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— *of inventorship (Rule 4.17(iv)) for US only*

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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.

(54) Title: USE OF TRIPTANS AS ANTIVIRAL AGENTS

(57) Abstract: The present invention relates to the use of triptans for the preparation of pharmaceutical compositions suitable to treat viral infections.

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USE OF TRIPTANS AS ANTIVIRAL AGENTS

Prior art

Triptans form a class of drugs obtained from indole.

They differ from one another according to different functional groups connected to the indole structure.

Triptans are drugs widely used to treat migraines and a certain number of them are cited in the literature and indicated for this type of therapy,

For example in Martindale (The complete drug reference, thirty-second edition, pages 443-452) the following triptans are quoted: almotriptan, elitriptan, frovatriptan, naratriptan hydrochloride, rizatriptan benzoate, sumatriptan succinate and zolmitriptan.

The efforts of pharmacological research, since the first synthesized and marketed triptan (sumatriptan), have been targeted at improving efficacy and decreasing side effects, always within the sphere of treating migraines.

The activity of triptans against migraines is attributed to the fact that they function as agonists at the $5HT_{1D}$ receptors and that their action on the similar $5HT_{1D}$ - receptors present in cranial circulation inhibits the release of neuropeptides (CGRP and substance P) by perivascular trigeminal sensory neurons (E. Seaber et al. British J. of Clinical Pharmacology, 1997, 43, pages 579-587).

No suggestion has ever been made for therapeutic treatments of affections other than migraines.

Summary

It has now surprisingly been found that the triptans used to treat migraines exert a powerful therapeutic effect on different infective pathologies of viral origin.

Therefore, the present invention relates to a new use of triptans as active ingredients for the preparation of pharmaceutical compositions suitable to treat viral affections.

The invention also relates to pharmaceutical compositions containing as active ingredient triptan mixed with pharmaceutically acceptable excipients or diluents, suitable to treat viral affections.

Finally, the invention relates to a therapeutic method for treating viral affections comprising the administration of an efficacious dose of a triptan.

Detailed description of the invention

The characteristics and advantages of the use of triptans to prepare compositions suitable to treat viral affections according to the present invention shall be explained in more detail during the following detailed description, with particular reference to clinical research conducted over a period of three years, according to the examples indicated hereunder.

In the course of this research numerous patients with viral affections were treated with triptans. During treatment the patients did not use anti-viral drugs of another kind.

Patients with the following viral affections were treated:

- herpes simplex type 1;
- herpes zoster;
- parainfluenza viruses or rhinovirus;
- orthomyxovirus;
- hepatitis B virus;
- hepatitis C virus;
- mononucleosis from cytomegalovirus

The triptans described in the examples were zolmitriptan, rizatriptan and sumatriptan, taken orally in doses ranging from 2.5 to 50 mg/day.

In all the cases treated the triptans were found to be extremely efficacious against viral pathologies. This efficacy, depending on the period in which the drugs were taken, ranged from simple improvement of the symptoms to total remission, and even true abortive forms of the infection.

In particular it was noted that when triptans were administered at the onset of the first symptoms of the infection, they were capable of totally blocking evolution of the disease.

Instead, when triptans were taken when the affection was already in progress, they considerably reduced the symptoms and drastically decreased the normal evolution and febrile period.

In any case, the extent of the anti-infective action of these drugs proved to be correlated to the evolutional phase of the disease. The earlier they were administered the more effective and rapid their action was, to the extent that taking

minimum but repeated doses simultaneously to the onset of the first symptoms was able to totally and rapidly resolve the symptoms of the various viral affections.

All triptans have proved to be extremely efficacious in the treatment of viral affections. Nonetheless some differences in efficacy were found, for example: sumatriptan < rizatriptan < zolmitriptan.

In view of their efficacy, triptans may be used successfully to prepare pharmaceutical compositions suitable to treat viral affections, mixed with acceptable pharmaceutical excipients. Said pharmaceutical compositions, preferably prepared in tablet form, may each contain from 1.25 to 50 mg of triptan (depending on the triptan used). For example, lactose, microcrystalline cellulose, mannitol, sodium starch glycolate, corn starch, aspartame, crospovidone, polyethyleneglycol, magnesium stearate, colloidal silica and ferric oxide may be employed as excipients.

The present invention also relates to a therapeutic method for treating viral affections comprising the oral administration of a dose ranging from 2.5 to 100 mg of triptan per day.

There is currently no information to describe a mechanism for the antiviral action of triptans which, as already described, are used to treat migraines in which efficacy is explained on the basis of their function as agonists at the $5HT_{1D}$ receptors.

Nonetheless, it seems that a simple antiphlogistic action similar to the one performed by NSAID drugs can be excluded, as in addition to acting on the symptoms, triptans are also capable of rapidly and radically resolving the infective episode.

Purely as a hypothesis, we may think of an antiviral action that could be implemented at the level of cellular receptors for viruses or through a mechanism that prevents viruses from being adsorbed and penetrating inside the cell or through a mechanism that impedes the capacity of virions that have entered the cell to induce the genome of the cell to allow their replication.

It is clear that this is a hypothesis that would require a great deal of research in order to be verified.

The following examples of antiviral efficacy in patients treated with triptans are

provided for the purpose of illustrating the invention.

Example 1

Five patients with herpes simplex type 1, with etiologic diagnosis verified on the basis of the clinical-epidemiological symptoms, were treated with zolmitriptan (ZOMIG ®) at a dose of 2.5 mg per day divided into two 1.25 mg doses.

Three out of these patients who commenced treatment after the emergence of the vesicles benefited by rapid disappearance of the characteristic mucocutaneous pathology.

The other two patients, who took the drug simultaneously to the first symptoms, obtained total blockage of evolution of the infection.

Moreover, three out of said patients who started to take the drug systematically to cure migraines no longer had recurrence.

Example 2

Four cases were studied in patients affected by herpes-zoster with infection confirmed by the appearance of specific IgM in the blood.

Two out of said patients, treated with a dose of 50 mg of sumatriptan (IMIGRAN ®) per day, divided into two 25 mg doses, developed an abortive form of the viral pathology which was resolved in five days.

The other two patients treated with common analgesics developed the characteristic long and bothersome herpes symptoms.

Example 3

Eight patients with parainfluenza or rhinovirus affections of the upper airways, diagnosed according to clinical-epidemiological symptoms, were treated with a daily dose of 2.5 mg of zolmitriptan (ZOMIG ®), divided into two 1.25 mg doses.

Complete remission of the infective symptoms occurred a few hours after administering the drug. Resolution of the infection was more rapid in patients who had taken the drug when the first inflammatory symptoms appeared.

Example 4

Six patients with orthomyxovirus influenza infection, diagnosed according to clinical-epidemiological symptoms, were treated with a daily dose of 5 mg of rizatriptan (MAXALT ®) divided into two 2.5 mg doses.

Fever and inflammatory symptoms of the airways disappeared a few hours after

administering the drug, with a more rapid effect in patients who had taken the drug precociously.

Example 5

Four patients with chronic hepatitis B virus infection with the HBs-Ag marker present in their blood, with high transaminase values and with high viral replication indices, were treated discontinuously with 50 mg of sumatriptan (IMIGRAN ®) per day divided into two 25 mg doses.

There was progressive regression of the transaminase values and the viral replication indices to normal values about 3 months after starting the treatment.

Moreover, after 12 months the HBsAg marker had disappeared from the blood of two patients.

Example 6

Five patients with chronic hepatitis C virus infection with the virus in the active phase of replication and with high transaminase values were treated discontinuously with 2.5 mg of zolmitriptan (ZOMIG ®) per day divided into two 1.25 mg doses.

After about 5 months of treatment there was a drastic regression of the transaminase values and the viral replication indices.

Example 7

Five patients with mononucleosis infection from cytomegalovirus diagnosed from the clinical-epidemiological symptoms confirmed by the presence of specific IgM antibodies in the blood, were treated with 2.5 mg of zolmitriptan (ZOMIG ®) per day divided into two 1.25 mg doses.

There was an extremely benign evolution of the infection with remission of cephalea and febrile pharyngitis after about two days of treatment.

Claims

1. Use of triptans as active ingredients for the preparation of pharmaceutical compositions suitable to treat viral affections.
2. Use as claimed in claim 1, characterized in that said triptans are selected from the group including sumatriptan, rizatriptan and zolmitriptan.
3. Use as claimed in claim 1, characterized in that said viral affections comprise herpes simplex type 1, herpes zoster, parainfluenza viruses or rhinovirus, orthomyxovirus, hepatitis B virus, hepatitis C virus and cytomegalovirus.
4. Pharmaceutical compositions suitable to treat viral affections containing as active ingredient a triptan mixed with pharmaceutically acceptable excipients.
5. Compositions according to claim 4, prepared in the form of tablets each containing from 1.25 to 25 mg of triptan.
6. Therapeutic method to treat viral affections comprising the oral administration of an efficacious quantity of triptan.
7. Therapeutic method according to claim 6, characterized in that said efficacious quantity ranges from 2.5 to 500 mg per day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/09435

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/404 A61K31/4196 A61P31/12 A61P31/22 A61P31/16

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)
IPC 7 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)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 01107 A (HOFMANN BO ARNE) 18 January 1996 (1996-01-18) page 26, line 10-15; example 1 page 28, line 13 -page 29, line 10; claims	1-7
X	AFZELIUS P ET AL: "Sumatriptan increases the proliferation of peripheral blood mononuclear cells from HIV- infected individuals and healthy blood donors in vitro." APMIS, (2000 JAN) 108 (1) 74-8. , XP009023377 the whole document, in particular the discussion	1,2,4

☐ Further documents are listed in the continuation of box C.

☒ 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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"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
9 January 2004	15/01/2004

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	Venturini, F

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/09435

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:

Although claims 6,7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 searched 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

International Application No
PCT/EP 03/09435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601107 A	18-01-1996	AU 2880495 A	25-01-1996
		AU 2880595 A	25-01-1996
		WO 9601106 A1	18-01-1996
		WO 9601107 A1	18-01-1996