

1. NAME OF THE MEDICINAL PRODUCT

GLUCOTRACE, 185 to 1850 MBq per multi-dose vial, Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 185 MBq [¹⁸F]-fludeoxyglucose at the date and time of calibration.

The activity per vial ranges from 185 MBq to 1850 MBq.

Fluorine-18 decreases into stable oxygen-18 with a half-life of 109.77 minutes by emitting a positronic radiation of maximum energy of 0.633 MeV, followed by photonic annihilation radiation of 0.511 MeV.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or slightly yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

[¹⁸F] fludeoxyglucose is indicated for use with positron emission tomography.

Oncology

GLUCOTRACE is indicated for imaging in patients undergoing oncologic diagnostic procedures describing function or diseases where enhanced glucose influx of specific organs or tissues is the diagnostic target. The following indications are sufficiently documented:

Diagnosis:

- Characterisation of solitary pulmonary nodules
- Metastatic cervical adenopathy of unknown origin.

Staging:

- Head and neck cancers including assistance in guiding biopsy (see also section 4.4)
- Primary lung cancer, including detection of distant lung metastases (see also section 4.4)
- Oesophageal cancer (Staging for oesophageal cancer by FDG-PET may be indicated when cancer remains in doubt after completion of a standard diagnostic workup using endoscopic ultrasound-fine needle aspiration, including conventional imaging.)
- Recurrent colorectal cancer
- Malignant lymphoma (see also section 4.4)
- Malignant melanoma (Breslow >1.5 mm or lymph node metastasis during first diagnosis - regarding metastases in the brain and coincidence cameras refer to section 4.4)

Monitoring of therapeutic response

- Malignant lymphoma (see also section 4.4)
- Head and neck cancers (see also section 4.4)

Detection in case of reasonable suspicion of recurrences:

- Glioma with high grade of malignancy (III or IV)
- Head and neck cancers (See also section 4.4)
- Thyroid cancer (non-medullary): patients with increased thyroglobulin serum levels and negative ¹³¹I whole body scintigraphy
- Primary lung cancer (see also section 4.4)
- Colorectal cancer
- Malignant lymphoma (see also section 4.4)
- Malignant melanoma: (see also section 4.4)

Cardiology

In the cardiologic indication, the diagnostic target is viable myocardial tissue that takes -up glucose but is hypo-perfused, as it must be assessed beforehand using appropriate blood-flow imaging techniques.

- Evaluation of myocardial viability in patients with severe impaired left ventricular function who are candidates for revascularisation when conventional imaging modalities are not contributive.

Neurology

In the neurologic indication the interictal glucose hypometabolism is the diagnostic target

- Localisation of epileptogenic foci in the presurgical evaluation of partial temporal epilepsy.

4.2 Posology and method of administration

Posology

The recommended activity for an adult weighing 70 kg is 100 to 400 MBq (this activity has to be adapted according to the body weight of the patient and the type of camera used), administered by direct intravenous injection.

Only few clinical data are available for patients aged under 18 years concerning safety and diagnostic efficacy of the product. Therefore, the use in oncologic paediatrics has to be carefully weighted.

The activity administered to children and to adolescents is a fraction of the activity recommended for adults. This activity can be determined from the recommended activity for adults on the basis of body mass, using the following multiplying coefficient:

3 kg = 0.10	22kg = 0.50	42 kg = 0.78
4 kg = 0.14	24 kg = 0.53	44 kg = 0.80
6 kg = 0.19	26 kg = 0.56	46 kg = 0.82
8 kg = 0.23	28 kg = 0.58	48 kg = 0.85
10 kg = 0.27	30 kg = 0.60	50 kg = 0.88
12 kg = 0.32	32 kg = 0.62	52-54 kg = 0.90
14 kg = 0.36	34 kg = 0.64	56-58 kg = 0.92
16 kg = 0.40	36 kg = 0.66	60-62 kg = 0.96
18 kg = 0.44	38 kg = 0.68	64-66 kg = 0.98
20 kg = 0.46	40 kg = 0.70	68 kg = 0.99

Method of administration

For specific patient preparation, see section 4.4

Administration of GlucoTrace and PET examination

The activity of FDG has to be measured with calibrator immediately prior to injection. The injection must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts. The emission scans are usually started 45 to 60 minutes after the injection of fludeoxyglucose (18F). Provided a sufficient activity remains for adequate counting statistics, fludeoxyglucose (18F)-PET can also be performed up to two or three hours after administration, thus reducing background activity. If required, repeated examinations can be carried out at short notice.

4.3 Contraindications

- Pregnancy.
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Indication of the examination

For all patients, the radiation exposure must be justifiable by the expected diagnostic achieved with the lowest possible radiation dose.

In patients with reduced kidney function, a very careful indication is required since an increased radiation exposure is possible in these patients.

It should be taken into consideration that the effective dose per MBq is higher in children than in adults (see section 11. dosimetry).

Patient preparation

In order to obtain images of best quality and to reduce the radiation exposure of the bladder, patients should be encouraged to drink sufficient amounts and to empty prior to and after the PET examination.

Oncology and neurology

GLUCOTRACE should be given to (sufficiently hydrated) patients fasting for a minimum of 4 hours, in order to obtain a maximum enrichment of activity, since glucose uptake in the cells is limited (“saturation kinetics”). The amount of liquid should not be limited (avoid beverages containing glucose!)

In order to avoid hyperfixation of the tracer in muscle, it is advisable for patients to avoid all strenuous physical activity prior to the examination and to remain at rest between the injection and examination and during acquisition of images (patients should be comfortably lying down without reading or speaking).

The cerebral glucose metabolism depends on the brain activity. Thus, neurological examinations should be performed after a relaxation period in a darkened room and with less background noise.

A blood glucose test should be performed prior to administration since hyperglycaemia may result in a reduced sensitivity of GLUCOTRACE, especially when glycaemia is greater than 8 mmol/l. Similarly, this product should be avoided in subjects presenting uncontrolled diabetes.

Cardiology

Since glucose uptake in the myocardium is insulin-dependent, for a myocardial examination a glucose loading of 50 g approximately 1 hour prior to the administration of GLUCOTRACE is recommended. Alternatively, especially for patients with diabetes mellitus, the blood sugar level can be adjusted by a combined infusion of insulin and glucose (Insulin-Glucose-Clamp) if needed.

Interpretation of the FDG PET images

Infectious and/or inflammatory diseases as well as regenerative processes after surgery can result in a significant uptake of FDG and therefore lead to false positive results.

False positive results cannot be excluded after radiotherapy within the first 2-4 months. If the clinical indication is demanding an earlier diagnosis by FDG-PET, the reason for earlier FDG-PET examination must be reasonably documented.

A delay of at least 4-6 weeks after the last administration of chemotherapy is optimal, in particular to avoid false negative results. If the clinical indication is demanding an earlier diagnosis by FDG-PET, the reason for earlier FDG-PET examination must be reasonably documented. In case of chemotherapy regimen with cycles shorter than 4 weeks, the FDG PET examination should be done just before re-starting a new cycle.

In low-grade lymphoma only positive predictive values have to be considered because of a limited sensitivity.

[¹⁸F] fludeoxyglucose is not effective in detecting brain metastases.

When applying a coincidence PET (positron emission tomography) scanner system, sensitivity is reduced in comparison to dedicated PET, resulting in a probably reduced detection of lesions smaller than 1 cm.

It is recommended that fludeoxyglucose (18F)-PET images shall be interpreted in relation with tomographic anatomical imaging modalities (e.g. CT, ultrasonography, MRI). Fusion of the functional fludeoxyglucose (18F)-PET images with morphologic images e.g. PET-CT can lead to an increased sensitivity and specificity, and is recommended in pancreas, head and neck tumors, lymphoma, melanoma, lung cancers and recurrent colorectal or ovarian cancers.

When a hybrid PET-CT scanner is used with contrast media, some artefacts may occur on the PET images.

General warnings

It is recommended to avoid any close contact between the patient and young children during the initial 12 hours following the injection.

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings and receipt, storage, use, transfer and disposal are subject to the regulations and appropriate licences of the competent authorities.

Radiopharmaceuticals should be prepared by the user in a manner that satisfies both radiation safety and pharmaceutical quality requirements.

GLUCOTRACE should be stored and handled in adequate shielding, so as to protect patients and hospital staff as much as possible. In particular, it is recommended to protect oneself from the effects of beta+ radiation by using a shielded syringe when performing withdrawals and injections.

4.5 Interaction with other medicinal products and other forms of interaction

All medicinal products that modify blood glucose levels can affect the sensitivity of the examination (e.g. corticosteroids, valproate, carbamazepine, phenytoin, phenobarbital and catecholamines).

Under administration of colony-stimulating factors (CSFs), there is an increased uptake of [¹⁸F]-fludeoxyglucose in the bone marrow and the spleen for several days. This must be taken into account for the interpretation of PET imaging. Separating CSF therapy from PET imaging by an interval of at least 5 days may diminish this interference.

The administration of glucose and insulin can influence the influx of [¹⁸F]-fludeoxyglucose into the cells. In the case of high blood sugar levels as well as low plasma insulin levels the influx of [¹⁸F]-fludeoxyglucose into organs and tumours is reduced.

In patients with highly reduced ventricle function, to whom high doses of catecholamines have to be given, the quality of cardiac imaging can be impaired.

4.6 Pregnancy and lactation

GLUCOTRACE must not be administered during pregnancy.

There is no clinical experience with the use of [¹⁸F]-fludeoxyglucose in pregnant women. No studies of reproductive function have been performed in animals.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques that do not involve ionising radiation have to be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Administration of GLUCOTRACE at activity of 400 MBq results in an absorbed dose to the uterus of 8.4 mGy. In general, a radiation burden to the foetus above the natural radiation exposure should be avoided.

[¹⁸F]-fludeoxyglucose is excreted into breast milk. Before administering [¹⁸F]-fludeoxyglucose to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding. If administration during lactation is unavoidable, breast feeding has to be interrupted for at least 12 hours and the expressed milk has to be discarded. Milk will have to be drawn before administration and stored for subsequent use. Moreover, for radioprotection reasons, it is recommended to avoid close contact between the mother and the infant during the initial 12 hours following injection.

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Undesirable effects after the administration [¹⁸F]-fludeoxyglucose have not been observed to date.

Since the administered substance quantity is very low, the major risk is caused by the radiation. Exposure to ionising radiation can lead to cancer or development of hereditary defects. Most examinations involving nuclear medicine involve levels of radiation (effective dose) less than 20 mSv.

These effects can be expected with a low probability. After administration of the maximum recommended activity of fludeoxyglucose [¹⁸F], the effective dose is about 7.6 mSv.

4.9 Overdose

An overdose in the pharmacological sense is unlikely given with the doses used for diagnostic purposes

If an overdose of [¹⁸F]-fludeoxyglucose has been administered; the dose delivered to the patient must be reduced by increasing as much as possible the elimination of the radionuclide by forced diuresis and frequent mictions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, ATC code: V09IX04.

Fludeoxyglucose[¹⁸F] is a glucose analogue, which is accumulated in all cells using glucose as primary energy source. Fludeoxyglucose[¹⁸F] is accumulated in tumours with a high glucose turnover.

5.2 Pharmacokinetic properties

Following intravenous injection, the pharmacokinetic profile of [¹⁸F]-fludeoxyglucose in the vascular compartment is biexponential. It has a distribution time of 1 minute and an elimination time of approximately 12 minutes.

The cellular uptake of [¹⁸F]-fludeoxyglucose is performed by tissue-specific carrier systems which are partly insulin-dependent and, thus, can be influenced by eating, nutritional condition and the existence of a diabetes mellitus. In patients with a diabetes mellitus a reduced uptake of [¹⁸F]-fludeoxyglucose into the cells occurs due to a changed tissue distribution and glucose metabolism.

[¹⁸F]-fludeoxyglucose is transported via the cell membrane in similar fashion to glucose, but only undergoes the first step of glycolysis resulting in formation of [¹⁸F]fludeoxyglucose-6-phosphate which remains trapped within the tumour cells and is not further metabolised. Since the following dephosphorylation by intracellular phosphatases is slow, [¹⁸F]fludeoxyglucose-6-phosphate is retained in the tissue over several hours (trapping-mechanism).

In healthy subjects, [¹⁸F]-fludeoxyglucose is widely distributed throughout the body, particularly in the brain and heart, and to a lesser degree in the lungs and liver.

Elimination of [¹⁸F]-fludeoxyglucose is chiefly renal, with 20 % of activity being excreted in urine in the 2 hours following injection.

Binding to renal parenchyma is weak, but because of renal elimination of [¹⁸F]-fludeoxyglucose, the entire urinary system, particularly the bladder, exhibits marked activity.

[¹⁸F]-fludeoxyglucose passes the blood-brain barrier. Approximately 7 % of the injected dose are accumulated in the brain within 80-100 minutes after injection. Epileptogenic foci exhibit a reduced glucose metabolism in the phases free of attacks.

Approximately 3 % of the injected activity are absorbed by the myocardium within 40 minutes. The distribution of [¹⁸F]-fludeoxyglucose in normal heart is mainly homogenous, however, regional differences of up to 15 % are described for the interventricular septum. During and after a reversible myocardial ischemia, an increased glucose uptake occurs into the myocardial cell.

0.3 % and 0.9 - 2.4 % of the injected activity are accumulated in pancreas and lung.

[¹⁸F]-fludeoxyglucose is also bound to a lesser extent to ocular muscle, pharynx and intestine. Binding to muscle may be seen following recent exertion and in the event of muscular effort during the examination.

5.3 Preclinical safety data

In preclinical studies of acute toxicity the 50fold human dose in dogs and the 1000fold human dose in mice did not reveal any signs of toxicity.

Studies of chronic toxicity, of mutagenic potential as well as studies of reproduction toxicity and cancerogenic potential have not been performed because of the intended clinical use of the substance (usually a single intravenous application of 1 µg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (0.06 -0.45%)

Sodium hydroxide (0.03 - 0.35%)

Sodium citrate dihydrate

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

11 hours after manufacturing time (6 hours after the calibration time)-

Maximum 8 hours after first-use.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

This product should be stored in accordance with national regulations concerning radioactive products.

6.5 Nature and contents of container

15 ml multi-dose vial, colourless glass, type I, closed with a chlorobutyl stopper and crimped with an aluminium seal.

One vial contains 1 to 10 ml of solution, corresponding to 185 to 1 850 MBq at calibration time.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MDS Nordion S.A., Zoning Industriel, B-6220 Fleurus, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The table below shows the dosimetry as calculated according to ICRP 80 Publication.

Organ	Dose absorbed per unit of activity administered (mGy/MBq)					
	Adult	15 yrs old	10 yrs old	5 yrs old	1 yr old	
Adrenal glands	0.012	0.015	0.024	0.038	0.072	
Bladder wall	0.160	0.210	0.280	0.320	0.590	
Bone surfaces	0.011	0.014	0.022	0.035	0.066	
Brain	0.028	0.028	0.030	0.034	0.048	
Breasts	0.009	0.011	0.018	0.029	0.056	
Bile duct	0.012	0.015	0.023	0.035	0.066	
Intestinal wall	0.011	0.014	0.022	0.036	0.068	
Small intestine	0.013	0.017	0.027	0.041	0.077	
Colon	0.013	0.017	0.027	0.040	0.074	
ULI wall	0.012	0.016	0.025	0.039	0.072	
LLI wall	0.015	0.019	0.029	0.042	0.076	
Heart	0.062	0.081	0.120	0.200	0.350	
Kidneys	0.021	0.025	0.036	0.054	0.096	
Liver	0.011	0.014	0.022	0.037	0.070	
Lungs	0.010	0.014	0.021	0.034	0.065	
Muscles	0.011	0.014	0.021	0.034	0.065	
Oesophagus	0.011	0.015	0.022	0.035	0.068	
Ovaries	0.015	0.020	0.030	0.044	0.082	
Pancreas	0.012	0.016	0.025	0.040	0.076	
Bone marrow	0.011	0.014	0.022	0.032	0.061	
Skin	0.008	0.010	0.016	0.027	0.052	
Spleen	0.011	0.014	0.022	0.036	0.069	
Testes	0.012	0.016	0.026	0.038	0.073	
Thymus	0.011	0.015	0.022	0.035	0.068	
Thyroid	0.010	0.013	0.021	0.035	0.068	
Uterus	0.021	0.026	0.039	0.055	0.100	
Other organs	0.011	0.014	0.022	0.034	0.063	
Effective dose (mSv/MBq)	0.019	0.025	0.036	0.050	0.095	

For GLUCOTRACE, the effective dose resulting from the administration of an activity of 400 MBq is about 7.6 mSv (for an individual weighing 70 kg).

For this activity of 400 MBq, the radiation doses delivered to the critical organs, bladder, heart and brain are respectively: 64 mGy, 25 mGy and 11 mGy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Delivered in multi-dose vial.

The product is for single intravenous injection. The activity of the solution is determined prior to administration. The solution may be diluted with sodium chloride 9mg/ml (0.9%) solution for injection. The administered volume depends on the time period between calibration and time of administration. It has to be calculated with respective decay correction factor and measured with a calibrator prior to injection.

The maximum volume of GLUCOTRACE administered to each patient should not exceed 10 ml.

Withdrawals should be performed under aseptic conditions.

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

The administration of radiopharmaceuticals creates risks for other people from external radiation or contamination from spills of urine, vomit, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Radioactive waste must be disposed of in conformity with the relevant national and international regulations.

Studies have shown that diluting GLUCOTRACE with sodium chloride 9mg/ml (0.9%) solution for injection did not affect its quality. Compatibility with other diluents has not been studied.

If necessary, GLUCOTRACE may be diluted up to 10 times with sodium chloride 9mg/ml (0.9%) solution for injection. This dilution must be carried out under aseptic conditions.