HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

22 September 2010

CISNAF 100 MBq/ml, solution for injection
B/1 vial of 0.5 to 15 ml (CIP: 5773184)

CIS BIO INTERNATIONAL

sodium fluoride (^{18}F)
ATC code: V09IX06

Date of Marketing Authorisation: 27/05/2010

List I
Medicinal product for hospital use only

Radiopharmaceutical products must be used by qualified persons only. They should be only supplied to practitioners who have obtained the special authorisation provided for under Article R 1333-24 of the Public Health Code.

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic, and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Sodium fluoride (18F)

1.2. Indication

“This medicinal product is for diagnostic use only.

Sodium fluoride (^{18}F) is intended for use in positron emission tomography (PET).

PET with CISNAF is indicated as a diagnostic imaging procedure allowing a functional approach to pathologies, bone structures or even organs where enhanced fluoride (^{18}F) capture in the normal, pathological or metaplastic bone matrix is sought.

The indication for PET with sodium fluoride (^{18}F) has been particularly documented for the research of bone metastases in prostate, breast or lung cancer.”

1.3. Dosage

“This product is for direct intravenous administration only.

The average activity recommended in adults is 4 MBq/kg body weight. The injected activity can vary between 2 and 6 MBq/kg body weight, depending on the PET system used.

Children and adolescents:

The safety and efficacy of this product have not been established in patients under 18 years old. Other techniques not involving ionising radiation should be considered.

The use of this product in children and adolescents should be decided after a careful assessment of clinical needs and risk / benefit ratio in this patient population. The activity administered must be adjusted in accordance with the recommendations of the Working Group in Pediatrics (Pediatric Task Group) of the EANM. This activity can be calculated from the formula below and a multiplier based on the patient's body mass (Table 1):

Recommended activity [MBq] = 14 MBq x factor (Table 1)

Table 1

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

A minimum activity of 14 MBq is recommended in case of acquisition with 3D PET system and 26 MBq in the case of acquisition with 2D PET system. In children images acquisition in 3D mode should be preferred.

Static images are acquired between 30 minutes and 4 hours, usually 60 minutes after injection.

In some cases a "three phases" protocol can be achieved by dynamic acquisition and / or static images beginning immediately after injection."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2010)

V : Various
V09 : Diagnostic radiopharmaceuticals
V09I : Tumour detection
V09IX : Other diagnostic radiopharmaceutical for tumour detection
V09IX06 : Sodium fluoride (^{18}F)

2.2. Strictly comparable medicines

IASOFLU (sodium fluoride (^{18}F)), solution for injection; a marketing authorisation has been granted in 2008 but this product is not approved for hospital use (not evaluated by the Committee).

2.3. Medicinal products with same diagnostic objective

Most of the available radiopharmaceuticals are used with planar-mode single-photon emission (SPECT) gamma cameras or tomographs, unlike CISNAF which is used with a PET machine.

DPD-Technetium pertechnetate (ATC code: V09BA04)

- TECEOS, kit for the preparation of technetium [99mTc] 3,3-diphosphono-1,2-propanedicarboxylic acid (DPD) injection
  Indication: after reconstitution with an injectable solution of sodium pertechnetate [99mTc], this product can be used to detect areas of abnormal osteogenesis by bone scintigraphy.

Oxidronate sodium (or sodium hydroxymethylene diphosphonate - HMDP) (ATC code: V09BA01)

- OSTEOCIS, powder for solution for injection. Kit for the preparation of technetium (^{99m}Tc) oxidronate solution for injection
  Indication: This medicinal product is for diagnostic use only. After reconstitution with an injectable solution of sodium pertechnetate (^{99m}Tc), the injectable technetium (^{99m}Tc) oxidronate solution can be used as a diagnostic aid for skeletal scintigraphy to detect areas of abnormal osteogenesis.

- TECHNESCAN HDP, powder and kit for the preparation of technetium (^{99m}Tc) oxidronate solution for injection
  Indication: bone scintigraphy for the delimitation of areas of altered osteogenesis.

Sodium medronate (ATC code: V09BA02)

- AMERSCAN MEDRONATE II, kit for the preparation of injectable technetium (^{99m}Tc) medronate solution
  Indication: after reconstitution with an injectable solution of sodium pertechnetate (^{99m}Tc), this product can be used to detect areas of abnormal osteogenesis by bone scintigraphy.

Fludeoxyglucose (ATC code: V09IX04)

- FLUDEOXYGLUCOSE [^{18}F)-IBA, solution for injection

- FLUCIS, fludeoxyglucose [^{18}F] solution for injection (250 MBq/ml)
  FLUDEOXYGLUCOSE [^{18} F] CIS BIO INTERNATIONAL, solution for injection
- GLUCOTEP, solution for injection
  Indication: Fludeoxyglucose (^{18}F) is indicated in oncology, in imaging examinations, for functional examinations of diseases, organs or tissues that are being checked for increased glucose consumption […].

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The studies presented in the dossier are the result of a literature search. These same studies were used in the marketing authorisation dossier.

Bisphosphonates (^{99m}Tc) are the best comparator for this product. In fact, other radiopharmaceutical products are not specifically indicated in the detection of bone lesions. Sodium fluoride (^{18}F) is an agent that has been used in bone PET for a number of years and was approved by the FDA in 1972.
The French Medicine Agency (AFSSAPS) therefore based its decision on a bibliographical dossier.
The results of the studies are presented in Table 2.

Table 2: Comparison of technical performance between PET with sodium fluoride (^{18}F) and gamma scintigraphy with technetium (^{99m}Tc)-labelled bisphosphonates.

Study reference Year	Objectives Methods	Treatments compared Dosages Duration of treatment Numbers per group (randomised and analysed)	Characteristics of the population included	Primary endpoint and most relevant secondary endpoints	Efficacy results for the primary endpoint (and the most relevant secondary endpoints)
Schirrmeister[1] 1999 A	Detection of bone metastases in prostate, thyroid (stage III or IV) and lung cancer.	Comparison of the performance of F Na PET and bone scintigraphy (planar BS)	Cancer of the: Prostate: n = 20 Thyroid: n = 19 Lung: n = 5	Overall sensitivity (Se) and specificity (Sp) of the 2 methods	Se F Na PET 15/15=100% BS 13/15=87% Sp F Na PET 29/29=100% BS 20/29=69% Area under the curve F Na PET 0.99 BS 0.64, p<0.05
Schirrmeister[2] 1999 B	Detection of bone metastases in breast cancer The gold standard was a panel of diagnostic examinations	Comparison of the performance of F Na PET and bone scintigraphy (planar BS) with 99mTc methylene diphosphonate	Breast cancer: n=34 Mean age = 52 years old [37-75]	Sensitivity and specificity of the 2 methods	Se F Na PET 17/17=100% BS 11/17=65% Sp F Na PET 17/17=100% BS 12/17=70% Area under the curve F Na PET 1.00 BS 0.82, p<0.05
Hetzel[3] 2003	Detection of vertebral bone metastases in lung cancer	Comparison of the performance of F Na PET and bone scintigraphy (planar BS and SPECT)	Lung cancer n = 103 72 men and 31 women Mean age = 62 years old [38-81]	Sensitivity of the 3 methods	Se F Na PET 28/33=85% BS 17/33=52% BSSPECT 26/33=79% Area under the curve F Na PET 0.99 BS 0.77 BS SPECT 0.87, p<0.005 Impact on patient management F Na PET 10/103=9,7% BS SPECT 8/103=7.8%

[1] Schirrmeister H [1999A], Guhlmann A, Kotzerke J, Santjohanser C, Kuhn T, Kreienberg R, Messer P, Nussle K, Elsner K, Glatting G, Trager H, Neumaier B, Diederichs C, Reske SN. Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. J Clin Oncol 1999; 17: 2381-89.
[2] Schirrmeister H [1999B], Guhlmann A, Elsner K, Kotzerke J, Glatting G, Rentschler M, Neumaier B, Trager H, Nussle K, Reske SN. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET. J Nucl Med 1999; 40: 1623-9.

Even-Sapir[4] 2006	Detection of bone metastases in prostate cancer	Comparison of the performance of F Na PET and bone scintigraphy (planar BS) and SPECT (technetium medronate)	Prostate cancer: N=44 Mean age: 71.6 years old	Sensitivity and specificity of the 3 methods	Se F Na PET 23/23=100% BS 13/23=57% BS SPECT 18/23=78% Sp F Na PET 21/21=100% BS 12/21=57% BS SPECT 14/21=67%
Beheshti[5] 2008	Detection of bone metastases in prostate cancer	Comparison of the performance of F Na PET and F Fluorocholine (FCH) PET	Prostate cancer: n = 38 men 321 sites Prostate cancer confirmed by biopsy. Mean age of patients: 69 years old	Sensitivity and specificity of the 2 methods	Se F Na PET 81% FCH PET 74% , p=0.12 NS Sp F Na PET 93% FCH PET 99%, p=0.01 No difference in patient management between the 2 groups.

[3] Hetzel M, Arslandemir C, Konig HH, Buck AK, Nussle K, Glatting G, Gabelmann A, Hetzel J, Hombach V, Schirrmeister H. F-18 NaF PET for detection of bone metastases in lung cancer: accuracy, cost-effectiveness, and impact on patient management. J Bone Miner Res 2003; 18: 2206-14.

[4] Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer : 99mTc-MDP planar bone scintigraphy, single- and multi-field-of-view TEMP, 18F-Fluoride PET, and 18F-Fluoride PET/CT. J Nucl Med 2006; 47: 287-97.

[5]Beheshti M, Vali R, Waldenberger P, Fitz F, Nader M, Loidl W, Broinger G, Stoiber F, Fogelman I, Langsteger W. Detection of bone metastases in patients with prostate cancer by F-18 fluorocholine and F-18 fluoride PET-CT: a comparative study. Eur J Nucl Med Mol Imaging 2008; 35: 1766-74

Small series of cases were run in other indications, mainly thyroid and renal cancer. Considering the low level of evidence of these studies, they are not presented in this document.

3.2. Adverse effects

The Summary of Product Characteristics states that no serious adverse effects have been observed to date.

Moreover, it says that “exposure to ionising radiation may induce cancer or lead to the development of hereditary defects. Experience shows that, for diagnostic examinations in nuclear medicine, the frequency of these adverse effects is very low because of the low levels of activity used”.

3.3. Conclusion

The performance of PET/CT after administration of sodium fluoride (18F) was found superior to that of gamma scintigraphy using bisphosphonates labelled with technetium-99m in 5 studies from the literature research which included a limited number of patients (34 to 103 patients). In examinations for bone metastases, the sensitivity of the product ranged from 81% to 100% (vs 52 to 87% for the comparator), the specificity from 93% to 100% (vs 57 to 70% for the comparator). The limited number of patients included is due to constraints linked to the performance of these studies (limited availability of machines, difficulty of performing several radiation-based diagnostic examinations in the same patient, etc.). Moreover, it is regrettable that these studies did not present a calculation of the positive and negative predictive value, since these indicators can be used to establish the probability of the disease being present if the test is positive and of the disease not being present if the test is negative.

Since it is a medicinal product for diagnostic use, sodium fluoride (18F) has no direct effect on quality of life or survival time.

The adverse effects of the technique as a whole are linked to the ionising radiation and are expected to occur with a low probability given the low levels of activity used.

This product should be used in compliance with radioprotection measures.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The severity of the condition is defined by the results of the investigation.

This medicinal product is for diagnostic use.

The efficacy/adverse effects ratio for this medicine is high.

There are alternatives.

> Public health benefit:
>
> Positron emission tomography (PET) examinations with fludeoxyglucose are indicated mainly in investigations for metastases and in the monitoring of patients in oncology, particularly for breast, prostate and lung cancer.
>
> Metastatic cancer is a disease that constitutes a major burden. Improving breast cancer screening is one of the priorities set out in the Law of 9 August 2004 on public health policy.
>
> In the light of the clinical study data, PET after administration of sodium fluoride (^{18}F) gives better diagnostic performance than the comparator, gamma scintigraphy using bisphosphonates radiolabelled with technetium-99m. However, the improvement in patient management has not been demonstrated.
>
> Consequently, the public health benefit of the medicinal product CISNAF is expected to be small.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

CISNAF provides a level IV (minor) in improvement in actual benefit (IAB) compared to technetium scintigraphy in the detection of bone metastases in lung, prostate and breast cancers because of its superiority in diagnostic performance and in the reduction in adverse effects compared with the comparator.

Moreover, PET acquisition improves patient comfort by shortening the examination time.

Finally, if technetium-99m is not available (shortage of molybdenum 99), sodium fluoride (^{18}F) is an alternative to bone scintigraphy, since sodium fluoride (^{18}F) does not require a nuclear reactor but a medical cyclotron for its production.

4.3. Role in diagnostic strategy

The initial assessment of the spread of lung, prostate and breast cancers usually comprises bone scintigraphy to check for metastases, at least with forms that are advanced on diagnosis, since these are osteophilic cancers[7]. During follow-up, there must be a reason for checking for bone metastases, in particular the onset of bone pain or an increase in the concentration of the tumour marker (CEA, CA 15.3, PSA). It is not intended that two successive examinations (scintigraphy and fluoride (^{18}F) PET) should deliberately be performed in the same patient, even if this is acceptable in some cases and, after discussion, that fluoride (^{18}F) PET should be performed to obtain clarification about a suspect image in skeletal scintigraphy. The discovery of a bone metastasis changes the stage of the disease and influences the treatment (cancellation of curative surgery and indication for

chemotherapy in initial staging, hormone therapy or radiotherapy in a single location if discovered during follow-up, etc.).

Positron emission tomography (PET) is a functional imaging technique that is of proven clinical value, mainly in oncology[6]. The most commonly used tracer is fluorodeoxyglucose (^{18}F) or FDG[7]. Moreover, a guide to good practice in medical imaging examinations has been prepared by the learned societies and the trade unions concerned, with the support of the Directorate General for Nuclear Safety and Radiological Protection (DGSNR), and by HAS[8]. It looks at the value of PET. This guide is in the process of being updated by HAS.

PET with FDG is indicated mainly in the pretreatment assessment of breast cancer, in checks for remote metastases in progressive forms that have a poor prognosis, and in monitoring breast cancer to check for parietal or lymph node recurrences or metastases (grade B recommendations).

For the assessment of metastatic spread, there is no consensus about the examinations to be carried out (chest X-ray, echography of the abdomen and pelvis, bone scintigraphy, etc.). They are therefore prescribed according to the patient's age, his/her general health condition, the clinical stage of the disease and the preferences of the teams treating the patient[9].

PET with FDG is also indicated in assessments of the spread of bronchopulmonary cancer (grade B recommendations), in patients eligible for surgical treatment, for the determination of locoregional or remote spread[10].

In assessments of the spread of prostate cancer, imaging examinations are performed only if they have an impact on the management of the patient and for localised tumours according to the risk of recurrence established using the D'Amico classification[11]:

- in patients at low risk: an assessment of lymph node involvement or metastasis is not indicated.
- in patients at intermediate or high risk: it can include bone scintigraphy, a scan or MRI of the pelvis and abdomen[12] .

Bone scintigraphy can be performed by planar mode or tomographic gamma scintigraphy (using bisphosphonates radiolabelled with technetium-99m), or by PET/CT after administration of sodium fluoride (^{18}F). Like scintigraphy, PET now includes "whole body" acquisition allowing the entire skeleton to be visualised in a single examination. PET/CT after the administration of sodium fluoride (^{18}F) can thus in theory replace bone scintigraphy performed by gamma scintigraphy, and offers better image quality.

Finally, the consequences of recurring shortages of ^{99m}Tc generators could be avoided since ^{18}F is produced in a medical cyclotron and not in a nuclear reactor.

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[6] NICE METHODS, EVIDENCE & GUIDANCE. The Diagnosis and Treatment of Lung Cancer, February 2005

[7] Standards, options and recommendations on the use of fludeoxyglucose [18F] positron-emission tomography (PET-FDG) in oncology. French Federation of Cancer Centres – February 2002

[8] HAS evaluation and status report on positron-emission tomography coupled with computed tomography; 2005.

[9] Place of breast MRI in the pretreatment assessment of the locoregional spread of breast cancer. HAS Technology evaluation report March 2010

[10] ALD 30 – Malignant tumour, malignancy of the lymphatic or haematopoietic tissue Lung cancer and malignant pleural mesothelioma, HAS-INCA 2009

[11] D'Amico A, Altschuler M, Whittington R, Kao G, Malkowicz SB, Wein A. The use of clinical parameters in an interactive statistical package to predict pathological features associated with local failure after radical prostatectomy for prostate cancer.,Clin Perform Qual Health Care. 1993 ;1(4):219-22.

[12] HAS-INCA ALD 30 Guide – Prostate cancer - September 2008

Role of CISNAF in diagnostic strategy

PET after administration of CISNAF can in theory replace bone scintigraphy performed by gamma scintigraphy, and offers better image quality and several other technical advantages (shorter examination time, tomographic images covering the whole of the field explored, better quantification of radiopharmaceutical binding) for "checks for bone metastases of prostate, breast or lung cancers." It has the advantage that it is not performed with bisphosphonates (^{99m}Tc), which avoids the deterioration in image quality seen with bisphosphonate treatments and tolerance incidents that have been reported with bisphosphonates, even at the low doses used in scintigraphy.

In two of the three osteophilic cancers mentioned (lung and breast), PET after administration of FDG is also indicated and logically comes before fluoride (^{18}F) PET, in that it can also be used to detect abdominal malignancies but also most bone metastases, including those in the intramedullary stage. Fluoride (^{18}F) PET could be performed in complicated cases, for example where osteocondensing bone metastases are suspected.

4.4. Target population

The indication for sodium fluoride (^{18}F) PET has been documented more particularly in investigations for bone metastases of prostate, breast or lung cancer. However, this examination covers broader indications.

The standardised incidence of prostate cancer in France is 128.8/100,000 in 2010[13].

The incidence of bone metastases in progressive prostate cancer is 70%[14]. These metastases are what reveal the disease in 30% of cases. In this indication, the target population is estimated at 28,000 patients (the French population is 64 million inhabitants, 33,000,000 of them women and 31,000,000 men, as at 1 January 2009[15]).

The incidence of breast cancer was 101.5/100,000 in 2005. The incidence of bone metastases in progressive breast cancer is 70%. At present, between 8 and 12% of breast cancers treated in France are already metastatic at the time of diagnosis[16]. In this indication, the target population is estimated at 23,000 patients.

The incidence of lung cancer was 51.9/100,000 for men in 2010 and 17.8 for women. The incidence of bone metastases in progressive lung cancer is 30%. It is these metastases which reveal the disease in 20% of cases. In this indication, the target population is estimated at 6600 patients.

Overall, the population likely to benefit from sodium fluoride (18F) PET would be 57,600 patients a year.

For information purposes, in 2007 the number of procedures involving whole-body positron-emission tomography with a dedicated PET camera (CCAM code: ZZQL016) performed in France was estimated at 113,734[17].

Under the cancer plan, the number of authorisations for PET or PET-CT was fixed at 1 per 800,000 inhabitants.

[13] Source InVS
[14] Clinical expert report on the marketing authorisation
[15] Source INSEE
[16] MRI of the breast in the assessment of local spread – HAS 2010
[17] INVS Exposure of the French population to ionising radiation linked to medical diagnostic procedures in 2007. http://www.invs.sante.fr

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indications and at the dosages stated in the Marketing Authorisation.