

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

GLUSCAN, 600 MBq/mL solution for injection

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection contains 600 MBq Fludeoxyglucose ( $^{18}\text{F}$ ) at the date and time of calibration. The activity per vial ranges from 300 MBq to 6 GBq.

Fluorine-18 decays to stable oxygen-18 with a half-life of 109.8 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

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.

Fludeoxyglucose ( $^{18}\text{F}$ ) is indicated for use with positron emission tomography (PET).

#### **Oncology**

GLUSCAN 600 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 (see also section 4.4):

#### Diagnosis:

- Characterisation of solitary pulmonary nodule
- Detection of a primary cancer of unknown origin revealed for example by cervical adenopathy, liver or bones metastases
- Characterisation of a pancreatic mass.

#### Staging:

- Head and neck cancers including assistance in guiding biopsy
- Primary lung cancer
- Locally advanced breast cancer
- Oesophageal cancer
- Carcinoma of the pancreas
- Colorectal cancer particularly in restaging recurrences
- Malignant lymphoma
- Malignant melanoma, Breslow >1.5 mm or lymph node metastasis at first diagnosis

#### Monitoring of therapeutic response:

- Malignant lymphoma
- Head and neck cancers

#### Detection in case of reasonable suspicion of recurrences:

- Glioma with high grade of malignancy (III or IV)
- Head and neck cancers
- Thyroid cancer (non-medullary): patients with increased thyroglobulin serum levels and negative radioactive iodine whole body scintigraphy
- Primary lung cancer (see also section 4.4)
- Breast cancer
- Carcinoma of the pancreas
- Colorectal cancer
- Ovarian cancer
- Malignant lymphoma
- Malignant melanoma.

#### **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**

### **Adults and elderly**

The recommended activity for adults is 200 to 500 MBq (depending on the body weight of the patient and the type of camera used), administered by direct intravenous injection.

### **Population aged less than 18 years**

Only few clinical data are available for patients below 18 years old 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 and must be determined from the recommended activity for adults on the basis of body mass, using the following multiplying coefficient as indicated below (Paediatric European Task Group EANM):

3 kg = 0.10	12 kg = 0.32	22kg = 0.50	32 kg = 0.65	42 kg = 0.78	52-54 kg = 0.90
4 kg = 0.14	14 kg = 0.36	24 kg = 0.53	34 kg = 0.68	44 kg = 0.80	56-58 kg = 0.92
6 kg = 0.19	16 kg = 0.40	26 kg = 0.56	36 kg = 0.71	46 kg = 0.82	60-62 kg = 0.96
8 kg = 0.23	18 kg = 0.44	28 kg = 0.58	38 kg = 0.73	48 kg = 0.85	64-66 kg = 0.98
10 kg = 0.27	20 kg = 0.46	30 kg = 0.62	40 kg = 0.76	50 kg = 0.88	68 kg = 0.99

### **Method of administration**

#### Preparation of the patient

For specific patient preparation, see section 4.4.

#### Administration of GLUSCAN and PET examination

The activity of Fludeoxyglucose (<sup>18</sup>F) has to be measured with a calibrator immediately prior to injection. The injection must be strictly intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

The emission scans are usually started 40 to 60 minutes after the injection of Fludeoxyglucose ( $^{18}\text{F}$ ). Provided a sufficient activity remains for adequate counting statistics, Fludeoxyglucose ( $^{18}\text{F}$ ) PET can also be performed up to two or three hours after administration, thus reducing background activity. If required, repeated Fludeoxyglucose ( $^{18}\text{F}$ )-PET examinations can be reiterated within a short period of time.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

#### Indication of the PET 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

GLUSCAN should be given to sufficiently hydrated patients fasting for a minimum of 4 hours, in order to obtain a maximum target of activity, since glucose uptake in the cells is limited ("saturation kinetics"). The amount of liquid should not be limited (beverages containing glucose must be avoided).

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*

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 hyperglycemia may result in a reduced sensitivity of GLUSCAN, especially when glycemia is greater than 8 mmol/L. Similarly Fludeoxyglucose ( $^{18}\text{F}$ )-PET 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 GLUSCAN 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 Fludeoxyglucose ( $^{18}\text{F}$ ) and therefore lead to false positive results.

False positive or false negative FDG-PET 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 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 Fludeoxyglucose ( $^{18}\text{F}$ )

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, lower oesophagus cancer and suspicion of recurrent ovarian cancer, only positive predictive values have to be considered because of a limited sensitivity of FDG-PET.

Fludeoxyglucose ( $^{18}\text{F}$ ) 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 reduced detection of lesions smaller than 1 cm.

It is recommended that Fludeoxyglucose ( $^{18}\text{F}$ )-PET images shall be interpreted in relation with tomographic anatomical imaging modalities (e.g. CT, ultrasonography, MRI). Fusion of the functional Fludeoxyglucose ( $^{18}\text{F}$ )-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 tumours, lymphoma, melanoma, lung cancers and recurrent colorectal or ovarian cancers.

### 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.

GLUSCAN 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<sup>+</sup> radiation and annihilation photons by using an appropriate shielding when performing withdrawals from the vial and injections.

## **4.5 Interaction with other medical 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 Fludeoxyglucose ( $^{18}\text{F}$ ) 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 influences the influx of Fludeoxyglucose ( $^{18}\text{F}$ ) into the cells. In the case of high blood glucose levels as well as low plasma insulin levels, the influx of Fludeoxyglucose ( $^{18}\text{F}$ ) into organs and tumours is reduced.

## **4.6 Pregnancy and lactation**

### Pregnancy

There is no clinical experience with the use of Fludeoxyglucose ( $^{18}\text{F}$ ) in pregnant women.

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.

Radionuclidic procedures carried out on pregnant women involve radiation doses to the foetus.

Administration of GLUSCAN at activity of 400 MBq results in an absorbed dose to the uterus of 8.4 mGy.

In this dose range, lethal effects and the induction of malformations, growth retardations and functional disorders are not to be expected; however, the risk of the induction of cancer and hereditary defects may be increased.

GLUSCAN should not be administered during pregnancy unless clearly necessary or when the benefit of the mother outweighs the risk of the foetus.

#### Lactation

Fludeoxyglucose ( $^{18}\text{F}$ ) is excreted into breast milk. Before administering Fludeoxyglucose ( $^{18}\text{F}$ ) 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. When appropriate, milk may be drawn off prior to administration of GLUSCAN. Moreover, for radioprotection purposes, it is recommended to avoid close contact between the mother and the infant during the initial 12 hours following injection.

#### Fertility

No studies on the effects on fertility have been performed.

### **4.7 Effects on 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 Fludeoxyglucose ( $^{18}\text{F}$ ) 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. Thus these effects can be expected with a low probability. After administration of the maximum recommended activity of Fludeoxyglucose ( $^{18}\text{F}$ ), the effective dose is about 9.5 mSv.

### **4.9 Overdose**

An overdose in the pharmacological sense is unlikely with the doses used for diagnostic purposes. If an overdose of Fludeoxyglucose ( $^{18}\text{F}$ ) has been administered, the radiation 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: Radiopharmaceutical product for diagnosis  
ATC code: V09IX04

At the chemical concentrations used for diagnostic examinations, Fludeoxyglucose ( $^{18}\text{F}$ ) does not appear to have any pharmacodynamic activity.

## 5.2 Pharmacokinetic properties

Fludeoxyglucose ( $^{18}\text{F}$ ) is a glucose analogue which is accumulated in all cells using glucose as primary energy source. Fludeoxyglucose ( $^{18}\text{F}$ ) is accumulated in tumours with a high glucose turnover. Following intravenous injection, the pharmacokinetic profile of Fludeoxyglucose ( $^{18}\text{F}$ ) 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 Fludeoxyglucose ( $^{18}\text{F}$ ) 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 Fludeoxyglucose ( $^{18}\text{F}$ ) into the cells occurs due to a changed tissue distribution and glucose metabolism.

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

In healthy subjects, Fludeoxyglucose ( $^{18}\text{F}$ ) is widely distributed throughout the body, particularly in the brain and heart, and to a lesser degree in the lungs and liver.

Elimination of Fludeoxyglucose ( $^{18}\text{F}$ ) 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 the renal elimination of Fludeoxyglucose ( $^{18}\text{F}$ ), the entire urinary system, particularly the bladder, exhibits marked activity.

Fludeoxyglucose ( $^{18}\text{F}$ ) 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 seizure free phases.

Approximately 3 % of the injected activity are taken-up by the myocardium within 40 minutes. The distribution of Fludeoxyglucose ( $^{18}\text{F}$ ) 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.

Fludeoxyglucose ( $^{18}\text{F}$ ) 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, 50fold human dose in dogs and 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 carcinogenic potential have not been performed because of the intended clinical use of the substance (usually a single intravenous application of the substance in the range of nanograms or micrograms).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium Chloride 0.9%,  
Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf life**

10 hours after production time and 8 hours following the first use.

The date and time of the expiration are indicated on the external side of the original packaging as well as on the vial.

### **6.4 Special precautions for storage**

The product should be stored at a temperature below +25°C in its original packaging.

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

### **6.5 Nature and contents of container**

10 mL glass vial, colourless Type I of the European Pharmacopoeia, closed by a rubber stopper covered by Teflon and sealed by an aluminium capsule.

One vial contains maximum 10 mL of solution, corresponding to an active concentration of 600 MBq per mL at calibration time.

### **6.6 Special precautions for disposal**

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.

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

## **7. MARKETING AUTHORISATION HOLDER**

Advanced Accelerator Applications SA (AAA)

20 rue Diesel

01630 SAINT GENIS POUILLY

FRANCE

tel: +33 4 50 99 30 70

telefax: +33 4 50 99 30 71

e-mail: [info@adacap.com](mailto:info@adacap.com)

## **8. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

## 11. DOSIMETRY

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

<b>Dose absorbed per unit of activity administered (mGy/MBq)</b>					
<b>Organ</b>	<b>Adult</b>	<b>15 yrs old</b>	<b>10 yrs old</b>	<b>5 yrs old</b>	<b>1 yr old</b>
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	0.0086	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
<b>Effective dose (mSv/MBq)</b>	<b>0.019</b>	<b>0.025</b>	<b>0.036</b>	<b>0.050</b>	<b>0.095</b>

For GLUSCAN, the effective dose resulting from the administration of an activity of 500 MBq is about 9.5 mSv (for an individual weighing 70 kg).

For this activity of 500 MBq, the radiation doses delivered to the critical organs, bladder, heart and brain are respectively: 80 mGy, 31 mGy and 14 mGy.

## 12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

GLUSCAN is delivered in multidose vial.

GLUSCAN package must be checked before use and the activity measured using a calibrator.

The medicinal product may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection.

Withdrawals should be performed under aseptic conditions. The vials must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

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

Control of radiochemical purity by thin layer chromatography (TLC)

This control is described in the European Pharmacopoeia (current edition) monograph 1325.

Examine by thin-layer chromatography (*Ph. Eur.* 2.2.27) using a TLC silica gel plate R (*Ph. Eur. Reference code: 1116700*).

Test solution: the preparation to be examined.

Apply 2 $\mu$ L of the test solution to the plate. Develop over a path of 8 cm (about 10 minutes) using a mixture of 5 volumes of water R and 95 volumes of acetonitrile R.

Allow the plate to dry in air for 15 min.

Determine the distribution of radioactivity using a suitable detector.

Not less than 95% of the total radioactivity is found in the spot corresponding to  $^{18}\text{F}$ -FDG ( $R_f$  about 0.45).

Possible contaminants are [ $^{18}\text{F}$ ]fluoride ( $R_f$  0.0) and partially acetylated  $^{18}\text{F}$ -FDG derivatives ( $R_f$  ranges from 0.8 to 0.95).