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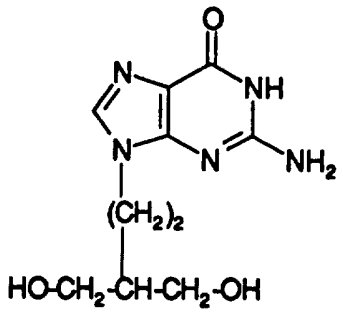
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF AMINOPURINE ANTIVIRAL AGENTS FOR THE TREATMENT AND PROPHYLAXIS OF LATENT HERPESVIRUS INFECTIONS

(57) Abstract

A method for the treatment of latent infection of herpes viruses in mammals, including humans, which method comprises administering to the mammal in need of such treatment, an effective amount of a compound of formula (A) or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing.



(A)

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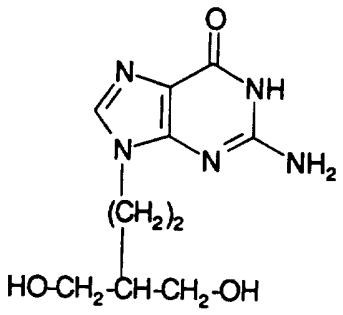
USE OF AMINOPURINE ANTIVIRAL AGENTS FOR THE TREATMENT AND PROPHYLAXIS OF LATENT HERPES VIRUS INFECTIONS

This invention relates to treatment of latent infection of herpesviruses. When used herein, 'treatment' includes prophylaxis as appropriate.

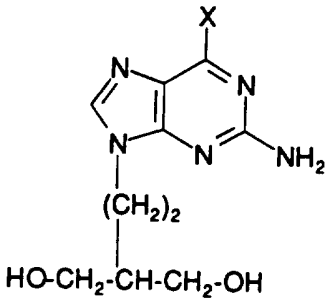
EP-A-141927 (Beecham Group p.l.c.) discloses penciclovir, the compound of formula (A):



(A)

and salts, phosphate esters and acyl derivatives thereof, as antiviral agents. The sodium salt hydrate of penciclovir is disclosed in EP-A-216459 (Beecham Group p.l.c.). Penciclovir and its antiviral activity is also disclosed in Abstract P.V11-5 p.193 of 'Abstracts of 14th Int. Congress of Microbiology', Manchester, England 7-13 September 1986 (Boyd et. al.).

Orally active bioprecursors of the compound of formula (A) are of formula (B):



(B)

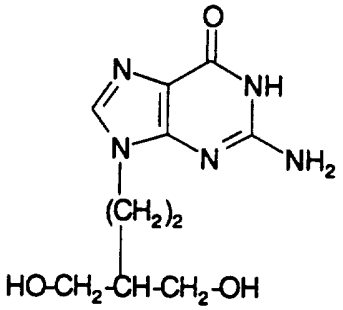
and salts and derivatives thereof as defined under formula (A); wherein X is C_{1-6} alkoxy, NH_2 or hydrogen. The compounds of formula (B) wherein X is C_{1-6} alkoxy or NH_2 are disclosed in EP-A-141927 and the compounds of formula (B) wherein X is hydrogen, disclosed in EP-A-182024 (Beecham Group p.l.c.) are preferred prodrugs. A particularly preferred example of a compound of formula (B) is that wherein X is hydrogen and wherein the two OH groups are in the form of the acetyl derivative, described in Example 2 of EP-A-182024, hereinafter referred to as famciclovir.

The compounds of formulae (A) and (B) and salts and derivatives thereof have been described as useful in the treatment of infections caused by herpesviruses, such as herpes simplex type 1 and herpes simplex type 2.

Previous work has shown that if antiviral treatment is delayed beyond a few hours after infection then latency is established. Once a latent infection is established, the infection can recurr.

It has now been shown in mice that famciclovir treatment can prevent the establishment of competent latency when treatment is commenced 18 h (first experiment) and up to 4 days (second experiment) after infection. It has also now been shown that latency can be prevented in an experiment in immunocompromised mice. The potential clinical advantage is that a patient, within 4 days of contact, may be treated with famciclovir to prevent not only the acute infection but also the development of latency and so avoid recurrences. Furthermore, it is thought that there may be a slow natural loss of latently infected cells and recurrent infections may be required in order to maintain the burden of latently infected cells by establishing latency in new cells. Therefore, suppressive treatment with famciclovir over a prolonged period (up to several years) may prevent new cells becoming latently infected. The result would then be curative treatment, the patient having no recurrences thereafter.

Accordingly, the present invention provides a method of treatment of latent infection of herpesviruses in humans, which method comprises the administration to the human in need of such treatment, an effective amount of a compound of formula (A):



(A)

or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing.

The term 'acyl derivative' is used herein to include any derivative of the compounds of formula (A) in which one or more acyl groups are present. Such derivatives are included as bioprecursors of the compounds of formula (A) in addition to those derivatives which are *per se* biologically active.

The compound of formula (A) may be in one of the forms disclosed in EP-A-216459 (Beecham Group p.l.c.).

Examples of bioprecursors, pharmaceutically acceptable salts and derivatives are as described in the aforementioned European Patent references, the subject matter of which are incorporated herein by reference.

A particular compound of formula (B) of interest is 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, known as famciclovir (FCV), the well-absorbed oral form of penciclovir (PCV).

The compound of formula (A), bioprecursors, salts and derivatives may be prepared as described in the aforementioned European Patent references.

The compound, in particular, famciclovir, may be administered by the oral route to humans and may be compounded in the form of syrup, tablets or capsule. When in the form of a tablet, any pharmaceutical carrier suitable for formulating such solid compositions may be used, for example magnesium stearate, starch, lactose, glucose, rice, flour and chalk. The compound may also be in the form of an ingestible capsule, for example of gelatin, to contain the compound, or in the form of a syrup, a solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl alcohol, glycerine, saline and water to which flavouring or colouring agents may be added to form syrups. Sustained release formulations, for example tablets containing an enteric coating, are also envisaged.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound depending on the vehicle and the

concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

Preferred parenteral formulations include aqueous formulations using sterile water or normal saline, at a pH of around 7.4 or greater, in particular, containing penciclovir sodium salt hydrate.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

A suitable dosage unit might contain from 50mg to 1g of active ingredient, for example 100 to 500mg. Such doses may be administered 1 to 4 times a day or more usually 2 or 3 times a day. The effective dose of compound will, in general, be in the range of from 0.2 to 40mg per kilogram of body weight per day or, more usually, 10 to 20 mg/kg per day. in the case of famciclovir, the dosage unit would be 125 mg, 250 mg, 500 mg or 750 mg, preferably 125 mg or 250 mg.

For prevention of establishment of competent latency, the treatment is preferably carried out as soon as possible after contact with the virus, preferably within 18 hours, although up to four days is acceptable. The treatment period is usually 3 to 14 days, more usually 5 to 10 days, often 7 days.

For treatment of established recurrent disease, the treatment period is up to 5 years, for example, up to 1, 2, 3, 4, and 5 years.

The present invention also provides the use of a compound of formula (A) or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing, in the preparation of a medicament for use in the treatment of latent infection of herpesviruses. Such treatment may be carried out in the manner as hereinbefore described.

The present invention further provides a pharmaceutical composition for use in the treatment of latent infection of herpesviruses, which comprises an effective amount of a compound of formula (A) or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing, and a

pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinafter described.

The compound of formula (A) and its prodrugs show a synergistic antiviral effect in conjunction with interferons; and treatment using combination products comprising these two components for sequential or concomitant administration, by the same or different routes, are therefore within the ambit of the present invention. Such products are described in EP-A-271270 (Beecham Group p.l.c.).

The following results from animal studies illustrate the invention.

EXPERIMENTS IN MICE INFECTED WITH HSV-1 VIRUS

A cutaneous infection was established by inoculation of the ear pinnae of mice with HSV-1 (SC16) and the effects of oral famciclovir on the latent virus infection was investigated.

BALB/c female mice (Bantin and Kingman, Kingston, Hull, UK) were purchased at 3 to 4 weeks old and inoculated one week later. Virus suspension (10ul) containing 5 x 10^4 p.f.u. were inoculated into the skin of the left ear pinna. Skin thickness was measured daily in individual mice by means of an Engineers' micrometre screw gauge. (ref. Nash *et al*, 1980, J. Gen. Virol. **48**, 351-357). These mice were kept for 3 (Experiment 1) or 4 (Experiment 2) months and then killled. The trigeminal ganglia and cervical dorsal root ganglia were removed and co-cultivated. Those cultures showing virus replication were recorded as positive.

Experiment 1

In a first experiment, mice were treated within 18h and treatment ceased on day 10 post infection.

Of the 24 untreated control mice, 12 showed latent infection in the trigeminal ganglia (TG) and 20 showed latent infection in the cervical dorsal route ganglia (DRG). All 24 control mice showed either TG or DRG latency. None of the FCV treated mice showed any latency.

Experiment 2

In a second experiment, antiviral treatment was initiated on days 1, 2, 3, 4 or 5 post-infection (p.i.) and and ceased on day 10 p.i.. The compounds were administered *ad libitum* in the drinking water, at 1 mg/ml (approximately 100 mg/kg/day).

The results are as shown in the following table:

(Note: The groups 1 and 2 received the same treatment regimens but the results were assayed separately.)

	Latency (Group 1)				Latency (Group 2)				Latency Total	Acute Total
Antiviral Therapy (days)	TG +ve/8		DRG +ve/8		TG +ve/8		DRG +ve/8		% Mice with virus +ve ganglia on day 120 (n=16)	% Mice with virus +ve ganglia on day 8 (n=8)
	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	L/RTG+DRG	L/RTG+DRG
None	8	4	8	5	8	6	8	2	100	100
5-10	4	0	4	0	2	0	2	0	38	100
4-10	2	0	2	0	0	0	0	0	13	100
3-10	0	0	0	0	0	0	0	0	0	0
2-10	0	0	0	0	0	0	0	0	0	0
1-10	0	0	0	0	0	0	0	0	0	0

Four months later, latent virus could be reactivated in ganglia explants (ipsilateral and contralateral trigeminal and dorsal root) from all of 16 control mice. Latent virus was not reactivated from the ganglia of FCV-treated mice, except ipsilateral ganglia, and only when the start of therapy was delayed until days 4 p.i. (2/16) or 5 p.i (6/16).

Similar results were obtained when compounds were administered twice daily by gavage at 50 mg/kg per dose.

Experiment 3

Mice were immunosupressed with Cyclosporin A (CyA) from day -2 to day =10 (day 0 being the day of infection). Groups of mice were untreated (control), or treated with famciclovir orally at 50mg/kg twice daily from 22h after infection to 5.5 or 10.5 days. The ganglia were examined for reactivation of infectious virus 1 or 4 months later and the results are shown in the Table below.

	LTG (n=6)	RTG (n=6)	LDR (n=6)	RDR (n=6)
Control	6	4	6	3
FCV	0	0	0	0

TG = trigeminal DRG = dorsal root ganglia L/R = left/right

EXPERIMENTS IN MICE INFECTED WITH HSV-2 VIRUS

A cutaneous infection was established by inoculation of the ear pinnae of mice with HSV-2 (Bry) and the effects of oral famciclovir on the latent virus infection was investigated. Treatment was 50 mg/kg twice daily for 5 days starting 22h post-infection.

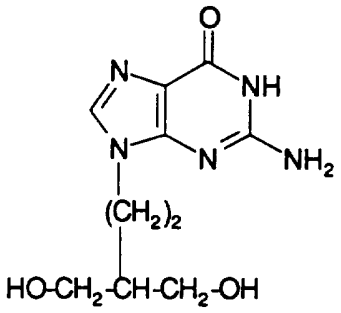
The table shows the number of mice/group with positive latent infection in the trigeminal or cervical dorsal root ganglia.

	No. of mice with +ve ganglia /number of mice tested				**% mice yielding at least one +ve ganglion**
Group	**Left T/G**	**Right T/G**	**Left CDR**	**Right CDR**	
Control	10/10	10/10	10/10	6/10	100
famciclovir	0/10	0/10	0/10	0/10	0

T/G = trigeminal CRG = Cervical dorsal root ganglia

Claims

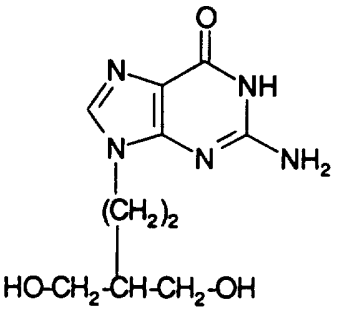
1. A method for the treatment of latent infection of herpesviruses in mammals, including humans, which method comprises administering to the mammal in need of such treatment, an effective amount of a compound of formula (A):



(A)

or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing.

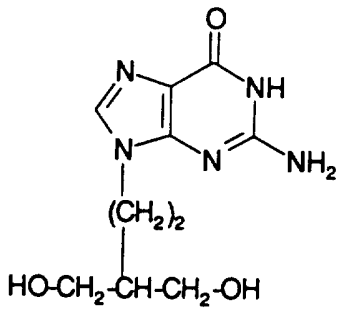
2. Use of a compound of formula (A):



(A)

or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing;
in the manufacture of a medicament for use in the treatment of latent infection of herpesviruses.

3. A pharmaceutical composition for use in the treatment of latent infection of herpesviruses, which method comprises administering to the mammal in need of such treatment, an effective amount of a compound of formula (A):



(A)

or a bioprecursor, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing.

4. A method, use, or composition according to claim 1, 2 or 3 wherein the treatment is for latent infection of herpes simplex type 1 infection.

5. A method use, or composition according to claim 1, 2 or 3 wherein the treatment is for latent infection of herpes simplex type 2 infection.

6. A method use, or composition according to claim 1, 2, 3, 4, or 5 wherein the Compound is famciclovir.

7. A method use, or composition according to claim 6 wherein famciclovir is administered at a dose of 125mg, 250 mg, 500 mg, 750 mg, or 1g, once, twice or three times a day.

INTERNATIONAL SEARCH REPORT

Internation pplication No
PCT/EP 95/04692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTIMICROB AGENTS CHEMOTHER, MAR 1988, 32 (3) P358-63, UNITED STATES, XP000567471 BOYD MR ET AL: "Antiherpesvirus activity of 9-(4-hydroxy-3-hydroxymethylbut-1-yl) guanine (BRL 39123) in animals." see abstract see page 360, left-hand column, line 17-27 --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* 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

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
18 April 1996	09.05.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Mair, J

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INTERNATIONAL SEARCH REPORT

Internation pplication No
PCT/EP 95/04692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 27, no. 5, May 1985, pages 763-8, XP000568644 KLEIN, R.J. ET AL: "Effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine on the acute local phase of herpes simplex virus induced skin infections in mice and the establishment of latency" see abstract see page 764, left-hand column, line 43-45 see page 765, right-hand column, line 31-35 ---	1-5
X	ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 15, no. 5, May 1979, pages 723-729, XP000568641 KLEIN, R.J. ET AL: "Latent herpes simplex virus infections in sensory ganglia of hairless mice prevented by acylguanosine" see abstract see page 724, right-hand column, line 40 - page 725, left-hand column, line 46 ---	1-5
X	DRUGS, OCT 1994, 48 (4) P528-48, NEW ZEALAND, XP000567542 NIKKELS AF ET AL: "Recognition and treatment of shingles." see page 540, right-hand column, line 41-44 ---	1-3
X	WO,A,92 00742 (BEECHAM GROUP PLC) 23 January 1992 see the whole document ---	3-7
X	DRUGS OF THE FUTURE, 1995, 20/4 (415-417), SPAIN, XP000567462 "Famciclovir. Famvir (R)"	3-7
A	see the whole document ---	1,2
X	ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 24, no. 1, July 1983, pages 129-131, XP000568642 KLEIN, R.J. ET AL: "Effect of discontinuous Acyclovir treatment on in vitro reactivation of herpes simplex virus from latently infected trigeminal ganglia" see the whole document ---	1-5

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INTERNATIONAL SEARCH REPORT

Internation pplication No
PCT/EP 95/04692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF GENERAL VIROLOGY, vol. 56, no. 2, October 1981, pages 259-265, XP000568615 FIELD, H.J. ET AL: "Effects of oral treatment with acyclovir and bromovinyldeoxyuridine on the establishment and maintenance of latent herpes simplex virus infection in mice" see the whole document especially page 262, line 12-15 -----	1-5

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/ 04692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1,4-7 are directed towards a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internation pplication No
PCT/EP 95/04692

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9200742	23-01-92	AP-A-	291	29-12-93
		AU-B-	647807	31-03-94
		AU-B-	8103291	04-02-92
		CA-A-	2086756	08-01-92
		EP-A-	0538305	28-04-93
		IL-A-	98749	30-03-95