SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FDG BioM® Multidose Injection – Fluorodeoxyglucose-(^{18}F)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The activity per vial ranges from 37 MBq to 222000 MBq (1 to 6000 mCi) at the date and time of dispensing.

Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

Excipient with known effect: sodium chloride 9 mg/ml. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile Solution for injection
Clear, colourless or slightly yellow solution, with a pH between 4.5 and 8.5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is for diagnostic use only.

Fluorodeoxyglucose-(^{18}F) is a positron emitting radiopharmaceutical used in PET (Positron Emission Tomography) for the

- identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures and tumour.
- assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

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4.2. Posology and method of administration

Posology

Adults and elderly

The recommended activity for an adult weighing 70 kg is 100 to 400 MBq or 2.7 to 10.8 mCi (this activity has to be adapted according to the body weight of the patient, the type of camera used and acquisition mode), administered by direct intravenous injection.

Renal impairment

Extensive dose-range and adjustment studies with this product in normal and special populations have not been performed. The pharmacokinetics of Fluorodeoxyglucose (^{18}F) in renally impaired patients has not been characterised.

Paediatric population

The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the EANM paediatric task group Dosage Card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the body-mass-dependent coefficients given in the table below.

$$A[MBq]_{Administered} = \text{Baseline Activity} \times \text{Coefficient}$$

The Baseline Activity for 2D imaging is 25.9 MBq or 0.7 mCi and for 3D imaging 14.0 MBq or 0.38 mCi (recommended in children).

Weight [kg]	Coefficient	**Weight [kg]**	Coefficient	**Weight [kg]**	Coefficient
3	1	**22**	5.29	**42**	9.14
4	1.14	**24**	5.71	**44**	9.57
6	1.71	**26**	6.14	**46**	10.00
8	2.14	**28**	6.43	**48**	10.29
10	2.71	**30**	6.86	**50**	10.71
12	3.14	**32**	7.29	**52-54**	11.29
14	3.57	**34**	7.72	**56-58**	12.00
16	4.00	**36**	8.00	**60-62**	12.71
18	4.43	**38**	8.43	**64-66**	13.43
20	4.86	**40**	8.86	**68**	14.00

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Method of administration

For patient preparation, see section 4.4.
The activity of Fluorodeoxyglucose (^{18}F) has to be measured with activimeter immediately prior to injection.
The injection of Fluorodeoxyglucose (^{18}F) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

Precautions to be taken before handling or administering the medicinal product
For intructions on dilution of the medical product before administration, see section 12.

Image acquisition
The emission scans are usually started 45 to 60 minutes after the injection of Fluorodeoxyglucose (^{18}F). Provided a sufficient activity remains for adequate counting statistics, Fluorodeoxyglucose (^{18}F)-PET can also be performed up to two or three hours after administration, thus reducing background activity.

If required, repeated Fluorodeoxyglucose (^{18}F) PET examinations can be reiterated within a short period of time.

4.3. Contraindications

Hypersensitivity to the active substance -and to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

- *Renal impairment*
  In patients with reduced kidney function, careful consideration of the indication is required since an increased radiation exposure is possible in these patients.

- *Inflammatory bowel disease*
  In the exploration of inflammatory bowel diseases, diagnostic performance of Fluorodeoxyglucose (^{18}F) has not been directly compared with that of scintigraphy using labelled white blood cells which may be indicated prior to Fluorodeoxyglucose (^{18}F) PET or after Fluorodeoxyglucose (^{18}F) PET when inconclusive.

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- *Paediatric population*
  Paediatric population, see section 4.2.
  Careful consideration of the indication is required since the effective dose per MBq is higher in children than in adults (see section 11).

Patient preparation

Fluorodeoxyglucose (^{18}F)-BioM® should be given to sufficiently hydrated patients fasting for a minimum of 4 hours, in order to obtain a maximum target 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 their bladder prior to and after the PET examination.

- *Oncology and neurology and infectious diseases*
  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 Fludeoxyglucose (^{18}F)-BioM®, especially when glycaemia is greater than 8 mmol/L. Similarly, PET with fludeoxyglucose (^{18}F) 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 Fludeoxyglucose (^{18}F)-BioM® 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 PET images with fludeoxyglucose (^{18}F)

Infectious and/or inflammatory diseases as well as regenerative processes after surgery can result in a significant uptake of fludeoxyglucose (^{18}F) and therefore lead to false positive results, when search for infectious or inflammatory lesions is not the aim of the fludeoxyglucose (^{18}F) PET. In cases where fludeoxyglucose (^{18}F) accumulation can be caused by either cancer, infection or inflammation, additional diagnostic techniques for the determination of the causative pathologic alteration may be required to supplement the information obtained by PET with fludeoxyglucose (^{18}F). In some settings e.g. staging of myeloma, both malignant and infectious foci are searched for and may be distinguished with a good accuracy on topographic criteria e.g. uptake at extramedullary sites and/or bone and joint lesions would be atypical for multiple myeloma lesions and identified cases

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associated with infection. There are currently no other criteria to distinguish infection and inflammation by means of fludeoxyglucose (^{18}F) imaging.

False positive or false negative PET with fludeoxyglucose (^{18}F) results cannot be excluded after radiotherapy within the first 2-4 months. If the clinical indication is demanding an earlier diagnosis by PET with fludeoxyglucose (^{18}F), the reason for earlier PET with fludeoxyglucose (^{18}F) 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 PET with fludeoxyglucose (^{18}F), the reason for earlier PET with fludeoxyglucose (^{18}F) examination must be reasonably documented. In case of chemotherapy regimen with cycles shorter than 4 weeks, the PET with fludeoxyglucose (^{18}F) 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 PET with fludeoxyglucose (^{18}F).
Fludeoxyglucose (^{18}F) is not effective in detecting brain metastases.

Sensitivity of coincidence PET (positron emission tomography using a gamma-camera or CDET) scanner systems, is reduced in comparison to dedicated PET, resulting in reduced detection of lesions smaller than 1 cm; as a consequence CDET is not recommended in any indication and should be used only if dedicated PET is not available.

It is recommended that fludeoxyglucose (^{18}F) PET images shall be interpreted in relation with tomographic anatomical imaging modalities (e.g. CT, ultrasonography, MRI).

When a hybrid PET-CT scanner is used with or without administration of CT contrast media, some artefacts may occur on the PET images.

<u>After the procedure</u>
It is recommended to avoid any close contact between the patient and young children and pregnant women during the initial 12 hours following the injection.

<u>Specific warnings</u>
Depending on the time when you administer the injection, the content of sodium given to the patient may in some cases be greater than 1 mmol (23 mg).
This should be taken into account in patient on low sodium diet.

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 (Ohira 2008**)**, valproate, carbamazepine, phenytoin, phenobarbital and catecholamines.

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Under administration of colony-stimulating factors (CSFs), there is an increased uptake of Fluorodeoxyglucose (^{18}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 Fluorodeoxyglucose (^{18}F) into the cells. In the case of high blood glucose levels as well as low plasma insulin levels, the influx of Fluorodeoxyglucose (^{18}F) into organs and tumours is reduced.

No formal studies on the interaction between Fluorodeoxyglucose (^{18}F) and any contrast for computed tomography have been performed.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.) alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus.
Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

Breastfeeding

Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 12 hours and the expressed feeds discarded.
Close contact with infants should be restricted during the initial 12 hours following injection.

4.7. Effects on ability to drive and use machines

Not relevant.

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4.8. Undesirable effects

Undesirable effects after the administration of Fluorodeoxyglucose (^{18}F) have not been observed to date.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 7.6 mSv when the maximal recommended activity of 400 MBq is administered these adverse reactions are expected to occur with a low probability.

4.9. Overdose

In the event of administration of a radiation overdose with Fluorodeoxyglucose (^{18}F) the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical
ATC code: V09IX 04
At the chemical concentrations used for diagnostic examinations, Fluorodeoxyglucose (^{18}F) does not appear to have any pharmacodynamic activity.

5.2. Pharmacokinetic properties

Distribution
Fluorodeoxyglucose (^{18}F) is a glucose analogue, which is accumulated in all cells using glucose as primary energy source. Fluorodeoxyglucose (^{18}F) is accumulated in tumours with a high glucose turnover.
Following intravenous injection, the pharmacokinetic profile of Fluorodeoxyglucose (^{18}F) in the vascular compartment is biexponential. It has a distribution time of 1 minute and an elimination time of approximately 12 minutes.
In healthy subjects, Fluorodeoxyglucose (^{18}F) is widely distributed throughout the body, particularly in the brain and heart, and to a lesser degree in the lungs and liver.

Organ uptake
The cellular uptake of Fluorodeoxyglucose (^{18}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 Fluorodeoxyglucose (^{18}F) into the cells occurs due to a changed tissue distribution and glucose metabolism.

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

Fluorodeoxyglucose (^{18}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.

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

5.3. Preclinical safety data

Toxicological studies have demonstrated that with a single IV injection of Fluorodeoxyglucose (^{18}F) and 50-fold human dose in dogs and the 1000-fold human dose in mice no deaths were observed. This medicinal product is not intended for regular and continuous administration.

Mutagenecity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Sodium chloride
- Water for injections

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6.2. Incompatibilities

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

6.3. Shelf life

16 hours from the end of synthesis time.
Date and time of expiry are indicated on the packaging and the certificate of conformity and analysis.

6.4. Special precautions for storage

Store in the original package at temperature below 30°C
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5. Nature and contents of the container

15 mL multi-dose, colourless glass vial, European Pharmacopoeia Type I, closed with a Teflon chlorobutyl stopper and an aluminium seal.

Pack size: One multidose vial contains 0.5 to 10 mL of solution, corresponding to 37 to 222000 MBq (1 to 6000 mCi) at calibration time.

6.6. Special precautions, for disposal and other handling

General warnings
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

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

For instructions on dilution of the medicinal product before administration, see section 12.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

MAL14075037AZ

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th July 2014

10. DATE OF REVISION OF THE TEXT

Created on 13th August 2013

11. INTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The package must be checked before use and the activity measured using an activimeter.

Withdrawals should be performed under aseptic conditions. The vials must not be opened before 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 or using an authorized automated application system.
If the integrity of this vial is compromised, the product should not be used.

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

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

12. DOSIMETRY

For Fluorodeoxyglucose (^{18}F)-BioM®, the effective dose resulting from the administration to an adult of an activity of 400 MBq is about 7.6 mSv.

For this activity of 400 MBq, the radiation doses delivered to the critical organs, bladder, heart and brain are respectively: 52 mGy, 27 mGy and 15 mGy.

The table below shows the dosimetry as calculated according to ICRP 106 Publication.

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ORGAN	DOSE ABSORBED PER UNIT OF ACTIVITY ADMINISTERED (mGy/MBq)				
	Adult	15 year old	10 year old	5 year old	1 year old
Adrenals	0.012	0.016	0.024	0.039	0.071
Bladder	0.130	0.160	0.250	0.340	0.470
Bone surfaces	0.011	0.014	0.022	0.034	0.064
Brain	0.038	0.039	0.041	0.046	0.063
Breast	0.009	0.011	0.018	0.029	0.056
Gall bladder	0.013	0.016	0.024	0.037	0.070
Gastrointestinal tract	0.011	0.014	0.022	0.035	0.067
Stomach	0.012	0.016	0.025	0.040	0.073
Small Intestine	0.013	0.016	0.025	0.039	0.070
Colon	0.012	0.015	0.024	0.038	0.070
-Upper Large Intestine	0.014	0.017	0.027	0.041	0.070
-Lower Large Intestine					
Heart	0.067	0.087	0.130	0.210	0.380
Kidneys	0.017	0.021	0.029	0.045	0.078
Liver	0.021	0.028	0.042	0.063	0.120
Lungs	0.020	0.029	0.041	0.062	0.120
Muscles	0.010	0.013	0.020	0.033	0.062
Oesophagus	0.012	0.015	0.022	0.035	0.066
Ovaries	0.014	0.018	0.027	0.043	0.076
Pancreas	0.013	0.016	0.026	0.040	0.076
Red marrow	0.011	0.014	0.021	0.032	0.059
Skin	0.008	0.010	0.015	0.026	0.050
Spleen	0.011	0.014	0.021	0.035	0.066
Testes	0.011	0.014	0.024	0.037	0.066
Thymus	0.012	0.015	0.022	0.035	0.066
Thyroid	0.010	0.013	0.021	0.034	0.065
Uterus	0.018	0.022	0.036	0.054	0.090
Remaining organs	0.012	0.015	0.024	0.038	0.064
EFFECTIVE DOSE (mSv/MBq)	**0.019**	**0.024**	**0.037**	**0.056**	**0.095**

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