(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 226 266 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
28.02.1996 Bulletin 1996/09

(51) Int. Cl.[6]: **A61K 31/415**

(21) Application number: **86304831.0**

(22) Date of filing: **24.06.1986**

(54) **Use of a tetrahydrocarbazolone derivative for the manufacture of medicaments**
Verwendung eines Tetrahydrocarbazolonderivates zur Herstellung von Arzneimitteln
Utilisation d'un dérivé du tétrahydrocarbazolone pour la fabrication de médicaments

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(30) Priority: **25.06.1985 GB 8516083**

(43) Date of publication of application:
24.06.1987 Bulletin 1987/26

(60) Divisional application : **90122615.9**

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- **Eur.J.Cancer 26(3), March 1990, 311-314**
- **Cancer Treatment Reports, vol.66, no.1, January 1982, pages 187-189 A.P.Florczyk et al: "Cisplatin-induced emesis in the ferret: A new animal model"**

Printed by Rank Xerox (UK) Business Services
2.9.9/3.4

EP 0 226 266 B1

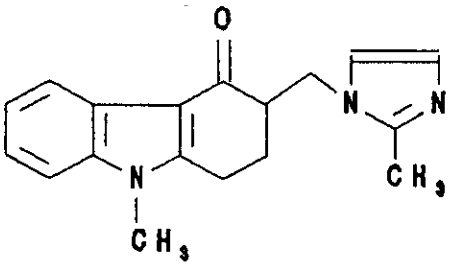
Description

This invention relates to the use of a certain tetrahydrocarbazolone derivative for the manufacture of a medicament, in particular for use as an anti-emetic agent.

A particularly important application for anti-emetic agents is in the prevention and treatment of nausea and vomiting associated with cancer chemotherapy. Emesis is a well-known and frequent side-effect of cancer chemotherapeutic agents, such as cisplatin. It causes serious problems in cancer chemotherapy, and in some patients emesis is so severe that therapy must be discontinued. Anti-emetic agents are therefore often administered in order to alleviate this side-effect of the cancer chemotherapeutic agent. The anti-emetic agents employed are usually benzamide derivatives, such as metoclopramide, which have dopamine antagonist activity.

In view of their dopamine antagonist activity benzamide derivatives such as metoclopramide themselves exhibit serious and undesirable side-effects, such as extra-pyramidal effects, i.e. tardive dyskinesia, acute distonia, akathisia and tremor. There is thus a need for a safe and effective anti-emetic agent.

In our British patent application No. 2153821A we disclose the compound 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one and physiologically acceptable salts and hydrates thereof. This compound may be represented by formula (I)



(I)

Suitable physiologically acceptable salts of the compound of formula (I) include acid addition salts formed with organic or inorganic acids, for example a hydrochloride, hydrobromide, sulphate, phosphate, citrate, fumarate or maleate.

The compound of formula (I) is described in the aforementioned specification as a potent and selective antagonist of 5-hydroxytryptamine (5-HT) at 'neuronal' 5-HT receptors of the type located on terminals of primary afferent nerves, and which are also believed to be present in the central nervous system. The compound is described as being of use in the treatment of a human or animal subject suffering from a condition caused by a disturbance of neuronal 5HT function, for example in the treatment of a human subject suffering from migraine pain or a psychotic disorder such as schizophrenia. It is also stated that the compound may be useful in the treatment of conditions such as anxiety, obesity and mania.

We have now surprisingly found that the compound of formula (I) is anti-emetic.

Accordingly, the invention provides the use of the compound of formula (I) or a physiologically acceptable salt or hydrate thereof for the manufacture of a medicament for the relief of nausea and vomiting.

Tests in animals have shown that the compound of formula (I) inhibits emesis. The compound is therefore of use as an anti-emetic agent, i.e. in the prevention and treatment of nausea and vomiting. The compound is especially valuable for the prevention of emesis induced by cancer chemotherapeutic agents such as cisplatin. Particular mention may also be made of the treatment of radiation-induced emesis. Thus, the compound of formula (I) may be used in the prevention of emesis induced by radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; or in the treatment of radiation sickness.

The compound of formula (I) does not possess dopamine antagonist activity and thus will not produce the undesirable side effects found with known anti-emetic agents such as metoclopramide.

It will be appreciated that the compound of formula (I) may be used prophylactically and references in this specification to treatment include prophylactic treatment as well as the alleviation of acute symptoms.

A preferred form of the compound of formula (I) is the hydrochloride dihydrate.

The compound of formula (I) is well absorbed from the gastro-intestinal tract. It does not prolong sleeping time in the pentobarbitone anaesthetised mouse indicating that there is no undesirable interaction with drug metabolising enzymes. Indeed it exhibits no effects on normal behaviour, is non-toxic and exhibits no undesirable effects in mice at doses up to 1mg/kg intravenously.

Medicaments containing the compound of formula (I) or a physiologically acceptable salt or hydrate thereof may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus the compound of formula (I) and its physiologically acceptable salts and hydrates may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compound of formula (I) may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compound of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compound may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compound of formula (I) may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For administration by inhalation the compound of formula (I) is conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound of formula (I) and a suitable powder base such as lactose or starch.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil,such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

A proposed dose of the compound of formula (I) for administration in man (of approximately 70kg body weight) is 0.05 to 20mg, preferably 0.1 to 10mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration and the body weight of the patient. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

For oral administration a unit dose will preferably contain from 0.5 to 8mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 8mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2mg to 4mg of the compound of formula (I) and each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 to 20mg of the compound of the invention. The overall daily dose by inhalation will be within the range of 0.4 to 80mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compound of formula (I) may be administered in combination with other therapeutic agents. It may be administered in combination with anticancer (e.g. cytostatic) drugs, for example to prevent nausea and vomiting associated with these agents. Cytostatic agents with which the compound of formula (I) may be administered include cyclophosphamide; alkylating agents; and platinum complexes such as cisplatin. Thus, the compound of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use, for the relief of nausea and vomiting. Such a combined preparation may be, for example, a twin-pack. A preferred combination comprises the compound of formula (I) with a cytostatic agent, especially cisplatin.

In general, the presently available dosage forms of the known therapeutic agents will be suitable for use in such combined preparations. Thus, cisplatin may be provided in vials containing 10, 25 or 50 mg of the active ingredient.

The compound of formula (I) may be prepared by the process described in British patent application No. 2153821A.

The anti-emetic activity of the compound of formula (I) has been demonstrated in standard animal models as described below.

Anti-Emesis

Test compound: 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate.

The effect of the test compound on emesis was demonstrated in ferrets according to the general method described by Florezyk, Schurig and Bradner (Cancer Treatment Report, 1982 66(1) 187-9) and summarised below. Both the test compound and cisplatin were prepared and administered in normal saline. The dose of test compound was calculated as the free base.

a) Control - without test compound

Emesis was induced in groups of 6 male ferrets weighing between 1.5-2kg, by intravenous administration of cisplatin at a dose of 10mg/kg. The onset of emesis occurred between 38 and 75 minutes after injection and over a period of 2 hours the number of vomits/retches (episodes) was in the range 30-62 (average 42±5 vomits/retches per 2h). Behavioural changes characteristic of emesis were also noted.

b) With test compound

The test compound was administered to groups of 6 male ferrets (1.5-2kg) by intravenous administration at doses of 0.01, 0.1 and 1mg/kg, immediately prior to administration of cisplatin as described above. The animals were observed for 3 hours.

The results obtained are given in Table 1 below.

Table 1

Compound	Onset of emesis (minutes)	Intensity of emesis (episodes 2h)	Duration of emesis (hours)	Other observations
Cisplatin (10mg/kg i.v.) (control)	38-75	42±5	2	Behavioural changes characteristic of emesis (e.g. increased or irregular respiration, backward locomotion, agitation)
Cisplatin (10mg/kg i.v.) + Test Compound				
0.01 mg/kg i.v.	89-109	17 ±2.9	1	Marked reduction in behavioural effects of cisplatin. In second and third hours after onset of emesis, the animals rested quietly and some slept
0.1 mg/kg i.v.) 1 mg/kg i.v.)	Emesis and behavioural changes were completely eliminated. After 30-40 minutes the animals rested quietly, and some slept.			

The effect of the test compound on emesis was also demonstrated following intraperitoneal administration, using a similar procedure to that described above. Thus cisplatin was administered intraperitoneally to a group of 4 male ferrets at a dose of 9 mg/kg, and the time to onset of emesis and the number of emetic episodes were recorded. In a second group of four male ferrets the test compound was administered at a dose of 1 mg/kg i.p. 30 minutes before and 1 hour

after intraperitoneal administration of cisplatin. The results are given in Table 2:

Table 2

Compound	Onset of emesis (minutes)	Mean no. of emetic (episodes)	Mean no. of retches
Cisplatin (9 mg/kg i.p.)	99.2(± 8.8)	6(± 2)	43(± 10)
Cisplatin (9 mg/kg i.p.) + test compound (1 mg/kg i.p.)	emetic response completely abolished		

The following example illustrates the preparation of the compound of formula (I). Temperatures are in °C. Where indicated, solutions were dried over Na_2SO_4 and solids were dried in vacuo over P_2O_5 at 50° overnight. Chromatography was carried out using the technique described by W.C. Still et al (J. Org. Chem., 1978, 43, 2923-2925), on kieselgel 9385.

Example

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidasol-1-yl)methyl]-4H-carbazol-4-one hydrochloride

A solution of 2,3,4,9-tetrahydro-N,N,N,9-tetramethyl-4-oxo-1H-carbazole-3-methanaminium iodide (2.0g) and 2-methylimidazole (5.0g) in dry dimethylformamide (30ml) was stirred, under nitrogen, at 95° for 16.75h and then allowed to cool. The solid that crystallised was filtered off, washed with ice-cold, dry dimethylformamide (3x2ml) and dry ether (2x10ml) and then dried. The resulting solid (0.60g) was suspended in a mixture of absolute ethanol (30ml) and ethanolic hydrogen chloride (1ml), and warmed gently to obtain a solution, which was filtered whilst warm. The filtrate was then diluted with dry ether to deposit a solid (0.6g) which was recrystallised from absolute ethanol to give the title compound as a solid (0.27g) m.p. 186-187°.

Analysis Found:	C, 61.9;	H, 6.4;	N, 11.8
$C_{18}H_{19}N_3O.HCl.H_2O$ requires	C, 62.3;	H, 6.1;	N, 12.1%

The following examples illustrate pharmaceutical formulations containing 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-l-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate as the active ingredient (1.25g of the hydrochloride dihydrate contains 1.00g of the free base).

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.
The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression

Tablet	mg/tablet	
Active Ingredient	4.688	28.125
Calcium Hydrogen Phospate BP*	83.06	87.75
Croscarmellose Sodium NF	1.8	1.8
Magnesium Stearate BP	0.45	0.45
Compression weight	90.0	118.0

* of a grade suitable for direct compression.

The active ingredient was passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix was compressed into tablets using a Manesty F3 tablet machine

fitted with 5.5mm, flat bevelled edge punches.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	2.5
Compressible Sugar NF	62.5
Magnesium Stearate BP	0.5
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

Wet Granulation

Conventional Tablet	mg/tablet
Active Ingredient	2.5
Lactose BP	151.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7mm diameter punches. Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	2.5
Mannitol BP	56.5
Hydroxypropylmethylcellulose	5.0
Magnesium Stearate BP	1.5
Compression Weight	65.5

The active ingredient is sieved through a suitable sieve and blended with the mannitol and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended into tablets using suitable punches. Tablets of other strengths may be prepared by altering the ratio of active ingredient to mannitol or the compression weight and punches to suit.

CAPSULES

	mg/tablet
Active Ingredient	2.5
* Starch 1500	97.0
Magnesium Stearate BP	1.0
Fill Weight	100.0

* a form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup	mg/5ml dose
Active Ingredient	2.5
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer)	
Flavour)	as required
Colour)	
Preservative)	
Purified Water BP to	5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-Free	mg/5ml dose
Active Ingredient	2.5
Hydroxypropylmethylcellulose USP (viscosity type 4000)	22.5
Buffer) Flavour) Colour) Preservative) Sweetener)	as required
Purified Water BP to	5.0ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION

The injection may be administered by the intravenous or subcutaneous route.

Injection	µg/ml	
Active Ingredient	50	800
Dilute Hydrochloric Acid BP	to pH 3.5	to pH 3.5
Sodium Chloride Injection BP	to 1ml	to 1ml

The active ingredient was dissolved in a suitable volume of Sodium Chloride Injection BP, the pH of the resultant solution was adjusted to pH 3.5 with dilute hydrochloric acid BP then the solution was made to volume with sodium chloride injection BP and thoroughly mixed. The solution was filled into Type 1 clear glass 5ml ampoules which were sealed under a headspace of air, by fusion of the glass then sterilised by autoclaving at 120° for not less than 15 minutes.

METERED DOSE PRESSURISED AEROSOL

Suspension Aerosol	mg/metered dose	Per can
Active Ingredient micronised	0.250	66mg
Oleic Acid BP	0.020	5.28mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high sheer

mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

Solution Aerosol

	mg/metered dose	Per can
Active Ingredient	0.25	30.0mg
Ethanol BP	7.500	1.80g
Trichlorofluoromethane BP	18.875	4.35g
Dichlorodifluoromethane BP	48.525	11.65g
(Oleic Acid BP, on a suitable surfactant e.g. Span 85 (Sorbitan trioleate) may also be included).		

The active ingredient is dissolved in the ethanol together with the Oleic Acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressued filled into them through the valves.

Inhalation Cartridges

	mg/cartridge
Active Ingredient (micronised)	0.5
Lactose BP to	25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are adminstered using a powder inhaler.

Claims

1. Use of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or hydrate thereof, for the manufacture of a medicament for the relief of nausea and vomiting.

2. Use according to claim 1 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of a hydrocholoride.

3. Use according to claim 1 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

4. Use according to any of claims 1 to 3 for the manufacture of a medicament to be used in combination with an anti-cancer therapeutic agent.

5. Use according to claim 4 wherein the anti-cancer therapeutic agent is cisplatin.

Patentansprüche

1. Verwendung von 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-on oder eines physiologisch annehmbaren Salzes oder Hydrats davon, zur Herstellung eines Arzneimittels zur Linderung von Übelkeit und Erbrechen.

2. Verwendung gemaß Anspruch 1, worin das 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-on in Form eines Hydrochlorids vorliegt.

3. Verwendung gemäß Anspruch 1, worin das 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-on in Form seines Hydrochlorid-Dihydrats vorliegt.

4. Verwendung gemäß einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels, das in Kombination mit einem therapeutischen Antikrebsmittel zu verwenden ist.

5. Verwendung gemäß Anspruch 4, worin das therapeutische Antikrebsmittel Cisplatin ist.

Revendications

1. Utilisation de la 1,2,3,9-tétrahydro-9-méthyl-3-[(2-méthyl-1H-imidazole-1-yl)méthyl]-4H-carbazole-4-one ou d'un sel physiologiquement acceptable ou d'un hydrate de celle-ci pour la fabrication d'un médicament pour soulager les nausées et vomissements.

2. Utilisation suivant la revendication 1, caractérisée en ce que la 1,2,3,9-tétrahydro-9-méthyl-3-[(2-méthyl-1H-imidazole-1-yl)méthyl]-4H-carbazole-4-one est sous la forme d'un chlorhydrate.

3. Utilisation suivant la revendication 1, caractérisée en ce que la 1,2,3,9-tétrahydro-9-méthyl-3-[(2-méthyl-1H-imidazole-1-yl)méthyl]-4H-carbazole-4-one est sous la forme de son chlorhydrate.

4. Utilisation suivant l'une quelconque des revendications 1 à 3 pour la fabrication d'un médicament à employer en combinaison avec un agent thérapeutique anti-cancer.

5. Utilisation suivant la revendication 4, caracterisée en ce que l'agent thérapeutique est la cisplatine.

REGISTER ENTRY FOR EP0226266

European Application No EP86304831.0 filing date 24.06.1986

Priority claimed:
25.06.1985 in United Kingdom - doc: 8516083

Divisional EP90122615.9

Designated States BE CH DE FR GB IT LI LU NL SE AT

Title USE OF TETRAHYDROCARBAZOLONE DERIVATIVES FOR THE MANUFACTURE OF MEDICAMENTS

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Classified to
A5B U1S
A61K

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Publication No EP0226266 dated 24.06.1987
Publication in English

Examination requested 24.06.1986

Patent Granted with effect from 28.02.1996 (Section 25(1)) with title USE OF A TETRAHYDROCARBAZOLONE DERIVATIVE FOR THE MANUFACTURE OF MEDICAMENTS

21.12.1989 EPO: Search report published on 24.01.1990
Entry Type 25.11 Staff ID. Auth ID. EPT

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Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

26.01.1996 Notification from EPO of change of EPO Representative details from
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20.06.1996 Notification of change of Address For Service address of
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to
FRANK B DEHN & CO, 179 Queen Victoria Street, LONDON, EC4V 4EL, United Kingdom [ADP No. 00000166001]
dated 24.06.1996. Written notification filed on GB9612106.6
Entry Type 7.3 Staff ID. AS1 Auth ID. HEO

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER EP0226266

PROPRIETOR(S)

GLAXO GROUP LIMITED, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, United Kingdom

DATE FILED 24.06.1986

DATE GRANTED 28.02.1996

DATE NEXT RENEWAL DUE 24.06.1997

DATE NOT IN FORCE

DATE OF LAST RENEWAL 17.06.1996

YEAR OF LAST RENEWAL 11

STATUS PATENT IN FORCE

**** END OF REPORT ****