AUSTRALIA
Patents Act 1990

P/OO/OO8
Section 29 (1)
Regulation 3.1(2)

NOTICE OF ENTITLEMENT

(To be filed before acceptance)
(PCT with Convention Claim)

I/We Y LE GALLIC
*authorised by CIS BIO INTERNATIONAL S.A.
of ROUTE NATIONALE 306 F-91000 SACLAY (FRANCE)

the applicant in respect of an application for a patent for an invention entitled PHARMACEUTICAL PRODUCT HAVING IN PARTICULAR A CARDIAC TROPISM COMPRISING A NITRURO COMPLEX OF A TRANSITION METAL AND PROCESS FOR PREPARATION THEREOF
filed under Australian Application No. 46392/89, state the following:-

CIS BIO INTERNATIONAL S.A.,
the person(s) nominated for the grant of the patent,

[ ] ~~*is/*are the actual inventor(s)~~
or
[X] has, for the following reasons, gained entitlement from the actual inventors(s):
The nominated persons are the assignees of the invention and priority rights from Compagnie ORIS Industrie S.A., who was entitled to have the application assigned to them by the inventors, listed on the basic application.

The person(s) nominated for the grant of the patent ~~*is~~/*are:

[ ] ~~the applicant(s) of the application(s) listed in the declaration under Article 8~~ of the PCT
or
[X] entitled to rely on the application(s) listed in the declaration under Article 8 of the PCT by reason of the following:-
CIS BIO INTERNATIONAL S.A. is the assignee of the invention from Compagnie ORIS Industrie S.A., who is a person who would, if a patent were granted upon application by the said actual inventors, be entitled to have the patent assigned to it.

And

The basic application(s) referred to in the declaration under Article 8 of the PCT ~~*is~~/*are the application(s) first made in a Convention country in respect of the invention.

Signed: ...e Presidente-Directeur General **Date:** 28 January 1992

Status: _____

Y. LE GALLIC

F B RICE & CO PATENT ATTORNEYS
PCT with Convention

(12) PATENT ABRIDGMENT (11) Document No. AU-B-46392/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 623204

(54) Title
PHARMACEUTICAL PRODUCT HAVING, IN PARTICULAR, A CARDIAC TROPISM COMPRISING A NITRURO COMPLEX OF A TRANSITION METAL AND PROCESS FOR PREPARATION THEREOF

International Patent Classification(s)
(51)[5] **C07F 013/00** **A61K 049/02**

(21) Application No. : **46392/89** (22) Application Date : **24.11.89**

(87) PCT Publication Number : **WO90/06137**

(30) Priority Data

(31) Number	(32) Date	(33) Country
88 15415	**25.11.88**	**FR FRANCE**
89 07731	**12.06.89**	**FR FRANCE**

(43) Publication Date : **26.06.90**

(44) Publication Date of Accepted Application : **07.05.92**

(71) Applicant(s)
CIS BIO INTERNATIONAL

(72) Inventor(s)
ROBERTO PASQUALINI; LUCIANO MAGON; ANDRE BARDY; ADRIANO DUATTI; ANDREA MARCHI

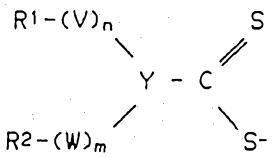
(74) Attorney or Agent
F B RICE & CO , 28A Montague Street, BALMAIN NSW 2041

(57) Claim

1. Radiopnarmaceutical product, characterized in that it comprises a complex of a transition metal complying with the formula:

$$(M \equiv N)\ L^1L^2$$

in which M is a transition metal and L^1 and L^2, which can be the same or different, comply with the formula:



(II)

in which V and W, which can be the same or different, represent O, S or Se, n and m, which can be the same or different, are equal to 0 or to 1, Y represents N, P or As, and R^1 and R^2, which can be the same or different, represent a straight or branched alkyl radical with 1 to 10 carbon atoms, which is either not substituted or substituted by $-O-R^3$, $OOC-R^3$, $OCNR^4R^5$ or $-NR^4R^5$ groups, in which R^3 is a straight or branched alkyl radical with 1 to 5 carbon atoms and R^4 and R^5, which can be the same or different, are hydrogen atoms or straight or branched alkyl radicals with 1 to 5 carbon atoms, or in which R^1 and R^2 together form a hydrocarbon cycle optionally containing one or more heteroatoms.

.../2

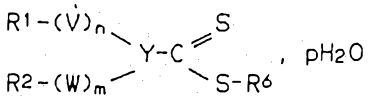
16. Process for the preparation of a radiopharmaceutical product according to any one of the claims 1 to 15, characterized in that it comprises the following successive stages:

1°) reacting an oxygenated compound of a transition metal M with:

a) a first ligand chosen from within the group of substituted or unsubstituted, aromatic and aliphatic phosphines and polyphosphines and

b) a second reagent chosen from among the ammonium and alkali metal nitrides and the nitrogenous ligands having a $\geq N\text{-}N\leq$ in which the N are connected to hydrogen atoms and/or to monovalent organic groups via a carbon atom, or in which one of the N is connected to the carbon atom of a divalent organic group via a double bond and the other N is connected to hydrogen atoms and/or monovalent organic groups via a carbon atom and

2°) reacting the intermediate obtained in the first stage with a compound in accordance with the formula:



(X)

in which R^1, R^2, V, W, n, m and Y have the meanings given hereinbefore, R^6 is an alkali metal ion, H^+ or NH_4^+ and p is equal to 0 or an integer between 1 and 5.

OPI DATE 26/06/90 APPLN. ID 46392 / 89

PCT AOJP DATE 26/07/90 PCT NUMBER PCT/FR89/00608

DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets 5 :
A61K 49/02, C07F 13/00

A1

(11) Numéro de publication internationale: WO 90/06137

(43) Date de publication internationale: 14 juin 1990 (14.06.90)

(21) Numéro de la demande internationale: PCT/FR89/00608

(22) Date de dépôt international: 24 novembre 1989 (24.11.89)

(30) Données relatives à la priorité:
88/15415 25 novembre 1988 (25.11.88) FR
89/07731 12 juin 1989 (12.06.89) FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: COMPAGNIE ORIS INDUSTRIE S.A. [FR/FR]; 33, rue de la Fédération, F-75015 Paris (FR).

(72) Inventeurs; et

(75) Inventeurs/Déposants *(US seulement)* : PASQUALINI, Roberto [FR/FR]; 223, avenue Victor-Hugo, F-92140 Clamart (FR). MAGON, Luciano [IT/IT]; Via Pietro Selvatico, 86, I-35100 Padova (IT). BARDY, André [FR/FR]; 48, les Genêts, F-92420 Morangis (FR). DUATTI, Adriano [IT/IT]; Via Galvana, 34, I-44040 Chiesuol Fosso (IT). MARCHI, Andrea [IT/IT]; Via Arianuova, 75, I-44100 Ferrara (IT).

(74) Mandataire: BREVATOME; 25, rue de Ponthieu, F-75008 Paris (FR).

(81) Etats désignés: AT (brevet européen), AU, BE (brevet européen), CH (brevet européen), DE (brevet européen), DK, ES (brevet européen), FI, FR (brevet européen), GB (brevet européen), IT (brevet européen), JP, LU (brevet européen), NL (brevet européen), NO, SE (brevet européen), SU, US.

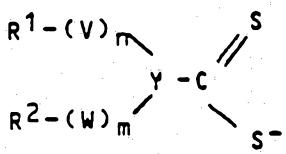
Publiée

Avec rapport de recherche internationale.

(54) Title: PHARMACEUTICAL PRODUCT HAVING, IN PARTICULAR, A CARDIAC TROPISM COMPRISING A NITRURO COMPLEX OF A TRANSITION METAL AND PROCESS FOR PREPARATION THEREOF

(54) Titre: PRODUIT RADIOPHARMACEUTIQUE AYANT NOTAMMENT UN TROPISME CARDIAQUE COMPORTANT UN COMPLEXE NITRURO D'UN METAL DE TRANSITION, ET SON PROCEDE DE PREPARATION

$$(M\equiv N)L^1L^2 \qquad (I)$$



(II)

(57) Abstract

The invention concerns a radiopharmaceutical product having, in particular, a cardiac tropism, comprising a nitruro complex of a transition metal, and process for preparation thereof. The complex has the formula $(M\equiv N)L^1L^2$ in which M is a transition metal, for example Tc99m, Re186 or Re188, and L^1 and L^2, which may be identical or different, have formula (II), whereby R^1 and R^2 may be alkyl radicals, V and W may be O, S or Se, n = 0 or 1, m = 0 or 1, and Y represents N, P or As.

(57) Abrégé

L'invention concerne un produit radiopharmaceutique ayant notamment un tropisme cardiaque, comportant un complexe nitruro d'un métal de transition, et son procédé de préparation. Ce complexe répond à la formule $(M\equiv N)L^1L^2$ (I) dans laquelle M est un métal de transition, par exemple Tc99m, Re186 ou Re188, et L^1 et L^2 qui peuvent être identiques ou différents, répondent à la formule (II) dans laquelle R^1 et R^2 peuvent être des radicaux alkyle, V et W peuvent être O, S ou Se, n = 0 ou 1, m = 0 ou 1, et Y représente N, P ou As.

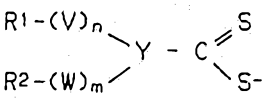
DESCRIPTIVE ABSTRACT

The invention relates to a radiopharmaceutical product more particularly having a cardiac tropism, incorporating a nitride complex of a transition metal and the process for the preparation thereof.

This complex complies with the formula:

$$(M \equiv N)L^1L^2 \qquad (I)$$

in which M is a transition metal, e.g. Tc99m, Re 186 or Re 188 and L1 and L2, which can be the same or different, comply with the formula:



(II)

in which R^1 and R^2 can be alkyl radicals, V and W can be O, S or Se, n=0 or 1, m=0 or 1, and Y represents N, P or As.

B. 9810/10169 MDT

RADIOPHARMACEUTICAL PRODUCT MORE PARTICULARLY HAVING A CARDIAC TROPISM INCORPORATING A NITRIDE COMPLEX OF A TRANSITION METAL AND ITS PREPARATION PROCESS

The present invention relates to a radiopharmaceutical product or radioactive drug in particular having a cardiac tropism, which comprises a nitride complex of a transition metal having a part M ≡ N, in which M represents the transition metal. It more particularly applies to radiopharmaceutical products having a cardiac tropism.

It is pointed out that the term transition metal means a metal whose coating d is partly filled in the standard oxidation degree of said metal. They are elements in periods III to XII of the periodic table of elements consisting of eighteen columns. Examples of such metals are Tc, Ru, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb and Ta.

Technetium nitride complexes have been described by J. Baldas et al in the following documents: International Patent Application WO-85/03063, J. Chem. Soc. Dalton Trans., 1981, pp.1798-1801 and in the book "Technetium in Chemistry and Nuclear Medicine", M. Nicolini, G. Bandoli and U. Mazzi, Cortine Int. Verona, 1986, pp.103 to 108.

These documents describe the preparation of technetium nitride complexes by a substitution reaction on $^{99m}TcNCl_4$ and it is stated that these complexes can be used as radiopharmaceutical products. However, these documents fail to provide any results giving evidence regarding the fixing of the complexes in the body and consequently give no indication of their tropisms with respect to certain organs and in particular the heart.

Among the radiopharmaceutical products having a cardiac tropism, technetium complexes are known, which contain as the ligand isonitriles substituted by an ether, in the manner described in European patent application EP-A-0 233 368 and dioxime-based technetium complexes as described in European patent EP-A-0 268 801. These complexes are formed from ligands which are difficult to synthesize.

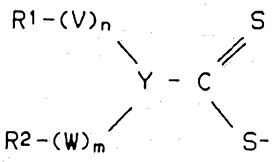
Thus, research has been carried out to find other radiopharmaceutical products having satisfactory properties for use as diagnosis or therapy products and more particularly radiopharmaceutical

products with a cardiac tropism, e.g. for myocardial scintigraphy.

The present invention specifically relates to a radiopharmaceutical product, which comprises a complex of a transition metal complying with the formula:

$$(M \equiv N)\ L^1L^2$$

in which M is a transition metal and L^1 and L^2, which can be the same or different, comply with the formula:



(II)

in which V and W, which can be the same or different, represent O, S or Se, n and m, which can be the same or different, are equal to 0 or to 1, Y represents N, P or As, and R^1 and R^2, which can be the same or different, represent a straight or branched alkyl radical with 1 to 10 carbon atoms, which is either not substituted or substituted by $-O-R^3$, $OOC-R^3$, $OCNR^4R^5$ or $-NR^4R^5$ groups, in which R^3 is a straight or branched alkyl radical with 1 to 5 carbon atoms and R^4 and R^5, which can be the same or different, are hydrogen atoms or straight or branched alkyl radicals with 1 to 5 carbon atoms, or in which R^1 and R^2 together form a hydrocarbon cycle optionally containing one or more heteroatoms.

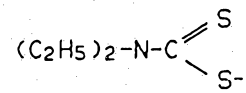
The radiopharmaceutical products incorporating transition metal complexes in accordance with the above formula in particular have a cardiac tropism, which makes them interesting as heart therapy or diagnosis products.

In the radiopharmaceutical products according to the invention, the transition metal nitride complex can be of different types.

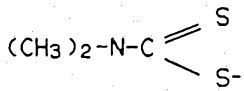
Thus, according to a first embodiment of the invention, in the aforementioned formula, Y represents N, m and n are equal to 0, L^1 and L^2 are identical and R^1 and R^2 are unsubstituted alkyl radicals.

In this first embodiment according to the invention, R^1 and R^2 are preferably also identical.

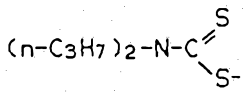
For example, L^1 and L^2 can be in accordance with the following formulas:



(III)



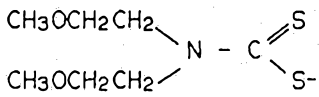
(IV)



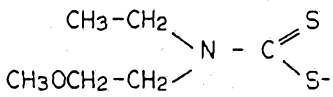
(V)

According to a second embodiment of the invention, Y represents N, m and n are equal to 0, L^1 and L^2 are identical and at least one of the R^1 and R^2 represents an alkoxy alkyl radical.

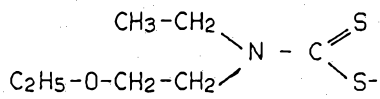
For example, L^1 and L^2 can comply with the following formulas:



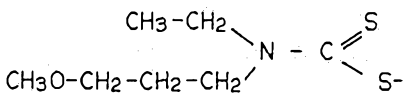
(VI)



(VII)



(VIII)

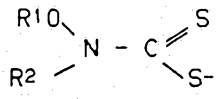


(IX)

According to a third embodiment of the invention, the transition metal complex is in accordance with the formula:

$$(M \equiv N)L^1L^2$$

in which M is a transition metal and L^1 and L^2 comply with the formula:



in which R^1 and R^2 have the meanings given in claim 1.

Examples of such complexes are those for which R^1 represents CH_3 and R^2 represents CH_3- or CH_3-CH_2-, or for which R^1 represents CH_3-CH_2- and R^2 represents CH_3- or CH_3-CH_2-.

In the complexes according to the invention, the transition metal used more particularly depends on the application of the radiopharmaceutical product. Thus, when it is wished to use the product for

diagnosis, use is made of a radioactive transition metal with a relatively short period, e.g. technetium ^{99m}.

In the case where it is wished to use the radiopharmaceutical product for therapy, use is made of a transition metal emitting an effective radiation for the therapy and which has a longer life, such as rhenium, e.g. Re-186 or Re-188.

The technetium nitride complexes used in the invention can be prepared by the Baldas process. However, preference is generally given to the preparation thereof by a simpler process, which is easier to carry out in a hospital department and which leads to high yields.

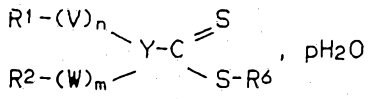
This process comprises the following successive stages:

1°) reacting an oxygenated compound of a transition metal M with:

a) a first ligand chosen from within the group of substituted or unsubstituted, aromatic and aliphatic phosphines and polyphosphines and

b) a second reagent chosen from among the ammonium and alkali metal nitrides and the nitrogenous ligands having a $\geq$N-N$\leq$ in which the N are connected to hydrogen atoms and/or to monovalent organic groups via a carbon atom, or in which one of the N is connected to the carbon atom of a divalent organic group via a double bond and the other N is connected to hydrogen atoms and/or monovalent organic groups via a carbon atom and

2°) reacting the intermediate obtained in the first stage with a compound in accordance with the formula:



$$R^1\text{-}(V)_n \diagdown \quad \diagup \; S \qquad \qquad R^2\text{-}(W)_m \diagup \quad \diagdown \; S\text{-}R^6 \qquad , \; pH_2O \qquad (X)$$

in which R^1, R^2, V, W, n, m and Y have the meanings given hereinbefore, R^6 is an alkali metal ion, H^+ or NH_4^+ and p is equal to 0 or an integer between 1 and 5.

When the process is performed using technetium as the transition metal, the oxygenated compound of the transition metal can be ammonium or alkali metal pertechnetate. In the case where the transition metal is rhenium, it is possible to use an ammonium or alkali metal perrhenate.

Thus, in the first stage of the process, preparation takes place of a technetium nitride complex, which is then reacted with the compound of formula (X) in order to exchange the first and second ligands by this

compound.

In order to carry out the reaction, it is possible to aseptically introduce the first ligand and namely either the ammonium or alkali metal nitride, or the nitrogenous ligand, into a container and then add the requisite quantity of the oxygenated transition metal compound, e.g. technetium ^{99m} pertechnetate, after adjusting the pH to an appropriate value by the addition of acid or base. It is then possible to carry out the reaction at ambient temperature or at a higher temperature between 50 and 100°C. The temperature and pH used in particular depend on the second nitrogenous ligand. Operation generally takes place between pH2 and 7.

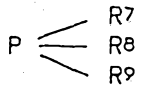
In the first stage, it is possible to use the first and second ligands in the form of alcoholic, hydroalcoholic or aqueous solutions and simply add these solutions to the oxygenated compound of the transition metal.

In the second stage, the product obtained in the first stage is reacted with the compound of formula (X) in aqueous solution, generally at a pH above 7 and e.g. in a sodium bicarbonate - carbonate buffer.

In this second stage, it is also possible to use an alcoholic or hydroalcoholic solution of compound (X).

The first ligand making it possible to obtain the formation of a nitride complex is an organic ligand with an electron donor phosphorus atom chosen from among substituted or unsubstituted, aliphatic and aromatic phosphines and polyphosphines.

The phosphines which can be used can comply with the formula:



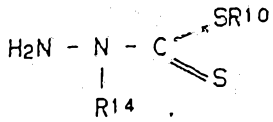
in which R^7, R^8 and R^9, which can be the same or different, represent a hydrogen atom, an alkyl radical, an aryl radical, an alkoxy radical or an alkyl or aryl radical substituted by a group chosen from among the amino, amido, cyano and sulphonate radicals.

Examples of phosphines of this type are triphenyl phosphine, trisulphonated triphenyl phosphine, diethyl phenyl phosphine, triethyl phosphine, trimethyl phosphine and tris(2-cyanoethyl)-phosphine $P(CH_2-CH_2CN)_3$.

In the first stage, it is possible to use as the second reagent

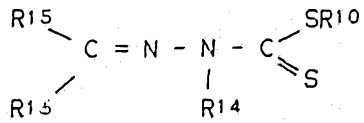
either an ammonium or alkali metal nitride, e.g. sodium nitride, or a nitrogenous ligand having the $\geq N\text{-}N \leq$, as in hydrazine and its derivatives. It is possible to use numerous nitrogenous ligands of this type. Generally, preference is given to the use as the nitrogenous ligand of dithiocarbazic acid or a derivative thereof.

Thus, the second nitrogenous ligand can be dithiocarbazic acid or a derivative thereof in accordance with the formula:



in which R^{10} represents a hydrogen atom, an alkyl radical or an aryl radical and R^{14} represents a hydrogen atom, an alkyl radical, an aryl radical, an alkoxy radical, an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals, or an aryl radical substituted by at least one group chosen from among the halogen atoms and the alkoxy, hydroxy, amino and mercapto radicals and the amino radicals substituted by at least one alkyl radical.

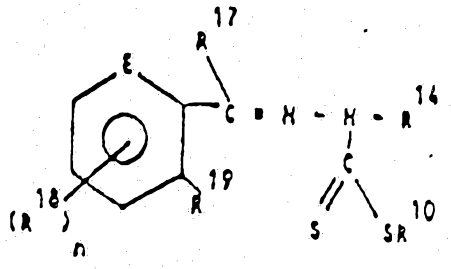
It can also be a condensation product obtained by the reaction of dithiocarbazic acid with a ketone or aliphatic aldehyde of formula $R^{15}\text{-}CO\text{-}R^{16}$. In this case, it complies with the formula:



in which R^{10} represents a hydrogen atom, an alkyl radical or an aryl radical; R^{14} represents a hydrogen atom, an alkyl radical, an aryl radical, an alkoxy radical, an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals, or an aryl radical substituted by at least one group chosen from among the halogen atoms and alkoxy, hydroxy, amino and mercapto radicals or amino radical substituted by at least one alkyl radical; and R^{15} and R^{16}, which can be the same or different, represent a hydrogen atom, an alkyl radical or an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals.

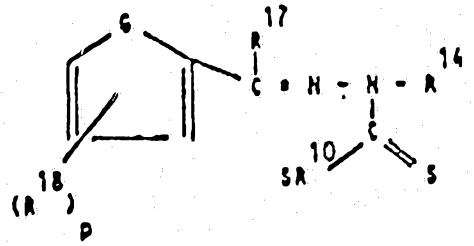
The dithiocarbazic acid derivative used as the second ligand can

also be the condensation product of dithiocarbazic acid with a ketone or aromatic aldehyde. In this case, the derivative complies with the formula:



In which R^{10} represents a hydrogen atoms, an alkyl radical or an aryl radical; R^{14} represents a hydrogen atom, an alkyl radical, an aryl radical, an alkoxy radical, an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals or an aryl radical substituted by at least one group chosen from among the halogen atoms and the alkoxy, hydroxy, amino and mercapto radicals and the amino radical substituted by at least one alkyl radical; R^{17} represents a hydrogen atom, an alkyl radical, an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals, R^{18} represents a hydrogen atom, a halogen atom, an alkoxy radical, an amino radical or an amino radical substituted by at least one alkyl group, R^{19} represents a hydrogen atom, a hydroxy radical or a mercapto radical, E represents a carbon atom or a nitrogen atom and n is an integer between 1 and 4, or in which n is equal to 2 and the two R^{18} are adjacent together forming an aromatic cycle.

It is also possible to use as the second ligand the product obtained by the condensation of dithiocarbazic acid with a ketone having a 5-link heterocycle. In this case, the second ligand complies with the formula:

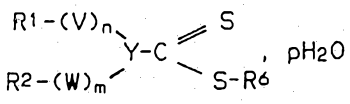


in which R^{10} represents a hydrogen atom, an alkyl radical or an aryl radical; R^{14} represents a hydrogen atom, an alkyl radical, an aryl radical, an alkoxy radical, an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals, or an aryl radical substituted by at least one group chosen from among the halogen atoms and the alkoxy, hydroxy, amino and mercapto radicals and the amino radical substituted by at least one alkyl radical; R^{17} represents a hydrogen atom, an alkyl radical, an alkyl radical substituted by at least one group chosen from among the hydroxy, carboxy, amino, amido and mercapto radicals, R^{18} represents a hydrogen atom, a halogen atom, an alkoxy radical, an amino radical or an amino radical substituted by at least one alkyl group, G is S or O, and p is 1, 2 or 3.

Examples of second nitrogenous ligands which can be used are S-methyl-beta-N(2-hydroxyphenyl)methylene dithiocarbazate, S-methyldithiocarbazate, S-methyl-N-methyl-dithiocarbazate, alpha-N-methyl-S-methyl-beta-N-pyridylmethylene dithiocarabazate, and alpha-N-methyl- S-methyl-beta-N(2-hydroxyphenyl)methylene dithiocarbazate.

When the radiopharmaceutical product according to the invention is for use in diagnosis, it is generally necessary to prepare it at the moment of use.

The invention also relates to a kit for the preparation of a radiopharmaceutical product with cardiac tropism and which comprises a first bottle containing a phosphine, a second bottle containing sodium nitride, dithiocarbazic acid or a derivative thereof and a third bottle containing a compound complying with the formula:



(X)

in which R^1, R^2, V, W, n, m and Y have the meanings given hereinbefore, R^6 is an alkali metal ion, H^+ or NH_4^+ and p is equal to 0 or is an integer from 1 to 5.

This kit makes it possible to directly prepare the desired radiopharmaceutical product in a nuclear medicine hospital department by mixing the content of the first two bottles with a solution of the oxygenated transition metal solution, e.g. an ammonium or alkali metal pertechnetate solution, followed by the addition to the thus obtained

product of the content of the third bottle.

The products respectively present in the first, second and third bottles can be in liquid or lyophilized form.

In certain cases, it is also possible to mix the content of the first two bottles prior to use. In this case, the kit will only have a first bottle containing a phosphine and the second reagent constituted either by sodium nitride or by dithiocarboxylic acid or a derivative thereof, and a second bottle containing the compound of the aforementioned formula (VII).

. In view of the fact that the products are intended for intravenous injection in living beings, it is necessary to use appropriate production and use conditions for obtaining appropriately sterile and apyrogenic solutions.

In order to prepare the solutions, it is possible to use sterile and apyrogenic water or sterile and apyrogenic alcoholic or hydro-alcoholic solutions and store the solutions under nitrogen.

In order to prepare the lyophilized compositions, solutions obtained under the conditions described hereinbefore are lyophilized in standard equipment.

The radiopharmaceutical products according to the invention can be more particularly used in myocardial scintigraphy. In this case, following the preparation of the technetium nitride complex, the latter is injected into the patient to be examined and the heart is then examined by scintigraphy.

For the injection of the product, the quantities of the different ligands are such that they substantially correspond to the stoichiometry of the complexes to be obtained. The final quantity injected is in particular dependent on the ligands used and their toxicity.

Generally, satisfactory results are obtained by using total ligand quantities of 0.05 to 0.40 mg/kg of body weight.

The total transition metal, e.g. technetium dose is generally 185 to 740 Mbq (5 to 20 millicuries).

Following the administration of the transition metal nitride complex, it is possible to carry out a satisfactory examination within 0.5 to 3h obtaining a good contrast, clear images and a good detection of lesions.

Other characteristics and advantages of the invention can be gathered from the following illustrative, non-limitative examples.

EXAMPLE 1: Preparation of the bis(diethyl dithiocarbamate) nitride complex ^{99m}Tc(V)(TcNDEDC).

a) Preparation of the intermediate.

Into a penicillin-type bottle are introduced 0.4ml of a solution containing $2 \cdot 10^{-2}$mole/l (2.5mg/ml) of S-methyl dithiocarbazate in ethyl alcohol, then 0.2 ml of a $2 \cdot 10^{-2}$mole/l (5mg/ml) triphenyl phosphine solution in ethyl alcohol and 0.1ml of 1N hydrochloric acid. This is followed by the addition of 0.5 to 1 ml of a sodium pertechnetate (Tc^{99m}) solution and the reaction is carried out at 80°C for 30 minutes or at 100°C for 15 minutes.

b) Preparation of the final complex.

To the content of the bottle obtained in stage a) are added 0.1ml of 1N NaOH solution and 0.5ml of a solution containing 0.18mole/l of trihydrated sodium diethyl dithiocarbamate (40mg/ml) in a 0.5mol/l-1 sodium bicarbonate - carbonate buffer at pH 9.0.

The reaction is carried out for 15 minutes at 100°C, 30 minutes at 80°C or 60 minutes at ambient temperature.

The radiochemical purity of the complex obtained is tested by carrying out thin film chromatography using a silica gel and toluene as the solvent. The complex obtained has a Rf of 0.3 to 0.4. The radiochemical purity is equal to or greater than 93%.

EXAMPLE 2: Preparation of the bis(diethyl dithiocarbamate) nitride complex ^{99m}Tc(V) (TcNDEDC).

a) Preparation of the intermediate.

Into a penicillin-type bottle are introduced 0.2ml of a solution containing $7.7 \cdot 10^{-2}$mole/l (5.0mg/ml) of sodium nitride in water, then 0.2ml of a $2 \cdot 10^{-2}$mole/l (5mg/ml) triphenyl phosphine solution in ethyl alcohol and 0.1ml of 1N hydrochloric acid. This is followed by the addition of 0.5 to 1ml of a sodium pertechnetate solution (Tc-99m) and the reaction is performed at 80°C for 30 minutes or at 100°C for 15 minutes.

b) Preparation of the end product.

To the content of the bottle obtained in stage a) are added, as in example 1, 0.1ml of a 1N NaOH solution and 0.5ml of a solution

containing 0.18mole/l (40mg/ml) of trihydrated sodium diethyl dithiocarbamate in a 0.5mole/l sodium bicarbonate - carbonate buffer and at pH 9. The reaction is carried out as in example 1.

Testing also takes place of the radiochemical purity of the product by thin film chromatography and the results are identical to those of example 1.

EXAMPLE 3: Preparation of the bis(diethyl dithiocarbamate) nitride complex $^{99m}Tc(V)$ (TcNDEDC).

a) Preparation of the intermediate.

Into a penicillin-type bottle are introduced 0.2ml of a solution containing $7.7 \cdot 10^{-2}$mole/l (5mg/ml) of sodium nitride in water, then 0.4ml of a solution containing $1 \cdot 10^{-2}$mole/l (2 mg/ml) of tris(2-cyanoethyl)-phosphine in water and 0.1ml of 1N hydrochloric acid.

This is followed by the addition of 0.5 to 5ml of a sodium pertechnetate (^{99m}Tc) solution and the reaction is performed at 80°C for 30 minutes or at 100°C for 15 minutes - preparation without alcohol.

b) Preparation of the final complex.

The same operating procedure as in example 1, paragraph b) is followed for the preparation of the TcNDEDC complex from the previously obtained intermediate.

EXAMPLE 4: Preparation of the bis(diethyl dithiocarbamate) nitride complex $^{99m}Tc(V)$ (TcNDEDC).

a) Preparation of the intermediate.

Into a penicillin-type bottle are introduced 0.2ml of a solution containing $7.7 \cdot 10^{-2}$mole/l (5mg/ml) of sodium nitride in water, then 0.4ml of a solution containing $1 \cdot 10^{-2}$mole/l of tris(2-cyanoethyl)-phosphine.

This is followed by the addition of 0.5 to 5ml of a sodium pertechnetate (^{99m}Tc) solution and the reaction is performed at 80°C for 30 minutes or 100°C for 15 minutes. This operation is carried out at a pH close to 7.

b) Preparation of the end product.

To the content of the bottle obtained in stage a) are added 0.5ml of a solution containing 0.18mole/l (40mg/ml) of trihydrated sodium diethyl dithiocarbamate in a 0.5mole/l sodium bicarbonate - carbonate buffer and at pH 9. The reaction is carried out as in example 1.

EXAMPLE 5: Preparation of the bis(dimethyl dithiocarbamate) nitride complex $^{99m}Tc(V)$ (TcNDMDC).

The same operating procedure as in example 1 is followed, whilst in the final stage the diethyl dithiocarbamate is replaced by 0.5ml of a solution containing 0.18mole/l of dihydrated sodium dimethyl dithiocarbamate (30mg/ml) in the same buffer. This gives the technetium complex TcNDMDC with a radiochemical purity equivalent to that of example 1.

EXAMPLE 6: Preparation of the bis(di-n-propyl dithiocarbamate) nitride complex $^{99m}Tc(V)$ (TcNDPDC).

The same operating procedure as in example 1 is followed, but the diethyl dithiocarbamate is replaced by 0.5ml of a solution containing 0.18mole/l (40.7mg/ml) of sesquihydrated sodium di-n-propyl dithiocarbamate in a mixture of the 0.5mole/l sodium bicarbonate - carbonate buffer and at pH 9 and ethyl alcohol in a volume ratio of 7:3.

This gives the technetium complex TcNDPDC having a radiochemical purity equivalent to that of example 1.

EXAMPLES 7 TO 9:

In these examples testing takes place of the properties of the complexes obtained in examples 1, 5 and 6, by determining their bio distribution in male rats of the Sprague Dawley strain weighing 200±20g.

In this case, into the rats, anesthetized with sodium pentobarbital, is injected a dose corresponding to 15µmole/kg of body weight of myotropic ligand, which corresponds to a radiation dose of 1 to 2.5µCi. 5, 30 or 60 minutes following the injection of the product, the rats are sacrificed and their organs removed. This is followed by the determination of the radioactivity present in each of the organs.

The results obtained are given in the following table 1 and expressed as a percentage of the injected radioactivity found in the organs, following sampling and counting.

The values given in each box in the table represent the mean value and the two extreme values.

This table makes it clear that these complexes have a good cardiac tropism.

TABLE 1

		TdMDMDC $(CH_3)_2N-C(=S)-S^-$			TdMDEDC $(C_2H_5)_2N-C(=S)-S^-$			TMDPDC $(C_3H_7)_2N-C(=S)-S^-$		
		number of animals: 3			number of animals: 5			number of animals: 5		
	Time between I.V. injection and sacrifice	5 min	30 min	60 min	5 min	30 min	60 min	5 min	30min	60 min
whole organs										
		17.5	18.2	27.5	20.2	24.1	25	27.2	33.2	28.5
Liver		16.6 -18.1	16.7 -20.0	27.6 -28.5	14.9-22.1	23.2-26.1	24.3-26.1	23.1-32.3	29.8-35.2	22.3-33.4
5.2	1.9	1.8	4.9	3.5	3.0	2.9	2.6	2.1		
Kidneys		5.1 - 5.3	1.8 - 2.1	1.7 - 2.2	4.6- 5.2	3.2- 4.1	2.8- 3.2	2.4- 3.6	2.0- 3.3	1.6- 2.6
		4.4	6.0	6.5	9.2	1.8	1.2	2.6	1.1	0.6
Lungs		3.9 - 4.6	4.5 - 7.5	4.5 -11.5	8.5- 9.5	1.6- 1.9	1.3- 1.4	2.1- 3.4	1.0- 1.3	0.4- 0.9
		0.52	0.18	0.15	0.7	0.2	0.1	0.2	0.2	0.2
Brain		0.48- 0.58	0.17- 0.19	0.14- 0.16	0.7- 0.7	0.2- 0.2	0.1- 0.1	0.1- 0.2	0.2- 0.2	0.1- 0.2
		2.3	0.70	0.60	2.6	1.6	1.4	1.8	1.5	1.3
Heart		2.1 - 2.5	0.6 - 0.9	0.5 - 0.7	2.4- 2.7	1.6- 1.7	1.3- 1.5	1.4- 1.9	1.4- 1.7	1.2- 1.4
		3.0	2.3	3.0	9.2	2.3	1.8	3.5	2.0	1.5
Whole blood		2.9 - 3.2	2.0 - 2.5	2.9 - 3.2	7.5-10.1	1.8- 3.0	1.6- 2.2	2.5- 4.6	1.8- 2.5	1.0- 1.9

EXAMPLE 10: Preparation of the bis(N,N-dimethoxydiethyl dithiocarbamate) nitride complex ^{99m}Tc(V) (TcNMEDC).

a) Preparation of the intermediate.

Into a penicillin-type bottle are introduced 0.5ml of a solution containing $0.8 \cdot 10^{-2}$mole/l (1mg/ml) of S-methyl-N-methyl dithiocarbazate in water, then 0.5ml of a $2 \cdot 10^{-2}$mole/l (10mg/ml) trisulphonated triphenyl phosphine solution in water and 0.1ml of 1N hydrochloric acid. This is followed by the addition of 0.5 to 5ml of a sodium pertechnetate (Tc^{99m}) solution and the reaction is carried out at 80°C for 30 minutes or at 100°C for 15 minutes.

b) Preparation of the final complex.

To the content of the bottle obtained in stage a) are added 0.1ml of 1N NaOH solution and 0.5ml of a solution containing 0.1mole/l of sodium dimethoxyethyl dithiocarbamate (23mg/ml) in a 0.5mole/l sodium bicarbonate - carbonate buffer at pH 9.5. The reaction is carried out for 30 minutes at ambient temperature.

This gives the nitride complex TcNMEDC or the complex of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing the compound of formula (VI).

EXAMPLE 11: Preparation of the bis(N-ethyl-N-(2-methoxyethyl)-dithiocarbamate) nitride complex ^{99m}Tc(V) (TcNEMEC).

The same operating procedure as in example 10 is followed for the preparation of the intermediate from S-methyl-N-methyl dithiocarbazate and trisulphonated triphenyl phosphine. This is followed by the preparation of the end product by adopting the operating procedure of example 10, but using 0.5ml of a 0.1mole/l solution of sodium N-ethyl-N-(2-methoxyethyl)-dithiocarbamate (20mg/ml) in place of the sodium dimethoxyethyl dithiocarbamate of example 10.

This gives the bis(N-ethyl-N-(2-methoxyethyl)-dithiocarbamate nitride complex ^{99m} Tc(V), i.e. the product of formula:

$$(Tc{\equiv}N)L^1L^2$$

with L^1 and L^2 representing the compound of formula (VII).

EXAMPLE 12: Preparation of the bis(N-ethyl-N-(3-methoxypropyl)-dithiocarbamate) nitride complex ^{99m} Tc(V) (TcNEMPC).

The same operating procedure as in examples 10 and 11 is adopted for the preparation of this complex from the intermediate obtained in

stage a) of example 10 and using as the reagent in stage b) 0.5ml of a 0.1mole/l solution of sodium N-ethyl-N-(3-methoxypropyl)-dithiocarbamate (22mg/ml).

This gives the nitride complex TcNEMPC or the complex of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing the compound of formula (VIII).

EXAMPLE 13: Preparation of the bis(N-ethyl-N-(2-ethoxyethyl)-dithiocarbamate) nitride complex ^{99m}Tc(V) (TcNEEDC).

The same operating procedure as in example 10 is used for the preparation of the intermediate and the end product, except that the reagent used for the preparation of the end product is 0.5ml of a 0.1mole/l solution of sodium N-ethyl-N-(2-ethoxyethyl)-dithiocarbamate (22mg/ml).

This gives the nitride complex TcNEEDC or the complex of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing the compound of formula (IX).

EXAMPLE 14: Preparation of the bis(N-methoxy-N-methyl dithiocarbamate) nitride comples ^{99m}Tc (TcNMEMC).

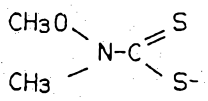
a) Preparation of the intermediate.

The same operating procedure as in example 10 is used for preparing an intermediate, whilst using the same reagents and the same reaction conditions.

b) Preparation of the final complex.

To the content of the bottle obtained in stage a) are added 0.1ml of a 1N NaOH solution and 0.5ml of a solution containing 0.13mole/l of sodium N-methoxy-N-methyl dithiocarbamate (20mg/ml) in a 0.5mole/l sodium bicarbonate - carbonate buffer at pH 9.5. The reaction is performed for 30 minutes at ambient temperature.

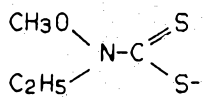
This gives the complex TcNMEMC, namely that of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing:



EXAMPLE 15: Preparation of bis(N-methoxy-N-ethyl dithiocarbamate) nitride complex ^{99m}Tc(V) (TcNMEEC).

The same operating procedure as in example 14 is adopted for preparing this technetium complex from the same intermediate and using for the preparation of the end product 0.5ml of a 0.12mole/l sodium N-methoxy-N-ethyl dithiocarbamate solution (20mg/ml). This gives the

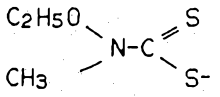
complex TcNMEEC, namely the complex of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing the formula:



EXAMPLE 16: Preparation of bis(N-ethoxy-N-methyl dithiocarbamate) nitride complex $^{99m}Tc(V)$ (TcNETMC).

This example adopts the operating procedure of example 14, except that the reagent used for preparing the end product is 0.5ml of a 0.12mole/l solution of sodium N-ethoxy-N-methyl dithiocarbamate (20mg/ml).

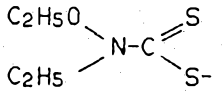
This gives the technetium complex of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing the formula:



EXAMPLE 17: Preparation of the bis(N-ethoxy-N-ethyl dithiocarbamate) nitride complex $^{99m}Tc(V)$ (TcNETEC).

The same operating procedure as in example 14 is followed for the preparation of this technetium complex using as the reagent in the second stage 0.5ml of a solution containing 0.11mole/l of sodium N-ethoxy-N-ethyl dithiocarbamate (20mg/ml).

This gives the complex of formula $(Tc{\equiv}N)L^1L^2$ with L^1 and L^2 representing the formula:



EXAMPLE 18:

The biological properties of the complexes obtained in examples 10 to 13 and 17 are tested by determining the retention of the myocardium in dogs weighing between 10 and 15kg.

In this case, into dogs anesthetized with sodium pentobarbital and kept under ventilation, is injected a dose corresponding to 2µmole/kg of body weight of myotropic technetium complex, which corresponds to a 2 to 5mCi radiation dose.

The retention of the radioactivity by the myocardium and the surrounding organs (lungs and liver) is determined by dynamic acquisition between injection and the end of the examination using a

gamma camera and by defining areas of interest for each organ. All the tested complexes allow a good visual display of the myocardium.

The heart/liver and heart/lung contrast values are measured by performing a simple ratio between the number of beats per surface unit (or pixel) in the organs. The heart/liver and heart/lung ratio values are given in table 2.

Therefore the target organ/background noise ratios are very favourable.

EXAMPLES 19 TO 21:

These examples test the properties of the complexes obtained in examples 15 to 18 by determining their biodistribution in male rats of the Sprague Dawley strain weighing 200±20g.

In this case, into rats, anesthetized with sodium pentobarbital, is injected a dose corresponding to 15µmole/kg of body weight of myotropic ligand, which corresponds to a radiation dose of 1 to 2.5µCi.

5, 30 or 60 minutes following the injection of the product, the rats are sacrificed and the organs removed. The radioactivity present in each of the organs is determined.

The results obtained are given in table 3 and expressed as a percentage of the injected radioactivity found in the organ, following sampling and counting. The values given in each box of the table represent the mean value and the two extreme values.

The table shows that these complexes have a good cardiac tropism.

TABLE 2

HEART/LIVER AND HEART/LUNG RATIOS FOR CERTAIN DITHIOCARBAMATE Tc=N COMPLEXES

Ex	$L_1=L_2=$ $R^1 \diagdown R^2 \diagup NCS_2$	t min / Ratios	5	15	30	75	90	120
17	$R^1 = C_2H_5-$ $R^2 = C_2H_5O-$	Heart./liver Heart./lung	2 01 1 10	1 39 1 33	1 24 1 61	0 90 1 75		0 82 2 64
11	$R^1 = C_2H_5-$ $R^2 = CH_3O(CH_2)_2-$	Heart./liver Heart./lung	1 44 2 75	1 02 2 60	0 86 2 41		0 66 1 66	
10	$R^1 = CH_3O(CH_2)_2-$ $R^2 = CH_3O(CH_2)_2-$	Heart./liver Heart./lung	1 27 2 02	0 61 1 70	0 38 1 35			
13	$R^1 = C_2H_5-$ $R^2 = C_2H_5O(CH_2)_2-$	Heart./liver Heart./lung	1 43 1 36	0 97 1 66	0 87 1 68	0 63 3 10	0 58 2 97	0 56 2 46
12	$R^1 = C_2H_5-$ $R^2 = CH_3O(CH_2)_3-$	Heart./liver Heart./lung	0 95 1 39	0 74 2 16	0 60 2 44	0 32 2 04	0 27 1 87	0 18 1 54

TABLE 3

L1 = L2	EX. 6 (TCNMEMC) CH3-O, NCS2, CH3			EX. 7 (TCNMEEC) CH3-O, NCS2, C2H5		
Time between I.V. injection and sacrifice	5 min	30 min	60 min	5 min	30 min	60 min
whole organs						
Liver	24.2	27.5	22.7	22.8	21.2	23.0
	16.1 -29.3	20-29.2	20.5 -24.2	20.1-23.5	20.0-24.0	21-25
Kidneys	5.8	3.9	5.4	6.0	6.7	8.7
	5.0 - 6.5	3.1 - 4.5	4.2 - 5.9	5.8- 6.2	6.5-7.0	7.5- 9.1
Lungs	4.6	6.2	7.8	4.4	3.7	2.5
	4.7 - 4.9	5.7 - 6.5	7.0 -8.2	4.0- 4.8	3.2-3.9	2.1- 3.0
Brain	0.46	0.18	0.17	0.40	0.23	0.16
	0.36- 0.59	0.15- 0.20	0.16-0.20	0.40-0.40	0.21-0.25	0.15- 0.1
Heart	2.2	0.80	0.20	1.5	0.80	0.50
	1.9 - 2.5	0.6 - 0.9	0.2 - 0.2	1.4- 1.7	0.75-0.83	0.48-0.53
Whole blood	2.4	4.5	7.8	7.2	6.1	6.0
	2.4 - 2.4	4.2 - 4.9	6.8 - 8.5	7.0-7.5	5.8-6.9	5.7- 6.5

TABLE 3 (continued)

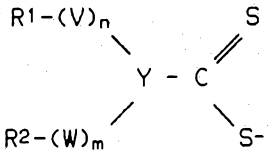
	EX. 8 (TCNETMC) CH_2H_5-O- ⟍ N-CS_2 ⟋ CH_3			EX. 9 (TCNETEC) C_2H_5-O ⟍ N-CS_2 ⟋ C_2H_5		
$L_1 = L_2$						
Time between I.V. injection and sacrifice	5 min	30 min	60 min	5 min	30 min	60 min
whole organs						
Liver	18.7	22.1	29.4	21.5	29.4	28,9
	17.5 -19.1	19.5 -23.0	26.1 -32.0	16.1-27.2	27.5-30.2	28.0-29.5
Kidneys	5.5	4.0	4,3	6.1	5.7	5.4
	5.0 - 5.9	3.8 - 4.3	4.0 - 4.5	5.5- 7.4	5.0- 6.0	4.9- 5.7
Lungs	5.3	9.0	6.5	4.9	2.4	1.6
	5.0 - 5.8	8.4 - 9.7	6.1 - 6.9	4.8- 5.1	2.1- 2.8	1.4- 1.8
Brain	0,65	0,18	0.18	0,65	0.34	0.20
	0.62- 0.69	0.15- 0.20	0.15- 0.20	0.54-0.75	0.30-0.40	0.20-0.21
Heart	1.70	0.81	0.41	2.70	2.26	1.91
	1.60- 1.80	0.80- 0.82	0.40- 0.42	2.32-3.08	2.1 -2.5	1.85-2,01
Whole blood	4.2	3.6	2.4	2.1	2.2	2.3
	3.9 - 4.4	3.5 - 3.7	2.3 - 2.5	1.8 -3 0	2.0 -2.2	2.0- 2.5

C L A I M S

1. Radiopharmaceutical product, characterized in that it comprises a complex of a transition metal complying with the formula:

$$(M \equiv N)\ L^1L^2$$

in which M is a transition metal and L^1 and L^2, which can be the same or different, comply with the formula:



(II)

in which V and W, which can be the same or different, represent O, S or Se, n and m, which can be the same or different, are equal to 0 or to 1, Y represents N, P or As, and R^1 and R^2, which can be the same or different, represent a straight or branched alkyl radical with 1 to 10 carbon atoms, which is either not substituted or substituted by $-O-R^3$, $OOC-R^3$, $OCNR^4R^5$ or $-NR^4R^5$ groups, in which R^3 is a straight or branched alkyl radical with 1 to 5 carbon atoms and R^4 and R^5, which can be the same or different, are hydrogen atoms or straight or branched alkyl radicals with 1 to 5 carbon atoms, or in which R^1 and R^2 together form a hydrocarbon cycle optionally containing one or more heteroatoms.

2. Radiopharmaceutical product according to claim 1, characterized in that M represents a rhenium or technetium isotope.

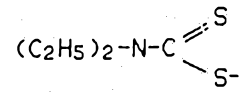
3. Radiopharmaceutical product according to claim 2, characterized in that the technetium isotope is Tc 99m.

4. Radiopharmaceutical product according to claim 2, characterized in that the rhenium isotope is Re-186 or Re-188.

5. Radiopharmaceutical product according to any one of the claims 1 to 4, characterized in that Y represents N, m and n are equal to 0 and L^1 and L^2 are identical.

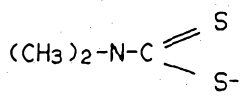
6. Radiopharmaceutical product according to claim 5, characterized in that R^1 and R^2 represent unsubstituted alkyl radicals.

7. Radiopharmaceutical product according to claim 6, characterized in that L^1 and L^2 represent:



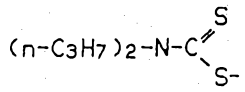
(III)

8. Radiopharmaceutical product according to claim 6, characterized in that L^1 and L^2 represent:



(IV)

9. Radiopharmaceutical product according to claim 6, characterized in that L^1 and L^2 represent:



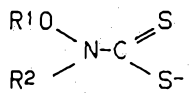
(V)

10. Radiopharmaceutical product according to claim 5, characterized in that at least one of the R^1 and R^2 is an alkoxyalkyl radical.

11. Radiopharmaceutical product according to claim 10, characterized in that R^1 represents $CH_3O-CH_2-CH_2-$ and R^2 represents CH_3-CH_2- or $CH_3OCH_2-CH_2-$.

12. Radiopharmaceutical product according to claim 10, characterized in that R^1 represents CH_3-CH_2- and R^2 represents $CH_3-O-CH_2-CH_2-CH_2-$ or $C_2H_5-O-CH_2-CH_2-$.

13. Radiopharmaceutical product according to any one of the claims 1 to 4, characterized in that Y represents N and L^1 and L^2 comply with the formula:



in which R^1 and R^2 have the meanings given in claim 1.

14. Radiopharmaceutical product according to claim 13, characterized in that R^1 represents CH_3- and R^2 represents CH_3- or CH_3-CH_2-.

15. Radiopharmaceutical product according to claim 13, characterized in that R^1 represents CH_3-CH_2- and R^2 represents CH_3- or CH_3-CH_2-.

16. Process for the preparation of a radiopharmaceutical product

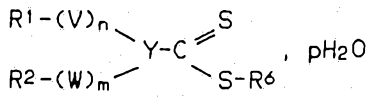
according to any one of the claims 1 to 15, characterized in that it comprises the following successive stages:

1°) reacting an oxygenated compound of a transition metal M with:

a) a first ligand chosen from within the group of substituted or unsubstituted, aromatic and aliphatic phosphines and polyphosphines and

b) a second reagent chosen from among the ammonium and alkali metal nitrides and the nitrogenous ligands having a $\geq N\text{-}N\leq$ in which the N are connected to hydrogen atoms and/or to monovalent organic groups via a carbon atom, or in which one of the N is connected to the carbon atom of a divalent organic group via a double bond and the other N is connected to hydrogen atoms and/or monovalent organic groups via a carbon atom and

2°) reacting the intermediate obtained in the first stage with a compound in accordance with the formula:



, pH_2O (X)

in which R^1, R^2, V, W, n, m and Y have the meanings given hereinbefore, R^6 is an alkali metal ion, H^+ or NH_4^+ and p is equal to 0 or an integer between 1 and 5.

17. Process according to claim 16, characterized in that the oxygenated compound of the transition metal is an ammonium or alkali metal pertechnetate.

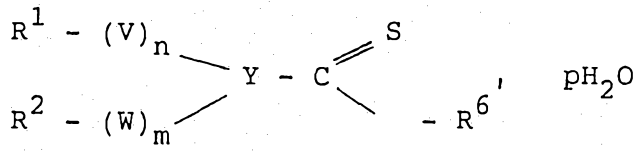
18. Process according to claim 16, characterized in that the oxygenated compound of the transition metal is ammonium or alkali metal perrhenate.

19. Process according to any one of the claims 16 to 18, characterized in that the first ligand is a phosphine chosen from among triphenyl phosphine, diethyl phenyl phosphine, triethyl phosphine, trimethyl phosphine, tris(2-cyanoethyl)-phosphine and trisulphonated triphenyl phosphine.

20. Process according to any one of the claims 16 to 19, characterized in that the second reagent is chosen from among S-methyldithiocarbazate, S-methyl-N-methyldithiocarbazate, alpha-N-methyl-S-methyl beta-N-pyridylmethylene dithiocarbazate, S-methyl-beta-N-(2-hydroxyphenyl)methylene dithiocarbazate and alpha-N-methyl-S-methyl-beta-N-(2-hydroxyphenyl)methylene dithiocarbazate.

21. Process according to any one of the claims 16 to 19, characterized in that the second reagent is sodium nitride.

22. A kit when used for the preparation of a radiopharmaceutical product according to any one of claims 16-21, characterized in that it comprises a first bottle containing a phosphine, a second bottle containing sodium nitride, dithiocarbazic acid or a derivative thereof and a third bottle containing a compound complying with the formula:



(X)

in which R^1, R^2, V, W, n, m and Y have the meanings given in claim 1, R^6 is an alkali metal ion, H^+ or NH_4^+ and p is equal to 0 or an integer from 1 to 5.

23. The transition metal complex as defined in any one of the claims 1 to 15 when used for the preparation of a radiopharmaceutical product with cardiac tropism.

DATED this 19th day of February 1992

CIS BIO INTERNATIONAL S.A.
Patent Attorneys for the
Applicant:

F.B. RICE & CO.

INTERNATIONAL SEARCH REPORT

International Application No PCT/FR 89/00608

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[5] A 61 K 49/02; C 07 F 13/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int. Cl.[5]	A 61 K; C 07 F; C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [9]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	INTERNATIONAL JOURNAL OF RADIATION/APPLICATIONS INSTRUMENTATION part A. vol. 38, No. 8, 1987, GB pages 665 - 668; BALLINGER J.R.: "Technetium-99m Diethyldithiocarbamate (DDC): Comparison with Thallium-201DDC as an Agent for Brain Imaging" see the whole document	1-23
Y	WO, A, 8503063 (THE COMMONWEALTH OF AUSTRALIA) 18 July 1985 see the whole document (cited in the application)	1-23
Y	INTERNATIONAL JOURNAL OF APPLIED RADIATION AND ISOTOPES. vol. 36, No. 2, February 1985, OXFORD GB pages 133 - 139; BALDAS J. et al: "Substitution reactions of 99m TcNCl4- A. Route to a new class of 99m Tc-Radiopharmaceuticals" see the whole document	1-23

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 February 1990 (15.02.90)	13 March 1990 (13.03.90)
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

PCT/FR 89/00608
SA 32762

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 15/02/90

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8503063	18-07-85	EP-A- 0166746	08-01-86
		JP-T- 61501087	29-05-86
		US-A- 4851515	25-07-89

RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale No PCT/FR 89/00608

I. CLASSEMENT DE L'INVENTION (si plusieurs symboles de classification sont applicables, les indiquer tous) 7

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

CIB 5 A61K49/02 ; C07F13/00

II. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée[8]

Système de classification	Symboles de classification
CIB 5	A61K ; C07F ; C07C

Documentation consultée autre que la documentation minimale dans la mesure où de tels documents font partie des domaines sur lesquels la recherche a porté[9]

III. DOCUMENTS CONSIDERES COMME PERTINENTS[10]

Catégorie °	Identification des documents cités, avec indication, si nécessaire,[12] des passages pertinents[13]	No. des revendications visées[14]
Y	INTERNATIONAL JOURNAL OF RADIATION/APPLICATIONS & INSTRUMENTATION Part A. vol. 38, no. 8, 1987, GB pages 665 - 668; BALLINGER J.R.: "Technetium-99m Diethyldithiocarbamate (DDC): Comparison with Thallium-201DDC as an Agent for Brain Imaging" voir le document en entier ---	1-23
Y	WO,A,8503063 (THE COMMONWEALTH OF AUSTRALIA) 18 juillet 1985 voir le document en entier (cité dans la demande) --- -/--	1-23

° Catégories spéciales de documents cités:[11]

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié postérieurement à la date de dépôt international ou à la date de priorité et n'appartenenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier.

"&" document qui fait partie de la même famille de brevets

IV. CERTIFICATION

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
15 FEVRIER 1990	13. 03. 90
Administration chargée de la recherche internationale	**Signature du fonctionnaire autorisé**
OFFICE EUROPEEN DES BREVETS	T.K. WILLIS

III. DOCUMENTS CONSIDERES COMME PERTINENTS [14] (SUITE DES RENSEIGNEMENTS INDIQUES SUR LA DEUXIEME FEUILLE)

Catégorie °	Identification des documents cités, [16] avec indication, si nécessaire des passages pertinents [17]	No. des revendications visées [18]
Y	INTERNATIONAL JOURNAL OF APPLIED RADIATION AND ISOTOPES. vol. 36, no. 2, février 1985, OXFORD GB pages 133 - 139; BALDAS J. et al: "Substitution reactions of 99m TcNCl4-_A. Route to a new class of 99m Tc-Radiopharmaceuticals" voir le document en entier ---	1-23

ANNEXE AU RAPPORT DE RECHERCHE INTERNATIONALE RELATIF A LA DEMANDE INTERNATIONALE NO.

PCT/FR89/00608
SA 32762

La présente annexe indique les membres de la famille de brevets relatifs aux documents brevets cités dans le rapport de recherche internationale visé ci-dessus.
Lesdits membres sont contenus au fichier informatique de l'Office européen des brevets à la date du
Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office européen des brevets. 15/02/90

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
WO-A-8503063	18-07-85	EP-A- 0166746	08-01-86
		JP-T- 61501087	29-05-86
		US-A- 4851515	25-07-89

EPO FORM P0472

Pour tout renseignement concernant cette annexe : voir Journal Officiel de l'Office européen des brevets, No.12/82