USE OF 4-(4-METHYLPIPERAZIN-1-YLMETHYL)-N-[4-METHYL-3-(4-PYRIDIN-3-YL)PYRIMIDIN-2-YLAMINO] PHENYL]-BENZAMIDE FOR TREATING SEMINOMAS

4-(4-methylpiperazin-1-ylmethyl)-n-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide of the formula (I) or a pharmaceutically acceptable salt thereof can be used in the treatment of seminomas.
The invention relates to 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide (hereinafter: "COMPOUND I") or a pharmaceutically acceptable salt thereof for the manufacture of pharmaceutical compositions for use in the treatment of seminomas, to the use of COMPOUND I or a pharmaceutically acceptable salt thereof in the treatment of seminomas, and to a method of treating warm-blooded animals including humans suffering from seminomas by administering to a said animal in need of such treatment an effective dose of COMPOUND I or a pharmaceutically acceptable salt thereof.

Testicular germ cell tumors are uncommon neoplasms, accounting for only 1% to 2% of malignancies in North American males. They are, however, the commonest malignancies in men aged 20-34 and epidemiological studies have shown a doubling of the incidence rate in the past 30 years. Approximately 45% of germ cell tumors are seminomas and the majority of patients will present with clinical stage I disease. Only 15% to 20% of patients have infradiaphragmatic lymph node involvement (stage II disease) and less than 5% present with distant metastatic disease.

Standard treatment for stage I seminomas, in which the tumor is confined to the testis and a lymphangiogram is negative, involves orchidectomy followed by ipsilateral irradiation of the para-aortic and pelvic lymph nodes. The treatment for Stage II seminomas, in which the tumor has spread to lymph nodes below the diaphragm, involves radiation treatment that extends to the involved anatomy.

About 10-20% of seminomas patients harbor micrometastases in the draining lymph nodes. Marks et al., J. Urol. 143:524 (1990). Therefore, the irradiation of regional lymph nodes as part of the standard treatment of Stage I seminomas is unnecessary in approximately 85% of all seminoma patients. Although post-orchidectomy radiation is generally well tolerated, local complications have been reported to include a higher incidence of second-site malignancies, impaired fertility, and persistent scrotal edema. Hunter, et al., Cancer 64:1608 (1989); Thomas, et al., J. Urol. 12:313 (1989).
The instant invention is a response to the need for an alternative therapy in the treatment of seminomas, especially to decrease the need for subsequent radiation or chemotherapy treatment and reduce consequent infertility.

It has now surprisingly been demonstrated that seminomas can be successfully treated with COMPOUND I, or pharmaceutically acceptable salt thereof.

The present invention thus concerns the use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide having the formula I

![Chemical Structure](structure.png)

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating seminomas.

The present invention particularly concerns the use of COMPOUND I for the manufacture of a medicament for treating seminomas associated with c-Kit mutations sensitive to COMPOUND I.

The present invention most particularly concerns the use of COMPOUND I for the manufacture of a medicament for treating seminomas associated with Y823D, N822K or D816H mutations in the c-Kit tyrosine kinase.

4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide or a pharmaceutically acceptable salt crystal form thereof will be referred herein as COMPOUND I.
The term "4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide" includes the β-crystal form as described in the European patent application No. 998 473.

The preparation of COMPOUND I and the use thereof, especially as an anti-tumour agent, are described in Example 21 of European patent application EP-A-0 564 409, which was published on 6 October 1993, and in equivalent applications and patents in numerous other countries, e.g. in US patent 5,521,184 and in Japanese patent 2706682.

By the term "seminomas associated with COMPOUND I-sensitive Kit mutations" the applicant means a seminoma disease in which the germ cell tumors contain c-Kit having one or more mutations, the c-Kit mutant being sensitive to inhibition of its tyrosine kinase activity by COMPOUND I with an in vitro IC₅₀ of approximately 10 nM to 50μM preferably 10 nM to 10μM most preferably 10 nM to 1μM.

By the term "seminomas associated with Y823D, N822K and/or D816H mutations in the c-Kit tyrosine kinase" the applicant means a seminoma disease in which the germ cell tumors contain human c-Kit tyrosine kinase having one or more of the following mutations Y823D, N822K or D816H.

The names of the amino acids are either written out or the one letter or three letter codes are used. Mutations are referred to by accepted nomenclature, e.g. "Ala380Thr" or "380 Ala→Thr" both indicating that alanine at position 380 is replaced by threonine. The amino acid numbers indicating the position of the mutation refer to the amino acid numbering of the native human c-Kit protein as given in the SwissProt database under Accession Number P10721.

Y823D indicating that the amino acid tyrosine at position 823 is replaced by aspartate
N822K indicating that the amino acid asparagine at position 822 is replaced by lysine
D816H indicating that the amino acid aspartate at position 816 is replaced by histidine
The term "treatment" as used herein means curative treatment and prophylactic treatment. The term "curative" as used herein means efficacy in treating ongoing episodes of seminomas.
The term "prophylactic" means the prevention of the onset or recurrence of seminomas.
Pharmaceutically acceptable salts of COMPOUND I are pharmaceutically acceptable acid addition salts, like for example with inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example aliphatic mono- or di-carboxylic acids, such as trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid or oxalic acid, or amino acids such as arginine or lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxycarboxylic acid, 2-acetoxy-benzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids, such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids, such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids, such as methane-, ethane- or 2-hydroxyethane-sulfonic acid, or aromatic sulfonic acids, for example benzene-, p-toluene- or naphthalene-2-sulfonic acid.

The monomethanesulfonic acid addition salt of COMPOUND I (hereinafter “COMPOUND I mesylate”) and a preferred crystal form thereof are described in PCT patent application WO99/03854 published on January 28, 1999.

Depending on species, age, individual condition, mode of administration, and the clinical picture in question, effective doses, for example daily doses of about 100-1000 mg, preferably 200-600 mg, especially 400 mg, are administered to warm-blooded animals of about 70 kg bodyweight. For adult patients with unresectable and/or metastatic malignant seminomas, a starting dose of 400 mg daily can be recommended. For patients with an inadequate response after an assessment of response to therapy with 400 mg daily, dose escalation can be safely considered and patients may be treated as long as they benefit from treatment and in the absence of limiting toxicities.

The invention relates also to a method for administering to a human subject having seminoma, a COMPOUND I or a pharmaceutically acceptable salt thereof, which comprises administering a pharmaceutically effective amount of COMPOUND I or a pharmaceutically acceptable salt thereof to the human subject. Preferably administered once daily for a period exceeding 3 months. The invention relates especially to such method wherein a daily dose of 200 to 600 mg, especially 400-600 mg, preferably 400 mg, of COMPOUND I mesylate is administered.
It can be shown by established test models and especially those test model described herein that the COMPOUND I or a pharmaceutically acceptable salt thereof, results in a more effective prevention or preferably treatment of seminomas. The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects. The pharmacological activity may, for example, be demonstrated in a clinical study or in the test procedure as essentially described hereinafter.

The Kit protooncogene encodes a 145-kd transmembrane tyrosine kinase (TK) closely related to platelet derived growth factor receptor (PDGFR), monocyte-colony stimulating factor receptor (c-fms) and fms-like tyrosine kinase 3 (FLT3). It is expressed on hematopoietic stem cells, mast cells, melanocytes, interstitial cells of Cajal, intraepithelial lymphocytes, and germ cells. Studies of naturally occurring murine models of Kit deficiency have demonstrated that Kit is required in utero for the survival of germ cells. Postnatally, Kit is expressed by Leydig cells, spermatogonia and round spermatids. Seminomas and intratubular germ cell neoplasias (ITGCN) almost always express membrane associated Kit (as demonstrated by immunohistochemistry). In contrast, only a minority of non-seminoma germ cell tumors (GCT) express cytoplasmic, but not membranous, Kit. In mixed GCTs, membranous Kit expression is limited to the seminoma component.

In one case of mixed ovarian dysgerminoma/yolk sac tumor the mutation was detected in both components of the tumor. However, membranous Kit immunoreactivity was limited to the dysgerminoma component, whereas the yolk sac component had only weak cytoplasmic Kit staining. These results suggest that mutational or autocrine/paracrine Kit activation may play a role in the development of ITGCN and seminomas/dysgerminomas but that downregulation or loss of normal Kit signaling in these cells is associated with progression to non-seminomatous GCT.

Thus, the applicant decided to study the efficacy of COMPOUND I in inhibiting some constitutively activated Kit kinase isoforms associated with seminoma tumors.

**METHODS**

**Analysis of Kit mutations:** Cases of pure seminomas were selected from archival pathology specimens. Sections were prepared from formalin-fixed, paraffin-embedded specimens and trimmed to enrich for tumor cells. In some cases, laser capture microscopy was used to enrich for tumor cells. In a minority of patients, fresh frozen tumor specimens
were available and were used to prepare genomic DNA and/or RNA, as described by Rader A, et col. (Cancer 2001; 93:275) and Lux ML, et al. (Am.J.Pathol. 2000; 156:791-795).

PCR of genomic DNA was performed as previously described (Rader A et al.), using the primer pairs listed below (5'-3' notation): Exon 9F ATGCTCTGCTTCTGTACTGCC; Exon 9R AGAGCCTAACATCCCCTTA; Exon 11F CCAGAGTGTCTAATGACTG; Exon 11R ACCCAAAAGGGTACATGGA; Exon 13F CATCAGTTGACCAGTTGTC; Exon 13R ACACGGCTTTACCCTCAATG; Exon 17F TGTATTCAGAGACTTTGCC; Exon 17R GGATTACATTATGAAAGTCACAGG.

Amplicons of Kit were analyzed by D-HPLC using a Transgenomic WAVE instrument as previously described by Choy YS, et al. (Annals of Human Genetics 1999; 63:383-391). Denaturing temperatures for detection of point mutations were optimized for each primer pair (Exon 9 58°C, Exon 11 57°C, Exon 13 59°C, Exon 17 58°C). Amplicons were bidirectionally sequenced and the identity of all mutations were confirmed by analysis of a second, independent amplification product (Rader A et al.). In cases with available frozen material, the entire Kit cDNA was sequenced (Lux ML, et al.).

**Reagents:** COMPOUND I mesylate. Fresh 10 mM stock solutions of inhibitor were made before each experiment by dissolving compound in 1 ml Phosphate-Buffered Saline (PBS; Gibco-BRL).

**Antibodies:** A polyclonal rabbit anti-Kit antibody (c- Kit Ab-1) was used at a dilution of 1:500 (c-Kit Ab-1; Oncogene, Cambridge, MA). An anti-phosphotyrosine antibody (PY20) was used at a dilution of 1:1000 (PY20 Transduction Laboratories; Lexington, KY). Peroxidase conjugated goat anti-mouse antibody was used at a dilution of 1:5000 and goat anti-rabbit antibody at a dilution of 1:10,000 (Pierce; Rockford, IL).

**In vitro studies:** Plasmids encoding mutant Kit cDNAs were generated by site directed mutagenesis of the wild-type cDNA. All mutations were confirmed by bi-directional sequencing. The CHO (Chinese hamster ovary) cell line was obtained from American Type Culture Collection (ATCC) and maintained as previously described by Bold G, et al. ([published erratum appears in J Med Chem 2000 Aug 10;43(16):3200]. Journal of Medicinal Chemistry 2000; 43:2310-2323).
Cells were transiently transfected with plasmids encoding cDNAs for wild-type or mutant Kit proteins using Lipofectamine PLUS (Invitrogen Life Technologies) according to the manufacturer's protocol. Twenty-four hours after transfection the cells were treated with control media or media containing various concentrations of COMPOUND I mesylate for 90 minutes. The cells were then harvested and protein lysates prepared and analyzed for Kit activation as described previously (Lux ML, et al.).

RESULTS

Example 1: Spectrum and frequency of Kit mutations in pure seminomas

To further investigate the type and frequency of KIT mutations occurring in seminomas, we analyzed forty-three archival cases. All tumors were pure seminomas; in cases with heavy lymphocytic infiltrates laser capture microdissection was performed to enrich for tumor DNA. PCR amplimers were screened by denaturing HPLC (Transgenomic WAVE system) and detected mutations were confirmed by direct DNA sequencing. Some cases contained in-frame point mutations in exon 17, including cases with the D816H mutation. Interestingly, the majority of the mutations were D816V, but examples of N822K and Y823D were also found (see Table for summary). The D816V, N822K, and Y823D mutations have not been previously described in seminomas.

COMPOUND I mesylate inhibits some constitutively activated Kit kinase isoforms associated with seminomas tumors.

The selectivity of COMPOUND I mesylate is related to its ability to reversibly bind to the ATP-binding pocket of ABL, Kit, and PDGFR but not other tyrosine kinases. While the molecular mechanism(s) by which mutations of Kit lead to kinase activation are not fully understood, it is possible that some mutations could inhibit the interaction of COMPOUND I mesylate with the ATP-binding pocket. To examine this possibility, representative constitutively-activated Kit oncoproteins from seminomas were expressed by transient transfection in CHO cells and examined for sensitivity to inhibition by COMPOUND I mesylate. As shown above, mutant Kit isoforms with amino acid substitutions at residue 822 or 823 were highly sensitive to COMPOUND I mesylate with an \textit{in vitro} IC\textsubscript{50} of approximately 100-200 nM. In contrast, the D816V mutation that is commonly associated with human mastocytosis, is completely resistant to COMPOUND I mesylate even using concentrations of 5-10 μM. The kinase activity of the D816H mutant isoform was less
inhibited by COMPOUND I mesylate than that of wild type Kit. The in vitro IC₅₀ was approximately 1 µM.

**DATA SUMMARY**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>D816V</th>
<th>D816H</th>
<th>N822K</th>
<th>Y823D</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPOUND I Sensitive</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Taken together, these results suggest that COMPOUND I has an unexpected potential for the treatment of seminomas. The efficacy of COMPOUND I in seminomas is tested by clinical trials in advanced metastatic disease refractory to chemotherapy or in a “window of opportunity” neoadjuvant setting in patients with low volume retroperitoneal disease prior to their radiotherapy.

Future development could include use of COMPOUND I as an adjuvant therapy in patients with Stage I disease in an attempt to decrease the need for subsequent radiation or chemotherapy treatment and perhaps reduce consequent infertility.

Very good tolerability of COMPOUND I mesylate treatment.

Treatment with COMPOUND I mesylate was well tolerated overall. No hair loss was observed, and the patient reported only mild occasional nausea related to swallowing of the drug capsules, lasting for about 15 minutes improved after taking drug with food. Blood cell count changes were unremarkable. Her blood haemoglobin level varied between 118 g/L and 125 g/L during COMPOUND I mesylate therapy (the pretreatment value was 120 g/L), the white blood cell count from 3.2 to 4.4 x 10⁹/L (5.5 x 10⁹/L), the granulocyte count from 1.52 to 2.39 x 10⁹/L (3.2 x 10⁹/L), and the platelet count from 261 to 365 x 10⁹/L (360 x 10⁹/L). No drug-related liver, renal or cardiac toxicity was observed. The main subjective toxicity [all Grade 1 (NCI CTC version 2.0)] consisted of increased frequency of bowel movements (2 to 4 times a day), occasional muscle cramps in the legs, slight transient ankle oedema, and a Herpes zoster infection with rash located on the left ventral (LV) dermatome was diagnosed during COMPOUND I mesylate therapy. The World Health Organization (WHO) performance status improved from 1 (cancer related symptoms present) to 0 (normal) during COMPOUND I mesylate therapy.
Example 2: Capsules with 4-[(4-methyl-1-piperazin-1-ylmethyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate, β-crystal form.
Capsules containing 119.5 mg of the compound named in the title (=COMPOUND I mesylate) corresponding to 100 mg of COMPOUND I (free base) as active substance are prepared in the following composition:

<table>
<thead>
<tr>
<th>Composition</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPOUND I mesylate</td>
<td>119.5 mg</td>
</tr>
<tr>
<td>Cellulose MK GR</td>
<td>92 mg</td>
</tr>
<tr>
<td>Crospovidone XL</td>
<td>15 mg</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>2 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

230 mg

The capsules are prepared by mixing the components and filling the mixture into hard gelatin capsules, size 1.

Example 3: Capsules with 4-[(4-methyl-1-piperazin-1-ylmethyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate, β-crystal form.
Capsules containing 119 mg of the compound named in the title (=COMPOUND I mesylate) as active substance are prepared in the following composition:

<table>
<thead>
<tr>
<th>Composition</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
<td>119 mg</td>
</tr>
<tr>
<td>Avicel</td>
<td>200 mg</td>
</tr>
<tr>
<td>PVPPXL</td>
<td>15 mg</td>
</tr>
<tr>
<td>Aerosil</td>
<td>2 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

337.5 mg

The capsules are prepared by mixing the components and filling the mixture into hard gelatin capsules, size 1.

These examples illustrate the invention without in any way limiting its scope.
Claims:
1. The use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino]phenyl]-benzamide of the formula I

   ![Chemical Structure](image1)

   (I)

or a pharmaceutically acceptable salt thereof for the manufacture of pharmaceutical compositions for use in the treatment of seminomas.

2. Use according to claim 1, wherein seminoma is associated with c-Kit mutations sensitive to COMPOUND I.

3. Use according to claim 1, wherein seminoma is associated with Y823D, N822K or D816H mutations in the c- Kit tyrosine kinase.

4. The use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino]phenyl]-benzamide of the formula I

   ![Chemical Structure](image2)

   (I)

or a pharmaceutically acceptable salt thereof in the treatment of seminomas.
5. A method of treating humans suffering from seminomas which comprises administering to a said human in need of such treatment a dose, effective against seminomas, of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide of the formula I

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof.

6. Use or method according to claim 5 wherein a pharmaceutically acceptable acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide of the formula I is administered.

7. Use or method according to claim 5 wherein a methanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide of the formula I is administered.

8. Use or method according to claim 7 wherein a daily dose of 200 to 600 mg of a monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide of the formula I is administered to an adult human.

9. A method for administering to a human subject having seminomas 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide of the formula I.
or a pharmaceutically acceptable salt thereof, which comprises administering a pharmaceutically effective amount of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof to the human subject once daily for a period exceeding 3 months.

10. A method according to claim 9 wherein a daily dose of 200 to 600 mg of the monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I is administered.

11. A method according to claim 5 wherein seminoma is associated with c-Kit mutations sensitive to COMPOUND I.

12. A method according to claim 5 wherein seminoma is associated with Y823D, N822K or D816H mutations in the c- Kit tyrosine kinase.

13. Use according to claim 1, wherein the pharmaceutically acceptable salt is monomethanesulfonate salt.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/506 A61P35/00

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, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 99 03854 A (NOVARTIS ERFINDB VERWALT GMBH ;NOVARTIS AG (CH); BUERGER HANS MICHA) 28 January 1999 (1999-01-28) cited in the application page 16, line 4 -page 17, line 16; claims</td>
<td>1-13</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Date of the actual completion of the international search

9 April 2003

Date of mailing of the international search report

29/04/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 651 eipo nl, Fax: (+31-70) 340-3016

Authorized officer

Venturini, F
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
INTERNATIONAL SEARCH REPORT

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. ☒ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 4–12 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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AU 8975998 A</td>
<td>10-02-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9810920 A</td>
<td>15-08-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1264375 T</td>
<td>23-08-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9903854 A1</td>
<td>28-01-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0003230 A2</td>
<td>28-06-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 3276359 B2</td>
<td>22-04-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2001510192 T</td>
<td>31-07-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 20000227 A</td>
<td>17-01-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 502295 A</td>
<td>21-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 338129 A1</td>
<td>25-09-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SK 432000 A3</td>
<td>12-06-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TR 2000000060 T2</td>
<td>21-09-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2002115858 A1</td>
<td>22-08-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 9806362 A</td>
<td>22-01-1999</td>
</tr>
</tbody>
</table>