HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 December 2011

ADREVIEW (^{123}I), solution for injection
1 glass vial of 74 MBq/ml (CIP code: 564 459-3)

Applicant: GE HEALTHCARE S.A.

iobenguane (sulfate)
ATC code: V09IX01 (diagnostic radiopharmaceuticals)

List I – Medicinal product reserved for hospital use
Radiopharmaceuticals should only be used by authorised personnel. They may only be delivered to practitioners who have obtained special authorisation covered by Article R 1333-24 of the Public Health Code.

Date of Marketing Authorisation (national procedure): 22 February 2005; Revision: 04 January 2010

Reason for request: Inclusion on this list of medicines approved for hospital use in the extension of the indication for cardiology use (assessment of the sympathetic innervation of the myocardium):
"as a prognostic indicator for the risk of progression of symptomatic heart failure, potentially fatal arrhythmic events or cardiac related deaths in patients with class II or III heart failure according to the NYHA[1] classification and for left ventricular dysfunction".

[1] NYHA: New York Heart Association

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

iobenguane (sulfate)

1.2. Indication

"Oncology:
- Diagnostic scintigraphic localisation of tumours originating in tissue that embryologically stems from the neural crest, such as phaeochromocytomas, paragangliomas, chemodectomas and neurogangliomas
- Detection, staging and follow-up on therapy of neuroblastomas
- Evaluation of the uptake of iobenguane when therapeutic use is proposed
- Investigation of adrenal medullary hyperplasia

Cardiology (assessment of the sympathetic innervation of the myocardium):
- Adults: ADREVIEW is a radiopharmaceutical product indicated in the assessment of sympathetic innervation of the myocardium **as a prognostic indicator for the risk of progression of symptomatic heart failure, potentially fatal arrhythmic events or heart related deaths in patients with class II or III heart failure according to the NYHA classification and for left ventricular dysfunction."**

in bold, addition of cardiology use to the pre-existing indication (assessment of the sympathetic innervation of the myocardium).

1.3. Dosage

"Cardiology:

For adults, the recommended activity for sympathetic innervation of the myocardium is from 200 to 400 MBq.
For elderly patients, no changes to the activity dose required."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

V : Various
V09 : Diagnostic radiopharmaceuticals
V09I : Tumour detection
V09IX : Other diagnostic radiopharmaceuticals for tumour detection
V09IX01 : ^{123}I-iodine iobenguane

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

- Kit for the preparation of a solution for injection of iobenguane [123 I]. [Reference: IK-4]
- IOBENGUANE (123 I) FOR DIAGNOSIS, MALLINCKRODT France, solution for injection

For these two medicinal products, the indication for cardiology use is:
"assessment of the sympathetic innervation of the myocardium"

3 ANALYSIS OF AVAILABLE DATA

In support of its request, the laboratory commissioned a study, ADMIRE HF (*ADREVIEW Myocardial Imaging for Risk Evaluation in Heart Failure*).

3.1. Diagnostic and prognostic value

ADMIRE HF Study[2,3]

Objective: Demonstrate the prognostic value of the heart/mediastinum (H/M) ratio via scintigraphy with ADREVIEW ^{123}I by defining the threshold value of 1.60 on planar images carried out at 4 hours post-injection of the product to identify heart failure patients the most at risk of having a cardiac event. This study did not aim to evaluate the diagnostic performance of iobenguane.

Methodology:
ADMIRE HF was a prospective, non-comparative phase III study, carried out on a cohort of 985 heart failure patients (and 110 reference patients) included between July 2005 and February 2008 and monitored over a two-year period. This was a prognostic study that combined the results from two identical prospective, controlled, open-label phase III studies, MBG311 and MBG312.

[2] Arnold F. Jacobson, Roxy Senior, Manuel D. Cerqueira, Nathan D. Wong, Gregory S. Thomas, Victor A. Lopez, Denis Agostini, Fred Weiland, Harish Chandna, Jagat Narula, and ADMIRE-HF* Investigators. Myocardial Iodine-123 Meta-Iodobenzylguanidine Imaging and Cardiac. Events in Heart Failure: Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study J Am Coll Cardiol published online Feb 24, 2010; doi:10.1016/j.jacc.2010.01.014

[3] Arnold F. Jacobson, John Lombard, Gopa Banerjee, Paolo G. Gamici. ^{123}I-*m*IBG Scintigraphy to predict risk for adverse cardiac outcomes in heart failure patients: Design of two prospective multicenter international studies. J Nucl Card 2009 Feb; 16. http://www.onlinejnc.com/journal/12350/16/1/9008_10.1007_s12350-008-9008-2/0/123I-mIBG_Scintigraphy_to_predict_risk_for_adverse_cardiac_outcomes_in_heart_failure_patients_Design_of_two_prospective_multicenter_internat.html

It was not stated in the protocol whether combining these two studies was previously planned. These two studies were carried out by the laboratory during the period of 2005-2008. In each study, a maximum of 587 patients (525 heart failure and 62 reference patients) were included.

- Main inclusion and non-inclusion criteria:

The main inclusion criteria were:
- age ≥ 18 years.
- not pregnant or breast feeding.
- with class II and III NYHA heart failure due to ischaemic heart disease, diagnosed at least 3 months prior to being included in the study, or due to non ischaemic heart disease, diagnosed at least 6 months prior to being included in the study.
- an LVEF ≤ 35%.
- treatment that complies with guidelines.

The main non-inclusion criteria were:
- having a ventricular pacemaker
- a previous medical history of de-fibrillation to treat a previous ventricular arrhythmic event
- having had a coronary bypass
- having a implantable cardioverter-defibrillator (ICD) or a myocardial infarction in the last 30 days
- poorly managed hypertension
- a serum creatinine level above 3.0 mg/dl (265 µmol/l)

- Endpoints:

The primary efficacy endpoint was the correlation between the H/M ratio and the time before the occurrence of a major coronary event (MCE) or:
- progression of heart failure evaluated by the change from a Class II to III or IV in the NYHA classification or the change from III to IV
- the occurrence of a potentially fatal ventricular rhythm disorder
- the occurrence of a cardiac related death.

For the initial analysis, patients were firstly classified in to two groups: H/M ratio <1.60 or H/M ratio ≥ 1.60.
The choice of this threshold value was based on published data.[4,5,6,7]. In a second analysis, the H/M ratio was investigated as a continuous variable.

Furthermore, a multivariate analysis (Cox analysis) allowed the H/M ratio to be compared with other prognostic criteria used in practice: LVEF (left ventricular ejection fraction) and BNP (B type natriuretic peptide).

Kaplan-Meier survival analyses were carried out for the primary and secondary endpoints.

[4] Merlet P, Benvenuti C, Moyse D, et al. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. J Nucl Med 1999; 40: 917–23.
[5] Wakabayashi T, Nakata T, Hashimoto A, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. J Nucl Med 2001; 42: 1757– 67.
[6] Cohen-Solal A, Esanu Y, Logeart D, et al. Cardiac metaiodobenzylguanidine uptake in patients with moderate chronic heart failure: relationship with peak oxygen uptake and prognosis. J Am Coll Cardiol 1999; 33: 759–66.
[7] Nakata T, Miyamoto K, Doi A, et al. Cardiac death prediction and impaired cardiac sympathetic innervation assessed by MIBG in patients with failing and non-failing hearts. J Nucl Cardiol 1998; 5: 579 –90.

- Study method:

ADMIRE HF was carried out using a standardised image analysis protocol (according to the American College of Cardiology/American Heart Association/Society of Nuclear Medicine):
SPECT and planar images were sent to an independent laboratory for analysis.
Qualified nuclear medicine technicians analysed all of the planar images to determine the H/M ratio using a specific procedure.
The SPECT and planar images were then looked at by three independent experts in nuclear cardiology who had no prior knowledge of the clinical data of the patients; thus they interpreted these images blind.
For each planar image, the investigator examined the regions of interest and the corresponding H/M ratio defined by a technician; they then determined if the values were a reflection of their visual interpretation. If they did not correspond, the investigator requested that the technician make changes to determine a new H/M ratio for the patient.
For the SPECT images, the standards[8,9] of the American Society of Nuclear Cardiology were taken into consideration when interpreting these images.

Results:
The benefit of iobenguane sulfate was evaluated in 961 heart failure patients. However, among the 985 patients who received the medicinal product, 24 could not be investigated, mainly due to non-compliance with the study protocol.
On average, the patients included were aged 62 years, had an LVEF of 27% and were monitored for 17 months.

- Primary efficacy endpoint:

During the 2 years of the study, 237 (25%) first cardiac events were observed (table 1). Fifty-two patients had a second cardiac event, giving a figure of 289 for the number of patients having had a first or a second cardiac event.
In total, 293 cardiac events were observed (table 2).

Table 1: the occurrence of a first MCE

	Number of patients (%)			
	Progression of heart failure	**Rhythm disorders**	**Cardiac related death**	**Total**
1st event	163 (69%)	50 (21%)	24 (10%)	237

Table 2: the total number of events that occurred

	Number of patients (%)			
	Progression of heart failure	**Rhythm disorders**	**Cardiac related death**	**Total**
total events	176 (60%)	64 (22%)	53 (18%)	293

Primary analyses:
- H/M threshold value < 1.60 or ≥ 1.60

The relative risk of developing an MCE in the group with an H/M ratio ≥ 1.60 was 0.40 (97.5% CI, [0.25; 0.64], p < 0.001). The rate of MCEs at 2 years in the H/M ≥ 1.60 group was 15% and 38% in the H/M < 1.60 group (p < 0.0001).

[8] Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002; 105: 539-42.
[9] Port SC, editor. Imaging guidelines for nuclear cardiology procedures, Part 2. J Nucl Cardiol 1999; 6: G49-84.

Sub-group analyses:
The patients at a lower risk of having one of the three MCEs (progression of heart failure, rhythm disorder or cardiac related death) were patients with a higher H/M ratio:

- progression of heart failure: 0.49 (p = 0.002)
- rhythm disorders: 0.37 (p = 0.02)
- cardiac related death: 0.14 (p = 0.006)

Furthermore, patients at risk from a cardiac related death or from any cause were those with an H/M ratio <1.60. For this group of patients, the probability of a cardiac related death was 11.2% (p = 0.001) and the probability of death from any cause was 16.1% (p < 0.001) at 2 years.
For the group with an H/M ratio ≥ 1.60, the probability of a cardiac related death was 1.8% (p = 0.001) and the probability of death from any cause was 3.0% (p < 0.001).

- H/M as a continuous variable

The H/M ratio, investigated as a continuous variable, highlighted the risk of developing an MCE as 0.22 (97.5% CI, [0.10; 0.47], p < 0.001).
By considering the H/M ratio as a continuous variable, a progressive decrease in cardiac related deaths and deaths from any cause was observed between the H/M ratio values of < 1.10 and ≥ 1.80:

- More than 20% of cardiac related deaths and deaths from any cause were observed in patients with an H/M ratio < 1.10 (p < 0.001)
- There were no cardiac related deaths or deaths from any cause observed in patients with an H/M ratio ≥ 1.80 (p < 0.001).

Secondary analyses:
The H/M ratio, the LVEF, the NYHA classification and BNP were investigated as individual parameters. For each of these, the risk of developing an MCE was:

- H/M ratio: 0.36 (95% CI, [0.17; 0.75], p = 0.006)
- LVEF: 0.95 (95% CI, [0.93; 0.97], p < 0.001)
- NYHA: 1.48 (95% CI, [1.08; 2.02], p = 0.015)
- BNP: 1.00 (95% CI, [1.00; 1.00], p < 0.001)

Multivariate analyses compared the prognosis characteristic of the H/M ratio with other markers such as the LVEF and BNP.

- BNP

The median value for BNP was 140 ng/l across 926 patients. A statistically significant negative correlation was observed between plasma BNP and the H/M ratio (RR = -0.247, p < 0.0001).
The rate of cardiac events at 2 years for patients with a BNP > 140 ng/l was 42% for the sub-group with an H/M ratio < 1.60 and 20.5% for the sub-group with an H/M ratio ≥ 1.60 (p = 0.003). There were no cardiac related deaths among the 57 patients with a BNP > 140 ng/l and an H/M ratio ≥ 1.60 (p = 0.011). There were 42 cardiac related deaths among the 406 patients with a BNP > 140 ng/l and an H/M ratio <1.60 (p = 0.011).

- LVEF

The median value for LVEF was 29% across 961 patients. A statistically significant positive correlation was observed between the LVEF and the H/M ratio (RR = 0.184, p < 0.0001).
However, the H/M ratio was able to provide additional information on the classification of heart failure patients in the two LVEF sub-groups < 30% or ≥ 30%.
A rate of cardiac events at 2 years of 40.3% was reported for patients with an LVEF < 30% (p < 0.0001). This rate was 17.6% for patients with an LVEF < 30% and an H/M ratio ≥ 1.60 (p = 0.0004).

There were 2 cardiac related deaths among the 81 patients (2.5%) with an LVEF < 30% and an H/M ratio ≥ 1.60 (p = 0.034).
There were 39 cardiac related deaths among the 409 patients (9.5%) with an LVEF < 30% and an H/M ratio < 1.60 (p = 0.034).
There were no cardiac related deaths among the 120 patients with an LVEF ≥ 30% and an H/M ratio ≥ 1.60 (p = 0.037).

- Arrhythmic events

In total, 86 patients (9%) had a non-fatal arrhythmic event (n = 56) or a sudden death (n = 23). All of these arrhythmic events were more common in patients with an H/M ratio < 1.60 (10.4% versus 3.5%; p < 0.01). The highest prevalence of arrhythmic events was observed for the group of patients with an H/M ratio of between 1.30 and 1.39 (13.1%). Five arrhythmic events were observed in the 191 patients with an H/M ratio > 1.60 (2.6%).

3.2. Adverse effects

The pharmacovigilance data available (PSURs[10] from 1st September 2001 to 31 May 2009) were taken into account, and did not change the tolerance profile of the medicinal product.
The observable adverse effects after the administration of ADREVIEW were: redness, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions.

"When the drug is administered too fast, palpitations, dyspnoea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration. These symptoms should disappear within one hour.

For each patient, exposure to ionizing radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable, bearing in mind the need to obtain the intended diagnostic or therapeutic result. Exposure to ionising radiation may potentially lead to cancer and/or the development of hereditary defects. For most nuclear medicine diagnostic investigations, it is generally considered that the frequency of these risks is negligible, given the low doses of radiation delivered." (Source: SPC)

3.3. Conclusion

ADMIRE HF was a prospective study, carried out on a cohort of 985 heart failure patients included between July 2005 and February 2008 and monitored over two years. The aim of this study was to demonstrate the prognostic value of the heart/mediastinum (H/M) ratio via scintigraphy with ADREVIEW ^{123}I, to identify the heart failure patients most at risk of having a major cardiac event (MCE), the threshold value being defined as 1.60 through planar images carried out 4 hours after injection of the product.

At 2 years, the relative risk of having an MCE in the group with an H/M ratio ≥ 1.60 was 0.40 (97.5% CI, [0.25; 0.64], p < 0.001). The rate of MCEs at 2 years in the H/M ≥ 1.60 group was 15% and 38% in the H/M < 1.60 group (p < 0.0001). The correlation was negative between the plasma type B natriuretic peptide concentration (BNP) and the H/M ratio (RR = -0.247, p < 0.0001) and positive between the LVEF and the H/M ratio (RR = 0.184, p < 0.0001).

This study raises the following issues:
- the choice of patients included. The diagnosis of symptomatic systolic heart failure is based on a consultation, a clinical examination (New York Heart Association, NYHA

[10] PSUR: Periodic Safety Update Report

classification) and the measurement of the ejection fraction (LVEF < 45%).[11] In this study, only patients who had an LVEF ≤ 35% were included. This point raises issues as to the transferability of results to current clinical practice. In addition, it was not possible to reliably stratify patients according to the severity of their heart failure. Also, in a real life usage situation for this medicinal product, patients with less severe forms of heart failure will benefit the most from the prognosis factor investigation.

- the choice of the events included as primary efficacy endpoints. Indeed, evaluating the worsening in NYHA classification level is very subjective and therefore inappropriate in the measurement of a prognosis criterion, especially in a non-comparative and thus open-label study. The results concerning this criterion raise even more problems, as the non-ischaemic patients in the study had more MCEs than the ischaemic patients, which contradicts what is seen in practice; this result may be due to the subjective nature of assessing the worsening in NYHA classification and/or by the selection of a less severely effected ischaemic patient population.
- no investigation of the peak in VO_2[12] as a prognostic factor.
- choice of the BNP threshold value of 140 ng/l for the assessment of BNP as a prognosis factor is questionable, given that it is higher than that normally used (100 ng/l according to experts).
- no comparison with any other radio markers, which means that it is difficult to draw conclusions concerning the relative prognostic value of this proprietary medicinal product.

It should be noted that the author of this study is an employee of the laboratory.

[11] HAS Guide LTC – Insuffisance cardiaque systolique symptomatique chronique (chronic symptomatic systolic heart failure) – update November 2010

[12] By definition, the measurement of VO_2 max. allows the effects of O_2 transport (cardiac output) and issues in O_2 use to be evaluated, based on the level of exercise. A peak in VO_2 is of prognostic value, independently of haemodynamic parameters at rest.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

ADREVIEW is a diagnostic radiopharmaceutical medicinal product, used primarily in myocardial scintigraphy.

The seriousness of the condition is defined based on the results of the investigation.

In the assessment of sympathetic innervation of the myocardium, as a prognostic indicator for the risk of progression of symptomatic heart failure, potentially fatal arrhythmic events or heart related deaths in patients with class II or III heart failure according to the NYHA (New York Heart Association) classification and for left ventricular dysfunction, scintigraphy is used as a third-line treatment, after echocardiography and the measurement of BNP.
During a scintigraphy examination, the patient is exposed to radiation.

The efficacy/adverse effects ratio for this proprietary medicinal product has not been clearly established in the indication investigated.

> *Public health benefit: on the basis of the available data, it is not expected that ADREVIEW will benefit public health in this indication.*

Alternative medicinal products exist: the kit for the preparation of the solution for injection of iobenguane [123 I] and IOBENGUANE (123 I) FOR DIAGNOSIS, MALLINCKRODT France, solution for injection. Both of these medicinal products are indicated in the assessment of the sympathetic innervation of the myocardium.

Given that there is insufficient data on the analysis of the prognostic value of iobenguane, as a radiopharmaceutical in iobenguane scintigraphy, for major cardiovascular complications of heart failure, and in the absence of information on its performance compared with other available diagnostic alternatives, the actual benefit of ADREVIEW in the extension of its indication is insufficient for it to be refundable by National Health Insurance.

4.2. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines approved for hospital use and various public services in the indication "as a prognostic indicator for the risk of progression of symptomatic heart failure, potentially fatal arrhythmic events or heart related deaths in patients with class II or III heart failure according to the NYHA classification and for left ventricular dysfunction".