(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2001 (27.12.2001)

PCT

(10) International Publication Number
WO 01/97804 A1

(51) International Patent Classification[7]: A61K 31/351, A61P 31/16

(21) International Application Number: PCT/AU01/00748

(22) International Filing Date: 22 June 2001 (22.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0015324.7 22 June 2000 (22.06.2000) GB

(71) Applicant *(for all designated States except US)*: **BIOTA SCIENTIFIC MANAGEMENT PTY LTD** [AU/AU]; Level 4, 616 St Kilda Road, Melbourne, Victoria 3004 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FUJIWARA, Masatoshi** [JP/JP]; c/o GlaxoSmithKline KK, 6-15, Sendagaya 4-Chome, Shibuya-ku, Tokyo 151-8566 (JP). **ITOU, Miyuki** [JP/JP]; c/o GlaxoSmithKline KK, 6-15, Sendagaya 4-Chome, Shibuya-ku, Tokyo 151-8566 (JP). **YOKOTA, Tomoyuki** [JP/JP]; c/o GlaxoSmithKline KK, 6-15, Sendagaya 4-Chome, Shibuya-ku, Tokyo 151-8566 (JP).

(74) Agent: **GRIFFITH HACK**; Level 3, 509 St Kilda Road, Melbourne, VIC 3004 (AU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/97804 A1

(54) Title: MEDICAMENTS

(57) Abstract: This invention relates to a new veterinary use for compounds having neuraminidase inhibitor activity, and to medicaments containing them.

Medicaments

This invention relates to a new veterinary use for compounds having neuraminidase inhibitor activity, and to medicaments containing them.

Enzymes with the ability to cleave N-acetyl neuraminic acid (NANA), also known as sialic acid, from other sugars are present in many microorganisms. These include bacteria such as Vibrio cholerae, Clostridium perfringens, Streptococcus pneumoniae, and Arthrobacter sialophilus, and viruses such as influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus, fowl plague virus, and Sendai virus. Most of these viruses are of the orthomyxovirus or paramyxovirus groups, and carry neuraminidase activity on the surface of the virus particles.

Many of the neuraminidase-possessing organisms are major pathogens of man and/or animals, and some, such as influenza virus, Newcastle disease virus, and fowl plague virus, cause diseases of enormous economic importance.

It has long been thought that inhibitors of neuraminidase activity might prevent infection by neuraminidase-bearing viruses. Many of the known neuraminidase inhibitors are analogues of neuraminic acid, such as 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA) and its derivatives. See, e.g., Meindl et al., Virology 1974 58 457-63. The most active of these is 2-deoxy-2,3-dehydro-N-trifluoroacetyl-neuraminic acid (FANA), which inhibits multi-cycle replication of influenza and parainfluenza viruses in vitro. See Palese et al., Virology 1974 59 490-498.

A variety of compounds which act as neuraminidase inhibitors are known in the art. These include 4-substituted-2-deoxy-2,3-didehydro derivatives of α-D-neuraminic acid such as those disclosed inter alia in published

International patent application No. WO 91/16320, incorporated herein by reference.

The compounds disclosed in the aforementioned patent specification have been described for use as antiviral agents, for example in the treatment of influenza virus infections.

Other compounds which act as neuraminidase inhibitors include those disclosed inter alia in published International patent application Nos. WO 96/26933 and WO 99/33781, incorporated herein by reference.

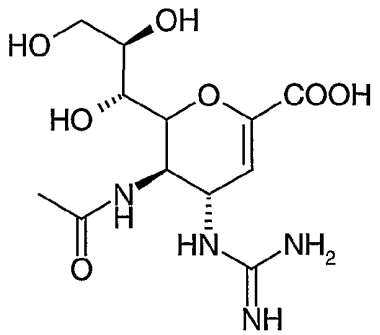
We now find that neuraminidase inhibitors are also of use in the treatment of equine influenza virus infections. The use of neuraminidase inhibitors in the treatment of equine influenza virus infections has not been disclosed in any of the aforementioned patent specifications. Equine influenza virus infection is one of the most important diseases of members of the genus Equus, including horses, donkeys and mules, throughout the world, and is one of the most common disorders requiring veterinary attention (see, e.g., Timoney, Comparative Immunology, Microbiology and Infectious Diseases 1996, 19: 205-11). Outbreaks of equine influenza virus infection have been reported frequently in horses, including epidemics in race horses, with high rates of morbidity and mortality.

Two types of equine influenza viruses have been identified on the basis of the difference between haemaglutinin (H) and neuraminidase (N), A/equine-1 (H7N7) and A/equine-2 (H3N8); they do not cross-react immunologically. Current equine influenza vaccines such as inactiviated alum-activated vaccine (see Nelson, K. M. et al.) offer only limited protection. Local and systemic isotype-specific antibody responses to natural equine influenza virus infection generate a protective immunity associated with mucosal IgA and humoral IgGa and IgGb sub-isotype reponses, a pattern of reponse not

generated by conventional vaccines. Therefore, effective antiviral agents are needed for the treatment of equine influenza virus infections.

Surprisingly, we have found that neuraminidase inhibitors which are effective in the treatment of human influenza virus infections are also effective in the treatment of equine influenza virus infections. Human influenza viruses differ from equine influenza viruses in that human influenza viruses have N1, N2 and N3 neuraminidase, whereas equine influenza viruses have N7 and N8 neuraminidase. It might be expected that the difference in the neuraminidase activity of human and equine influenza viruses would lead to a difference in the effectiveness of neuraminidase inhibitors in the treatment of human and equine influenza virus infections. Therefore, it is surprising and unexpected that neuraminidase inhibitors which are effective in the treatment of human influenza virus infections have now been found to be effective in the treatment of equine influenza virus infections. Suitable neuraminidase inhibitors include those described in published International patent Nos. WO 91/16320, WO 96/26933 and WO 99/33781. Zanamivir is particularly preferred.

5-acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-*glycero*-D-*galacto*-non-2-enoic acid which may be represented by the formula (I)

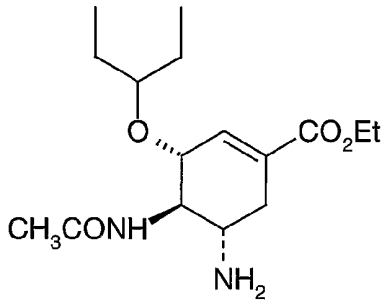


(I)

and its pharmaceutically acceptable derivatives thereof, are disclosed in published International patent application No. WO 91/16320, which is incorporated herein by reference. The compound of formula (I) is also

known as zanamivir, GG167 or RELENZA™. "Zanamivir" when used hereinafter means the compound 5-acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-*glycero*-D-*galacto*-non-2-enoic acid. Zanamivir exhibits neuraminidase inhibitor activity and is useful in the treatment of viral infections, in particular, human influenza virus infections. It has not previously been disclosed for use in the treatment of equine influenza virus infections.

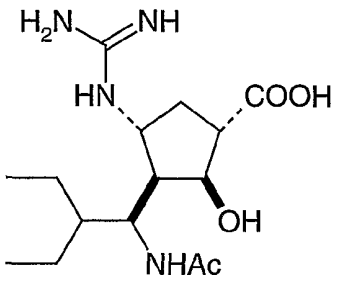
Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate, which may be represented by the formula (II)



(II)

and its pharmaceutically acceptable derivatives thereof, are disclosed in published International patent application No. WO96/26933 which is incorporated herein by reference. The compound of formula (II) is also known as oseltamivir or TAMIFLU™. "Oseltamivir" when used hereinafter means the compound ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate. Oseltamivir exhibits neuraminidase inhibitor activity and is useful in the treatment of viral infections, in particular, human influenza virus infections. It has not previously been disclosed for use in the treatment of equine influenza virus infections.

(1S,2S,3R,4R)-3-[(1R)-1-(acetylamino)-2-ethylbutyl]-4-{[amino(imino)methyl]amino}-2-hydroxycyclopentanecarboxylic acid, which may be represented by the formula (III)



(III)

and its pharmaceutically acceptable derivatives thereof, are disclosed in published International patent application No. WO99/33781 which is incorporated herein by reference. The compound of formula (III) is also known as RWJ-270201 or BCX-1812. "RWJ-270201" when used hereinafter means the compound (1S,2S,3R,4R)-3-[(1R)-1-(acetylamino)-2-ethylbutyl]-4-{[amino(imino)methyl]amino}-2-hydroxycyclopentanecarboxylic acid. RWJ-270201 exhibits neuraminidase inhibitor activity and is useful in the treatment of viral infections, in particular, human influenza virus infections. It has not previously been disclosed for use in the treatment of equine influenza virus infections.

Accordingly, one aspect of the invention provides a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of equine influenza virus infection wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

In a further aspect of the invention there is provided the use of a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof for the treatment of equine influenza virus infection wherein the neuraminidase inhibitor is not is not oseltamivir or a pharmaceutically

acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

In a further aspect of the invention there is provided the use of a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of equine influenza virus infection wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

In a further aspect, the invention provides a medicament for the treatment of equine influenza virus infection in an animal, such as a horse, a donkey or a mule, comprising as active ingredient a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

A further aspect of the invention provides a method of treating an animal, such as a horse, a donkey or a mule, suffering from or susceptible to equine influenza virus infection which comprises administering to said animal an effective amount of a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

Preferably the neuraminidase inhibitor is zanamivir or a pharmaceutically acceptable derivative thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester of a neuraminidase inhibitor specifically oseltamivir, RWJ-270201 or zanamivir or any other compound which upon administration to the animal

is capable of providing (directly or indirectly) a neuraminidase inhibitor specifically oseltamivir, RWJ-270201 or zanamivir or an antivirally active metabolite or residue thereof.

It will be appreciated by those skilled in the art that zanamivir may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds. Compounds of interest include ester, ether and amino derivatives of zanamivir.

It will be appreciated by those skilled in the art that zanamivir may be derivatised at more than one position.

Pharmaceutically acceptable salts of zanamivir include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Suitable pharmaceutically acceptable salts of zanamivir are described in published International patent No. WO 91/16320.

It will be appreciated that reference to treatment is intended to include prophylaxis.

Conveniently, the medicament according to the invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Thus, the medicament according to the

invention may for example be formulated for oral, parenteral or rectal administration, or in a form suitable topical for administration to the respiratory tract, for instance, intranasally or by inhalation or insufflation (either through the mouth or nose).

For oral administration, the medicament 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 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, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

The medicament according to the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, optionally with an added preservative.

The medicaments for parenteral administration 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 dry form such as a powder, crystalline or freeze-dried solid for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or isotonic saline before use. They may be presented, for example, in sterile ampoules or vials.

The medicament for use according to the invention 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 glyceride.

For intranasal administration the medicament according to the invention may be used, for example, as a liquid in the form of, for example, a solution, suspension or emulsion, presented in the form of a spray or drops, or as a powder. Preferably the preparation for intranasal administration is delivered in the form of a spray or aerosol from an insufflator or from a pressurised pack or nebuliser with the use of a suitable propellant.

For administration by inhalation the medicament according to the invention is conveniently delivered in the form of a dry powder or an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 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, or blisters of e.g. laminated aluminium foil, for use in a dry powder intranasal device, inhaler or insufflator may contain the active ingredient in powder form or formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Suitable formulations of zanamivir are described in published International patent No. WO 91/16320.

In a preferred embodiment of the invention, there is provided a medicament for the treatment of equine influenza virus infection adapted for topical administration to the respiratory tract, for instance intranasally, by inhalation or insufflation (either through the mouth or nose) wherein the active ingredient is zanamivir.

It will be appreciated that the precise dose administered will depend on the size and condition of the animal, and the frequency and route of administration and will be at the ultimate discretion of the attendant veterinarian. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

A proposed dose of the active ingredient for use according to the invention for oral, parenteral, rectal or topical administration to the respiratory tract for the treatment of equine influenza virus infection may be 0.1 to 30 mg of the active ingredient per unit dose per kg bodyweight of the animal which could be administered, for example, 1 to 4 times per day.

In a preferred embodiment of the invention, the medicament may be administered as the raw chemical comprising the active ingredient of from 0.1 to 30 mg per kg bodyweight of the animal.

The new use according to the present invention has been demonstrated in the following studies.

The neuraminidase inhibitors were examined for their inhibitory effects on the replication of four equine influenza virus strains in Madin–Darby canine kidney (MDCK) cells. One human influenza virus strain was also tested as

a control. MDCK cells were grown and maintained in Eagle's modified minimal essential medium supplemented with 8 % heat-inactivated foetal calf serum, 100 units/ml penicillin G and 100 µg/ml streptomycin. The four strains of equine influenza A virus used were Prague/1/56 (H7N7), Newmarket/1/77 (H7N7), Miami/1/63 (H3N8) and Tokyo/2/71 (H3N8); the strain of human influenza A virus was Puerto Rico/8/34 (H1N1). The virus strains were propagated in MDCK cells. Titres of the virus stocks to show their viral infectivity were determined by the 50 % Tissue Culture Infectivity Dose ($TCID_{50}$) method in MDCK cells, and the stocks were stored at –80 °C until use.

Antiviral activity was assayed by cytopathic effect (CPE) inhibition test and the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. For CPE test, MDCK cells were seeded into a 96-well tissue culture plate at 5.0×10^4 cells/well and incubated at 37 °C in 5 % CO_2 for two days. When the cell cultures were confluent, the growth medium was withdrawn. The wells were then filled with 50 µl of different concentrations of test compounds in Dulbecco's modified minimum essential medium supplemented with 0.1 % bovine serum albumin and antibiotics. 50 µl of virus solution ($100TCID_{50}$) was added to each well and the plates were incubated for 4 to 5 days and virus-induced CPE was observed by microscopy. The 50 % antiviral effective concentration (EC_{50}) values were expressed as the concentration that achieved 50 % protection of virus-infected cells from the virus-induced destruction (CPE). Cytotoxicity of the compounds was evaluated in parallel with their antiviral activity by the MTT method, based on the viability of mock-infected cells at the 50 % cytotoxic concentration (CC_{50}). Selectivity index (SI) values were estimated from 50 % cytotoxic concentration (CC_{50})/50 % effective concentration (EC_{50}).

Results

Table 1 shows that zanamivir and oseltamivir have an inhibitory effect on the replication of the viruses. The EC_{50} values of zanamivir to A/equine-1

(H7N7) and A/equine-2 (H3N8) were 0.002 - 0.006 and 0.006 μg/ml, respectively. These values are approximately 83300 to 250000-fold lower than the corresponding CC_{50} values, indicating the specificity of zanamivir to viral specific neuramindase. EC_{50} values of zanamivir against the four equine influenza virus strains were similar. In contrast, the antiviral activity of zanamivir against equine influenza virus showed increased potency in comparison with human influenza virus.

Similarly, the EC_{50} values of oseltamivir to A/equine-1 (H7N7) and A/equine-2 (H3N8) were 0.003 - 0.016 and 0.006 μg/ml, respectively. These values are approximately 6250 to 166700-fold lower than the corresponding CC_{50} values, indicating the specificity of oseltamivir to viral specific neuraminidase. EC_{50} values of oseltamivir against the four equine influenza virus strains were similar. In contrast, the antiviral activity of oseltamivir against equine influenza virus showed increased potency in comparison with human influenza virus.

Table 1

Antiviral activity of zanamivir and oseltamivir

virus strain	zanamivir		oseltamivir	
	EC_{50}* (µg/ml)	SI**	EC_{50}* (µg/ml)	SI**
Puerto Rico/8/34 (H1N1)	0.032	>15600	0.4	>1250
Eq/Prague/1/63 (H7N7)	0.006	>83300	0.003	>166700
Eq/Newmarket/1/77 (H7N7)	0.002	>250000	0.016	>31250
Eq/Miami/1/63 (H3N8)	0.006	>83300	0.016	>31250
Eq/Tokyo/2/71 (H3N8)	0.006	>83300	0.006	>83300

* Effective concentration (EC_{50}) values were obtained by virus-induced cytopathic effect inhibition test

** Selectivity index (SI) values were estimated from cytotoxic concentration (CC_{50})/EC_{50} values; CC_{50} values were obtained using MDCK cells

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The application of which this description and claims form part may be used as a basis for a claim for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims

1. A neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of equine influenza virus infection wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

2. Use of a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof for the treatment of equine influenza virus infection wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

3. Use of a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of equine influenza virus infection wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

4. A method of treating an animal, such as a horse, a donkey or a mule, suffering from or susceptible to equine influenza virus infection which comprises administering to said animal an effective amount of a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

5. The use or method as claimed in any of Claims 1 to 4 wherein the neuraminidase inhibitor is zanamivir or a pharmaceutically acceptable derivative thereof.

6. A medicament for the treatment of equine influenza virus infection in an animal, such as a horse, a donkey or a mule, comprising as active ingredient a neuraminidase inhibitor or a pharmaceutically acceptable derivative thereof wherein the neuraminidase inhibitor is not oseltamivir or a pharmaceutically acceptable derivative thereof or RWJ-270201 or a pharmaceutically acceptable derivative thereof.

7. A medicament as claimed in claim 6 wherein the neuraminidase inhibitor is zanamivir or a pharmaceutically acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/00748

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 31/351, A61P 31/16

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)

IPC7 IPC AS ABOVE

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

AU: IPC AS ABOVE AND C07D 309/28

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

World Patent Index, Chemical Abstracts: equine/ horse, flu/ influenza, neuraminidase inhibitor/ Relenza/ GG167/ Zanamivir/139110-80-8

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Rogers, G. N. et al, Virology Vol 127 pages 361 to 373 (1983). See pages 361, 366 and 367 in particular	1 2 to 7
Y X	WO 99/33781 A (Biocryst Pharmaceuticals, Inc) 8 July 1999. See pages 2 to 3 in particular.	1 to 7 1
X Y	WO 01/29021 A (Abbott Laboratories) 26 April 2001. See pages 1 to 3, 19, 65, 66 and 75 in particular.	1 2 to 7

[X] Further documents are listed in the continuation of Box C [ ] See patent family 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 application or patent 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 when the document is taken alone

"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

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2001	29 August 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer K.G. ENGLAND Telephone No : (02) 6283 2292

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/00748

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 98/21243 A (Biota Scientific Management Pty. Ltd.) 22 May 1998. See pages 3 and 4 in particular.	1 2 to 7
X A	WO 96/34603 A (University of Alabama at Birmingham) 7 November 1996. See whole document.	1 2 to 7
A	WO 91/16320 A (Biota Scientific Management Pty. Ltd.) 31 October 1991. See page 1	1 to 7

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/00748

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9933781	AU	22001/99	BR	9813480	EP	1040094
		HU	200100142	NO	20003084	PL	341431
		SK	200000871				
WO	200129021	NONE					
WO	9821243	AU	48576/97	BR	9714299	CN	1238783
		CZ	9901679	EP	951480	HU	9904009
		NO	992297	PL	333364		
WO	9634603	AU	56745/96	BR	9608239	EP	824349
		US	5714509	US	6114386		
WO	9116320	AP	249	AU	77590/91	AU	75338/91
		CN	1057260	CN	1150020	CN	1184108
		CS	9101145	EP	526543	EP	786458
		FI	924790	FI	20001231	HK	1003834
		HU	61989	HU	9500070	IE	911372
		IL	97936	LU	90468	NO	923944
		NO	974670	NZ	237936	PT	97460
		SG	43170	SI	9110745	US	5360817
		US	5648379	HR	930455	ZA	9103086

END OF ANNEX