edotreotide is reflected in the published scientific literature. Indeed, the European consensus clinical and procedural guidelines include gallium (68) edotreotide for diagnostic management of GEP-NET patients.

The CHMP considers that the applicant has fulfilled the criteria for the legal basis for well-established use of edotreotide in the EU.

Efficacy data and additional analyses

Technical performance of gallium (^{68}Ga) edotreotide has been demonstrated in the publications submitted which showed that tumour/no tumour uptake was better for gallium (^{68}Ga) edotreotide than Octreoscan in all lesions previously seen by CT/MRI. ^{68}Ga edotreotide provides several advantages for physicians and patients. The gallium (^{68}Ga) isotope has the advantage of being produced from a generator, so it can be more widely available in departments without the need of a cyclotron. The time window for ^{68}Ga imaging acquisition is relatively short, in line with the radio- nucleide's half-life of 68 minutes, thus having an added value in terms of lower irradiation to patients and shorter scan timing (in one single day versus a higher irradiation and a 2-day scan for Octreoscan). Thus, gallium (^{68}Ga) edotreotide appears to have technical advantages over somatostatin receptor scintigraphy with Octreoscan for diagnosis of GEP-NET and a similar safety profile.

For diagnostic performance, a substantial number of publications have been provided and the results are positive in terms of sensitivity, specificity and lesion detection rate of gallium (^{68}Ga) edotreotide PET. For the detection of the primary GEP-NET site in case of rising levels of a relevant biochemical tumour marker or in case of proven NET metastasis, patient-based sensitivity and specificity of gallium (^{68}Ga) edotreotide PET were 100% (4/4) and 89% (8/9), respectively, in the prospective study of Gabriel et al. 2007. Lesion-detection rate was 75% (3/4) in the subgroup of patients with unknown primary tumour site of the prospective study of Frilling et al. 2010. In the retrospective paper of Schreiter et al. 2014, the intra-individual comparison in a subgroup of 20 patients showed that gallium (^{68}Ga) edotreotide permitted to localise the primary tumour in 9/20 (45%) patients while indium (^{111}In) pentetreotide did in 2/20 (10%).

A prospective intra-individual comparison showed that gallium (^{68}Ga) edotreotide is able to detect lesions better than indium (^{111}In) pentetreotide. A lesion detection rate of 100% (40/40) versus 85% (34/40) was observed in the study of Hofmann et al. 2001 recruiting patients with histologically proven bronchial (n=2) or midgut (n=6) NETs. In the study of Buchmann et al. 2007, conducted in 27 patients mostly with GEP-NET (59%) or NETs of unknown primary (30%), gallium (^{68}Ga) edotreotide identified 279 lesions versus 157 lesions seen with indium (^{111}In) pentetreotide. In the study of Van Binnebeek et al. 2015 in 53 patients with metastatic GEP-NET [mostly GEP-NET (n=39) or NET of unknown origin (n=6)], the lesion-based detection rate of gallium (^{68}Ga) edotreotide was 99.9% (1098/1099) versus 60% (660/1099) for indium (^{111}In) pentetreotide based on the follow-up scans. In the study of Lee et al. 2015 in 13 GEP-NET patients, a total of 35 positive lesions were detected in 10 patients on either gallium (^{68}Ga) edotreotide PET/CT or indium (^{111}In) pentetreotide SPECT/CT while 3 patients did not exhibit any positive lesions on either imaging method. Gallium (^{68}Ga) edotreotide detected 35/35 (100%) lesions vs 19/35=54% for indium (^{111}In) pentetreotide SPECT/CT. In the study of Kowalski et al. 2003 in 4 patients with GEP-NET, gallium (^{68}Ga) edotreotide showed better patient-based detection rate (100%) than indium (^{111}In) pentetreotide (50%).

The results provided comparing gallium (^{68}Ga) edotreotide with Octreoscan have some drawbacks related to the limited number of patients included in the publications (as expected for a rare disease), the use of the ideal comparator (Octreoscan) only in a limited number of studies, and the assessment based on lesions rather on patients in some publications. However, the overall efficacy data, including the results from the meta-analysis, are consistent where gallium (^{68}Ga) edotreotide detects more primary and/or metastatic GEP-NET lesions than Octreoscan. The applicant has not provided data of impact on diagnostic thinking (higher probability of correct diagnosis after the test than before the test, or change in diagnosis) for gallium (^{68}Ga) edotreotide. Data available on the impact of gallium (^{68}Ga) edotreotide on patient management are limited.

Frilling et al. analysed the added value of ^{68}Ga-edotreotide PET/CT in diagnostic algorithm of 52 patients with NET (Frilling 2010). The examinations were performed in terms of tumour staging and, in some instances, also of primary tumour site identification to evaluate the patient’s eligibility for different types of treatment.

In each patient, the CT and/or MRI were performed and consecutively underwent ^{68}Ga-edotreotide PET/CT. In all 52 patients, ^{68}Ga-edotreotide PET/CT demonstrated pathologically increased uptake for at least 1 tumour site, yielding a patient based sensitivity of 100%. In 3 of 4 patients with unknown primary tumour site, ^{68}Ga-edotreotide PET/CT visualised the primary tumour region (jejunum, ileum, and pancreas, respectively) not identified on CT and/or MRI. ^{68}Ga-edotreotide PET/CT detected additional hepatic and/or extrahepatic metastases in 22 of the 33 patients diagnosed with hepatic metastases on CT and/or MRI. Of the 15 patients evaluated for liver transplantation, 7/15=46.6% were omitted from further screening because of evidence of metastatic lesions not seen by conventional imaging. Overall, ^{68}Ga-edotreotide PET/CT impacted the treatment decisions based on CT and/or MRI alone, in 31/52 patients =59.6%.

In the study of Gabriel et al. ^{68}Ga-edotreotide PET provided further clinically relevant information in comparison with diagnostic CT alone in 18/84=21.4% of patients in different clinical situations of NET (Gabriel 2007). Compared with SRS with 99mTc-HYNIC-TOC or 111In-edotreotide, ^{68}Ga-edotreotide PET provided further valuable clinical information (impact on diagnostic thinking) in 12/84=14.3% of patients. Finally, in 21/84=25% of patients with NET, Surgical intervention was omitted in 3 patients because widespread disease was detected by ^{68}Ga-edotreotide, showing additional unknown distant tumour lesions.

Similar results were obtained in the study of Froeling et al. who evaluated the impact of ^{68}Ga-edotreotide PET/CT on diagnosis and therapeutic management of 21 patients with MEN (Froeling 2012). The impact of ^{68}Ga-edotreotide PET/CT on diagnosis and therapeutic management of patients were assessed by the records of the interdisciplinary NET tumour board including histological findings, clinical and radiological follow-up. It was observed in 10/21 (47.6%) MEN patients. The author concluded that ^{68}Ga-edotreotide PET/CT allows a high detection rate of NET lesions in the context of MEN-1 syndrome as well as influence therapeutic management in nearly up to half of the patients. ^{68}Ga-edotreotide PET/ CT should include a CE- CT to improve MEN-associated NET lesion detection.

A retrospective evaluation of impact of ^{68}Ga-edotreotide PET/CT (including triple-phase CE CT) in 64/66 patients with known or suspected was performed by Ruf et al. (Ruf 2010). An impact on therapeutic management was observed in 24/64=38% of NET patients: primary resection (n=5), curative lymph node resection (n=1), initiation/switch of chemotherapy (CTx) due to progressive disease (n=10), no surgery due to systemic disease (n=2), PRRT instead of CTx (n=1), additional bisphosphonate therapy (n=4), and hepatic brachytherapy (n=1). In 12/24=50% of these patients, relevant findings were detected by a single submodality only: CT (n=5), PET (n=7); (p=0.774).

The impact of whole-body PET/CT and MRI imaging on the treatment decision was evaluated by an interdisciplinary tumour board (Schraml 2013). The imaging results impacted the treatment decision in 30/51 patients=59% with comparable information from PET/CT and wbMRI in 30 patients, additional relevant information from PET/CT in 16 patients and from wbMRI in 7 patients.

Solid tumours represent a highly heterogeneous group of cells with different susceptibility to anti-cancer therapy where malignant cells survive by activation of multiple oncogenic pathways, including the phenotypic transformation. This becomes even more evident in patients with advanced disease and history of multiple drug-resistance. Within this context of advanced stage disease (metastatic NET) where detection rate becomes less critical, a positive impact of ^{68}Ga-edotreotide PET imaging (over ^{111}In-pentetreotide SPECT) on patient management has been observed. In two studies (Buchmann et al. 2007; Van Binnebeek et al. 2015) the pooled impact rate of ^{68}Ga-edotreotide PET/CT on this category of patients was 8/80=10%.

Errors in PET findings interpretation have been included as potential important risks in the RMP.

The proposed dose and time window of gallium (^{68}Ga) edotreotide scan PET images have been justified and are based on the 2010 Procedure guidelines forPET/CTtumour imaging with ^{68}Ga-DOTA-conjugated peptides of the European association of Nuclear Medicine (EANM) (Virgolini et al. 2010) and some published papers.

Based on the clinical efficacy data of gallium (^{68}Ga) edotreotide presented, the wording of the indication was modified as follows:

"This medicinal product is for diagnostic use only.
After radiolabelling with gallium (^{68}Ga) chloride solution, the solution of gallium (^{68}Ga) edotreotide obtained is indicated for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases."

The CHMP was not convinced that the efficacy data showed that ^{68}Ga edotreotide demonstrated a clinical benefit at predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET. A statement has been included in section 5.1 of the SmPC to highlight to healthcare professionals that data supporting efficacy of gallium (^{68}Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited. Five studies have been submitted, one of them prospective (Gabriel et al. 2009) and four retrospective studies (Kroiss et al. 2013, Ezziddin et al. 2012, Kratochwil et al. 2015 and Luboldt et al.2010a).

In the study by Gabriel et al. 2009 pre-PRRT gallium (^{68}Ga) edotreotide was compared with CT or MRI using the Response Evaluation Criteria in Solid Tumors (RECIST). Gallium (^{68}Ga) edotreotide PET and CT showed a concordant result in 32 patients (70%) and discrepancies in 14 patients (30%) presenting 9 with progressive disease and 5 with remission.

The retrospective study of Kroiss et al. 2013 in 249 NET patients showed that PRRT does not significantly influence semiquantitative uptake of gallium (^{68}Ga) edotreotide PET, except in liver metastases of patients with NET, but the study lacked histological confirmation. The three remaining retrospective studies recruited small samples (ranging from 20 to 28 GEP-NET patientsor those with cancer of unknown origin) and found that semiquantitative uptake in the pre-PRRT gallium (^{68}Ga) edotreotide PET scan correlated with the tumour-absorbed doses per injected activity of the subsequent first treatment cycle, differed between those lesions classified as responding and non-responding after three PRRT cycles, and helped to separate hepatic metastases from normal liver tissue.

Paediatric population

The safety and efficacy of gallium (^{68}Ga) edotreotide has not been established in paediatric populations, where the effective dose might be different than in adults. There is no recommendation for use of SomaKit TOC in paediatric patients.

Method of administration

SomaKit TOC is for intravenous use and for single use only.

This medicinal product should be radiolabelled before administration to the patient.

The activity of gallium (^{68}Ga) edotreotide has to be measured with activimeter immediately prior to injection.

The injection of gallium (^{68}Ga) edotreotide must be administered intravenously in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

For instructions on extemporaneous preparation of the medicinal product before administration, see sections 6.6 and 12 of the SmPC.

For patient preparation, see section 4.4 of the SmPC.

Image acquisition

Radiolabelled SomaKit TOC is suitable for PET medical imaging. The acquisition must include a whole body acquisition from skull to mid-thigh. The recommended time for imaging is 40 to 90 minutes post-injection. Imaging acquisition start time and duration should be adapted according to the equipment used, the patient and the tumour characteristics in order to obtain the best image quality possible.

2.5.4. Conclusions on the clinical efficacy

Technical and diagnostic performance of gallium (^{68}Ga) edotreotide has been demonstrated in patients with GEP-NET in comparison versus the standard of truth (histology) and/or the appropriate comparator indium (In111) pentetreotide (Octreoscan). Data on impact of gallium (^{68}Ga) edotreotide on diagnostic thinking was not provided and data available on the impact of gallium (^{68}Ga) edotreotide on patient management are limited.

2.6. Clinical safety

Patient exposure

The patient population exposed to ^{68}Ga-endotreotide from the published results of the clinical studies on efficacy and safety in the claimed indication of GEP-NET include 977 examinations performed in 970 patients.

The safety data of gallium (^{68}Ga) edotreotide were obtained from the available published data.

In the study of safety and tolerability of SomaKit TOC (EudraCT# 2014-002741-21), the activity administered was 2 MBq/kg of body weight, but ranging between 100 and 200 MBq.

Adverse events

From available literature data, no adverse reaction related to gallium (^{68}Ga) edotreotide has been reported so far, when used in the specified diagnostic dose range. There is, however, a hypothetical risk of hypersensitivity and adverse events related to exposure to ionising radiation (induction of cancer and potential of hereditary defects).

Serious adverse event/deaths/other significant events

There was no serious adverse event reported in the published literature.

There were no deaths reported in the published literature.

There were no other significant events reported in the published literature.

Laboratory findings

There were no laboratory findings reported from the published literature.

Safety in special populations

Liver and renal impairment

Norenberg et al. (2006) assessed the acute toxicity of unlabelled and 213Bi-labelled edotreotide in CA20984 tumour-bearing Lewis rats. While nephrotoxicity was described in the study of Norenberg, the data cannot be extrapolated to ^{68}Ga as 213Bi is an alpha emitter and ^{68}Ga is a beta+ emitter. Alpha emitters such as 213Bi, are known to cause nephrotoxicity. For ^{68}Ga-labelled edotreotide, the dosimetric data and bibliographic data support the findings that no nephrotoxic effects of gallium (^{68}Ga) edotreotide were observed.

Paediatric population

There were no data on the paediatric population reported from the published literature.

Pregnancy

There were no data on the administration of gallium (^{68}Ga) edotreotide in pregnant women reported in the published literature. The risk of administration of gallium (^{68}Ga) edotreotide is related to the estimation of radiation dose to the foetus. This assumption may be done from the following assumptions:

- The absorbed dose for gallium (^{68}Ga) edotreotide per unit of activity for uterus is 0.015 mGy/MBq (3mGy/200MBq) and the effective dose after administration of maximal recommended activity of gallium (^{68}Ga) edotreotide of 200 MBq is 4.2 mSv (Sandstrom et al., 2013).
- With fludeoxuglucose (^{18}F) (FDG), the use of which is not contraindicated during pregnancy, the absorbed dose per unit of activity for uterus is 0.018 mGy/MBq (7.2 mGy/400MBq) and the effective dose after administration of maximal recommended activity of FDG of 400 MBq is 7.6 mSv (ICRP 106, Core SmPC FDG).

Breastfeeding

There were no data on the administration of gallium (^{68}Ga) edotreotide in breastfeeding women reported in the published literature. For other PET agents such as 18-fluorinated PET radiopharmaceuticals, the breastfeeding and the close contact with infants is recommended to be interrupted during 12 hours following their administration (=720 minutes, corresponding to 6.6 physical half-lives of ^{18}F).
Similarly, for ^{68}Ga with a physical half-live of 68 minutes the breastfeeding and the close contact with infants are recommended to be interrupted during 68min x 6.6 = 449 minutes following its administration, corresponding to approximately 8 hours.

Safety related to drug-drug interactions and other interactions

There were no data on clinical drug interaction reported in the published literature.

SST receptors expressed by malignant cells appear not to be saturable by exogenous somatostatin analogues (Velikyan 2010, Sabet 2013, Giesel 2013). Furthermore, the results of Velikyan et al. (2010), show that high levels (250 and 500 µg) of edotreotide are suboptimal with respect to tumour-background ratio (compared to lower levels of edotreotide).

Discontinuation due to adverse events

There were no data on discontinuation due to adverse events reported in the published literature.

Post marketing experience

There were no data on post marketing experience reported in the published literature.

2.6.1. Discussion on clinical safety

As this is an application based on well-established use, safety data of gallium (^{68}Ga) edotreotide is presented from published studies. No pivotal study from the applicant has been performed.

The extent of population exposure to gallium (^{68}Ga) in the literature references provided amounts to 977 examinations in 970 patients. Taking into account the rarity of GEP-NET, this number could be considered acceptable.

No adverse reactions related to gallium (^{68}Ga) edotreotide have been reported and hence, no important identified risks have been noted. Gallium (^{68}Ga) edotreotide is generally well tolerated. There is only the risk of hypersensitivity and the adverse reactions due to occupational and inadvertent exposure to ionising radiation, which have been included in the RMP as important potential risks. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is about 4.5 mSv when the maximal recommended activity of 200 MBq is administered, these adverse reactions are expected to occur with a low probability. This is in line with the safety profile of the competitor Octreoscan. Occupational and inadvertent exposure has been included as an important potential risk.

Safety of the gallium (^{68}Ga) edotreotide solution has not been the subject of specific clinical studies in special populations. Several published studies included elderly patients and no safety concern was reported in such subpopulation. In the paediatric population, the safety and efficacy of gallium (^{68}Ga) edotreotide has not been established in paediatric populations, where the effective dose might be different than in adults (see SmPC section 4.4). This has been included in the RMP as an important potential risk. There is no recommendation for use of SomaKit TOC in paediatric patients. Use in paediatric population has been included as missing information.

Taking into consideration that pregnancy is not a contraindication for the use of unlabelled “cold” somatostatin analogues which are administered in significantly higher amounts than present in radiolabelled edotreotide for diagnostic PET imaging, the sole factor implicating the contraindication of this radiopharmaceutical would be the potential radiation exposure. No data are available regarding the use of this product during pregnancy. Radionuclide procedures carried out on pregnant women also involve radiation doses to the fœtus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and fœtus.

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionizing radiation (if there are any) should be offered to the patient.

Before administering radiopharmaceuticals to a mother who is breastfeeding, 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 the administration is considered necessary, breastfeeding should be interrupted for 8 hours and the expressed feeds discarded. Close contact with infants should be restricted during the initial 8 hours following injection. Use in lastation has been included as an important potential risk.

The proposal by the applicant to interrupt breastfeeding for 8 hours post-injection was justified and this information was reflected in section 4.6 of the SmPC and has been included in the RMP as an important potential risk.

No studies were conducted to assess the impact on fertility. Embryofoetal toxicity and impact on fertility has been included as an important potential risk.

No studies were conducted to assess the impact on embryofoetal toxicity and impact on fertility. These have been included in the RMP as important potential risks.

In patients with renal or hepatic impairment, it is proposed to use SomaKit TOC with careful consideration of the activity to be administered since an increased radiation exposure is possible in these patients (see SmPC section 4.4). The use of Somakit TOC in patients with renal and hepatic impairment is included as missing information in the RMP.

Gallium (^{68}Ga) edotreotide has no or negligible influence on the ability to drive and use machines.

In the event of administration of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by reinforced hydration and by frequent micturition. It might be helpful to estimate the effective dose that was applied.

It is contraindicated if patients have hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

Potential for hypersensitivity or anaphylactic reactions

Although no hypersensitivity or anaphylactic reactions have been reported, if hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube must be immediately available. Hypersensitivity is included as an important potential risk.

Contraindications in the SmPC: Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

Potential for hypersensitivity or anaphylactic reactions

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube must be immediately available.

Individual benefit/risk justification

For each patient, the 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.

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 examination in order to reduce radiation.

After the procedure

Close contact with infants and pregnant women should be restricted during the first 8hours after administration.

Specific warnings

Depending on the time when you administer the injection, the content of sodium may in some cases be greater than 1 mmol. This should be taken into account in patient on low sodium diet.

Due to the acidic pH of the radiolabelled gallium (^{68}Ga) edotreotide solution, accidental extravasation may cause local irritation. In case of extravasation, the injection must be stopped, the site of injection must be changed and the affected area should be irrigated with sodium chloride solution.

Precautions with respect to environmental hazard are in section 6.6 of the SmPC.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

For information on instructions for preparation of radiopharmaceuticals (radiation safety, method of preparation and quality control, see section 12 of the SmPC.

For information on incompatibilities, shelf-life, special precautions for storage and nature and contents of container and special equipment for use see section 6.2, 6.3, 6.4 and 6.5.

2.6.2. Conclusions on the clinical safety

No adverse reactions have been reported in the published literature with gallium (^{68}Ga) edotretotide. However, given that this product is administered by injection and is radioactive, there is only the potential risk of hypersensitivity and adverse reactions related to the exposure to ionising radiation to the patient and healthcare professionals. This risk is minimised by the recommendations of product handling and preparation in the SmPC (section 12). The safety of gallium (^{68}Ga) edotretotide appears to be acceptable.

2.7. Risk Management Plan

Safety concerns

Table 25: Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Hypersensitivity PET findings interpretation errors Embryofoetal toxicity and impact on fertility Occupational and inadvertent exposure
Missing information	Use in lactation Use in paediatric population Use in patients with renal impairment Use in patients with hepatic impairment

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 26: Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypersensitivity	The proposed SmPC includes information to minimize the risk of hypersensitivity. Special warning in section 4.4 Contraindications in section 4.3	None
PET findings interpretation errors	The proposed SmPC includes information to the interpretation of images Special warning in section 4.4 Information on interaction with other medicinal products and other forms of interaction in section 4.5	None
Embryofoetal toxicity and impact on fertility	The proposed SmPC includes information in section 4.6 Special warning in section 4.4	None
Occupational and	The proposed SmPC includes information/warning in section	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
inadvertent exposure	4.4 Recommendations in section 4.2 Recommendations in section 6.6	
Use in lactation	The proposed SmPC includes contraindication/warning about administration to breast feeding women in section 4.6	None
Use in paediatric population	The proposed SmPC includes warning to minimize the risk in paediatric population in section 4.4 Information on posology in section 4.2	None
Use in patients with renal impairment	The proposed SmPC includes information/warning in section 4.4 Information on posology in section 4.2	None
Use in patients with hepatic impairment	The proposed SmPC includes information/warning in section 4.4 Information on posology in section 4.2	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. 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.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, SomaKit TOC (edotreotide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

The application for a marketing authorisation of gallium (^{68}Ga) edetreotide under a “well established use” legal basis has been justified by providing data

1) on the extensive use of the medicinal product in the EU in clinical practice for at least 10 years,

2) on its use in more than 1,000 patients in published European studies and

3) by demonstrating the interest in the community by including recommendations of its use in current clinical and procedural European guidelines in the diagnosis and treatment of patients with GEP-NETs.

Benefits

Beneficial effects

In terms of technical performance, gallium (^{68}Ga)-labelled edotreotide has the technical advantage versus Octreoscan for better spatial resolution, whole-body scanning in a short time, and the added value of fusion imaging using a PET/CT hybrid scanner. The gallium (^{68}Ga) isotope has the advantage of being produced from a generator which is available in hospital departments without a cyclotron. For patients, the main advantage is through a shorter scanning time with less exposure to radiation
The diagnostic performance of gallium (^{68}Ga) edotreotide for the detection of the primary NET site in case of rising levels of a relevant biochemical tumour marker or in case of proven NET metastasis, was initially based on two prospective studies (Gabriel et al. 2007 and Frilling 2010). Gabriel's study obtained a patient-based sensitivity and specificity of 100% (4/4) and 89% (8/9) for gallium (^{68}Ga) edotreotide PET, better the values when compared to SPECT with 99mTc-HYNIC-TOC and/or ^{111}In-DOTATOC (40% and 89%, respectively). Frilling’s study used CT or MRI as comparators and detected that PET with gallium (^{68}Ga) edotreotide visualized the primary tumour region in 75% of patients compared to 25% for the comparators. In a publication from Schreiter et al. 2014, the retrospective analysis showed that in an intra-individual comparative images from a subpopulation of 20 patients, gallium (^{68}Ga) edotreotide localised the primary NET in 9/20 (45%) compared to Octreoscan in 2/20 (10%). Imaging with gallium (^{68}Ga) edotreotide PET/CT was able to identify the primary tumour in 7/15=47% patients who had negative findings according to Octreoscan performed at the first examination. In two patients with a primary tumour detected by Octreoscan, gallium, (^{68}Ga) edotreotide confirmed the result.
For staging in previously untreated GEP-NET or restaging in post-therapeutic GEP-NET in whom recurrence was suspected during the follow-up, the applicant presented a number of studies. A head-to-head comparison versus Octreoscan was performed in 3 prospective studies for initial staging or re-staging. In all studies, data showed that gallium (^{68}Ga) edotreotide is able to detect lesions better.

Concerning the impact on patient management of (^{68}Ga) edotreotide, it varied in the five studies from 14% to 59% (Schraml et al al. 2013, Frilling et al. 2010, Gabriel et al. 2007, Froeling et al. 2012 and Ruf 2010[88]). However, given the high sensitivity and specificity, it is acknowledged that this should eventually translate into better staging of the disease as well as changes in the treatment modalities. Thus, the clinical benefit from the diagnostic agent gallium (^{68}Ga) edotreotide is considered to be demonstrated.

Uncertainty in the knowledge about the beneficial effects

Although there was a considerable number of publications submitted to support the use of gallium (^{68}Ga) edotreotide in the claimed indication, the number of patients recruited in the studies was small and in many cases, they did not use the appropriate comparator (fludeoxyglucose (^{18}F), endoscopic ultrasound/multidetector CT, whole body MRI and contrast-enhanced CT instead of Octreoscan), the analyses were lesion-based instead of patient-based and in some studies the analyses were retrospectively performed. Nevertheless, the overall data, including the meta-analysis, appear to be consistent and robust considering that this is an orphan disease, with few patients diagnosed every year in the EU.

For predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET, there was a greater uncertainty with similar limitations identified in the studies provided (not the ideal comparator, the small patient population and the retrospective assessment) and the lack of robust data to support the patient population. Therefore, the CHMP was not convinced by the data presented and was not in favour of the indication of the product in this population. Therefore, a recommendation has been included in the SmPC section 4.4 that data supporting efficacy of gallium (^{68}Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited (see section 5.1 of the SmPC).

Risks

Unfavourable effects

No adverse reactions have been published or described in the studies submitted. There are no important identified risks in the RMP. Gallium (^{68}Ga) edotreotide appears to be well tolerated. The main potential risks are for hypersensitivity and exposure to ionising radiation, which are minimised through routine pharmacovigilance.

Uncertainty in the knowledge about the unfavourable effects

There is missing information on the use of gallium (^{68}Ga) edotreotide in renal and hepatic impaired patients. There is also a lack of data in breastfeeding, fertility and in paediatric patients. These are being monitored through routine pharmacovigilance.

[88] Ruf, J., F. Heuck, J. Schiefer, T. Denecke, F. Elgeti, A. Pascher, M. Pavel, L. Stelter, S. Kropf, B. Wiedenmann, and H. Amthauer. 2010. 'Impact of Multiphase ^{68}Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors', Neuroendocrinology, 91: 101-9.

Table 27: Effects Table for Somakit TOC

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Detection of the primary NET site						
Sensitivity	S=(Number of patients with primary NET sites detected by PET/Total number of patients with confirmed primary NET sites)x100	%	S=100	SPECT with 99mTc-HYNIC-TOC and/or ^{111}In-DOTATOC: S=40	Uncertainties: Small sample size (n=14). Inadequate comparator and not homogeneous for the whole sample.	Gabriel et al, 2007
Specificity	Sp=(Number of patients with no primary NET site detected by PET/Total number of patients without primary NET sites) x100	%	Sp=89	Sp=89		
Lesion-detection rate	(Number of NET lesions detected by PET/Total number of NET lesions)x100	%	75	CT or MRI: 25	Uncertainties: Small sample size (n=4). Assessment based on lesions and not in patients. Inadequate comparator.	Frilling et al, 2010
Sensitivity	S=(Number of patients with primary NET sites detected by PET/Total number of patients with confirmed primary NET sites)x100	%	45	Octreoscan: 10	Uncertainties: Small sample subpopulation size (n=20)	Schreiter et al, 2014
Staging in previously untreated GEP-NET and restaging in postherapeutic GEP-NET						
Lesion-detection rate + Image quality	(Number of NET lesions detected by PET/Total number of NET lesions)x100 Tumour/no tumour uptake	%	100 Better than in comparator	Octreoscan: 85	Uncertainties: Lesion-based and not patient-based analysis. Small sample size (n=8). Strength: Adequate comparator.	Hofmann et al, 2001
Lesion-detection	Number of NET lesions detected by PET	N. of lesions	279 In all patients, a total of 52 regions were interpreted as concordantly positive on both radiopharmaceuticals with verification	Octreoscan: 157	Uncertainties: Lesion-based and not patient-based analysis. Small sample size (n=27). Strength: Adequate comparator.	Buchmann et al, 2007

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			performed with MRI or CT. In all patients, a total of 31 regions were discordant and 18 of those discrepant were true positive with 68Ga-DOTATOC while were false negative with Octreoscan			
Lesion-detection rate	(Number of NET lesions detected by PET/Total number of NET lesions)x100	%	99.9 Atotalof439/1098(40%) lesionsin42/53(79%) patients were only detected by gallium (68Ga) DOTATOC.	Octreoscan: 60 A total of one incremental lesion in 1 patient was only detected by Octreoscan.	Uncertainties: Lesion-based and not patient-based analysis. Small sample size. (n=53) Strength: Adequate comparator.	Van Binnebeek et al, 2015
		%	100	Fludeoxyglucose (^{18}F) PET: 92	Uncertainties: Inadequate comparator. No most recruited patients were GEP-NET but NET.	Koukouraki et al, 2006a
Sensitivity Specificity	S=(Number of patients with NET lesions detected by PET/Total number of patients with NET lesions)x100 Sp=(Number of patients with no NET lesions detected by PET/Total number of patients without NET lesions)x100	% %	S=92 Sp=92 S=83 Sp=83	Endoscopic ultrasound: S=100 and multidetector CT: Sp=91 Endoscopic ultrasound: S=67 and multidetector CT: Sp=80	Uncertainties: Inadequate comparator. Retrospective assessment.	Versari et al, 2010
Lesion-detection	(Number of NET lesions detected by PET/Total		PET/CT with 68Ga-	Whole-body contrast	Uncertainties: Inadequate comparator.	Schraml et al, 2013

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
rate	number of NET lesions)x100	%	DOTATOC 92 (overall) 100 (lymph nodes) 100 (pulmonary lesions) 92 (liver) 82 (bone lesions)	enhanced MRI: 91 (overall) 73 (lymph nodes) 87 (pulmonary lesions) 99 (liver) 96(bone)	Not most of sample were GEP-NETs (max 61%). No separation of different indications. Retrospective assessment.	
Impact on patient management	Patients in whom imaging results influenced the treatment decision (% of patients)	%	59	Whole-body contrast enhanced MRI: N/A	Uncertainties: Not most of sample were GEP-NETs (max 61%). Strength: Prospective	Schraml et al, 2013
Sensitivity Specificity	S=(Number of patients with NET lesions detected by PET/Total number of patients with NET lesions)x100 Sp=(Number of patients with no NET lesions detected by PET/Total number of patients without NET lesions)x100	%	S=73.5 Sp=88.2	Whole-body PET/MRI: S=91.2 Sp=95.6	Uncertainties: Inadequate comparator. Lesion-based analysis but not patient-based. Retrospective assessment.	Scheiter et al., 2012b
		%	S=64 Sp=100	Fluorodopa (^{18}F) PET: S=64 Sp=100	Uncertainties: No most recruited patients were GEP-NET but NET Inadequate comparator	Putzer et al, 2010
		%	S=82 Sp=67	Triple-phase contrast-enhanced CT: S=84.6 Sp=50	Uncertainties: Inadequate comparator. Retrospective assessment	Ruf et al, 2011
		%	S=97 Sp=92	CT: S=58 Sp=100	Uncertainties: Lack of adequate comparator. Retrospective assessment. Reference standard not well-established	Putzer et al, 2009
Lesion-detection rate	(Number of NET lesions detected by PET/Total number of NET lesions)x100	%	100	Contrast-enhanced CT: 75	Uncertainties: Inadequate comparator. No European study.	Kumar et al., 2011

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Sensitivity Specificity	S=(Number of patients with NET lesions detected by PET/Total number of patients with NET lesions)x100 Sp=(Number of patients with no NET lesions detected by PET/Total number of patients without NET lesions)x100	%	For initial staging: S=97 Sp=100 For restaging: S=97 Sp=100	SPECT with 99mTc-HYNIC-TOC and/or ^{111}In-DOTATOC: For initial staging: S=42 Sp=14 For restaging: S=62 Sp=100	Uncertainties: Inadequate comparator and not homogeneous for the whole sample.	Gabriel et al, 2007
Impact on patient management	Patients in whom PET provided further valuable information in comparison to scintigraphy (% of patients)	%	3	SPECT with 99mTc-HYNIC-TOC and/or ^{111}In-DOTATOC: Not applicable	Uncertainties: No separation of different indications (all 3 subgroups combined).	Gabriel et al, 2007
Lesion-detection rate	(Number of NET lesions detected by PET/Total number of NET lesions)x100	%	100	CT or MRI: N/A	Uncertainties: No assessment of specificity. Retrospective assessment. Inadequate comparator.	Frilling et al, 2010
Impact on patient management	Patients in whom PET caused changed in their initial treatment decision (% of patients)	%	59.6	CT or MRI: N/A	Uncertainties: Retrospective assessment Long inclusion period Unknown inclusion criteria	Frilling et al, 2010
Lesion-detection rate	(Number of NET lesions detected by PET/Total number of NET lesions)x100	%	91.7	Contrast-enhanced CT: 56.8 Non contrast-enhanced CT: 21.7	Uncertainties: Calculation of lesion detection rate but not specificity. Retrospective assessment.	Froeling et al. 2012
Impact on patient management	Patients in whom PET findings led to a change in treatment (% of patients)	%	47.6	Contrast-enhanced CT and non-contrast-enhanced CT: N/A	Uncertainties: Inadequate comparator Sample with MEN and not only GEP-NET. Retrospective assessment.	Froeling et al. 2012

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Impact on patient management	Patients in whom PET/CT findings had an impact on further therapeutic management (% of patients)	%	38	None	Uncertainties: Calculation combining different clinical situations. Retrospective assessment.	Ruf et al. 2010
Lesion-detection rate + Interobserver reliability	(Number of NET lesions detected by PET/Total number of NET lesions)x100	% Kappa	80 0.916	Whole-body PET/MRI: 100 1	Uncertainties: Small sample (n=8) and combining 3 different clinical situations. No patient-based calculations. Inadequate comparator.	Beiderwellen et al. 2013
Predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET						
Concordance	Patients with concordant findings PET and CT	%	70	CT: Not applicable	Uncertainties: Inadequate comparator.	Gabriel et al. 2008
Uptake in pre-PRRT 68Ga-DOTATOC scan	Uptake as predictor of therapy response to PRRT		N/A	None	Uncertainties: Inadequate comparator Absence of standard of truth	Kroiss et al. 2013
			N/A	None	Uncertainties: Inadequate comparator Small sample (n=21). Retrospective assessment.	Ezziddin et al. 2012
			N/A	None	Uncertainties: Inadequate comparator Small sample (n=30). Retrospective assessment.	Kratochwil et al. 2015
			N/A	None	Uncertainties: Inadequate comparator. Small sample (n=21). Retrospective assessment.	Luboldtetal.2010a
Not indication specified						
Lesion-detection	Number of NET lesions detected by PET		A total of 35 positive lesions were detected in 10 patients on either Octreoscan SPECT/CT or Gallium (68Ga) DOTATOCPET/CT. Three patients did not exhibit any positive lesions on either imaging method. Gallium		Uncertainties: Small sample (n=10). Strength: Adequate comparator	Lee et al. 2015

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			(68Ga) DOTATOC detected 35/35 (100%) vs 19/35=54% for Octreoscan SPECT/CT. .			
Sensitivity	(Number of patients with NET lesions detected by PET/Total number of patients with NET lesions)x100	%	100	50	Uncertainties: Small sample (n=4). Strength: Adequate comparator.	Kowalski et al. 2003

Unfavourable Effects

No specific effects have been reported in published literature.

The main hypothetical risk remains hypersensitivity.

The administration of radiopharmaceutical products implies exposure to ionising radiation increase which is linked with cancer induction and a potential for development of hereditary defects, with a very low probability for this particular product.

Balance

Importance of favourable and unfavourable effects

The technical performance of gallium (^{68}Ga) edotreotide has been demonstrated in GEP-NET lesions where no tumour/tumour uptake was better for gallium (^{68}Ga) edotrotide than Octreoscan in all lesions previously seen by CT/MRI (Hofmann et al. 2011). The gallium (^{68}Ga) edotreotide has several advantages over Octreoscan for the patient in terms of scanning timing, irradiation time, and also for physicians where it is produced from a generator and hence more readily available in hospital departments without a cyclotron. For diagnostic performance, a substantial number of publications have been provided and the results are positive in terms of sensitivity, specificity and lesion detection rate of gallium (^{68}Ga) edotreotide PET. Overall, the data is positive and consistent where gallium (^{68}Ga) edotreotide appears to detect more primary and/or metastatic GEP-NET lesions than Octreoscan. Data available on the impact of gallium (^{68}Ga) edotreotide on patient management are limited. The safety data of (^{68}Ga) edotreotide shows that it is well tolerated and acceptable with no major issues so far identified.

Benefit-risk balance

Discussion on the benefit-risk assessment

GEP-NET are relatively rare neoplasms with an increase incidence and consist of an heterogenous group of tumours. Many different imaging techniques are used to localize GEP-NETs and their metastases. Anatomic techniques (ultrasound, CT and MRI) are the primary imaging modalities used in the initial phase of the diagnostic workup. Besides localization, staging and restaging of primary and metastatic tumors, imaging with some radiopharmaceuticals allows for the functional characterization of lesions and the therapy selection with cold or radiolabelled somatostatin analogues.

According to the Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev 1) the simple visualisation of an anatomic structure, which does not confer benefits to the patient, is considered insufficient. In order to establish an indication for a diagnostic agent, it is necessary to demonstrate its benefit by assessing its technical performance (including procedural convenience), diagnostic performance, impact on diagnostic thinking, on patient management, and on clinical outcome, as well as its safety.

Sensitivity and specificity of PET with gallium (^{68}Ga)-labelled somatostatin analogs for the diagnostic work-up of GEP-NET are important to be established, and also in comparison with sensitivity and specificity of scintigraphy using Octreoscan. The impact on diagnostic thinking and on patient management of gallium (^{68}Ga)-labelled somatostatin analogs is also of paramount importance as they refer to the impact of this radiopharmaceutical on clinical decisions.

Gallium (^{68}Ga) edotreotide was shown to be regularly used in the diagnostic work-up of patients with NET tumours, including GEP-NETs, for at least 10 years as a medicinal product in the European Union. The degree of scientific interest in the use of gallium (^{68}Ga) edotreotide is reflected in the published scientific literature as well as its inclusion in the European consensus clinical and procedural guidelines for the diagnostic management of GEP-NET patients.

The technical and diagnostic performance of gallium (^{68}Ga) edotrotide has been demonstrated where the diagnostic agent has proven to be convenient for both patients and healthcare professionals with its high sensitivity, specificity and lesion detection rate. The applicant has not provided with data of impact on diagnostic thinking (higher probability of correct diagnosis after the test than before the test, or change in diagnosis) for gallium (^{68}Ga) DOTATOC. Data available on the impact of gallium (^{68}Ga) edotreotide on patient management of GEP-NET are limited. There are some limitations on the use of gallium (^{68}Ga) edotreotide. An increase in somatostatin receptor density can exist in different pathological conditions (e.g. Cushing syndrome) and that, somatostatin receptors are present at baseline in different organs and cells of the body. Hence, the interpretation method of gallium (^{68}Ga) edotreotide images should be visual while semiquantitative measurement is not recommended. In addition, data supporting efficacy of gallium (^{68}Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited. Nevertheless, as GEP-NETs are neoplasms with increasing incidence, there is a need for new diagnostic tools such as gallium (^{68}Ga) edotreotide with improved technical and diagnostic performance as compared to what is currently available to patients and physicians.

Gallium (^{68}Ga) DOTATOC seems to be well tolerated with no adverse reactions reported in the publications submitted. There is a potential risk of hypersensitivity and adverse reactions due to exposure to ionising

radiation but with a very low probability. This would be in line with the safety profile of the comparator Octreoscan.

3.1. Conclusions

The overall B/R of Somakit TOC is positive in the indication for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NETs) for localizing primary tumours and their metastases.

4. Recommendations

Outcome

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

This medicinal product is for diagnostic use only.

After radiolabelling with gallium (^{68}Ga) chloride solution, the solution of gallium (^{68}Ga) edotreotide obtained is indicated for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases.

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

Other conditions or restrictions regarding supply and use

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

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.