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(54) Title: METHODS OF TREATING INFLAMMATORY AND AUTOIMMUNE DISEASES WITH NATALIZUMAB

(57) Abstract: Natalizumab is a safe and efficacious treatment for inflammatory and autoimmune diseases, such as multiple sclerosis, Crohn's Disease, and rheumatoid arthritis. Rare occurrences of progressive multifocal leucoencephalopathy during treatment suggest the possibility that it may be related to natalizumab treatment. Monitoring for JCV and informing caregivers and patients about the manifestations of progressive multifocal leucoencephalopathy can improve the safety of natalizumab therapy.



WO 2007/100770 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/04943

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 39/395(2006.01);G01N 33/53(2006.01)

USPC: 424/131.1;435/7.1

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)

U.S. : 424/131.1; 435/7.1

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 practicable, search terms used)
USPTO, US PGPub, EPO, JPO, STN Easy, NCBI, Google (Natalizumab, PML, Multiple Sclerosis)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	ANNETTE LANGER-GOULD et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. The New England Journal of Medicine. July 28, 2005, Vol. 353, pages 375-381, see pages 375-376.	1-19, 40-57 ----- 20-39, 58-76
Y	US 6,238,859 (LUKE et al.) 29 May 2001 (29.05.2001), see column 4, lines 43-45.	20-39
Y	KNOWLES et al. The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leukoencephalopathy. Journal of Clinical and Diagnostic Virology, Vol. 4, No.2, August 1195, pp 183-194 (12), see abstract.	58-76
A	KLEINSCHMIDT-DEMASTERS et al. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. The New England Journal of Medicine, July 28, 2005, Vol. 353, pages 369-374.	1-76

☒ 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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"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	"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/04943

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

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 additional fees, this Authority did not invite payment of any additional fees.
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 and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/04943

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MILLER et al. A controlled trial of natalizumab for relapsing multiple sclerosis. The New England Journal of Medicine, January 2, 2003, Vol. 348, pages 15-23.	1-76

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/04943

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claims 1-19 are drawn to a first method of using natalizumab to treat a patient with an inflammatory or autoimmune disease comprising administering a pharmaceutically effective amount of natalizumab, monitoring the patient for indicators of progressive multifocal leukoencephalopathy and discontinuing the administration of natalizumab in the presence of indicators of progressive multifocal leukoencephalopathy.

Group II, claims 20-39 are drawn to a second method of using natalizumab to treat a patient with an inflammatory or autoimmune disease comprising removing a sample of blood from the patient, testing the serum or plasma of the sample for the presence of IgG antibodies to JCV, initiating treatment of the patient with natalizumab in the event the sample is negative for IgG antibodies to JCV, monitoring the patient for indicators of progressive multifocal leukoencephalopathy and discontinuing the administration of natalizumab in the presence of indicators of progressive multifocal leukoencephalopathy.

Group III, claims 40-57 are drawn to a third method of using natalizumab to treat a patient with an inflammatory or autoimmune disease comprising removing a sample of blood from the patient, testing the serum or plasma of the sample for the presence of IgG antibodies to JCV, initiating treatment of the patient with natalizumab in the event the sample is positive for IgG antibodies to JCV, monitoring the patient for indicators of progressive multifocal leukoencephalopathy and discontinuing the administration of natalizumab in the presence of indicators of progressive multifocal leukoencephalopathy.

Group IV, claims 58-76 are drawn to a fourth method of using natalizumab to treat a patient with an inflammatory or autoimmune disease comprising removing a sample of blood from the patient, testing the sample for the presence of IgG antibodies to JCV, initiating treatment of the patient with natalizumab, informing the prescribing physician about the mental and physical syndromes of progressive multifocal leukoencephalopathy, informing the patient about the mental and physical syndromes of progressive multifocal leukoencephalopathy and instructing the patient to report to the physician in the presence of at least one symptom, monitoring the patient for indicators of progressive multifocal leukoencephalopathy and discontinuing the administration of natalizumab in the presence of indicators of progressive multifocal leukoencephalopathy.

The International Searching Authority considers that the international application does not comply with the requirement of unity of invention (PCT Rule 13.1, 13.2 and 13.3) for the reason indicated below:

The inventions are linked by the technical feature of a method of using natalizumab to treat a patient with an inflammatory or autoimmune disease. However, this feature is not special because it does not constitute an advance over the prior art. Taylor et al (US 2004/0009169 A1) teach use of natalizumab in the treatment of chronic autoimmune and inflammatory diseases (see paragraph 0236). Furthermore, each of these groups involves method steps not required by the other groups.