FORM 1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

613720

I\We,

JOHNSON MATTHEY
PUBLIC LIMITED COMPANY

of 78 HATTON GARDEN
LONDON EC1N 8JP
ENGLAND

hereby apply for the grant of a standard patent for an invention entitled:

PLATINUM CHEMOTHERAPEUTIC PRODUCT

which is described in the accompanying complete specification

Details of basic application(s):

Number of basic application	Name of Convention country in which basic application was filed	Date of basic application
8806224	GB	16 MAR 88

My/our address for service is care of GRIFFITH HACK & CO., Patent Attorneys, 601 St. Kilda Road, Melbourne 3004, Victoria, Australia.

DATED this 08th day of March 1989

JOHNSON MATTHEY
PUBLIC LIMITED COMPANY
GRIFFITH HACK & CO.

TO: The Commissioner of Patents.

M007217 08/03/89

Commonwealth of Australia
The Patents Act 1952

DECLARATION IN SUPPORT

In support of the (Convention) Application made by:

Johnson Matthey Public Limited Company

for a patent for an invention entitled:

Platinum Chemotherapeutic Product

I (We) I.C. Wishart

of and care of the applicant company do solemnly and sincerely declare as follows:

---

a) I am (We are) the applicant(s) for the patent

or

b) I am (We are) authorised by the applicant(s) for the patent to make this declaration on its behalf.

Delete the following if not a Convention Application.

The basic application(s) as defined by section 141 (142) of the Act was (were) made

in United Kingdom on 16th March 1988

in on

in on

by Johnson Matthey Public Limited Company

The basic application(s) referred to in this paragraph is (are) the first application(s) made in a Convention country in respect of the invention the subject of the application.

---

a) I am (We are) the actual inventor(s) of the invention.

or

b) Kenneth Reginald Harrap
of Grundlewood,
Park Gate Road, Newdigate,
Surrey RH5 5DZ, England

is (are) the actual inventor(s) of the invention and the facts upon which

Johnson Matthey Public Limited Company

is (are) entitled to make the application are as follows:

By virtue of an Agreement dated 19th November 1982, the Applicant would be entitled to have assigned to it a patent granted to the actual inventor in respect of the said invention.

Declared at Reading this 21st day of February 1984

For and on behalf of Johnson Matthey Public Limited Company

Signed I.C. Wishart Status Manager, Patents Agreements

Declarant's Name I.C. WISHART

(12) PATENT ABRIDGMENT (11) Document No. AU-B-31127/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 613720

(54) Title
PLATINUM CHEMOTHERAPEUTIC PRODUCT

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(51)[4] **A61K 031/445** **A61K 031/28** **A61K 031/555**

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8806224	**16.03.88**	**GB UNITED KINGDOM**

(43) Publication Date : **21.09.89**

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(71) Applicant(s)
JOHNSON MATTHEY PUBLIC LIMITED COMPANY

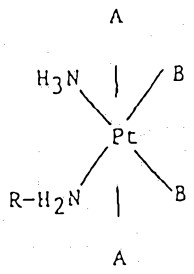
(72) Inventor(s)
KENNETH REGINALD HARRAP

(74) Attorney or Agent
GRIFFITH HACK & CO , GPO Box 1285K, MELBOURNE VIC 3001

(57) This invention relates to platinum chemotherapeutic products forthe treatment of cancer.

CLAIM

1. A pharmaceutical composition comprising a platinum coordination compound of the general formula I,



(I)

wherein R is hydrogen, methyl, ethyl or a straight chain or branched chain or cyclic alkyl group having from 3 to 9 carbon atoms, A is a chlorine atom or hydroxyl group and is present when the platinum atom is in the Pt (IV) state, and each B is a chlorine atom or together form a malonate or substituted malonate, providing B is not chlorine when R is hydrogen, and loperamide.

AUSTRALIA

PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

613720

Short Title:

Int. Cl:

Application Number:
Lodged:

Complete Specification-Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: JOHNSON MATTHEY
PUBLIC LIMITED COMPANY

Address of Applicant: 78 HATTON GARDEN
LONDON EC1N 8JP
ENGLAND

Actual Inventor:

Address for Service: GRIFFITH HACK & CO.,
601 St. Kilda Road,
Melbourne, Victoria 3004,
Australia.

Complete Specification for the invention entitled:
PLATINUM CHEMOTHERAPEUTIC PRODUCT

The following statement is a full description of this invention including the best method of performing it known to me:-

PLATINUM CHEMOTHERAPEUTIC PRODUCT

This invention relates to platinum chemotherapeutic products forthe treatment of cancer.

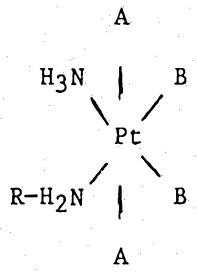
Certain platinum coordination compounds are known for clinical use in the treatment of various forms of cancer, and are generally analogues of the first compound recognised as exhibiting anti-cancer activity, namely cis-diammine-dichloroplatinum (II), known generically as cisplatin. However, indices of activity and toxicity vary widely from compound to compound and it has for several years been an objective of the researcher to provide a compound with a combination of good activity with low toxicity, particularly since the toxicity generally manifests itself in the

form of extreme vomiting and diarrhoea which the patient finds extremely unpleasant and has difficulty in tolerating, leading to a tendency to voluntary rejection of the therapy. However, some success has been achieved and certain compounds show desirable properties, although it remains a goal to improve activity, either in terms of spectrum of activity in absolute terms or against certain specified cancers, while reducing toxicity.

A further objective of the researcher has been to provide a compound which exhibits useful anti-tumour activity following oral administration. It has been found, however, that such activity cannot be predicted on the basis of or by extrapolation from results following intraperitoneal administration and much effort has been expended on pharmacokinetics studies, in an attempt to determine the factors which affect absorption and retention in the systemic circulation following oral administration.

It is an object of the present invention to provide a chemotherapeutic product for the treatment of cancer and which exhibits enhanced activity following oral administration.

According to the invention, a chemotherapeutic product comprises a platinum coordination compound having the general formula



(I)

in which R is H, methyl, ethyl or a straight chain, branched chain or cyclic alkyl group having from 3 to 9 carbon atoms, A is a chlorine or hydroxyl group and is present only when the platinum atom is in the Pt (IV) state, and each B is a chlorine atom or together form a malonate or substituted malonate, providing B is not chlorine when R is hydrogen, and loperamide, as a combined preparation for simultaneous, separate or sequential use in the treatment of cancer.

The invention also includes pharmaceutical products containing a platinum coordination compound having the general formula (I) and loperamide. Furthermore, the invention includes pharmaceutical compositions comprising such products together with a pharmaceutically acceptable carrier or diluent. Suitable carriers and diluents are well known, as are the principles of formulation of compositions in unit dosage form and for oral administration.

In a further aspect, the invention includes a method for the treatment of cancer in an animal or human body, the method comprising the simultaneous, separate or sequential administration to the said body of a platinum coordination compound having the general formula (I) and loperamide.

Loperamide (4-p-chlorophenyl)-4-hydroxy-N,N-dimethyl-α, α-diphenyl-1-piperidinebutyramide) is a known antidiarrhoel agent and its preparation and characterisation were first described in French Patent No. 2,100,711, corresponding to U.S. Patent No. 3,714,159. We have found according to the invention that loperamide significantly increases the absorption of the platinum compound into the systemic circulation following oral administration and causes a marked increase in anti-tumour activity as measured by reduction in tumour size in test animals. Furthermore, we have found that the beneficial effects of loperamide are not shown by combined administration with any platinum compound selected at random from the range of known such compounds exhibiting anti-tumour activity, but rather appear to have a selective effect with certain platinum compounds or classes of platinum compound only. For example, no beneficial effect is apparent from the administration of loperamide and cisplatin, but a marked effect is noted from the administration of loperamide and carboplatin, diammine-1,1-cyclobutanedicarboxylateplatinum (II), which is a platinum (II) compound according to general formula (I) in which R is H and the B's together form 1,1-cyclobutanedicarboxylate.

Other platinum coordination compounds which show a beneficial effect in combination with loperamide include mixed amine compounds with halogen leaving groups ligands, such as cis-dichloro (ammine) (iso-butylamine) platinum (II) and platinum (IV) compounds such as
cis-diammine-dichloro-trans-dihydroxyplatinum (IV),
cis-(ammine)- (cyclopentylamine)-tetrachloroplatinum (IV) and
cis-dichloro-(ammine)(t-butylamine)-trans-dihydroxyplatinum (IV).

We have obtained the results as shown in the attached Table 1 for combined administration of loperamide with the indicated platinum compounds, where loperamide at a dosage level of 10mg/kg was administered to mice simultaneously with administration of the platinum compound at a dosage level of 10 μmole/kg. Results are expressed as average percentage (number of animals per test was 3 or 4) of total platinum metal excreted in the urine over 48 hours following administration, plus/minus standard deviation, where a higher urine concentration is indicative of a higher level of absorption into the bloodstream.

It is seen from Table 1 that all compounds tested, except cisplatin, gave a marked beneficial effect in combination with loperamide, to the extent that absorption was increased to approximately 20-25% of the given dose.

Tests were also carried out in bioavailability of the compound carboplatin (cis-diammine-cyclobutanedicarboxylatoplatinum (II)) following combined administration with loperamide. Bioavailability is a measure of the absorption following oral (p.o.) administration compared with intravenous (i.v.) injection and is expressed as:

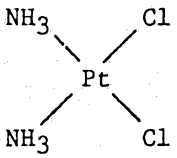
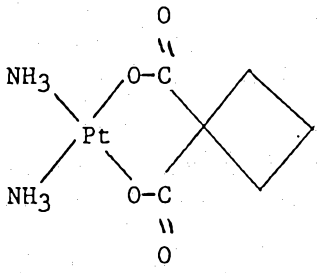
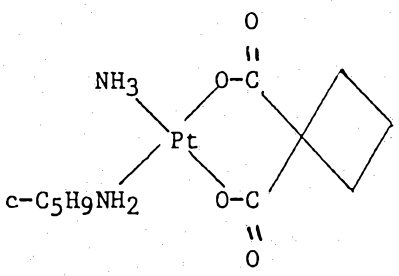
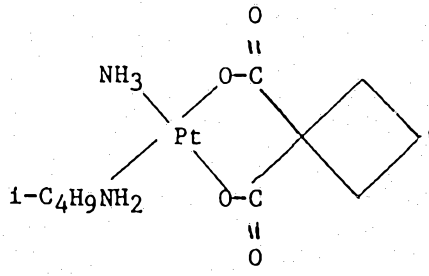
$$\frac{\%\text{ dose in urine following p.o.}}{\%\text{ dose in urine following i.v.}}$$

Results are given in the attached Table 2, from which it can be seen that loperamide enhances the bioavailability of carboplatin following oral administration by over 100%, compared with administration of the compound alone.

Further tests were carried out to determine anti-tumour effectiveness by assessing the reduction in tumour size 10 days after administration to mice bearing the ADJ/PC6 tumour. Dosage levels were 8mg/kg for the compound carboplatin and 3mg/kg for the compound cisplatin, in each case with and without loperamide. Results are given in the attached Table 3, from which it can be seen that the selective effect of loperamide, already noted from Table 1, is reinforced. Results are quoted as average volume reduction over 5 animals per test, plus/minus standard error.

TABLE 1

ABSORPTION STUDIES

Compound	% Dose in Urine	
	Control	+ Loperamide
	21 ± 2	18 ± 10
	9 ± 2	21 ± 5
	15 ± 3	27 ± 7
	6 ± 4	24 ± 10

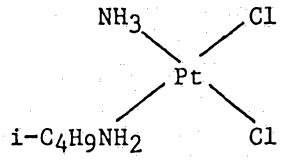
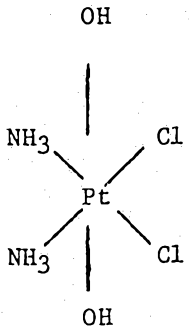
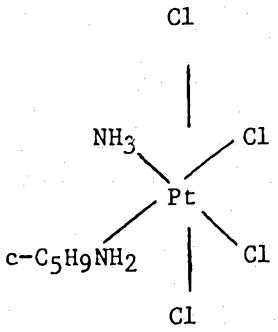
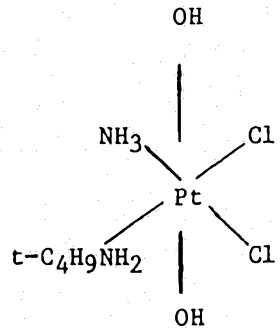
Compound	% Dose in Urine	
	Control	+ Loperamide
	7 ± 2	19 ± 3
	15 ± 2	23 ± 2
	6 ± 2	19 ± 3
	11 ± 0.2	17 ± 5

TABLE 2

BIOAVAILABILITY

DRUG	% DOSE IN URINE 0-48 HR		BIOAVAILABILITY
	p.o.	i.v.	
Carboplatin	11 ± 2	66 ± 13	16%
Carboplatin + loperamide	25 ± 10	72 ± 12	34%

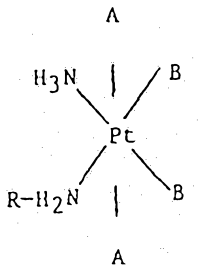
TABLE 3

ANTI-TUMOUR EFFECTIVENESS

DRUG	% REDUCTION IN TUMOUR SIZE
Cisplatin	88.1 ± 3.5
Cisplatin + loperamide	81.6 ± 2.6
Carboplatin	25.9 ± 7.1
Carboplatin + loperamide	74.3 ± 11.8

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition comprising a platinum coordination compound of the general formula I,



(I)

wherein R is hydrogen, methyl, ethyl or a straight chain or branched chain or cyclic alkyl group having from 3 to 9 carbon atoms, A is a chlorine atom or hydroxyl group and is present when the platinum atom is in the Pt (IV) state, and each B is a chlorine atom or together form a malonate or substituted malonate, providing B is not chlorine when R is hydrogen, and loperamide.

2. A composition according to claim 1, wherein the platinum compound has B substituents which together form a 1,1-cyclobutanedicarboxylate.

3. A product according to claim 2, wherein the platinum compound is carboplatin.

4. A pharmaceutical composition comprising a platinum compound of formula I and loperamide, together with a pharmaceutically acceptable carrier or diluent.

5. A composition according to claim 4, in oral unit dosage form.

6. A composition according to claim 4 or 5, wherein the platinum compound has B substituents which together form a 1,1-cyclobutanedicarboxylate.

7. A composition according to claim 6, wherein the platinum compound is carboplatin.

DATED THIS 5TH DAY OF JUNE 1991
JOHNSON MATTHEY PUBLIC LIMITED COMPANY
By its Patent Attorneys:
GRIFFITH HACK & CO.
Fellows Institute of Patent
Attorneys of Australia.