ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
France		Advanced Accelerator Applications 20 rue Diesel 01630 Saint Genis Pouilly FRANCE	GLUSCAN 500	500MBq/mL at calibration time	Solution for injection	Intravenous use	For 1mL of drug product: Fludeoxyglucose (18F) – 500MBq at calibration time, Water for injection – 1.00g, Sodium citrate – 0.62% (v/v), Sodium chloride – 0.41% (v/v), Hydrochloric acid 0.39% (v/v), Ethanol 0.31% (v/v) Sodium hydroxide 0.24% (v/v)
Germany		Advanced Accelerator Applications 20 rue Diesel 01630 Saint Genis Pouilly FRANCE	GLUSCAN 500	500MBq/mL at calibration time	Solution for injection	Intravenous use	For 1mL of drug product: Fludeoxyglucose (18F) – 500MBq at calibration time, Water for injection – 1.00g, Sodium citrate – 0.62% (v/v), Sodium chloride – 0.41% (v/v), Hydrochloric acid 0.39% (v/v), Ethanol 0.31% (v/v) Sodium hydroxide 0.24% (v/v)
Poland		Advanced Accelerator Applications 20 rue Diesel 01630 Saint Genis Pouilly FRANCE	GLUSCAN PL	500MBq/mL at calibration time	Solution for injection	Intravenous use	For 1mL of drug product: Fludeoxyglucose (18F) – 500MBq at calibration time, Water for injection – 1.00g, Sodium citrate – 0.62% (v/v), Sodium chloride – 0.41% (v/v), Hydrochloric acid 0.39% (v/v), Ethanol 0.31% (v/v) Sodium hydroxide 0.24% (v/v)
Portugal		Advanced Accelerator Applications	GLUSCAN 500	500MBq/mL at calibration time	Solution for injection	Intravenous use	For 1mL of drug product: Fludeoxyglucose (18F) – 500MBq

		20 rue Diesel 01630 Saint Genis Pouilly FRANCE					at calibration time, Water for injection – 1.00g, Sodium citrate – 0.62% (v/v), Sodium chloride – 0.41% (v/v), Hydrochloric acid 0.39% (v/v), Ethanol 0.31% (v/v) Sodium hydroxide 0.24% (v/v)
Spain		Advanced Accelerator Applications 20 rue Diesel 01630 Saint Genis Pouilly FRANCE	GLUSCAN 500	500MBq/mL at calibration time	Solution for injection	Intravenous use	For 1mL of drug product: Fludeoxyglucose (18F) – 500MBq at calibration time, Water for injection – 1.00g, Sodium citrate – 0.62% (v/v), Sodium chloride – 0.41% (v/v), Hydrochloric acid 0.39% (v/v), Ethanol 0.31% (v/v) Sodium hydroxide 0.24% (v/v)

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF GLUSCAN 500 AND ASSOCIATED NAMES (SEE ANNEX I)

Gluscan is a radiopharmaceutical medicinal product composed of fludeoxyglucose (^{18}F), abbreviated as FDG. Fludeoxyglucose (^{18}F) is a glucose analogue which is accumulated in all cells using glucose as a primary energy source. Fludeoxyglucose (^{18}F) is accumulated in tumours with a high glucose turnover. Fludeoxyglucose (^{18}F) passes the blood-brain barrier, and epileptogenic foci exhibit a reduced glucose metabolism in the seizure free phases. Fludeoxyglucose (^{18}F) is also accumulated by the myocardium, especially during and after a reversible myocardial ischemia when an increased glucose uptake occurs into the myocardial cell.

Gluscan is intended to be used in the oncological, cardiological, neurological indications and infectious or inflammatory diseases. The three indications oncology, cardiology and neurology are established in the core SmPC for this active substance. These indications were each based on a biological process, i.e. glucose uptake by specific organs or tissues: increased uptake by the malignant cells, persistent uptake by the viable jeopardised myocardial cells and decreased uptake by the neurons of the cortex responsible for promoting epilepsy when patient is not presenting with a crisis.

The particularity of the present application is that the proposed indication in infectious or inflammatory diseases is currently not part of the core SPC for FDG. As with the other indications in the core SmPC, the indication in infectious or inflammatory diseases is also based on a biological process: glucose uptake in tissue or structures with an abnormal content of activated white blood cells. It is intended to be used in patients with infectious or inflammatory diseases in the proposed settings. A technique for specific imaging of tissues or structures with an abnormal content of activated white blood cells is likely to provide important information in the management of patients with infectious and inflammatory diseases.

The legal basis for this application refers to: Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well established medicinal use supported by bibliographic literature.

However, a number of concerns were raised by the objecting CMS which did not consider the application for Gluscan acceptable. The issue was referred to the CMD(h) and an assessment was carried out by the RMS. Because no agreement was reached at Day 60, the procedure was referred to the CHMP. The CHMP assessed the dossier and the available data, including the issues raised by the objecting CMS.

Overall 6125 patients worldwide have to date been reported in published series (excluding cases reports) who benefited from FDG PET indicated for inflammation/and infection (excluding incidental findings of infection/inflammation in patients referred for another indication**).** The first publication of a series in 7 patients with sarcoidosis dates from 1994 and a total of 1988 patients have been reported in published series for EU series from 1999 to 2009. In addition FDG has already been registered in 3 EU Member States (EI, UK & CZ) for this "new" indication in infectious or inflammatory diseases, and the early results seen to be favourable in these countries, have been confirmed with experience of continuous use. The CHMP agreed that there has been a long experience of continuous use of FDG, which support its well-established use.

The quality of data used for assessment of efficacy has been checked (homogeneity of the series in a given setting according to explicit inclusion criteria, images acquired according to an accepted protocol available for FDG and also for the comparator in comparative studies and description of the standard of truth obtained in all evaluable patients, except in case of a study of the impact on management only) and shown to be in line with the requirements of the Points to Consider (PtC) on the Evaluation of Diagnostic Products (CPMP/EWP/1119/98). The quality of the studies that have been retained for the analysis, after many other have been discarded, has been confirmed in published meta-analysis or recent review articles, in several settings.

Furthermore for all the requested infectious and inflammatory diseases, the diagnostic performance has been determined and found to be at least equal to that of the comparator, when the studies of the same disease have been pooled together. A high overall impact on patient management has been reported for the overall indication and for every specific disease. This impact was addressed indirectly for two settings.

The CHMP agreed that the clinical efficacy (diagnostic performance and impact on diagnostic thinking) of PET/PET-CT with FDG had been adequately demonstrated.

The technical performance - the superiority of FDG over all radiopharmaceutical comparators has been documented in articles, and is applicable to all the proposed settings of these indications.

It was concluded that:

- that the intrinsic resolution of a PET scanner is twice as good as that of a gamma-camera with a low energy collimator used for technetium-99m and more than twice with a medium energy collimator used for gallium-67 or indium-111,
- that the waiting time for the patient (1h between injection and image acquisition) is the shortest of all registered radiopharmaceuticals in this field,
- that the other inconveniences/risks for the patient are less than those of gallium-67 (cumbersome patient preparation) or of labelled white blood cells (WBC) which requires withdrawal of a large quantity of blood and encompasses risk of errors in re-injection;
- that the dosimetry of FDG PET is similar to that of technetium-99m labelled products and more favourable than that of gallium-67 or indium-111 radiopharmaceuticals.

The CHMP therefore acknowledged that the technical performance and procedural convenience of FDG are of overall benefit in this indication. This should be carefully differentiated to diagnostic performance.

Concerning the diagnostic efficacy of fludeoxyglucose (^{18}F) in patients with immunodeficiency, the Applicant has provided data from literature that demonstrates that FDG PET is effective in AIDS patients to detect malignancies and/or infectious disease.

For the effect of a decrease in leukocytes counts in patients with leukocyte dysfunction, it has been demonstrated in myeloma patients (Mahfouz (2005)), that “FDG-PET can be diagnostic in the setting of severe neutropenia, unlike most other nuclear imaging techniques”. It is obvious that *in vitro* labelling of circulating WBC, which is requested with some of the comparators (^{111}In oxine or ^{99m}Tc HMPAO labelled WBC) is impeded by a poor leukocytes count. However this is not the case for FDG which targets *in vivo* foci of activated leukocytes. The Applicant claims that to the best of their knowledge (at this point in time), there has been no report about leukocyte dysfunction that leads to the fact they are unable to be activated in the vicinity of targets cells.

For patients under specific concomitant medications such as antibiotics and anti-inflammatory drugs, common sense indicates that in the corresponding claimed settings in long lasting or chronic illness (fever of unknown origin (FUO), chronic infection of bone, suspicion of infected hip prosthesis, active inflammatory bowel disease (IBD) …), they were not effective since the patient was referred to FDG PET. Since FDG PET accurately diagnoses those conditions, the interference of those unavoidable therapies would certainly be considered to be minor. This has been confirmed in 2000 by Meller: “Antibiotic and immunosuppressive therapy did not seem to influence the results of FDG scanning, as 66% of the patients who were treated exhibited a pathological uptake that clarified the cause of fever.”

Corticosteroids have been shown to decrease profoundly or suppress FDG uptake. This was mostly reported in sarcoidosis and also in vasculitis (Rehàk 2006). In this setting, Walter (2005) reported a detection rate of pathological large vessel of 8/9=89% without treatment vs. 10/21=48% with corticosteroids. A paragraph highlighting the effect of corticosteroids on FDG uptake in the infection and inflammation indication, and consideration of the possible temporary withdrawal of this therapy was proposed by a CMS in section 4.5 of

the SmPC (Intercation with other medicinal products and other forms of interaction), and was subsequently endorsed by the CHMP.

It should be borne in mind that the pharmacodynamic effects of these drugs (e.g. corticosteroids) on leukocytes that are taking-up FDG is identical in all settings, and that there is no need for a setting-by-setting demonstration of the interference, even though the consequence on diagnostic thinking may be different from one setting to another.

There is no reason to anticipate a lower efficacy in children as compared to adults for a diagnostic examination that is useful in a large spectrum of causes, which are both found in children and adults, without any metabolic specificity in children. It is also noted that FDG has been registered in childhood lymphoma for a long time, even though there were not at that time, more published data in children than currently in infection/inflammation. It is also true that a careful weighting of the indication is requested in the SmPC for any paediatric use. The CHMP therefore agreed that the current wording of the SmPC concerning the use in children is adapted also for infection/inflammation (by deleting the word "oncology").

The Applicant also refers to some specific studies that have been performed for IBD (Lemberg 2005, Löffler 2006) in a total of 88 patients, and for chronic granulomatous disease with a gut lesion in 5 of the 7 patients of Güngör (2001), and to some children who have also been included in a series with other conditions (e.g. 13 children with FUO). The impact on management was as obvious as in adults (FUO, IBD) and even more striking in the case of granulomatosis (Güngör 2001). It would seem to be detrimental and against the Euratom Directives (optimisation of irradiation) to exclude children from the benefit of FDG PET in infection and inflammation (in particular FUO or IBD), since some other scintigraphic options (gallium-67 scintigraphy, indium-111 WBC scintigraphy) are actually more irradiating and/or more demanding and would lead to the management of children in a less convenient way than adults.

Although it is argued that the effective dose of irradiation from ^{99m}Tc labelled compounds is similar to that of FDG, the easiest to use ^{99m}Tc labelled comparator, immunoscintigraphy, is contraindicated in children for a well documented reason; that the occurrence of antibodies will impede further use. The inconveniences and risks of ^{99m}Tc HMPAO *in vitro* labelled leukocytes are obvious: withdrawal of a large quantity of blood in a child for *in vitro* labelling and anaphylaxia. Furthermore, the ^{99m}Tc HMPAO *in vitro* labelled leukocytes are not indicated for the whole spectrum covered by FDG, since non-circulating WBC involved in many chronic infectious and inflammatory conditions are not labelled, and the background in the bone marrow is high, impeding detection of foci in the axial skeleton.

As mentioned above, it would be against the optimisation principle of the Euratom Directive (implemented in the law of all EU Member States) to exclude children from the benefit of FDG PET in infectious/inflammatory diseases, since the other scintigraphic options are actually more irradiating for the child (gallium-67 scintigraphy, indium-111 WBC scintigraphy) or for the personnel (*in vitro* labelling with technetium-99m HMPAO), without any benefit in efficacy. By this substitution of gallium-67 by FDG, radiation exposure is reduced by a factor 3-5, which is of major significance in children with benign conditions. The CHMP therefore agreed that the paediatric population aged less than 18 years should be included in the SmPC. The subheading 'Population aged less than 18 years' under the section 4.2 Posology and method of administration has been amended, and the word "oncologic" has been deleted.

The Dosimetry Tables in section 11 already include calculated children's doses.

The use of FDG PET-CT has been reported in all of the 10 proposed indications in 'Infectious or inflammatory diseases', except for the detection of infection of hip prostheses, at this point in time. In this setting CT is of poor help due to artefacts induces by beam hardening in the vicinity of the metallic prosthesis. Conversely this is not a contra-indication as the non-attenuation corrected images of PET remain artefact-free.

The posology (in fact the injected activity) recommended in the Core SmPC, 100-400MBq with adaptation in children, is in line with the activity used in the reported clinical studies for infection/inflammation, whatever the machine used PET, CDET or PET-CT. No adaptation is necessary according to the clinical setting, while an adaptation is necessary (within the above range) according to the body weight of the patient and the type of PET(/CT) machine used for imaging.

The use of PET-CT is a matter of equipment of the PET centre and of professional guidelines (including the above mentioned Euratom Directive defining justification and optimisation of the irradiation), and does not need to be addressed in the SmPC, except when PET-CT has been shown to increase efficacy. This has been demonstrated for some settings in oncology and is reported in the Core SmPC, but is not currently the case in infection/inflammation.

The safety data for the combined PET/CT technology does not differ from that of PET; the only difference being an increase in radiation dose, due to the low dose CT, which produces no detectable consequence. The total effective dose of FDG PET/CT with a low dose CT is less than that of a full contrast enhanced diagnostic CT of the same area.

As radiation protection is a part of safety, it is also noted that, although all the registered diagnostic radiopharmaceuticals are globally safe, FDG is thought to be among the safest, and much less irradiating than gallium-67 or indium-111.

PET/CT is now the state-of-the-art for FDG detection and it is clear from literature and expert opinion that it cannot deteriorate technical and diagnostic performances when compared to PET alone. Most data have been obtained with PET alone and are therefore still valid; one could only consider that they would represent the minimum performance that could be anticipated with PET/CT. The CHMP therefore does not see the need for additional information to support the use of this technique in the ten requested infectious and inflammatory diseases and the proposed posology in these indications.

There is no impact on the SmPC at the moment since it has not been demonstrated that any of the settings of this indication significantly benefit from PET/CT fusion as compared to PET alone.

In a large majority of FDG studies published in oncology, cases of infection/inflammation have been reported as a source for false-positive findings: those FDG foci did not correspond to malignant tissue. This is already reported in the Core SmPC. It is clear that FDG is able to detect infection/inflammation as an incidental finding in patients referred for cancer. In the particular case of myeloma (which is now considered part of lymphoma) and indicates FDG as such, FDG has been deliberately used to search for infection prior to starting chemotherapy, in relation with the depletion of immunity and WBC.

Mahfouz (2005) performed 2,631 FDG-PET examinations in 1,110 patients with multiple myeloma for cancer staging and/or for the diagnosis of suspected infection. The medical records of the 248 patients with multiple myeloma whose FDG-PET was reported as showing increased radiotracer uptake at extramedullary sites and/or bone and joint lesions (that would be atypical for multiple myeloma) were reviewed, to identify cases associated with infection. A perfect positive predictive value (PPV) and a considerable impact on management were reported.

Although PPV was favourable, and impact on management was available, according to the PtC, it was agreed during previous discussions with the RMS, CMS and Applicant, that this important information would remain in section 4.4 of the SmPC as its inclusion would be of value for the prescription and interpretation of FDG-PET in this indication. The CHMP also agreed with this approach.

Thus the benefit/risk ratio is clearly favourable for FDG than for any of the other registered radiopharmaceuticals in the requested indication ‘Infectious and inflammatory diseases’.

GROUNDS FOR POSITIVE OPINION

In conclusion the CHMP considers that the benefit-risk profile is favourable for Gluscan (FDG) in the indication 'infectious or inflammatory diseases' addressed above.

Whereas

- the body of evidence on infectious or inflammatory diseases considered in the evaluation of this well-established use dossier is a careful selection of the studies according to the criteria of the Points to Consider (PtC) on the Evaluation of Diagnostic Products (CPMP/EWP/1119/98) and limited to the best documented clinical settings

- a high impact on patient management has been reported for the overall indication and for every infectious or inflammatory diseases

- the technical performance has been documented in articles, and is applicable to all the proposed infectious or inflammatory diseases

- satisfactory consideration has been given to situations such as patients with immunodeficiency, with leukocyte dysfunction and patients under specific concomitant medications affecting the viability and/or function of leukocytes (such as antibiotics, non-steroid anti-inflammatory drugs, etc)

- the use of Gluscan can be recommended in children also, for indications of infectious and inflammatory diseases

- PET-CT is now the state-of-the-art for FDG detection and does not show a deterioration in technical and diagnostic performances when compared to PET alone

the CHMP has recommended the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for GLUSCAN 500 and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.