Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

STAMICIS
Kit for preparation of
Technetium (^{99m}Tc), Sestamibi injection
[Tetrakis(2-methoxy-2-methylpropyl-1 isocyanide)copper(I)] tetrafluoroborate]

FR/H/356/01/MR

Applicant: CIS bio international

This module reflects the scientific discussion for the approval of STAMICIS, Kit for preparation of Technetium (^{99m}Tc) Sestamibi injection. The procedure was finalised on 1 September 2009. For information on changes after this date please refer to the module 'Update'.

Date of the PAR: July 2009

Information about the initial procedure:

Application type/Legal basis	*Generic Art 10(1) Dir 2001/83/EC*
Active substance	*[Tetrakis(2-methoxy-2-methylpropyl-1 isocyanide)copper(I)] tetrafluoroborate]*
Pharmaceutical form	*Kit for the preparation of technetium (^{99m}Tc)Sestamibi injection*
Strength	*One mL contains 0.3 GBq*
Applicant	*CIS bio international*
EU-procedure number	*FR/H/356/01/MR*
End of procedure	*1st September 2008*

1. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the French Health Products Safety Agency (AFSSAPS) has granted a marketing authorization for STAMICIS, Kit for the preparation of technetium (^{99m}Tc) Sestamibi injection on 21 April 2008 to CIS bio international and on 1st September 2008, a MRP with AT, BE, CZ, DE, DK, EL, ES, FI, IE, IT, LU, NL, NO, PT, SE, SI, SK and UK was positively ended.

It concerns a generic application with reference to article 10(1) of Directive 2001/83/EC. The originator product is Cardiolite from Bristol-Myers Squibb Pharma Belgium, registered in Sweden since 21st June 1990 and in France since 21st September 1990.

The active ingredient of labelled STAMICIS, (^{99m}Tc) Sestamibi belongs to a class of cationic technetium compounds, the hexakis alkylisonitrile technetium (I) complexes. After intravenous injection, (^{99m}Tc) Sestamibi distributes within the myocardium according to myocardial perfusion and viability. It diffuses passively through the capillary and cell membrane. Within the cell it is localised in the mitochondria, where it is trapped. Retention is based on intact mitochondria, reflecting viable myocytes.

STAMICIS, Kit for the preparation of technetium (^{99m}Tc) Sestamibi injection has the following indications:

This medicinal product is for diagnostic use only.

After reconstitution with sodium technetium pertechnetate (99mTc) solution for injection, the solution of technetium (99mTc) sestamibi obtained is indicated for:

Myocardial perfusion scintigraphy
Detection and localisation of coronary artery disease and myocardial infarction.

Assessment of global ventricular function
First-pass technique for determination of ejection fraction and/or ECG-triggered, gated SPECT for evaluation of left ventricular ejection fraction, volumes and regional wall motion.

Scinti-mammography for the detection of suspected breast cancer

Detection of suspected breast cancer when mammography is equivocal, inadequate or indeterminate.

Localisation of hyperfunctioning parathyroid tissue in patients with recurrent or persistent hyperparathyroidism, and in patients scheduled to undergo surgery of the parathyroid glands.

A comprehensive description of the therapeutic indications and doses is given in the SmPC.

Sestamibi has been used for more than 20 years for myocardial perfusion studies and for more than 10 years in oncology and endocrinology. The current application was filed on the ground of bibliographical data in a context of well-established use. The included bibliography contained 147 references. This bibliographic application was supported by detailed references to the published pharmacology, efficacy and safety of the product.

2. QUALITY ASPECTS

2.1 Introduction

The drug product, STAMICIS, kit for the preparation of technetium (^{99m}Tc) Sestamibi injection, developed by CIS bio international (FRANCE) is a generic form of Cardiolite. The drug substance is tetrakis (2-methoxyisobutyl isonitrile) copper (I) tetrafluoroborate. After reconstitution with sodium pertechnetate (^{99m}Tc) injection, the labeled product complies with the European Pharmacopoeia, monograph 1926 "technetium (^{99m}Tc) Sestamibi injection".

The pharmaceutical data do not indicate any particular risk on the basis of the reproducibility studies of the analysis and stability methods.

At the chemical concentration and recommended activity STAMICIS does not seem to have any pharmacodynamic activity.

2.2 Drug Substance

The description of the synthesis is satisfactory.
Characterisation of the drug substance is satisfactory.
Specifications for unknown and total impurities have been added.
A shelf-life of 12 months/ store at 5°C is proposed for the drug substance.

2.3 Medicinal Product

The composition of the product is clearly defined. The formula meets in-house specifications based on the current European Monograph on Radiopharmaceuticals.
The quality control of the raw materials and the finished product is documented. The results comply with the European Pharmacopoeia when monographs are available and the other specific methods are validated.

The drug product Stamicis, kit for the preparation of technetium (^{99m}Tc) Sestamibi injection, is a lyophilised powder for solution for injection for preparation of a radiopharmaceutical.

A shelf-life of 12 months/ store below 25°C is proposed for the kit and for the reconstituted product a shelf-life of 10 hours/ store at 2-8°C is proposed. The proposed shelf-lives are supported by data obtained in accordance with stability guidelines.
Approved shelf-life/storage conditions: 12 months/ do not store above 25 °C/keep the vials in the outer carton in order to protect from light.
After reconstitution: 10 hours/ store at 2-8°C.

A number of questions have been raised related to characterisation and as well to manufacturing process, controls of materials, specifications and analytical procedures. Satisfactory answers and/or complementary information and related modifications have been brought to the original documents which, now, fulfil present European regulatory requirements.

III. NON-CLINICAL ASPECTS

Pharmacodynamics, Pharmacokinetics, and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of (^{99m})Tc Sestamibi are well known. As (^{99m})Tc Sestamibi is a widely used, well-known active substance and the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended no further studies are required and the applicant provides none.
A literature search on non-clinical findings after approval of the reference product Cardiolite has been conducted. The results of this literature search are being discussed in the non-clinical overview. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.
(^{99m}Tc) Sestamibi is a cationic complex which accumulates in viable myocardium in a rate proportional to the regional blood flow in normal and infarcted and ischemic cardiac tissue. (^{99m}Tc) Sestamibi from the blood is rapidly distributed into the tissue: 5 minutes after injection only about 8% of the injected dose is still in the circulation. Myocardial uptake which is dependent on coronary flow is 1.5% of the injected dose at stress and 1.2% on the injected dose at rest.

Animal experiments have demonstrated that uptake is dependent on the lipophilicity and charge distribution of (^{99m}Tc) Sestamibi. Direct analysis of heart cell aggregates has demonstrated specific mitochondrial retention. At equilibrium it is sequestered within mitochondria by a large negative transmembrane potential. The agent is fixed intracelluIarly as long as cell membrane integrity is intact and nutrient blood flow persists. This retention is a mechanism common to most tissues. The accumulation in tissue is a function of regional blood flow and dependent on metabolic activity of the tissue. The use of (^{99m}Tc) Sestamibi in tumor imaging is related to increased metabolism and neovascularization of these cells. In plasma, less than 1% of the tracer is protein bound. The primary route of excretion is hepatobiliary. Activity in the gallbladder appears in the intestine within one hour after injection. About 27% of the injected dose is cleared through renal elimination after 24 hours and approximately 33% of the injected dose is cleared through the faeces within 48 hours.

Toxicology. The originator reported in acute studies and subacute toxicity tests in mice, rats and dogs, toxic signs could be seen at doses 500 fold the human dose of 0.014 mg/kg bodyweight.

Environmental risk assessment
The only environmental danger is the radioactivity which in the present case is only to be taken into account during delivery and handling for the diagnostics, given the very short half life.

Approval is recommended from the non-clinical point of view.

IV. CLINICAL ASPECTS

No specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended. A literature search on clinical findings after approval of the reference product Cardiolite has been conducted. The clinical overview is a review of

the literature during the past 16 years and it documents the diagnostic accuracy of Sestamibi-SPECT in coronary heart disease. Myocardial perfusion scintigraphy is an established imaging technique and the indications ischemic heart disease, localisation of myocardial infarction and global ventricular function (first pass technique for determination of ejection fraction and/or regional wall motion) are acceptable. Several studies have documented that (^{99m}Tc) Sestamibi scintigraphy add information to mammography in very restricted but well-defined clinical settings. As stated in the current SmPC the indication can be accepted.

The indication of using (^{99m}Tc) Sestamibi scintigraphy in recurrent or persistent hyperparathyroidism can be considered as well documented in the updated clinical overview dated October 2008 has been submitted in response to answers.
A literature review focusing on the last 10 years was carried out on the following databases BIOSIS, DDFU, EMBASE, MEDLINE, SciSearch and TOXCENTER. Concerning (^{99m}Tc) Sestamibi, the adverse drug reactions and preclinical data commonly reported in publications are currently mentioned in the product safety information. In a Japanese survey the authors estimated the frequency of adverse events related to the administration of (^{99m}Tc) Sestamibi to be of 0.0073%. The adverse reaction types have been appropriately reflected in the "undesirable effects" and "special warnings and special precautions for use" sections of the proposed SmPC. (^{99m}Tc) Sestamibi can be considered to have a very safe profile and to be well tolerated.

The consolidated clinical overview on the clinical pharmacology, efficacy and safety is considered adequate.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The benefit risk is, therefore, considered to be positive.

The following commitments were made during the procedure:

Clinical

A commitment was given to provide an update of module 5 and Clinical Overview for the indication of STAMICIS in patients scheduled to undergo parathryroidectomy (any kind of intervention) by October 17th, 2008 as this indication was not initially approved for the innovator product.

A commitment is given to submit a variation to update the SmPC according to European Core SmPC for Sestamibi products once this European Core SmPC has been published.

No safety concern requiring additional risk minimisation activities have been identified with the reference (^{99m}Tc) Sestamibi product. In consequence, the routine pharmacovigilance is adequate to monitor the safety of the « Kit for the Preparation of Technetium (^{99m}Tc) Sestamibi Injection CIS bio international » and there is no need for a Risk Management Plan.