

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 May 2009 (28.05.2009)

PCT

(10) International Publication Number
WO 2009/067067 A1

- (51) **International Patent Classification:**
A61K 33/18 (2006.01) A61P 11/08 (2006.01)
A61K 33/44 (2006.01) A61P 11/00 (2006.01)
A61P 11/06 (2006.01)
- (21) **International Application Number:**
PCT/SE2008/000644
- (22) **International Filing Date:**
18 November 2008 (18.11.2008)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
0702587-7 23 November 2007 (23.11.2007) SE
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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report



WO 2009/067067 A1

(54) **Title:** METHOD AND MEANS FOR OBTAINING BRONCHORELAXATION

(57) **Abstract:** A method for producing bronchorelaxation in a human or an animal affected by airway obstruction comprises administration of a pharmacologically effective amount of elemental iodine on activated charcoal (iodinated activated charcoal) to the intestine of said human or animal. A pharmaceutical composition comprising elemental iodine on activated charcoal and uses thereof is also disclosed.

METHOD AND MEANS FOR OBTAINING BRONCHORELAXATION

FIELD OF THE INVENTION

5 The present invention relates to a method and a means for obtaining bronchorelaxation in the airways of a human or an animal. The present invention also relates to a method and a pharmaceutical composition and the use thereof for treating chronic obstructive pulmonary disease and asthma.

10 BACKGROUND OF THE INVENTION

 Chronic obstructive pulmonary disease (COPD) and asthma are important causes of morbidity, mortality and health-care costs worldwide. The estimated prevalence of COPD in many western countries is more than 10 % of the population (Mannino and
15 Buist, 2007). In the USA, COPD was the primary reason for hospital discharge 9.8 million times and a secondary reason for discharge an additional 37.5 million times from 1979 to 2001. COPD is estimated to cause more than 80,000 deaths every year in the USA. It has been estimated that the total national cost in the USA for COPD was US\$ 32.1 billion for the year 2003.

20 Approximately 300 million people worldwide currently have asthma. Most are found in the industrialized countries, which have an asthma prevalence of ~10 % in adults and almost 20 % in children. The rate of emergency hospital admissions during the early 2000 was 10/100,000 each year in adults and 100/100,000 in young children in the UK (Anderson et al., 2007). Asthma causes 1,200 deaths each year in the United
25 Kingdom alone. The financial burden of patients with asthma in different western countries amounts to around US\$ 300 billion every year.

 COPD is associated with tobacco smoking and is characterized by inflammation in the airways and a gradual decline in lung function. Often, the patients experience cough, sputum production and wheezing, as well as repeated bouts of
30 pneumonia, often several times per winter. The airway obstruction is usually irreversible, which means that it persists in spite of treatment with corticosteroids and beta2-agonists. As the disease progresses during many years, the airway obstruction can become very severe, leading to severe dyspnea during both exercise and rest and, eventually, lung failure. At this stage, lung function examinations with spirometry usually reveal a loss of

lung capacity by 50 % or more. Other severe symptoms often appear at this time as well, such as weight loss, depression and cardiac disease. The mortality risk is high in these patients. The only established pharmaceutical treatment for these patients is anti-cholinergics, which only gives minor effects. Steroids and bronchodilators have minimal beneficial effects.

Asthma is characterized by chronic inflammation in the airways with reversible airway obstruction and bronchial hyper-reactivity. In contrast to COPD, asthma is usually treatable with steroids and bronchodilators. However, 10 % of asthmatics have severe symptoms in spite of maximum treatment. There is also an overlap between COPD and asthma, often rendering a firm diagnosis difficult to obtain (Chang & Mosenifar, 2007).

COPD in horses (also known as heaves, broken wind, alveolar emphysema and equine asthma) is characterized by inflammation in the airways. It can be caused by dusty or mouldy hay, dust and moulds in bedding, or pollens, dust and other irritants in the environment, but the cause is often unknown. The horses show symptoms like coughing, increased respiration, laboured breathing and yellow nasal discharge. The symptoms range in severity from mild, to so severe that the horse appears listless, has difficulty breathing and develops a muscular “heave line” along the horse’s barrel from taking a double exhalation (The Columbia Encyclopedia, 2007). COPD in horses is often treated with β_2 -agonists but the bronchorelaxing effect by these drugs is poor (Törneke, K. and Ingvast-Larson, C. 1999).

There have also been reports about obstructive pulmonary diseases, mainly asthma, in other animals such as cats and dogs. As in humans, these animals get an obstruction of the airways when the bronchi fill up with mucous and go into spasms (bronchoconstriction). It is far more common in cats than dogs, and particularly in Siamese and Himalayan cat breeds (AnimalHospitals-USA, 2007).

Clearly, there are many individuals with COPD and asthma who urgently need better treatments for their disease.

In US 6,063,363 is disclosed a method of treating upper respiratory tract infections with potassium salts, including potassium iodide and bromide. The potassium salt is introduced into the lungs and/or the nasal area and/or the oral cavity as a liquid solution, nasal spray, etc. However, the effect on the upper respiratory tract infections is said to be caused by the potassium cation saturation of the cells and tissues involved in upper respiratory tract infection. The anions of the administrated salts are of no

importance in the treatment. Furthermore, US 6,063,363 discloses treatment of infection and not of bronchoconstriction.

In WO 00/36915 is disclosed a method of treating chronic obstructive airway disease by administering an osmotically active compound such as a salt, including
5 potassium iodide and potassium bromide, sugar, sugar alcohol or organic osmolyte to the afflicted airway surface. The osmotically active compound is administered to the airways in order to increase the volume of the liquid on airway surfaces. No bronchorelaxing effect is reported.

In US 6,696,041 and US 6,171,611 are disclosed the use of iodine-
10 containing nasal solutions for the treatment of nasal congestion caused by, i.e., common cold, flu or sinusitis. Both disclosed iodine-containing nasal solutions may also contain various salts including sodium iodide. US 6,171,611 further discloses a mouthwash solution comprising iodine and iodine salts, including potassium and sodium iodide.

US patents nos. 5,910,318 and 5,955,101 disclose starch-iodine
15 pharmaceutical formulations for the preparation of capsules and tablets. The pharmaceutical formulations are suitable for administration to patients suffering from iodine deficiency diseases, in particular breast dysplasia, breast cancer, endometriosis, premenstrual syndrome, ovarian cysts and radiation sickness. In the formulation iodine is complexed with starch containing amylose, forming triiodide ions or polyiodide ions (I_3^-
20 up to I_{11}^-). Iodine is released in the upper small bowel after hydrolysis of the starch by α -amylase. Since the triiodide ions cannot exist in non-complexed form I_2 is released.

Iodine toxicity may be a concern when high amounts of iodine are administered to a human. Iodine toxicity is manifested by, among other symptoms, thyroiditis, goiter, hypothyroidism and hyperthyroidism. It has been suggested that some
25 individuals can tolerate very high levels of iodine with no apparent side effects and that iodine intakes less than or equal to 1,000 mg/day are probably safe for the majority of the population, but may cause adverse effects in some individuals (Pennington, 1990).

Administration of a bromide salt, in particular sodium bromide, to animals suffering from the effects of iodine toxicity helps to reverse the symptoms (Baker et al., 2003). Sodium
30 bromide is well tolerated by humans and it has been found to have a no-effect level of 4 mg/kg body weight (van Gelderen et al., 1993).

Activated charcoal is used in medical applications to treat poisoning and oral overdose of various medicaments. Activated charcoal has a very large surface area; 1 gram has a surface area of 300-2000 m² (Greenwood et al., 1984).

Impregnated activated charcoals are carbonaceous adsorbents which have chemicals finely distributed on their internal surface. The impregnation optimizes the existing properties of the activated charcoal giving a synergism between the chemicals and the charcoal (Carbo Tech-Aktivkohlen GmbH, Germany). Iodinated activated charcoal has
5 been used for many years to bind heavy metals in gas.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide a method and a means for
10 producing bronchorelaxation in a human or an animal lung affected by airway obstruction.

Another object of the present invention is to provide a method for producing bronchorelaxation in a human or an animal with chronic obstructive pulmonary disease.

A further object of the present invention is to provide a method for
15 producing bronchorelaxation in a human or an animal with asthma.

A still further object of the present invention is to provide a pharmaceutical composition and the use thereof for producing bronchorelaxation in a human or an animal lung affected by airway obstruction.

An additional object of the present invention is to provide a pharmaceutical
20 composition and the use thereof for producing bronchorelaxation in humans or animals with chronic obstructive pulmonary disease.

Another object of the present invention is to provide a pharmaceutical composition and the use thereof for producing bronchorelaxation in humans or animals with asthma.

25 Further objects of the invention will become evident from the following summary of the invention, preferred embodiments and the appended claims.

SUMMARY OF THE INVENTION

30 According to the present invention is disclosed a method for producing bronchorelaxation in the lungs of a human or an animal affected by airway obstruction, comprising administration of a pharmacologically effective amount of elemental iodine, I₂, on activated charcoal to the intestine of said human or animal.

In this specification the term iodine refers to elemental iodine, I₂, and the term iodine on activated charcoal refers to iodinated activated charcoal.

According to the present invention is also disclosed a method for producing bronchorelaxation in the lungs of a human or an animal with chronic obstructive pulmonary disease (COPD) and/or asthma, comprising administration of a pharmacologically effective amount of iodine on activated charcoal to the intestine of said human or animal.

According to the present invention is furthermore disclosed a pharmaceutical composition comprising iodine on activated charcoal for use in the method of the invention.

Preferred administration forms for the pharmaceutical composition of the invention are tablets, tablets with disintegrants, capsules which disintegrate relatively fast in the stomach such as gelatin capsules and pullulan capsules, wherein the tablets and capsules comprise iodine on activated charcoal and optionally comprise a bromide salt and any of flavor, colour, preservative, sweetener excipient.

Preferred iodine concentration is from 1 % to 10 % w/w of the activated charcoal, in particular from 2 % to 8 % w/w of the activated charcoal, most preferred from 3 to 7 w/w of the activated charcoal.

Preferred daily doses to a human of iodine administered in form of the pharmaceutical composition of the invention are from 5 mg to 5,000 mg, in particular from 25 mg to 1,000 mg, most preferred from 50 mg to 250 mg.

Preferred daily doses of iodine administered to an animal in form of the pharmaceutical composition of the invention are from 0.07 mg/kg to 70 mg/kg body weight, in particular from 0.35 mg/kg to 15 mg/kg body weight, most preferred from 0.7 mg/kg to 3.5 mg/kg body weight.

Preferred doses administered to a human of activated charcoal are from 0.10 g to 100 g daily, in particular from 0.50 g to 20 g daily, most preferred from 1 g to 5 g daily.

Preferred daily doses administered to an animal of activated charcoal are from 1.5 mg/kg to 1,400 mg/kg body weight, in particular from 7 mg/kg to 285 mg/kg body weight, most preferred from 14 mg/kg to 70 mg/kg body weight.

According to a first preferred aspect of the invention iodinated activated charcoal is administered to the intestine of a human or an animal in need of

bronchorelaxation, in a pharmaceutically acceptable form, in particular in form of a tablet or capsule comprising elemental iodine on activated charcoal.

According to a second preferred aspect of the invention the iodinated activated charcoal is administered to the intestine of a human or an animal in form of a tablet, wherein the tablet comprises disintegrant for fast release of the tablet contents in the stomach.

According to a third preferred aspect of the invention the iodinated activated charcoal is administered to the intestine of a human or an animal in form of a capsule, wherein the capsule shell is comprised by gelatin or pullulan for fast release of the capsule contents.

According to a fourth preferred aspect of the invention a bromide salt is co-administered to a human or an animal in need of bronchorelaxation with the iodinated activated charcoal to minimize the risk of iodine toxicity.

Preferred bromide salts are sodium, potassium, magnesium, lithium, ammonium and calcium bromide.

A preferred concentration of the co-administered bromide salt is from 0.5 % to 5 % w/w of the iodinated activated charcoal.

The invention will now be described in more detail by reference to preferred but not limiting embodiments.

DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

EXAMPLE 1. *Administration of iodine on activated charcoal.*

A male Caucasian, born 1935, had been smoking cigarettes daily for many years, but quit about 10 years ago. The decision to quit smoking was caused by increasing problems from the airways, with repeated episodes of pneumonia and airway obstruction. These symptoms were usually treated with antibiotics, steroids and bronchodilators. The COPD diagnose was first suggested in June 2000.

After that, the airway symptoms increased considerably, with month-long episodes of cough and exercise-induced dyspnea. Spirometric evaluation some years later showed a Forced Expiratory Volume in one second, FEV₁, of 1.44 L, corresponding to 49.7 % of his reference value, and a Peak Expiratory Flow, PEF, of 282 L/min, corresponding to 60.1 % of his reference value.

In the following months the situation continued to worsen with loss of appetite, reduction of weight and severe dyspnea during rest, in spite of maximum treatment with anti-cholinergics, steroids and bronchodilators. The patient now felt desperately ill, and questioned how long he would be able to survive.

5 The severity of his condition prompted the patient to look for alternative treatments. When ingesting iodinated activated charcoal, in form of rods (1×1×5 mm) of activated charcoal comprising about 5 % iodine by weight, I₂, (Sigma-Aldrich, Inc.) the patient experienced immediate relief of airway obstruction and dyspnea. A few days
10 intake of 1-2 g iodinated activated charcoal twice per day (equivalent of 50-100 mg iodine twice per day), suspended in yoghurt, produced a dramatic increase in lung function and stamina, and completely removed the dyspnea. Sputum production was also considerably reduced. A renewed spirometric evaluation a few months later confirmed the subjective improvements (FEV₁ = 2.79 L, corresponding to 97.1 % of his reference value and PEF = 427 L/min, corresponding to 92.5 % of his reference value).

15 The patient has continued to regularly take the combination for more than a year and still experiences the full benefit of it. A temporary discontinuation of the intake for a few days led to the reappearance of many of the symptoms. However, they quickly disappeared upon the resumption of the intake of iodinated activated charcoal. The patient now lives a normal life, being able to pursue gardening, cycling and even to play an
20 occasional game of badminton.

To test the bronchorelaxing effect of activated charcoal without addition of iodine, the same patient took 5 g of iodine-free activated charcoal (Medikol, Selena Fournier) for a few days. However, no bronchorelaxing effect was observed, instead his condition worsened.

25 To clarify if iodine in itself has bronchorelaxing properties, 50 mg elemental iodine (Sigma-Aldrich, Inc.), placed in a gelatin capsule, was taken by the same patient for a few days. However, no distinct bronchorelaxing effect was observed.

EXAMPLE 2. Tablets comprising iodine on activated charcoal.

30 Tablets comprising iodine on activated charcoal were compressed in a conventional tableting machine from 500 mg iodinated activated charcoal (Sigma-Aldrich, Inc.) mixed with 122 mg lactose monohydrate, 6 mg magnesium stearate and 122 mg sodium methyl cellulose to form a 750 mg tablet comprising about 25 mg iodine. Optionally, sodium bromide (0.5-5 % w/w) can be added to the tableting mixture.

EXAMPLE 3. *Tablets comprising iodine on activated charcoal - for fast release in the stomach.*

Tablets comprising iodine on activated charcoal for fast release of the tablet content in the stomach were compressed in a conventional tableting machine from 500 mg iodinated activated charcoal (Sigma-Aldrich, Inc.) mixed with 108 mg lactose monohydrate, 6 mg magnesium stearate, 16 mg croscarmellose sodium and 120 mg sodium methyl cellulose to form a 750 mg tablet comprising about 25 mg iodine. Optionally, sodium bromide (0.5-5 % w/w) can be added to the tableting mixture.

EXAMPLE 4. *Capsules comprising iodine on activated charcoal and sodium bromide.*

Capsules comprising iodine on activated charcoal and sodium bromide were manufactured by mixing 350 mg iodinated activated charcoal (Sigma-Aldrich, Inc.) with 5 mg sodium bromide. Gelatin capsules were filled with the mixture in a conventional capsule filling machine to form capsules containing about 17 mg iodine.

EXAMPLE 5. *Capsules comprising iodine on activated charcoal and sodium bromide - for fast release in the stomach.*

Capsules comprising iodine on activated charcoal and sodium bromide were manufactured by mixing 350 mg iodinated activated charcoal (Sigma-Aldrich, Inc.) with 5 mg sodium bromide. Pullulan capsules were filled with the mixture in a conventional capsule filling machine to form capsules containing about 17 mg iodine.

EXAMPLE 6. *Absorption by activated charcoal of Hg dissolved in water.*

A solution of metallic Hg in water was prepared by placing a droplet of mercury in a 250 ml beaker, adding 150 ml of distilled water, and stirring for 1 h at 40 °C. 100 mL of the aqueous phase was decanted into another 250 ml beaker and a sample of 30 mL was withdrawn. Iodinated activated charcoal (0.7 g) was added to the aqueous phase and the suspension stirred at 40 °C; samples (30 ml each) were taken at 30 min and 60 min. The samples were filtered into glass tubes provided with polypropylene stoppers, 2 % nitric acid (0.6 ml) was added to each sample, and the samples sent for analysis. Hg²⁺, mg/mL: 0.075 prior to addition of iodine on charcoal; 0.0055 after 30 min; < 0.0001 after 60 min. Thus, 1 h exposure to 1 g iodinated activated charcoal/100 ml water removed 99.9 % of Hg (0) from the solution.

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CLAIMS

1. A method for producing bronchorelaxation in a human or an animal affected by airway obstruction, comprising administration of a pharmacologically effective amount of
5 elemental iodine on activated charcoal (iodinated activated charcoal) to the intestine of said human or animal.
2. A method for producing bronchorelaxation in a human or an animal with chronic obstructive pulmonary disease, comprising administration of a pharmacologically
10 effective amount of elemental iodine on activated charcoal (iodinated activated charcoal) to the intestine of said human or animal.
3. A method for producing bronchorelaxation in a human or an animal with asthma, comprising administration of a pharmacologically effective amount of elemental iodine
15 on activated charcoal (iodinated activated charcoal) to the intestine of said human or animal.
4. The method of any of claims 1-3, wherein administration is in form of a tablet.
- 20 5. The method of any of claims 1-3, wherein administration is in form of a tablet comprising disintegrant for fast release in the stomach of the tablet contents.
6. The method of any of claims 1-3, wherein administration is in form of a capsule.
- 25 7. The method of any of claims 1-3, wherein administration is in form of a gelatin capsule.
8. The method of any of claims 1-3, wherein administration is in form of a pullulan
30 capsule.
9. The method of any of claims 1-3, wherein the amount of elemental iodine is from 1 % to 10 % w/w of the activated charcoal.

10. The method of any of claims 1-3, wherein the amount of elemental iodine is from 2 % to 8 % w/w of the activated charcoal.
11. The method of any of claims 1-3, wherein the amount of elemental iodine is from 3 %
5 to 7 % of the activated charcoal.
12. The method of any of claims 1-3, wherein the daily dose of elemental iodine administered to a human is from 5 mg to 5,000 mg.
- 10 13. The method of any of claims 1-3, wherein the daily dose of elemental iodine administered to a human is from 25 mg to 1,000 mg.
14. The method of any of claims 1-3, wherein the daily dose of elemental iodine administered to a human is from 50 mg to 250 mg.
15
15. The method of any of claims 1-3, wherein the daily dose of elemental iodine administered to an animal is from 0.07 mg/kg to 70 mg/kg body weight of the animal.
16. The method of any of claims 1-3, wherein the daily dose of elemental iodine
20 administered to an animal is from 0.35 mg/kg to 15 mg/kg body weight of the animal.
17. The method of any of claims 1-3, wherein the daily dose of elemental iodine administered to an animal is from 0.7 mg/kg to 3.5 mg/kg body weight of the animal.
- 25 18. The method of any of claims 1-3, wherein the daily dose of activated charcoal administered to a human is from 0.10 g to 100 g.
19. The method of any of claims 1-3, wherein the daily dose of activated charcoal administered to a human is from 0.50 g to 20 g.
30
20. The method of any of claims 1-3, wherein the daily dose of activated charcoal administered to a human is from 1 g to 5 g.

21. The method of any of claims 1-3, wherein the daily dose of activated charcoal administered to an animal is from 1.5 mg/kg to 1,400 mg/kg body weight.
22. The method of any of claims 1-3, wherein the daily dose of activated charcoal administered to an animal is from 7 mg/kg to 285 mg/kg body weight.
23. The method of any of claims 1-3, wherein the daily dose of activated charcoal administered to an animal is from 14 mg/kg to 70 mg/kg body weight.
24. The method of any of claims 1-3, wherein a bromide salt is co-administered with the elemental iodine on activated charcoal.
25. The method of claim 24, wherein the bromide salt is sodium bromide, potassium bromide, magnesium bromide, lithium bromide, ammonium bromide or calcium bromide.
26. The method of claims 24-25, wherein the bromide salt administration is in an amount of from 0.5 to 5 % w/w of the elemental iodine on activated charcoal.
27. The use of elemental iodine on activated charcoal (iodinated activated charcoal) for the manufacture of a medicament for producing bronchorelaxation in human or animal airways affected by obstruction.
28. The use of elemental iodine on activated charcoal (iodinated activated charcoal) for the manufacture of a medicament for producing bronchorelaxation in a human or an animal with chronic obstructive pulmonary disease.
29. The use of elemental iodine on activated charcoal (iodinated activated charcoal) for the manufacture of a medicament for producing bronchorelaxation in a human or an animal with asthma.
30. The use of claims 27-29, wherein the medicament comprises a bromide salt.
31. The use of claim 30, wherein the bromide salt is sodium bromide, potassium bromide, magnesium bromide, lithium bromide, ammonium bromide or calcium bromide.

32. The use of claims 30-31, wherein the bromide salt is in an amount of from 0.5 to 5 % w/w of the elemental iodine on activated charcoal.

5 33. A pharmaceutical composition for producing bronchorelaxation in a human or an animal lung affected by airway obstruction, comprising a pharmacologically effective amount of elemental iodine on activated charcoal (iodinated activated charcoal).

34. The pharmaceutical composition of claim 33, wherein the airway obstruction is caused by chronic obstructive pulmonary disease.

10

35. The pharmaceutical composition of claim 33, wherein the airway obstruction is caused by asthma.

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36. The pharmaceutical composition of claim 33, comprising a bromide salt for co-administration with the elemental iodine on activated charcoal.

37. The pharmaceutical composition of claim 33, wherein the bromide salt is sodium bromide, potassium bromide, magnesium bromide, lithium bromide, ammonium bromide or calcium bromide.

20

38. The pharmaceutical composition of claims 36-37, wherein the bromide salt administration is in an amount of from 0.5 to 5 % w/w of the elemental iodine on activated charcoal.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2008/000644

A. CLASSIFICATION OF SUBJECT MATTER		
IPC: see extra sheet 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: A61K, A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9604787 A1 (THE CENTER FOR INNOVATIVE TECHNOLOGY), 22 February 1996 (22.02.1996), page 27, line 1 - line 12, claims 1-2 --	1-38
A	WO 2007015102 A1 (IMPERIAL COLLEGE INNOVATIONS LIMITED), 8 February 2007 (08.02.2007), page 4, line 30 - line 32; page 5, line 12; page 6, line 5 - line 10, page 6, line 24 - line 25; page 9, line 6 - line 10 --	1-38
A	GB 2255718 A (HOOPER O.E. ET), 18 November 1992 (18.11.1992), page 3, line 27 - line 29 --	1-38
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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
20 January 2009		23-01-2009
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Helena Pantzare/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2008/000644**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.: 1-26
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-26. relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic
.../...
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:

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 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/SE2008/000644

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.

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International patent classification (IPC)

A61K 33/18 (2006.01)

A61K 33/44 (2006.01)

A61P 11/06 (2006.01)

A61P 11/08 (2006.01)

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