PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

NeuraCeq™

Florbetaben (^{18}F)

3 µg/mL Solution for Intravenous Administration

Diagnostic Radiopharmaceutical

IsoLogic Innovative Radiopharmaceuticals Ltd.
1855 32nd Avenue, Lachine, Quebec H8T 3J1

Date Approval:
February 22, 2017

Submission Control No: 193105

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

NeuraCeq (florbetaben [^{18}F]) is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.

A negative NeuraCeq scan indicates sparse to no amyloid neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive NeuraCeq scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.

NeuraCeq is an adjunct to other diagnostic evaluations.

Limitations of Use:

- A positive NeuraCeq scan does not establish the diagnosis of AD or any other cognitive disorder.
- Safety and effectiveness of NeuraCeq have not been established for:
    - Predicting development of dementia or other neurologic conditions;
    - Monitoring responses to therapies.

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Of the 872 subjects in clinical studies of NeuraCeq, 603 (69%) were 65 years or over, while 304 (35%) were 75 years or over. No overall differences in safety were observed between these subjects and younger subjects

2 CONTRAINDICATIONS

NeuraCeq 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 *Dosage Forms, Strengths, Composition and Packaging*.

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

NeuraCeq is not authorized for pediatric use.

4.2 Dosage

The recommended dose of NeuraCeq is 300 ± 60 MBq, corresponding at most to a 30 µg mass dose of florbetaben.

4.3 Administration

- Do not use NeuraCeq after the expiration date stated on the label.
- Inspect the solution prior to administration and do not use if cloudy, discolored, or found to contain particulate matter.
- Use aseptic technique and radiation shielding to withdraw and administer NeuraCeq solution
- Measure the activity of NeuraCeq with a dose calibrator immediately prior to injection
- Do not dilute NeuraCeq.
- Ensure injection is intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artifacts. Verify patency of the indwelling catheter by a saline test injection prior to administration of NeuraCeq.
- Slowly (6 sec/mL) inject into a large vein in the arm followed by a saline flush of approximately 10 mL.
- Dispose of unused product in a safe manner in compliance with applicable regulations

4.4 Image Acquisition and Interpretation

Image Acquisition

Acquire PET images over 15 to 20 minutes starting 45 to 130 minutes after NeuraCeq injection. Keep the patient supine with the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reduce head movement with tape or other flexible head restraints if necessary. Reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm.

Image Interpretation

NeuraCeq images should be interpreted only by readers who successfully complete electronic media or in-person training provided by the manufacturer. The objective of NeuraCeq image interpretation is to estimate β-amyloid neuritic plaque density in brain gray matter, not to make a clinical diagnosis.

Image interpretation is performed independently of a patient's clinical features and relies upon the recognition of image features in certain brain regions.

Image Display

PET images should be displayed in the transaxial orientation using gray scale or inverse gray scale. The sagittal and coronal planes may be used for additional orientation purposes. CT or MR images may be helpful for anatomic reference purposes. However, visual assessment should be performed using the axial planes according to the recommended reading methodology.

Image Interpretation

Interpretation of the images is made by visually comparing the activity in cortical gray matter with activity in adjacent white matter. Regions displayed in the PET images which 'anatomically' correspond to white matter structures (e.g., the cerebellar white matter or the splenium) should be identified to help the readers orient themselves. Images should be viewed and assessed in a systematic manner, starting with the cerebellum and scrolling up through the lateral temporal and frontal lobes, the posterior cingulate cortex/precuneus, and the parietal lobes. For a gray matter cortical region to be assessed as showing 'tracer uptake', the majority of slices from the respective region must be affected.

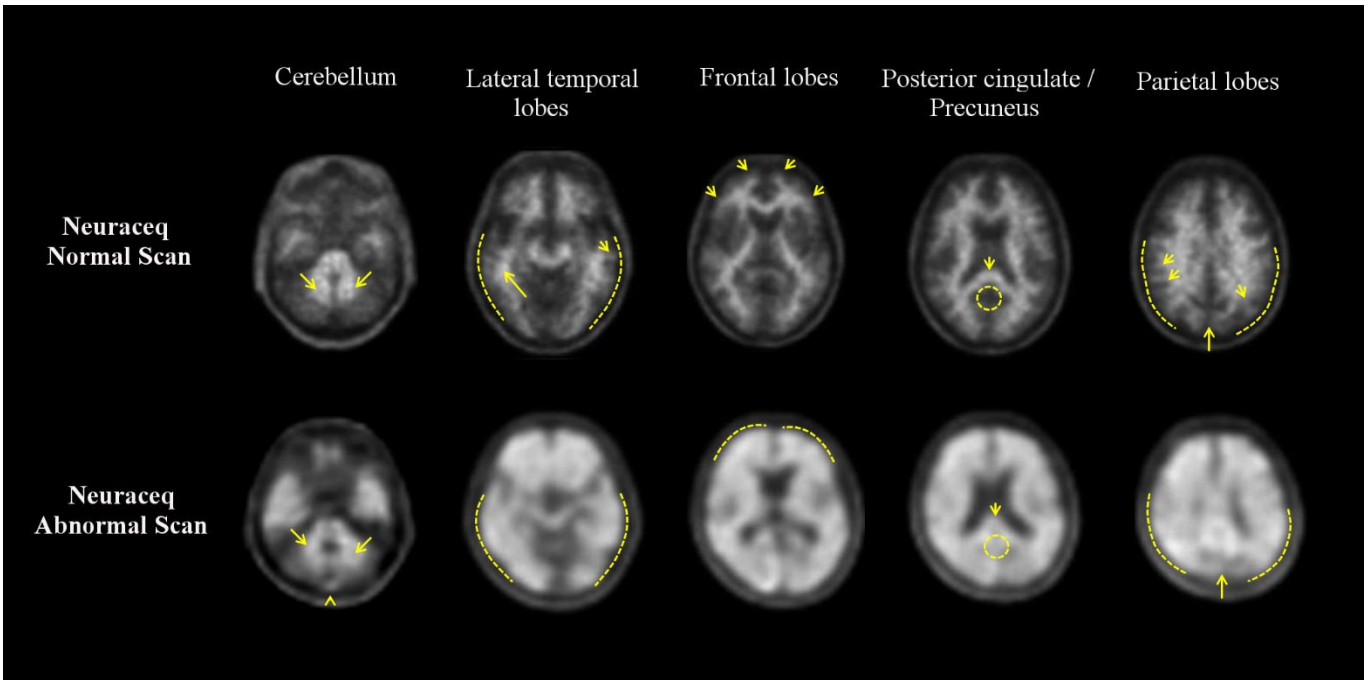
For each patient, the PET image assessment is categorized as either "β-amyloid-positive" or "β-amyloid-negative". This determination is based on the assessment of tracer uptake in the gray matter of the following four brain regions: the temporal lobes, the frontal lobes, the posterior cingulate cortex/precuneus, and the parietal lobes; according to the following 'rules for assessment':

- β-amyloid negative - tracer uptake (i.e., signal intensity) in gray matter is lower than in white matter in all four brain regions (no β-amyloid deposition)
- β--amyloid positive - smaller area(s) of tracer uptake equal to or higher than that present in white matter extending beyond the white matter rim to the outer cortical margin involving the majority of the slices within at least one of the four brain regions ("moderate" β-amyloid deposition), or a large confluent area of tracer uptake equal to or higher than that present in white matter extending beyond the white matter rim to the outer cortical margin and involving the entire region including the majority of slices within at least one of the four brain regions ("pronounced" β-amyloid deposition).

Some scans may be difficult to interpret due to image noise, atrophy with a thinned cortex, or image blur. If a coregistered computerized tomography (CT) image is available, the CT image may be used to clarify the relationship of the NeuraCeq uptake and the gray matter anatomy.

Examples of positive and negative scans for each of the four brain regions are illustrated in Figure 1.

Figure 1: Examples of Positive and Negative NeuraCeq PET scans



Cerebellum: *A contrast between the white matter (arrows) and gray matter is seen in both normal and abnormal scans. Extracerebral tracer uptake in scalp and in the posterior sagittal sinus (arrowhead) can be seen.* ***Lateral temporal lobes:*** *Spiculated or "mountainous" appearance of the white matter (arrows) is seen in the normal scan, and. radioactive signal does not reach the outer rim of the brain (dashed line) due to lower tracer uptake in the gray matter. The abnormal scan shows a "plumped", smooth appearance of the outer border of the brain parenchyma (dashed line) due to tracer uptake in the gray matter.* ***Frontal Lobes:*** *Spiculated appearance of the white matter in the frontal lobes (arrows) is seen in the normal scan. The abnormal scan shows the tracer uptake in these regions has a "plumped", smooth appearance due to the increased gray matter signal (dashed line).* ***Posterior cingulate/precuneus:*** *Adjacent and posterior to the splenium (arrow), these regions appear as a hypo-intense "hole" (circle) in the normal scan, whereas this hole is "filled-up" (circle) in the abnormal scan.* ***Parietal lobes:*** *In the normal scan, the midline between the parietal lobes can be easily identified (long arrow); white matter has a spiculated appearance (short arrow) with low signal near the outer rim of the brain (dashed line). In the abnormal scan, the midline between the parietal lobes is much thinner. The cortical areas are "filled-up" and are smooth in appearance as tracer uptake extends to the outer rim of the brain.*

4.5 Instructions for Preparation and Use

NeuraCeq is provided as an intravenous solution ready for injection. No preparation is required. 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.

4.6 Directions for Quality Control

NeuraCeq is provided as an intravenous solution ready for injection. No quality control testing is required.

5 RADIATION DOSIMETRY

The effective dose coefficient is 1.93E-02 mSv/MBq. The effective dose following a single injected activity of 300 MBq is 5.8 mSv. The total effective dose of a NeuraCeq PET/CT procedure will be higher due to the CT component of the procedure. The contribution from CT will vary according to the equipment used and the acquisition protocol.

Table 1: Radiation Dose Estimates

Organ/Tissue	mGy/MBq
Adrenals	1.30E-02
Brain	1.25E-02
Breasts	7.40E-03
Gallbladder Wall	1.37E-01
Heart Wall	1.39E-02
Kidneys	2.38E-02
Liver	3.86E-02
Lower Large Intestine-Wall	3.51E-02
Lungs	1.48E-02
Muscle	9.48E-03
Osteogenic Cells	1.48E-02
Ovaries	1.56E-02
Pancreas	1.39E-02
Red Marrow	1.22E-02
Skin	6.89E-03
Small Intestine	3.14E-02
Spleen	1.02E-02
Stomach Wall	1.16E-02
Testes	9.13E-03
Thymus	8.92E-03
Thyroid	8.42E-03
Upper Large Intestine-Wall	3.82E-02
Urinary Bladder Wall	6.95E-02
Uterus	1.63E-02
Effective Dose (mSv/MBq)	**1.93E-02**

Biokinetic data from 8 male and 7 female healthy volunteers.
Estimates calculated using OLINDA, male (hermaphrodite) phantom.

6 OVERDOSAGE

Cases of overdose are not known to have occurred with NeuraCeq. In case of overdose, the patient should be monitored and managed as clinically indicated.

7 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

NeuraCeq is supplied as a sterile, non-pyrogenic clear solution of 50 to 5000 MBq/mL florbetaben (^{18}F) at EOS, in a 30 mL multi-dose glass vial containing up to 30 mL. Each vial contains multiple doses and is enclosed in a shielded container to minimize external radiation exposure. The pH of the solution is between 4.5 and 7.

Table 2: Dosage form, strength, composition

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients	
Intravenous	Solution Florbetaben: 3 µg/mL ^{18}F: 50 to 5000 MBq/mL	Ascorbic acid	4.4 mg
		Ethanol	118.0 mg
		Macrogol 400	200.0 mg
		Sodium ascorbate	28.8 mg

8 DESCRIPTION

8.1 Physical Characteristics

NeuraCeq is radiolabeled with fluorine (^{18}F) that decays by positron (ß+) emission to ^{18}O with a half-life of 109.8 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons resulting from the interaction of the emitted positron with an electron (Table 3).

Table 3: Principal Emission Data for Fluorine (^{18}F)

Radiation	Energy Level (keV)	Abundance
Positron	249.8	96.7
Gamma	511	193.4

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after calibration are shown in Table 4.

Table 4. Physical Decay

Time from EOS (min)	Fraction remaining	Time from EOS (min)	Fraction remaining
60	68.5%	420	7.1%
120	46.9%	480	4.8%
180	32.1%	540	3.3%
240	22.0%	600	2.3%
300	15.1%	660	1.6%
360	10.3%	720	1.1%

Exact amounts can be calculated as percent remaining = $100*e^{(-0.006311*t)}$ where *t* is time from calibration in minutes.

8.2 External Radiation

The point source air-kerma coefficient[a] for ^{18}F is 3.74E-17 Gy m^2 s^{-1} Bq^{-1}. The first half-value thickness of lead for ^{18}F gamma rays is approximately 6 mm[b]. The relative reduction of radiation emitted by ^{18}F that results from various thicknesses of lead shielding is shown in Table 5. The use of approximately 8 cm of lead (Pb) will decrease the radiation transmission (i.e. exposure) by a factor of about 10,000.

Table 5: Radiation Attenuation by Lead Shielding

cm Pb	0.6	2	4	6	8
Coefficient of Attenuation	0.5	0.1	0.01	0.001	0.0001

9 WARNINGS AND PRECAUTIONS

9.1 Risk for Image Misinterpretation and other Errors

Errors may occur in the Neuraceq estimation of brain neuritic β-amyloid plaque density during image interpretation (see section 16, *Clinical Studies*). Image interpretation should be performed independently of the patient's clinical information. The use of clinical information in the interpretation of Neuraceq images has not been evaluated and may lead to errors. Errors may also occur in cases with severe brain atrophy that limits the ability to distinguish gray and white matter on the Neuraceq scan. Errors may also occur due to motion artifacts that result in image distortion. Neuraceq scan results are indicative of the presence of brain neuritic β-amyloid plaques only at the time of image acquisition and a negative scan result does not preclude the development of brain neuritic β-amyloid plaques in the future."

a Eckerman KF and A Endo. MIRD: Radionuclide Data and Decay Schemes, 2nd Edition, 2008.
b Derived from data in NCRP Report No. 49. 1998, Appendix C

9.2 General

Florbetaben (^{18}F) is radioactive and therefore adequate shielding of the radiopharmaceutical must be maintained.

The product 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.

The radiopharmaceutical product 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.

9.3 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential of florbetaben (^{18}F).

Florbetaben (^{18}F) did not demonstrate mutagenic potential in an *in vitro* bacterial mutation assay (Ames test) using five strains of *Salmonella typhimurium* and one strain of *Escherichia coli* or in an *in vitro* chromosomal aberration assay using human peripheral lymphocytes in the absence and presence of a metabolic activator.

No study on impairment of male or female fertility and reproductive performance was conducted in animals.

9.4 Contamination

To minimize the risk of contamination of clothing and bed linen by radioactive urine, for up to 12 hours after receiving NeuraCeq:

- incontinent patients should be catheterized; and
- bed-ridden patients should use the toilet, not hand-held urinals.

Urine-soiled clothes or linen should be immediately removed and washed or quarantined for 12 hours.

9.5 Special Populations

9.5.1 Pregnant Women

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse reactions on the fetus, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the potential benefits outweigh the potential hazards to the fetus.

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.

9.5.2 Breast-feeding

Where an assessment of the risk-benefit ratio suggests the use of this product in nursing women, breast feeding should be temporarily interrupted for at least 12 hours and the expressed feeds discarded following the PET scan. Formula feeding can be substituted or, when appropriate, milk may be expressed prior to florbetaben (^{18}F) administration to minimize close contact between the mother and infant to help limit radiation exposure to the infant.

9.5.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

9.5.4 Geriatrics

Of the 872 subjects in clinical studies of NeuraCeq, 603 (69%) were 65 years or over, while 304 (35%) were 75 years or over. No overall differences in safety were observed between these subjects and younger subjects.

10 ADVERSE REACTIONS

10.1 Overview

No serious adverse reactions related to NeuraCeq administration have been reported. The most frequently observed adverse drug reactions were injection site reactions consisting of erythema, irritation, and pain. All adverse reactions were mild to moderate in severity and of short duration.

10.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in clinical practice.

The overall safety profile of Neuraceq is based on data from 1090 administrations of Neuraceq to 872 subjects

The most commonly reported adverse reactions (occurring in at least 0.5% of subjects) during Neuraceq clinical trials are shown in Table 6.

Table 6: Adverse Reactions in Clinical Trials

Adverse Reaction	n	%
Injection site pain	38	3.5
Injection site erythema	18	1.7
Injection site irritation	13	1.2
Injection site reaction NS	13	1.2

10.3 Post-Market Adverse Reactions

From routine clinical use, there has been a single post-marketing report of an adverse reaction: injection site pain and dysgeusia. From post-marketing investigator-initiated studies, there have been eight reports (nine events): nausea, injection site pain (n=5), scan abnormal, dizziness, and hypertension.

11 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed in patients to establish the extent, if any, to which concomitant medications may alter NeuraCeq image results.

In vitro studies show that metabolism of florbetaben is predominantly catalyzed by CYP2J2 and CYP4F2. In *in vitro* studies using human liver microsomes, florbetaben did not inhibit cytochrome P450 enzymes at concentrations present *in vivo*.

12 ACTION AND CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Florbetaben (^{18}F) a fluorine-18-labeled stilbene derivative, which binds to β-amyloid plaques in the brain. ^{3}H-florbetaben *in vitro* binding experiments reveal two binding sites (Kd of 16 nM and 135 nM) in frontal cortex homogenates from patients with AD. Binding of florbetaben (^{18}F) to β-amyloid plaques in post-mortem brain sections from patients with AD using autoradiography correlates with both immunohistochemical and Bielschowsky silver stains. Florbetaben (^{18}F) does not bind to tau or α-synuclein in tissue from patients with AD. Neither NeuraCeq nor non-radioactive florbetaben (^{19}F) bind to AT8 positive tau deposits in brain tissue from patients with frontotemporal dementia (FTD), using autoradiography and immunohistochemistry, respectively.

12.2 Pharmacodynamics

At the low mass dose administered, florbetaben (^{18}F) does not have any detectable pharmacodynamic activity.

Following intravenous administration, NeuraCeq crosses the blood brain barrier and shows differential retention in brain regions that contain β-amyloid deposits. Differences in signal intensity between brain regions showing specific and nonspecific NeuraCeq uptake form the basis for the image interpretation method.

12.3 Pharmacokinetics

Ten minutes after intravenous bolus injection of 300 MBq of NeuraCeq in human volunteers, approximately 6% of the injected radioactivity was distributed to the brain. Florbetaben (^{18}F) plasma concentrations declined by approximately 75% twenty minutes post-injection, and by approximately 90% at 50 minutes. The ^{18}F in circulation during the 45- to 130-minute imaging window was principally associated with polar metabolites of florbetaben. Florbetaben (^{18}F) was 98.5% bound to plasma proteins and was eliminated from plasma primarily via the hepatobiliary route with a mean biological half-life of approximately 1 hour. *In vitro* studies show that metabolism of florbetaben is predominantly catalyzed by CYP2J2 and CYP4F2. At 12 hours post-administration, approximately 30% of the injected radioactivity had been excreted in urine.

Almost all ^{18}F radioactivity in urine was excreted as polar metabolites of florbetaben (^{18}F) and only trace amounts of florbetaben (^{18}F) were detected.

In *in vitro* studies using human liver microsomes, florbetaben did not inhibit cytochrome P450 enzymes at concentrations present *in vivo*.

Studies on the pharmacokinetics of NeuraCeq in special populations, including patients with hepatic or renal impairment, have not been performed.

As florbetaben (^{18}F) is eliminated primarily through the hepatobiliary system, a somewhat increased radiation exposure in patients with hepatic impairment may be possible.

13 STORAGE, STABILITY, AND DISPOSAL

Store NeuraCeq at room temperature 25°C.

The product does not contain a preservative. Store NeuraCeq within the original container or equivalent radiation shielding.

NeuraCeq must not be diluted.

NeuraCeq should be used within 10 hours of the end of synthesis.

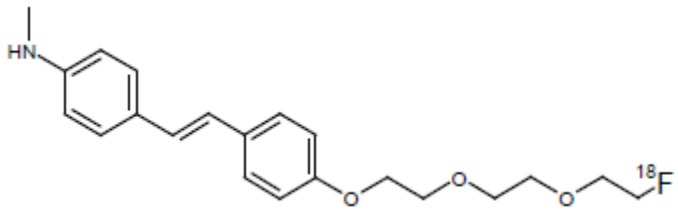
14 SPECIAL HANDLING INSTRUCTIONS

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.

PART II: SCIENTIFIC INFORMATION

15 PHARMACEUTICAL INFORMATION

15.1 Drug Substance

Proper name:	Florbetaben (^{18}F)
Chemical name:	4-{(E)-2-[4-(2-{2-[2-(^{18}F) fluoroethoxy]ethoxy}ethoxy)phenyl]vinyl}-N-methylaniline
Molecular formula:	$C_{21}H_{26}{}^{18}FNO_3$
Molecular mass:	358.5 g/mol
Structural formula:	
Physicochemical properties:	Clear colorless solution
pH	4.5 - 7.0

15.2 Product Characteristics

NeuraCeq is florbetaben (^{18}F) solution, at a radioconcentration of 50 to 5000 MBq/mL.

Each mL of the aqueous solution contains up to 3 μg of florbetaben labelled with 50 to 5000 MBq of ^{18}F, 4.4 mg of ascorbic acid, 118 mg of ethanol, 200 mg of macrogol 400, and 28.8 mg of sodium ascorbate.

The pH of the solution is 4.5 to 7.0.

Florbetaben is designated chemically as $C_{21}H_{26}{}^{18}FNO_3$ (MW 358.5, CAS 902143-01-5).

16 CLINICAL TRIALS

NeuraCeq was evaluated in three single arm clinical studies that examined images from adults with a range of cognitive function, including some end-of-life patients who had agreed to participate in a post-mortem brain donation program. Subjects underwent NeuraCeq injection and scan, then had images interpreted by independent readers masked to all clinical and histopathological information.

Study A had two parts, each reported separately. The first part was a regional (tissue-matched) analysis with MRI co-registration, designed as a “target validation” study. This part of the study validated the ability of florbetaben (^{18}F) PET imaging to detect amyloid aggregates in precisely the same tissue as that examined by histopathology. The pre-planned sample size for the first part of the study was at least 30 histopathological specimens; the analysis was done on 31. Study A continued into the second part, enrolling 216 patients and providing 82 evaluable autopsy cases.

The primary efficacy support comes from the original 3-reader assessment of the 82-autopsy sub-set; and from a re-read of the same sub-set by a panel of five readers (Study B). The first three readers had undergone in-person reader training; the set of 5 readers had undergone electronic media training. All readers were blinded to all other clinical information. The five-reader re-read also assessed inter- and intra-reader reliability.

The SoT was based on the histopathologic examination using Bielschowsky silver staining (BSS) of six brain regions, assessed by a Pathology Consensus Panel masked to all clinical information (including PET scan results). The histopathology-derived plaque score was based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria using neuritic plaque counts (Table 7). For the subject-level SoT, if in any of the six regions β-amyloid neuritic plaques were more than sparse, the subject was classified as positive; if in none of the regions the β-amyloid neuritic plaques were assessed as being more than sparse, the subject was classified as negative.

Table 7. CERAD Scoring

	Plaque Count			
	<1	1-5	6-19	≥ 20
CERAD score	None	Sparse	Moderate	Frequent
SoT Classification	Negative	Negative	Positive	Positive

At autopsy, the subject level brain β-amyloid neuritic plaque density category was: frequent (n = 31); moderate (n = 21); sparse (n = 17); or none (n = 13), giving a disease prevalence of 63% (52/82).

The median age of the 82 patients was 81 years (range 48 to 98 years); 57% of the subjects were male. By medical history, 60 had AD, 9 had other non-AD dementia, 4 had dementia with Lewy Bodies (DLB), and 9 had no clinical evidence of dementia. The interval between the NeuraCeq scan and death was less than one year for 45 patients, between one and two years for 23 patients and more than two years for 14 patients.

When the 82-patient sub-set was read by the three in-person-trained readers from the phase 3 study, NeuraCeq had a median sensitivity of 98% and a median specificity of 80% (Table 8).

When re-read by the five electronic-media-trained readers, NeuraCeq had a median sensitivity of 96% and a median specificity of 77% (Table 8), not different from the original read.

The reliability and reproducibility of the clinically applicable image interpretation methodology using the Electronic Media Training was assessed using 461 images from previous clinical studies, which included subjects with a range of diagnoses (Study C). The five readers assessed randomly provided images from subjects with a truth standard (54 subjects who underwent an autopsy) and without a truth standard (51 subjects with mild cognitive impairment, 182 subjects with AD, 35 subjects with other dementias, 5 subjects with Parkinson's Disease and 188 healthy volunteers). Among the 461 subjects, the median age was 72 years (range 22 to 98), 197 were females, and 359 were Caucasian. Image reproducibility data for these various groups are presented in Table 9. Inter-reader agreement across all 5 readers had a kappa coefficient of 0.79 (95% CI 0.77, 0.83). The performance characteristics in 54 subjects with SoT were similar to those measured in Studies A and B. Additionally, intra-reader reproducibility was assessed from 46 images (10%); the percentage of intra- reader agreement for the 5 readers ranged from 91% to 98%.

Table 8. Diagnostic Accuracy

	In-person-trained readers (n=82)			Electronic-media-trained readers (n=82)				
	1	2	3	4	5	6	7	8
TP	50	51	51	49	51	47	50	52
TN	25	23	24	24	14	24	23	17
FP	5	7	6	6	16	6	7	13
FN	2	1	1	3	1	5	2	-
Sensitivity	96%	98%	98%	94%	98%	90%	96%	100%
Specificity	83%	77%	80%	80%	47%	80%	77%	57%
PPV	91%	88%	89%	89%	76%	89%	88%	80%
NPV	93%	92%	92%	92%	88%	92%	92%	89%
Accuracy	91%	90%	91%	89%	79%	87%	89%	84%

Table 9. Inter-reader agreement

				Percent Reader Agreement		
	n*	Positive scan†	Kappa ($CI_{95\%}$)	3/5 readers	4/5 readers	5/5 readers
All subjects	454	212	0.80 (0.77, 0.83)	6	15	78
Subjects without SoT	394	175	0.80 (0.77, 0.83)	6	15	79
Subjects with SoT	60	37	0.75 (0.67, 0.83)	10	15	75
AD	176	139	0.77 (0.72, 0.81)	7	10	83
HV	188	26	0.55 (0.49, 0.58)	7	15	77
MCI	50	28	0.84 (0.75, 0.92)	0	20	80
Other Dementias	40	18	0.65 (0.55, 0.74)	8	33	60

* *Subjects with missing scan interpretation (2 to 6% per group) were excluded from the analyses.*
† *Shown is the median number of scans interpreted as positive across the 5 readers.*
AD: Alzheimer's disease; MCI: Mild cognitive impairment; HV: healthy volunteer.

17 NON-CLINICAL TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. The potential toxicity of 28 days of repeated intravenous injections of florbetaben was tested in rats and dogs, and the NOAEL was found to be at least 20 times the maximum human dose.

Chronic studies and carcinogenicity studies have not been carried out, since the medicinal product is not intended for regular or continuous administration.

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether <product name> affects fertility in males or females.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NeuraCeq

Florbetaben (^{18}F) Solution

Read this carefully before you receive NeuraCeq ("neura-seek"). 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 NeuraCeq.

Serious Warnings and Precautions

- NeuraCeq should not be administered to pregnant women.
- If you are breastfeeding, you must temporarily interrupt breastfeeding 12 hours.

What is NeuraCeq used for?

NeuraCeq is given to people with memory problems so that doctors can perform a type of brain scan, called a PET scan (Positron Emission Tomography). A NeuraCeq PET scan, along with other brain function tests, can help your doctor determine whether or not you may have β-amyloid plaques in your brain.

How does NeuraCeq work?

Shortly after it is injected, NeuraCeq attaches to a portion of a protein in the brain called beta-amyloid. Its radioactive portion can then be seen when using a PET camera. NeuraCeq has no effect of its own. The radioactivity decreases by half every two hours so that by the end of 10 hours, over 98% over the radioactivity has disappeared.

What are the ingredients in NeuraCeq?

Medicinal Ingredients	Non-medicinal ingredients
3 µg/mL of the drug florbetaben	4.4 mg of ascorbic acid (vitamin C)
from 50 to 5000 MBq of radioactive fluoride (^{18}F)	118.0 mg of ethyl alcohol
	28.8 mg of sodium ascorbate (a salt of vitamin C)
	200.0 mg of macrogol 400

NeuraCeq comes in the following dosage forms:

An injectable solution with 50 to 5000 MBq/mL florbetaben (^{18}F).

Do not use NeuraCeq if:

- You are allergic to any of the ingredients

Warnings and Precautions

Some radioactivity will be eliminated in your urine for up to 12 hours. To minimize the risk of urine contaminating your clothes or bed:

- If you have trouble retaining your urine (incontinence) ask about a catheter;
- Do not use hand-held urinals or bedpans but use the toilet.

Urine-soiled clothes or linen should be immediately removed and washed or put aside for 12 hours.

How to take NeuraCeq
This product will be given to you (administered) under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

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

- are pregnant
- are breast feeding

What are possible side effects from using NeuraCeq?
No side effects directly related to NeuraCeq have been reported. The most frequently observed side effects were injection site reactions consisting of injection/application site redness (1.7%), irritation (1.1%) and pain (3.4%). All side effects were mild to moderate in severity and of short duration.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

Keep out of reach and sight of children.

If you want more information about NeuraCeq:

- 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.

This leaflet was prepared by IsoLogic Innovative Radiopharmaceuticals Ltd., 1855 32nd Avenue, Lachine, Quebec H8T 3J1.

Last Revised February 02, 2017