PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

NETVISION™

gallium (^{68}Ga) oxodotreotide injection

Sterile Solution for intravenous injection

≤ 122 MBq/mL at End of Synthesis

Diagnostic Radiopharmaceutical

University Health Network (UHN)
UHN Radiotheranostics Core (UHNRC)
Toronto General Hospital
200 Elizabeth St., Suite B-PMB-174A
Canada
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Date of Initial Authorization:
February 24, 2022

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May 1, 2023

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NETVISION™ (gallium (^{68}Ga) oxodotreotide injection) is indicated for use with positron emission tomography (PET), as an adjunct to other diagnostic tests, for the detection and localization of somatostatin receptor-positive neuroendocrine tumours (NETs).

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of NETVISION™ in pediatric patients has not been established; therefore, Health Canada has not authorized a specific indication for pediatric use (see 7.1 SPECIAL POPULATIONS).

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies of gallium (^{68}Ga) oxodotreotide in the literature do not provide sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

2 CONTRAINDICATIONS

Gallium (^{68}Ga) oxodotreotide is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING;
- Patients who are taking disulfiram (Antabuse).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Before administration, visually inspect NETVISION™ behind a lead glass shield. NETVISION™ should be a clear, colourless solution without visible particles. Discard if the solution is cloudy or discoloured. Refer to 12 SPECIAL HANDLNG AND INSTRUCTIONS. Using a single-dose syringe fitted with a sterile needle and protective shielding, aseptically withdraw NETVISION™ from the vial.
- Advise the patient to frequently drink water and void their bladder after NETVISION™ injection to decrease the radiation exposure, especially to the bladder and kidney.
- Furosemide (20 mg) can be administered intravenously immediately pre- or post-injection of NETVISION™ to increase renal washout.
- NETVISION™ should be administered 45 to 90 minutes prior to imaging.
- Health Canada has not authorized an indication for pediatric use.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose for PET imaging in adult patients is 100 - 200 MBq (2.7 - 5.4 mCi). The dose should be adjusted within this range taking PET camera parameters into consideration. A minimum dose of 100 MBq is required to yield acceptable image quality.

4.3 Reconstitution

NETVISION™ is intended for direct intravenous administration. It does not require reconstitution or dilution prior to use.

4.4 Administration

NETVISION™ must be administered by intravenous bolus injection.

The patient dose should be measured by a suitable radioactivity calibration system prior to administration. Ensure that the injected radioactivity is within ± 10% of the target dose.

NETVISION™ is provided ready-to-use, and a Certificate of Analysis (CoA) documenting all release testing results must be received before administering the product.

4.5 Missed Dose

Not applicable.

4.6 Image Acquisition and Interpretation

Whole-body positron emission tomography (PET) imaging from skull to mid-thigh should be acquired 45 to 90 minutes (60 minutes recommended) after the intravenous administration of NETVISION™. Adapt imaging acquisition parameters and duration according to the equipment used and the patient and tumour characteristics in order to obtain the best possible image quality.

Based upon the intensity of the signals, PET images obtained using NETVISION™ indicate the presence and density of somatostatin receptors in tissues. Tumours that do not bear somatostatin receptors will not be visualized.

4.7 Instructions for Preparation and Use

NETVISION™ is provided ready-to-use. Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product. Transfer of product from the product vial to the shielded syringe must be performed aseptically.

4.8 Radiation Dosimetry

The effective dose of gallium (^{68}Ga) oxodotreotide has been calculated to be 0.020 - 0.026 mSv/MBq; using the highest value of 0.026 mSv/MBq (Walker 2013) and the recommended 100 - 200 MBq dose, this yields a total dose of 2.6 - 5.2 mSv. Table 1 presents estimated absorbed organ doses obtained from studies in the literature. Based on the most recent calculations using the data from Josefsson 2018 (who used the updated ICRP 110 voxelized reference phantoms with ICRP 103 tissue-weighting factors), the organs receiving the highest absorbed doses are as follows in decreasing order (assuming 100 - 200 MBq): the spleen (25 - 50 mGy), pituitary gland (15 - 30 mGy), kidneys (14 - 28 mGy), adrenals (11 - 22 mGy), liver (8.4 - 16.8 mGy), gallbladder wall (4.3 - 8.6 mGy) and urinary bladder wall (4 - 8 mGy).

Dose calculations by Machado 2016, based on the weight-independent effective dose model for use in pediatric nuclear medicine, reported estimated effective doses for ^{68}Ga-labelled peptides as follows (compared to 0.023 mSv/MBq for an adult): newborn (0.35 mSv/MBq), 1 year old (0.13 mSv/MBq), 5 year old (0.064 mSv/MBq), 10 year old (0.040 mSv/MBq), 15 year old (0.025 mSv/MBq). This demonstrates the scaling of doses that occurs with smaller body size in the pediatric population.

Table 1: Estimated Final Dose Absorbed per Unit Activity and Targeted Organ

Target organ	Walker 2013	Sandström 2013	Josefsson 2018
	Organ specific dose (mSv/MBq)	Absorbed dose (mGy/MBq)	Absorbed dose (mGy/MBq)
Adrenals	0.015	0.086	0.11
Brain	0.001	--	< 0.01
Breasts	0.001	--	< 0.02
Gallbladder wall	0.015	0.016	0.043
Lower large intestine wall	0.013	--	< 0.02
Upper large intestine wall	0.013	--	
Small intestine	0.014	--	< 0.02
Stomach wall	0.014	--	< 0.03
Heart wall	0.012	--	≤ 0.03
Kidneys	0.092	0.093	0.14
Liver	0.045	0.050	0.084
Lungs	0.012	0.006	~0.018 - 0.035

Target organ	Walker 2013	Sandström 2013	Josefsson 2018
	Organ specific dose (mSv/MBq)	**Absorbed dose (mGy/MBq)**	**Absorbed dose (mGy/MBq)**
Muscle	0.011	--	< 0.01
Ovaries	0.013	--	< 0.02
Pancreas	0.017	--	< 0.03
Pituitary gland	0.042	--	0.15
Hematopoietic cells	0.001	0.015	< 0.02
Bone-forming cells	0.016	--	< 0.01
Salivary glands	0.012	--	< 0.03
Skin	0.001	--	< 0.01
Spleen	0.282	0.109	0.25
Testes	0.011	--	< 0.02
Thymus	0.011	--	< 0.02
Thyroid	0.019	--	< 0.02
Urinary bladder wall	0.134	0.098	0.040
Uterus	0.015 (estimate)	--	< 0.02
Total body (mSv/MBq)	0.013	0.014	--
Effective dose (ED) (mSv/MBq)	**0.026**	**0.020 (♂), 0.022 (♀)**	**0.023**
ED/scan (mSv) per 100 - 200 MBq	**2.6 – 5.2**	**2.0 – 4.0 (♂), 2.2 – 4.4 (♀)**	**2.3 - 4.6**
Patient population	6♂ (newly diagnosed lung cancer or indeterminate pulmonary nodules)	6♂ & 3♀ (disseminated NETs, mainly liver)	5♂ & 11♀ (mixed NETs)
^{68}Ga-oxodotreotide dose	185 - 260 MBq	72 - 120 MBq	82 - 178 MBq
PET/CT Imaging	Whole body: 48, 90 & 120 min p.i. (5/6 pts)	Abdominal: 0 - 45 min dynamic Whole body: 60, 120 & 180 min p.i.	Whole-body 2 - 240 min p.i.
Absorbed dose calculations	OLINDA/EXM	OLINDA/EXM	ICRP 110
Reference Phantom	♂ and ♀ (not specified)	♂ and ♀ (MIRDOSE)	ICRP 110

5 OVERDOSAGE

It should be noted the estimated effective dose of gallium (^{68}Ga) oxodotreotide is well within the range of other commonly used positron-emitting radiopharmaceuticals. Consequently, in the event of a potential overdose, the inherent risk from additional radiation exposure (within the limits of the maximum activity that can be provided) is low.

In the event of a radiation overdose, the absorbed dose should be reduced by increasing the elimination of the radionuclide from the body using fluids and frequent bladder voiding.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution for injection ≤ 122 MBq/mL (radioactive strength at end of synthesis) ≤ 50 µg ^{68}Ga-oxodotreotide peptide (chemical dose)	Phosphate-buffered saline, ethanol

NETVISION™ is a clear colourless aqueous solution supplied in a sterile endotoxin-free Type I USP glass vial sealed with a latex-free halobutyl rubber stopper. The formulation contains phosphate-buffered saline, ≤ 10% ethanol (v/v) and, at the stated reference time, the radioactive amount of gallium (^{68}Ga) oxodotreotide ± 10% (≤ 50 µg peptide) specified on the label. The pH of NETVISION™ is 4.0 - 6.5.

6.1 Physical Characteristics

The drug substance gallium (^{68}Ga) oxodotreotide contains the radioisotope gallium-68 (^{68}Ga) which decays by positron (β+) emission (89%) and electron capture (11%), with a half-life of 68 minutes, to the stable isotope zinc-68 (^{68}Zn); maximum and mean β+ energies are 1899 keV and 836 keV, respectively, while gamma emissions are negligible: 1077 keV (3.2%) and others (< 0.31%).

Table 3 - Physical Decay Chart for ^{68}Gallium

Time (min)	Time (hours)	Fraction Remaining
0	0	1.000
15	0.25	0.858
30	0.5	0.736
60	1	0.542
90	1.5	0.398
120	2	0.293
180	3	0.159
360	6	0.025

6.2 External Radiation

Table 4 - Radiation Attenuation of 511 keV Photons by Lead Shielding

Pb shield thickness (mm)	Coefficient of attenuation
5.12 (HVL - half-value layer)	0.50
17 (TVL - tenth value layer)	0.10
34	0.01

The specific gamma ray constant at 1 metre is 1.8 x 10^{-4} mSv/hr per MBq.

7 WARNINGS AND PRECAUTIONS

NETVISION™ should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

NETVISION™ may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

General

Standard radiopharmaceutical practices should be used to minimize radioactive contamination post-administration. NETVISION™ contains the radioactive isotope gallium-68 (^{68}Ga); therefore, it contributes to a patient's overall long-term cumulative radiation exposure which is associated with an increased risk of cancer. Assuming the maximum adult dose of 200 MBq, the radiation dose would be 5.2 mSv which is equivalent to ~1.7 years of exposure to natural background radiation in Canada.

To reduce radiation exposure, ensure patients are well hydrated prior to administration of NETVISION™ and advise patients to drink and void frequently during the first hours following administration. A diuretic might also be considered.

Contamination

Standard radiopharmaceutical practices should be used to minimize radioactive contamination. Following administration, a toilet should be used instead of a urinal and the toilet should be flushed several times after use.

Special precautions such as bladder catheterisation should be taken following administration to incontinent patients to minimise the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Immune

Prior to administration, the patient should be questioned for a history of allergic reactions to oxodotreotide, other somatostatin analogues and the non-medicinal ingredients in the product.

Monitoring and Laboratory Tests

The uptake of gallium (^{68}Ga) oxodotreotide reflects the level of somatostatin receptor density in NETs. However, uptake can also be seen in some other tumour types, in other pathologic conditions (e.g. thyroid disease or subacute inflammation) or as a normal physiological uptake (e.g., uncinated process of the pancreas and the organs described in 4.8 Radiation Dosimetry). Increased uptake should be interpreted cautiously and by appropriately trained individuals, and may need to be confirmed by histopathology, other imaging modalities, or other assessments.

7.1 Special Populations

7.1.1 Pregnant Women

Ideally, examinations using radiopharmaceuticals, especially those elective in nature of women of childbearing capability, should be performed during the first ten days following the onset of menses, or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

There are no studies with gallium (^{68}Ga) oxodotreotide in pregnant women. As with all radiopharmaceuticals, gallium (^{68}Ga) oxodotreotide has the potential to cause fetal harm. Animal reproduction studies have not been conducted with NETVISION™.

7.1.2 Breast-feeding

Information from the literature indicates gallium (^{68}Ga) oxodotreotide is excreted in human milk. Where an assessment of the risk to benefit ratio suggests the use of this product in nursing mothers, formula feeding should be substituted for breast feeding for 12 hours after NETVISION™ administration. Breast milk expressed during this period should be pumped and discarded before resuming breastfeeding.

7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of NETVISION™ in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. The use in children and adolescents must be considered carefully, based on clinical needs and by assessing the risk/benefit ratio in this patient group. The effective dose resulting from administration of gallium (^{68}Ga) oxodotreotide may be higher in children than in adults (see 4.8 Radiation Dosimetry).

7.1.4 Geriatrics

Clinical studies of gallium (^{68}Ga) oxodotreotide in the literature do not provide sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of gallium (^{68}Ga) oxodotreotide was evaluated in a survey of the scientific literature. No serious adverse reactions were identified in these studies.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

A meta-analysis of the available published literature (Deppen 2016b), which included 17 studies and a total of 971 participants, found no serious adverse events after the use of gallium (^{68}Ga) oxodotreotide. These studies administered representative radioactive and chemical amounts of gallium (^{68}Ga) oxodotreotide. Of those studies, the following isolated non-serious adverse events, considered possibly related to gallium (^{68}Ga) oxodotreotide, were reported:

- One (1) case of post-scan tachycardia resolving without treatment;
- Two (2) cases of abdominal pain in patients with a history of gastritis;
- One (1) case of unilateral whole-body edema ipsilateral to the injected upper extremity, occurring within 24 h of injection and resolving spontaneously in less than 48h;
- One (1) case of itching at the injection site (spontaneously resolved).

The meta-analysis also found no changes in glucose levels among insulinoma patients.

In addition, the following non-serious events considered possibly or probably related to gallium (^{68}Ga) oxodotreotide were reported by sponsors of clinical trials using UHN-manufactured product:

- Vomiting (uncommon);
- Nausea (uncommon);
- Allergic reaction (temporary generalized itching that resolved spontaneously) (uncommon);
- Metallic taste in mouth (uncommon);
- Injection site reactions (e.g. pain, itching, redness, burning, stinging, tingling) (common).

In addition, hypersensitivity reactions may occur such as rash and pruritus, and less frequent reactions include angioedema or cases with features of anaphylaxis.

An independent literature review of safety information was conducted by the sponsor to support the market authorization for NETVision™, and identified no other adverse reactions in the literature.

8.5 Post-market Adverse Reactions

No post-market adverse reactions involving NETVISION™ have been reported to date.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interactions have not been investigated. However, given that NETVISION™ is administered intravenously as a single sub-pharmacological dose and that ^{68}Ga decays rapidly, no interactions are expected.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been investigated. However, given that NETVISION™ is administered as a sub-pharmacological single dose, ^{68}Ga decays rapidly, and the drug product is cleared quickly from the body, no drug substance-related interactions are expected.

The gallium (^{68}Ga) oxodotreotide formulation contains ≤10% ethanol, which would yield a maximum blood alcohol concentration (BAC) of ~8.9 mg/dL assuming the maximum administered volume of 4.5 mL and human blood volume of 4 L. For individuals >55 kg this is well below the BAC that would occur following the consumption of one alcoholic drink. Although some patients may feel slight effects from this low amount of ethanol, by 1 hour post-administration (well before discharge from the clinic following PET imaging) the BAC would be 0 mg/dL.

This BAC is also well below the level which would cause ethanol sensitization to most drugs (e.g., metronidazole, pentobarbital). However, patients taking disulfiram (Antabuse) should not receive gallium (^{68}Ga) oxodotreotide due to potentially serious side-effects at a BAC as low as 5 mg/dL.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted. The drugs listed in the table below are based on potential (theoretical) interactions and guidance from the literature.

Table 5 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Clinical comment
Corticosteroids	T	Some evidence indicates that corticosteroids can induce down-regulation of $SSTR_2$ receptors (Hofland 2010). It is theorized that repeated administration of high-dose glucocorticosteroids prior to ^{68}Ga-oxodotreotide administration may cause insufficient $SSTR_2$ receptor expression for adequate visualization of somatostatin receptor-positive NETs.

Proper/Common name	Source of Evidence	Clinical comment
Long-acting (e.g. lanreotide) and short-acting (e.g. octreotide) somatostatin analogs (SSAs)	T, CT	Non-radioactive SSAs are commonly used for symptomatic treatment of NET patients and bond to the same receptor ($SSTR_2$) as gallium (^{68}Ga) oxodotreotide. It has been theorized that these SSAs could interfere with gallium (^{68}Ga) oxodotreotide uptake in tumour and impede tumour visualization. Studies in the literature show that use of both short- and long-acting SSAs prior to gallium (^{68}Ga) oxodotreotide PET/CT does not decrease tumour uptake. In contrast, tumour uptake was increased whereas the uptake in normal organs was decreased. This led to increased tumour-to-liver ratios, although not deemed clinically relevant. There is no current clinical consensus on suspension of SSA treatment before ^{68}Ga-oxodotreotide imaging, with various guidelines indicating the following: • No suspension of SSA treatment is required • When possible, long-term SSA should be suspended 3 - 4 weeks pre-administration (or perform ^{68}Ga-oxodotreotide imaging immediately before start of next cycle) • When possible, short-term SSAs should be suspended 24 - 48 hours before ^{68}Ga-oxodotreotide imaging. In conclusion, the decision whether or not to suspend SSA therapy should be made by the treating physician considering the goals of the PET imaging and the patient's clinical situation.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Drug-food interactions have not been investigated. However, given that NETVISION™ is administered intravenously no interactions are expected. Most trials in the literature did not require fasting prior to administration and imaging.

9.6 Drug-Herb Interactions

Drug-herb interactions have not been investigated. However, given that NETVISION™ is administered as a single dose and that ^{68}Ga decays rapidly, no interactions are expected.

9.7 Drug-Laboratory Test Interactions

Drug-laboratory test interactions have not been investigated. However, given that NETVISION™ is administered as a single dose and that ^{68}Ga decays rapidly, no interactions are expected.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Gallium (^{68}Ga) oxodotreotide binds with nanomolar affinity to somatostatin receptors, with highest affinity for subtype 2 receptors ($SSTR_2$), which are characteristically overexpressed by NET cells. Gallium-68 is a β+ emitting radionuclide with an emission yield that allows positron emission tomography (PET) imaging.

10.2 Pharmacodynamics

No pharmacodynamic studies in humans were identified. This product is administered at microdose levels and is not intended to elicit any pharmacological effects.

10.3 Pharmacokinetics

Absorption

Gallium (^{68}Ga) oxodotreotide is administered intravenously, thus it is immediately and completely bioavailable.

Distribution

Gallium (^{68}Ga) oxodotreotide uptake occurs in $SSTR_2$-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. There is no significant uptake in the cerebral cortex or in the heart, and usually thymus and lung uptakes are low.

Uptake in all organs plateaued by ~50 min post-injection (p.i.) and remains relatively stable through 200 min p.i. while tumour uptake rises continually over this period. Blood clearance is rapid, with maximum activity observed within 5 minutes p.i. and decreasing to 5.3% and 2.2% of this peak level by 45 min and 195 min, respectively.

Elimination

Gallium (^{68}Ga) oxodotreotide is cleared via the kidneys, and by 4 h p.i. the total excreted in the urine is ~12%.

Special Populations and Conditions

No studies evaluating the pharmacokinetics of gallium (^{68}Ga) oxodotreotide in special populations were conducted.

11 STORAGE, STABILITY AND DISPOSAL

Store the product vial upright at room temperature (15 to 30 °C) within the secondary lead pig.

Use within 5 hours post-end of synthesis, as indicated on the product label.

12 SPECIAL HANDLING INSTRUCTIONS

Radiopharmaceuticals should be used only by healthcare professionals who are appropriately qualified in the use of radiopharmaceuticals in humans. The receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent organization.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

It is recommended to use protective equipment (e.g. gloves, safety glasses, lab coat, tongs) and appropriate shielding to minimize the radiation exposure.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Gallium (^{68}Ga) oxodotreotide is a somatostatin receptor (SSTR)-targeted positron-emitting radiopharmaceutical (PER) for positron emission tomography (PET) imaging. It consists of the radioisotope gallium-68 (^{68}Ga) conjugated to the octapeptide somatostatin analog (SSA) octreotate via the universal chelator DOTA.

Proper name:

- Gallium (^{68}Ga) oxodotreotide (INN)
- Also referred to as ^{68}Ga-DOTATATE, ^{68}Ga-gallium DOTA-octreotate, ^{68}Ga-DOTA-(Tyr^3)-octreotate.

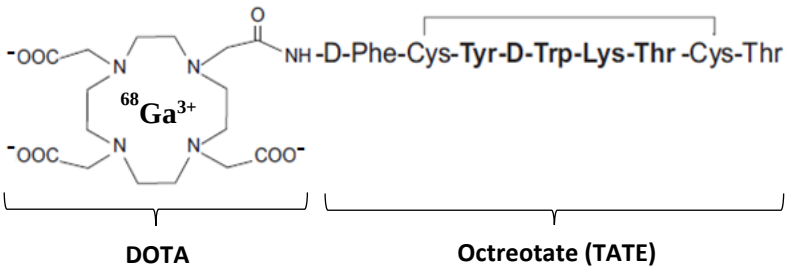
Chemical name:

- ^{68}Ga-tetraazacyclododecane tetra-acetic acid-octreotate
- (68Ga)gallium(3+) 2-[4-({[(1R)-1-{[(4R,7S,10S,13R,16S,19R)-10-(4-aminobutyl)-4-{[(1S,2R)-1-carboxy-2-hydroxypropyl]carbamoyl}-7-[(1R)-1-hydroxyethyl]-16-[(4-hydroxyphenyl)methyl]-13-[(1H-indol-3-yl)methyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-19-yl]carbamoyl}-2-phenylethyl]carbamoyl}methyl)-7,10-bis(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetate

Molecular formula: $C_{65}H_{87}N_{14}O_{19}S_2{}^{68}Ga$

Molecular mass: 1500.5 g/mol

Structural formula:



Physicochemical properties:

^{68}Ga decays with a half-life of 68 minutes to stable zinc (^{68}Zn) through positron emission followed by photonic annihilation radiations, through orbital electron capture (X-ray or Auger emissions), and through gamma transitions.

Product Characteristics:

NETVISION™ is a clear colourless aqueous solution supplied in a sterile endotoxin-free vial. The formulation contains phosphate-buffered saline, ≤ 10% ethanol (v/v) and, at the stated time of calibration, the radioactive amount of gallium (^{68}Ga) oxodotreotide ± 10% (≤ 50 mcg peptide/dose) specified on the label. The pH of NETVISION™ is 4.0 - 6.5.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The safety and efficacy of NETVISION™ is based on a systematic review of the scientific literature on the use of gallium (^{68}Ga) oxodotreotide (^{68}Ga-oxodotreotide) as a radiodiagnostic agent in patients with neuroendocrine tumours. No serious adverse reactions were identified in these literature reports. The key factor linking the selected studies are that well-differentiated NETs (Grade 1 or 2 as confirmed by mitotic counts and/or the Ki67 index) characteristically overexpress somatostatin subtype 2 receptor ($SSTR_2$) irrespective of NET subtype and location, primary tumour or metastases, clinical status (staging versus restaging), age of population (pediatric, adult or geriatric), or particular mutant carriers.

The efficacy of gallium (^{68}Ga) oxodotreotide was supported in 15 clinical studies identified through systematic literature review, which enrolled patients with well-differentiated (Grade 1 or Grade 2) or suspected NETs and described diagnostic performance data (sensitivity, specificity) based on the use of histological confirmation, clinical follow up, other imaging modalities (e.g. ^{111}In-DTPA-octreotide (^{111}In-DTPA-OC), CT or MRI) or a combination thereof. All studies were non-randomized. For all studies, ^{68}Ga-oxodotreotide was administered intravenously and the mean start of imaging was reported as 40 to 65 min post-injection (p.i). In the majority of studies, the administered dose was 100 - 200 MBq. Study results are described below according to NET subtype. See 14.2 Study Results for pooled sensitivity and specificity calculations.

Gastroenteropancreatic (GEP)-NETs

Three studies (Haug 2014, Ilhan 2015, Yu 2019) retrospectively evaluated ^{68}Ga-oxodotreotide performance in 166 patients (median cohort size: 45 patients; range cohort size: 44 – 77 patients) with GEP-NETs (approximately 44% females, 56% males)[1]. The mean patient age was 56 years[1] (range: 18 – 84 years of age). Histology and/or clinical follow up were used as reference standards. Patients from Haug 2014 and Ilhan 2015 were administered a median dose of 200 MBq ^{68}Ga-oxodotreotide (range of 100 – 200 MBq for all three studies). PET/CT imaging was performed 60 minutes p.i. Scans were evaluated by two readers who interpreted by consensus and were unblinded (Haug 2014), blinded except for clinical information (Ilhan 2015), or for whom no reference to blinding was provided (Yu 2019). In these studies, the median sensitivity was 92% (range: 68 – 100%; three studies) and median specificity was 89% (range: 89 – 100%; two studies).

Pheochromocytoma and Paraganglioma (PPGL)

Four prospective studies (Archier 2016, Janssen 2015, Janssen 2016a, Janssen 2016b) and one retrospective study (Kong 2019) evaluated ^{68}Ga-oxodotreotide performance in 108 patients (median cohort size: 20 patients; range cohort size: 17 – 30 patients) with PPGL (51% females, 49% males). The mean patient age was 46 years[1] (range: 16 – 84 years of age). Histology, clinical follow up, conventional imaging or a combination of imaging modalities were used as reference standards. For Janssen 2015, Janssen 2016a, Janssen 2016b and Kong 2019,

[1]Estimated based on available numbers provided within corresponding studies.

patients were administered a median dose of 192 MBq ^{68}Ga-oxodotreotide (range: 176 – 202 MBq) and PET/CT imaging was performed a median 60 minutes p.i. (range: 59 – 60 min). Patients in Archier 2016 were administered a median dose of 2.3 MBq/kg (1.4 – 2.9 MBq/kg) and PET/CT imaging was performed a median 45 minutes p.i. (range: 40 – 80 min). For the prospective studies, scans were evaluated by two readers who were fully blinded (Archier 2016), or by two readers in consensus blinded to all imaging and clinical data except for diagnosis, sex and age of the patient (Janssen 2015, 2016a, 2016b). Kong 2019 made no reference to image assessment details, number of readers or blinding. In these five studies, the median sensitivity was 100% (range: 93 – 100%) and the specificity in one study (Kong 2019) was 100%.

Mixed/Unknown NETs

Five retrospective studies (Srirajaskanthan 2010, Haug 2012, Haug 2014, Kazmierczak 2016, Lawal 2017) and two prospective studies (Deppen 2016, Fallahi 2019) evaluated ^{68}Ga-oxodotreotide performance in 517 patients (median cohort size: 51 patients; range cohort size: 18 – 203 patients) with Mixed/Unknown NETs (approximately 50% females, 50% males)[2]. The mean patient age was 56 years (range: 1 – 87 years of age). Histology, clinical follow up, conventional imaging or a combination of imaging modalities were used as reference standards. Patients from Haug 2012, Haug 2014, Kazmierczak 2016, Deppen 2016 and Fallahi 2019 were administered a median dose of 200 MBq ^{68}Ga-oxodotreotide (120 – 302 MBq for all seven studies). PET/CT imaging was performed a median 61 minutes p.i. (range: 55 – 93 min). Scans were evaluated by two readers who were blinded (Srirajaskanthan 2010, Kazmierczak 2016, Fallahi 2019), unblinded (Haug 2014, Deppen 2016), or for whom no reference to blinding was provided (Haug 2012, Lawal 2017). For studies where consensus was used to evaluate scans, consensus was reached with either two readers (Haug 2014, Kazmierczak 2016), or a third reader was used to resolve discordant results (Srirajaskanthan 2010, Fallahi 2019). In these studies, the median sensitivity was 94% (range: 81 – 96%; seven studies) and median specificity was 92% (range: 50 – 100%; six studies).

Medullary Thyroid Carcinoma (MTC)

Yamaga 2017 prospectively examined ^{68}Ga-oxodotreotide performance in 15 patients (53% females, 47% males). The mean patient age was 44 years (range: 20 – 68 years of age) with histologically confirmed medullary thyroid carcinoma (MTC) but negative conventional imaging after thyroidectomy. Patients received 185 MBq of ^{68}Ga-oxodotreotide and images were acquired 60 minutes p.i. Two teams of nuclear medicine physicians independently interpreted the ^{68}Ga-oxodotreotide PET/CT images while blinded to clinical and imaging data. Discordant results were resolved by consensus. Using histology, conventional imaging and clinical/imaging follow up as the reference standard, sensitivity was 100% (15/15 patients) while specificity was not calculated.

[2] Estimated based on available numbers provided within corresponding studies.

14.2 Study Results

Fifteen studies evaluating gallium (^{68}Ga) oxodotreotide as a radiodiagnostic agent in the management of patients with NETs were identified through a systematic review of the scientific literature described in Section 14.1 Trial Design and Study Demographics. Efficacy data pooled from these published studies and grouped by NET subtype are summarized below with respect to median sensitivity (Table 6) and median specificity (Table 7). Overall, the median sensitivity was 91.5 - 100% across four NET subtype groupings (GEP-NET, PPGL, mixed/unknown and MTC) while the median specificity was 89 - 100% across three NET subtype groupings (GEP-NET, PPGL and mixed/unknown).

Table 6 ^{68}Ga-oxodotreotide PET/CT - per patient pooled sensitivity by NET subtype

NET subtype	Studies (n)	Patients with confirmed NET (n)	Median Sensitivity (%)	Range (%)
GEP-NET	3[1]	135	91.5	68 - 100
PPGL	5[2]	102	100	93 - 100
Mixed/Unknown	7[3]	333	94	81 - 96
MTC	1[4]	13	100[5]	--

GEP = gastroenteropancreatic; Mixed/Unknown = mixed NET subtypes, suspected NET and unknown primary NET; MTC = medullary thyroid carcinoma; PPGL = pheochromocytoma/paraganglioma, including SDHx mutants

[1]Haug 2014, Ilhan 2015, Yu 2019

[2]Archier 2015, Janssen 2015, Janssen 2016a, Janssen 2016b, Kong 2019

[3]Haug 2012, Haug 2014, Deppen 2016a, Fallahi 2019, Kazmierczak 2016, Lawal 2017, Srirajaskanthan 2010

[4]Yamaga 2017

[5]As this value is based on a single study, median does not apply

Table 7 ^{68}Ga-oxodotreotide PET/CT - per patient pooled specificity by NET subtype

NET subtype	Studies (n)	Total number of patients (n)	Median Specificity (%)	Range (%)
GEP-NET	2[1]	89	89	89 - 100
PPGL	1[2]	19	100[4]	--
Mixed/Unknown	6[3]	499	92	50 - 100

GEP = gastroenteropancreatic; Mixed/Unknown = mixed NET subtypes, suspected NET and unknown primary NET; PPGL = pheochromocytoma/paraganglioma, including SDHX mutation-associated and sporadic PPGL

[1]Haug 2014, Ilhan 2015

[2]Kong 2019

[3]Deppen 2016a, Haug 2012, Fallahi 2019, Kazmierczak 2016, Lawal 2017, Srirajaskanthan 2010

[4]As this value is based on a single study, median does not apply

In these studies, the most commonly reported causes of false positive results were inflammation (including $SSTR_2$-expressing macrophages) and misinterpretation of faint ^{68}Ga-oxodotreotide uptake. False positive uptake has also been reported due to benign tumoral lesions (e.g., hemangioma, meningioma, fibrous dysplasia and breast fibroadenoma) and other non-neoplastic uptake (e.g., arthritis, reactive lymph nodes and accessory spleen). Uptake in the pancreas should also be interpreted cautiously due to high physiological uptake in the pancreatic head. The most commonly reported causes of false negative results were small lesion size (<5 mm) and poorly differentiated/high grade NETs which have low or no $SSTR_2$ expression.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Non-clinical toxicity studies have not been conducted with gallium (^{68}Ga) oxodotreotide. In a single-dose acute toxicity study, healthy male Wistar rats and male BALB/c mice were administered a single dose of 752 mcg/kg unlabeled oxodotreotide (n = 5/species) via i.v. penile injection. Animals showed no behavioral abnormalities (eating, sleeping, motion, posture) over the 24 h observation period and post-mortem examinations showed no macroscopic pathology or histological abnormalities. Based on these findings, a No Observed Adverse Effects Level (NOAEL) could not be determined.

The mass of oxodotreotide administered to rats is equivalent to ~200 mcg/kg in a human; assuming a 50 kg individual, this equals an administered mass of ~10 mg oxodotreotide in a human, which yields a safety margin of ≥ 200 fold considering the intended human dose is ≤ 50 mcg.

Carcinogenicity:

No long-term animal studies have been performed to evaluate the carcinogenic potential of NETVISION™. However, radiation is a carcinogen and mutagen.

Genotoxicity:

No long-term animal studies have been performed to evaluate the genotoxic potential of NETVISION™. As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

Reproductive and Developmental Toxicology:

No long-term animal studies have been performed to evaluate whether NETVISION™ affects fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NETVISION™

Gallium (^{68}Ga) oxodotreotide injection

Read this carefully before you receive **NETVISON™**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NETVISION™**.

Serious Warnings and Precautions

Because NETVISION™ is a radioactive substance, it can only be given by doctors and other health professionals who are specially trained and experienced in the safe use and handling of these substances.

What is NETVISION™ used for?

NETVISION™ (gallium (^{68}Ga) oxodotreotide injection) is indicated for use with positron emission tomography (PET), as an adjunct to other diagnostic tests, for the detection and localization of somatostatin receptor-positive neuroendocrine tumours (NETs).

How does NETVISION™ work?

NETVISION™ contains oxodotreotide, a molecule that attaches to the somatostatin receptors present on the surface of some tumour types such as NETs. The oxodotreotide molecule is attached to a radioactive ingredient called Gallium-68 (^{68}Ga). The radioactivity of the gallium allows the doctors to see the tumours via an imaging procedure called positron emission tomography (PET).

The use of NETVISION™ involves exposure to small amounts of radioactivity. Before you receive NETVISION™, your doctor will determine whether the benefits outweigh the potential risks due to radiation exposure.

What are the ingredients in NETVISION™?

Medicinal ingredient: gallium (^{68}Ga) oxodotreotide

Non-medicinal ingredients: ethanol, phosphate-buffered saline.

NETVISION™ comes in the following dosage forms:

Solution for intravenous injection.

Do not use NETVISION™ if:

- You are allergic to gallium (^{68}Ga) oxodotreotide or any of the other ingredients of this medicine;
- You are taking disulfiram (Antabuse).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NETVISION™. Talk about any health conditions or problems you may have, including:

- If you have previously experienced any allergic reaction after receiving gallium (^{68}Ga) oxodotreotide or other somatostatin analogs (e.g. lanreotide);
- If you are taking the drug disulfiram (Antabuse);
- If you have or have had a thyroid disease or subacute inflammation;
- If you have signs of dehydration (feeling very thirsty or no need to urinate) before, during or shortly after the administration;
- If you are pregnant or think you may be pregnant;
- If you are breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NETVISION™:

- Somatostatin analogues;
- Corticosteroids.

How to take NETVISION™:

- NETVISION™ will be given to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.
- You will receive only one injection intravenously (directly into your vein).
- After the injection, you will be asked to drink a lot of fluids and to urinate as often as possible. This helps remove the medicine and the radioactivity from your body.
- Avoid close contact with young children and pregnant women for 8 hours after the injection.
- If you are breastfeeding and your doctor decides it is appropriate for you to receive NETVISION™, you must not breastfeed for 12 hours after receiving this product and be sure to pump and discard any breast milk during that period.

Usual dose:

Your healthcare professional will calculate the dose of NETVISION™ depending on your clinical situation, the type of PET camera being used, and other factors. The dose will be between 100 - 200 MBq (MBq = megabecquerel, which is the unit used to express radioactivity).

Overdose:

An overdose is unlikely because NETVISION™ will be administered by a trained healthcare professional and the exact amount of product will be measured immediately before it is injected. In the unlikely event of an overdose, your doctor will let you know. Drinking water and emptying your bladder frequently will help remove the medicine from your body more quickly.

What are possible side effects from using NETVISION™?

These are not all the possible side effects you may have when taking NETVISION™. If you have any side effects not listed here, tell your healthcare professional. There have been no serious side effects reported to date from patients receiving NETVISION™. Possible non-serious side effects that you may have when taking NETVISION™ are summarized below, which are all either common (less than 1/10 patients) or uncommon (less than 1/100 patients).

- Injection site reaction: itching, swelling, redness, pain, burning, stinging, tingling warm feeling at the injection site (common)
- Tachycardia: Shortness of breath, light headedness, a racing, uncomfortable or irregular heartbeat, chest pain, fainting (uncommon)
- Abdominal pain (uncommon)
- Swelling (uncommon)
- Nausea or vomiting (uncommon)
- Allergic reactions, for example itching (uncommon)
- Metallic taste in mouth (uncommon)

Other allergic reactions such as rash, itching, hives, swelling, or anaphylaxis (a severe allergic reaction) may occur.

Drinking a lot of water and emptying your bladder frequently will speed up the removal of NETVISION™ from your body.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

You will not have to store this medicine. It will be stored by the hospital or clinic.

If you want more information about NETVISION™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html or the manufacturer's website www.uhnrc.ca.

This leaflet was prepared by University Health Network.

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