



Oxy-17[®] MRI Contrast Media Kit

Oxy-17[®] is a registered Trade Mark (# 3,421,019) of Rockland Technimed Ltd for: Oxygen-based diagnostic agent for use with MRI diagnostic apparatus, and diagnostic scanning agent in the nature of contrast media for use in In-Vivo imaging.

Indications for use and target patient population:

Oxy-17[®] is to be used to follow in situ metabolic processes with magnetic resonance imaging such as cerebral ischemia, cardiac ischemia and neoplastic tissue. Determination of oxygen metabolic rate and blood oxygen extraction fraction (OEF) are key indicators of tissue viability and treatment outcome in cerebral and cardiac ischemia. Molecular oxygen levels in neoplastic tissues are key indicators of radiation treatment response. The target population for the use of this agent is middle aged and elderly in whom these disease entities are most frequent.

Product Description.

Oxygen-17 (¹⁷O) is a naturally occurring, stable non-radioactive component of oxygen. It has identical chemical properties to ¹⁶O, and is abundantly available in the form of oxygen in the atmosphere. It differs only in the net 5/2 spin property of its nucleus which makes it visible on magnetic resonance imaging, both in its molecular gas form (¹⁷O₂) and after metabolism to tissue water (H₂¹⁷O). The other two stable isotopes of oxygen, ¹⁶O and ¹⁸O, have net nuclear spins of zero and therefore are not visible on magnetic resonance imaging.

Magnetic resonance imaging methods for quantitative detection of ¹⁷O₂ and H₂¹⁷O in tissue have been developed over the past 20 years. These methods, combined with inhalation of ¹⁷O₂, intra-vascular injection of ¹⁷O₂ with an oxygen carrier (e.g. autologous blood or blood substitute) or intra-vascular injection of H₂¹⁷O, allow the in vivo, quantitative determination of molecular oxygen concentration, oxygen extraction fraction, oxygen metabolism and blood flow. Validation of the tracer methods and compartmental models for quantitative evaluation of oxygen metabolism have been developed for ¹⁵O-PET over the past 20 years and can be adapted for use with ¹⁷O₂.

Alternative practices and procedures.

The only other human imaging method that allows the in vivo quantitative assessment of molecular oxygen concentration, oxygen extraction fraction, oxygen metabolism and blood flow is positron emission tomography (PET) using the radioactive isotope of oxygen, ¹⁵O. ¹⁵O-PET has been used extensively for brain research applications but has limited clinical utility because of its limited availability, high cost and substantial radiation dose.

Marketing history.

Oxygen-17 gas has been commercially available in various enrichments and various packaging, for over 20 years; And has been sold commercially in the USA, EU and Asia Pacific countries since the past 20 years.

Product Composition and Purity

Oxygen-17 (¹⁷O), is manufactured in compliance with the 21 Code US Federal Regulations part 210 and 211 (cGMP) for medical gases. It is isotopically enriched ultrapure gas with the following composition.

OXYGEN-17	>70.20 at %
Oxygen-16	19.2 at %
Oxygen-18	10.6 at %
Purity	99.900 wt%
<i>Other elements</i>	
CO	<1 vppm
CO2	< 13 vppm
H2	< 4 vppm
N2	<60 vppm

Product summary of studies.

Oxygen-17 (¹⁷O), a safe, non-radioactive, abundantly available naturally occurring form of oxygen, can be used in MRI-guided measurements of cerebral metabolic rate of oxygen consumption (CMRO₂) and oxygen extraction fraction (OEF). Measuring CMRO₂ and OEF is necessary to monitor significant changes in hemodynamic status of the brain before, during, and after various pathological states, such as stroke, transient ischemic attacks, carotid stenosis and occlusion. When cerebral perfusion pressure (CPP) drops, for example, as a result of stenosis, occlusion, or low arterial blood pressure, compensatory vasodilation known as Stage 1 cerebral autoregulation maintains normal cerebral blood flow (CBF). If CPP reaches levels below which vasodilation is no longer helpful, then CBF is compromised, oxygen levels decrease, and the brain extracts more oxygen to keep CMRO₂ levels normal. OEF increase and CBF decrease mark Stage 2 hemodynamic failure, or "misery perfusion," so named because maximal OEF is a precursor to tissue infarction. Imaging Stage 2 tissue is of critical importance in guiding treatment to restore and maintain tissue viability (1).



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¹⁷O-MRI is sensitive to H₂¹⁷O, the end product of oxidative metabolism, while insensitive to ¹⁷O₂. This unique specificity of ¹⁷O-MRI, different from ¹⁵O-PET in which both ¹⁵O gas and water are detectable, allows for the detection of metabolically generated H₂¹⁷O without confounding signals from ¹⁷O₂ bound to hemoglobin or dissolved in water. MRI sensitivity to H₂¹⁷O results from the effect of ¹H-¹⁷O scalar coupling on the transverse relaxation time, T₂, of water protons, which is shortened by the presence of the ¹⁷O nucleus in the water molecule (2).

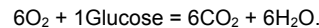
Both human and animal studies have illustrated the feasibility, significance, and safety of using ¹⁷O-MRI to measure CMRO₂ and OEF. Fiat and colleagues successfully used 1.5 Tesla (T) clinical MRI scanners to image the human brain with ¹⁷O and utilized this technique to determine CMRO₂ and CBF (3). Extensive studies in both rodents and primates have shown that it is possible not only to detect H₂¹⁷O with relatively high sensitivity on commercially available clinical scanners at 1.5 and 3.0T, but also to calculate CMRO₂ via indirect ¹⁷O-MRI at concentrations as low as natural abundance (4, 5). Reliable measures of CMRO₂ and OEF are important because both increased OEF and Stage 2 hemodynamic failure have been shown to be independent predictors for risk of subsequent stroke in patients with carotid occlusion (6-8).

Exact calculation of CMRO₂ requires not only measurement of dynamic changes of H₂¹⁷O in the brain (C_b), but also the arterial (C_a) input function (AIF), H₂¹⁷O concentration in the venous blood (C_v), and CBF, according to the original Kety-Schmidt equation:

$$dC_b(t)/dt = 2\alpha f_1 CMRO_2 + m CBF(C_a(t) - C_v(t))$$

Where α is the enrichment fraction of ¹⁷O₂ gas, f_1 is a unit converter with a value of 1.266, and m is the extraction fraction of water. The measurement of AIF often requires withdrawing arterial blood, and is not desirable in humans. To simplify the calculation of CMRO₂ and avoid the invasive procedure of direct arterial sampling, MRI methods and specialized hardware modifications is be used for direct detection of ¹⁷O₂ in tissue (10).

¹Tissue concentration of 4% H₂¹⁷O produces 50% signal reduction on T2W SE images at 1.5T. (Rogers, et. al., ISMRM, p. 309, 1999; Ronen, et. al., ISMRM, p. 315, 1999). Signal reduction is not caused by the PFC carrier. (Arena, et. al., ISMRM, p. 631, 1998). In aerobically metabolizing tissue, such as brain,



Safety and Effectiveness.:

Oxygen-17 (¹⁷O) is a naturally occurring component of atmospheric Oxygen (See Safety References).

Administration:

Oxygen-17 (¹⁷O) is administered by loading it on to autologous blood using a desktop pump (Oxynator™) and a closed loop single use disposable collection kit consisting of blood collection bag and a closed loop membrane Oxygenator Cartridge (OxyCart™) to formulate the contrast agent namely Oxy-17. The autologous blood saturated with Oxygen-17 namely Oxy-17® is administered intravenously, considered non invasive administration, or intra-arterially via an indwelling catheter as required. This is followed by imaging as per the standard imaging protocols given below. Oxy-17® is a diagnostic aid for following metabolic processes in situ where cellular water is produced in real-time using an unaltered Magnetic Resonance Imaging system.

Storage and Handling:

The Oxy-17 kits with each of its components, namely the Oxygen-17 gas 70% at % and the OxyCart™, and the Oxynator™ are all stored in a dry place at room temperature. Care must be taken to ensure that the integrity of the sterile packaging is maintained. Do not use if the sterile packaging is open or contents damaged during the peruse inspection. Care must be taken not to loose the Oxygen-17 gas during the oxygenation procedure and that the autologous blood is saturated by observing the color change to bright red. The disposable blood collection circuit is a single use item and must be discarded after its use. Care must be taken to wipe down the reusable pump with gas source.

Warning: Potential Biohazard: Healthcare professionals using this system on patients should be aware that all products or objects that come in contact with human blood, even after cleaning, should be handled as if capable of transmitting viral disease.

Oxygen-17 MRI Imaging Protocols (Brain)

T2W

- 1) Sagittal, Coronal and Axial scout GRE images to ensure correct positioning and orientation of the brain (1:00 min:sec)
- 2) Diffusion weighted image (DWI) images (SE EPI, b=1000 and b=2000, 128x128 matrix, 22cm FOV) (0:40 x2)
- 3) FLAIR (FSE ETL 36, TR 8000, TE 133ms, 288x288, 22cm FOV) (1:36)



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- 4) Baseline T2W Fast Spin Echo images (FSE ETL 16, TR 5000, TE 120ms, 320x224, 22cm FOV) (2:20).
- 5) Continuous repeated single echo T2W SE EPI (TE 120) imaging beginning 1 minutes before 17O delivery and continuing for 5 minutes afterward.
- 6) Post 17O T2W Spin Echo images (as above) repeated 9 times (21:00) to monitor H2 17O generation by oxidative metabolism and equilibration with recirculating H217O.
- 7) Serial rapid T2W gradient echo EPI images during bolus tail injection of gadolinium to measure perfusion (CBF for calculation of oxygen extraction fraction, OEF) (1:10). Total imaging time: 33:24

T1p (T1rho)

- 1) Sagittal, Coronal and Axial scout GRE images to ensure correct positioning and orientation of the brain (1:00 min:sec)
- 2) Diffusion weighted image (DWI) images (SE EPI, b=1000 and b=2000, 128x128 matrix, 22cm FOV) (0:40 x2)
- 3) FLAIR (FSE ETL 36, TR 8000, TE 133ms, 288x288, 22cm FOV) (1:36)
- 4) Baseline T1p-weighted high spin lock frequency = 1500 Hz, Fast Spin Echo images (FSE ETL 16, TR 1000, TE 17ms, 320x224, 22cm FOV, , time of spin-locking, TSL 120ms) 5 repeats (0:14 x 5 = 1:10).
- 5) Continuous T1p-weighted low spin lock frequency = 125 Hz, Fast Spin Echo images (FSE ETL 16, TR 1000, TE 17ms, 320x224, 22cm FOV, , time of spin-locking, TSL 120ms) 50 repeats beginning with 17O delivery and continuing for 10 minutes afterward. (0:14 x 50 = 11:40).
- 6) Serial rapid T2W gradient echo EPI images during bolus tail injection of gadolinium to measure perfusion (CBF for calculation of oxygen extraction fraction, OEF) (1:10). Total imaging time: 17:56 T1p

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