PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/70, 38/44, 38/19

A1

(11) International Publication Number: **WO 99/55315**

(43) International Publication Date: 4 November 1999 (04.11.99)

(21) International Application Number: PCT/GB99/01310

(22) International Filing Date: 28 April 1999 (28.04.99)

(30) Priority Data:

9809082.2	28 April 1998 (28.04.98)	GB
9810429.2	14 May 1998 (14.05.98)	GB

(71) Applicant *(for all designated States except US)*: EUROGENE LIMITED [GB/GB]; Marquis House, 67/68 Jermyn Street, London SW1Y 6NY (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MARTIN, John, Francis [GB/GB]; The Cruciform Project, Saint Martin's House, Tottenham Court Road, London W1P 9LN (GB). YLÄ–HERTTUALA, Seppo [FI/FI]; A.I. Virtanen Institute, University of Kuopio, P.O. Box 1627, FIN–70211 Kuopio (FI). BARKER, Stephen, George, Edward [GB/GB]; The Middlesex Hospital, The Vascular Unit, Dept. of Surgery, Sir Jules Thorn Building, Mortimer Street, London W1N 8AA (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: PERIADVENTITIAL DELIVERY DEVICE

(57) Abstract

A biodegradable matrix material is provided in a form that can be wrapped around a body part, in combination or impregnated with an agent that can be delivered to treat a condition *via* the adventitial surface of a body part, the agent being in a form that can be taken up by the matrix material. These components are provided for use in the treatment of the condition, e.g. by using a sealant to form a seal around the matrix material when impregnated with the agent.

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PERIADVENTITIAL DELIVERY DEVICE

Field of the Invention

The present invention relates to a device that can be used for delivering an active agent, in therapy.

Background of the Invention

Intimal hyperplasia is the increase in the number of cells between the endothelium and internal elastic lamina of a blood vessel, particularly in the intimal layer found there, or in an artery. Intimal hyperplasia is often caused by smooth muscle cell (SMC) proliferation in the blood vessel wall.

When intimal hyperplasia occurs, *de novo* thickening of the intimal layer or of the vessel wall, i.e. stenosis, may result. Thus, the blood vessel may become occluded.

Also, when an obstruction in a blood vessel has been cleared, intimal hyperplasia occurring after surgery may lead to the artery's becoming occluded again. This is known as restenosis.

Intimal hyperplasia, whether it leads to stenosis or restenosis, remains a major problem after various surgical procedures.

GB-A-2298577 discloses a non-restrictive, porous, external stent for arteriovenous bypass grafting procedures. This stent has beneficial effects on luminal size and on medial and intimal thickening.

WO-A-9423668 discloses a device for the local delivery of an agent into a blood vessel, including a reservoir formed between two elements thereof. Its use requires implantation, i.e. cutting through the vessel and then securing the device to the vessel walls. The device is partially porous. The reservoir is in direct contact with luminal blood flow. This involves the risk of infection.

US-A-3797485 discloses a device for delivering a drug to the adventitial surface of a blood vessel. It is provided with permanent walls and transcutaneous tubes for the delivery of drug in liquid form. The intention is that the drug should pass to another site.

US-A-5540928 and related patent publications (inventors: Edelman *et al*) disclose an extraluminal device in the form of a disc comprising a polymer matrix, with a central hole. In order to ensure that the agent, e.g. heparin, is delivered at the blood vessel wall, a radial hole may be bored in the coating; see Edelman *et al*, PNAS USA 87:3773-7 (May 1990).

Summary of the Invention

The present invention is based on initial experiments in which a collar was placed around the outside of the artery of a rabbit. This procedure normally causes intimal hyperplasia in the rabbit artery, leading to thickening of the arterial wall, which is similar to the stenosis that can occur in human arteries following bypass operations. When the collar was used to deliver DNA encoding VEGF to the arterial wall using a plasmid/liposome vector, the VEGF gene was overexpressed in the arterial wall, including the endothelial layer. Intimal hyperplasia was inhibited. It has been found that adventitial delivery is suitable for all tested systems.

The new findings demonstrate that effective agents can be delivered to the exterior of the blood vessel, to treat intimal hyperplasia. This has several advantages. In particular, the therapeutic agent is not washed away from the site of the hyperplasia by blood flow as with intralumenal delivery. A delivery reservoir can be maintained around the blood vessel, and there is no need for any intralumenal manipulations which damage the endothelium of the blood vessel (and can themselves trigger intimal hyperplasia).

According to one aspect of the invention, a device for use in the delivery of a therapeutic agent to a blood vessel or other elongate, internal member in a patient, comprises an outer layer adapted to provide a seal around the member, the agent being held within or associated with the device so that, in use, the agent comes into contact with the outer surface of the member. Such devices can be biodegradable, and do not require permanent transcutaneous delivery tubes.

One aspect of a method of application of a therapeutic agent, according to the invention, comprises surgical exposure of a body part; application, around the part, of an outer layer or of a matrix material; introduction of a pharmaceutical formulation containing the agent, either into the volume defined between the outer layer and the outer surface of the body part or into the matrix material (followed by providing a seal around the matrix material); and closure of the surgical wound.

Description of the Invention

Various agents, including peptidic and non-peptidic compounds, genes that can express active products etc, are suitable for use in the invention. As described in WO-A-9820027 (the content of which is incorporated herein by reference), an illustrative agent is the VEGF protein or nucleic acid. Herein, references to such agents, and to VEGF itself, are given by way of example.

Nucleic acids may be delivered in a "naked" form unassociated with a vector, or by means of a gene therapy vector. It is preferred to deliver them by means of any suitable gene therapy vector. In particular, viral or non-viral vectors may be used.

The body part to which the invention may be applied is typically a duct, and will typically be essentially tubular or cylindrical. For example, it may be a nerve, Fallopian tube, bile duct, aortic aneurism or blood vessel. In particular, anti-thrombotic agents may be administered to act on blood platelets or the coagulation cascade, growth factors to the nerves, and anti-rejection agents to transplanted organs.

For example, the active agent may be delivered to the outside of the body part to be treated, e.g. artery. This may be achieved by means of an implant placed externally to the blood vessel, in proximity to a site of hyperplasia to be treated. Such an implant may contain VEGF protein or nucleic acid or the vector and provides a reservoir of the agent.

The agent (preferably in association with a vector) may be introduced into the implant before or after the implant is introduced into the subject to be treated. For example, the implant may be fitted in the vicinity of the blood vessel; the agent is introduced into the implant, e.g. by injection, subsequently.

Preferably, the implant is placed in direct contact with the blood vessel, e.g. artery. This is especially preferred when retroviral vectors are used to deliver nucleic acids, as the physical distortion of the blood vessel may induce smooth muscle cell proliferation, which increases the efficiency of gene transfer by retroviral vectors. This proliferation, like the proliferation induced by the hyperplasia itself, is overcome or at least ameliorated, by the delivery of the agent. Similarly, it is preferred for the implant to be in contact with the artery when employing other vectors that exhibit increased efficiency of gene transfer when their target cells are dividing. For example, cell proliferation may also enhance gene transfer efficiency with plasmid/liposome complexes.

Such implants may be in any suitable form. An implant in the form of a collar which surrounds, partially or completely, preferably completely, the artery, at or near the site of the hyperplasia to be treated or prevented, is fully described and illustrated (see the drawings) in WO-A-9820027.

Extravascular delivery avoids procedures such as balloon catheterization or high pressure fluid which may lead to endothelial damage or denudation. Transfected genes are preferably applied *via* a silastic or biodegradable implant, placed next to, preferably

around, the outside of the blood vessel. The endothelium suffers little or no damage. This is a major advantage of this form of delivery.

Implants may be made of any suitable material. Silastic implants, i.e. implants comprising silicone rubbers, are one preferred alternative. Most preferred are biodegradable implants. Any suitable biodegradable material may be used.

In a preferred aspect of this invention, treatment comprises surgical exposure of the body part; application, around the part, of a strip of a matrix material including, or to include, the agent; covering the matrix material with an outer, sealing layer; and closure of the surgical wound.

Particularly in this latter aspect, the agent may be contained within a medium within the device, e.g. a solid or gel medium. This may help to prevent the agent escaping into the tissue.

For example, a sheet or strip of a biodegradable material may be impregnated with the therapeutic agent. The strip is cut to a desired size, before or after being wound around the body part to be treated. It is then sealed *in situ* by the application of, for example, a tissue glue around the matrix material. The glue may advantageously be activated remotely, e.g. by light.

Alternatively, the agent may be coated onto the surface of the implant which is in contact with the body part, in use. Alternatively, the agent may be dispersed throughout the structure of the implant.

Some advantages of such implants are that: (i) they provide a delivery reservoir, allowing for sustained delivery; (ii) no intralumenal manipulations are required and the, say, arterial endothelium remains intact; and (iii) the distortion (e.g. constriction in the case of a collar) created by the implant may enhance the efficiency of gene delivery, as explained above.

The invention provides a relatively or substantially impermeable outer layer. It may provide a diffusion barrier.

As indicated above, the therapeutic agent that is used in the present invention may be a nucleic acid from which a gene product is derived, *in situ*, e.g. following transport across the wall of the body part to which the device is applied. By way of example, a suitable gene may be provided in a polymer solution. If it is desired that a long-acting effect is provided, continuous expression of a gene may be provided, e.g. using fibroblasts.

The present invention may be understood with reference to the accompanying drawing, in which:

Figure 1 is a schematic view of a "wrap" embodying the invention in place around an arterial anastomosis.

Particularly where a strip of flexible matrix material is used as a wrap, it may be provided in a kit with a sealant and the agent. These components may be separate, or two or more may be combined. Thus, the agent may be pre-impregnated in the matrix material. The material may be in bi-layer form, one layer being of the matrix and the other of a relatively impermeable material, e.g. both of collagen but of different characteristics. Any or each component may be aseptically packaged, in generally known manner, ready for use.

The sealant may be a conventional "tissue glue", such as the thrombin glue sold under the name Tisseal, or a cyanomethacrylate-based glue.

The matrix material is, advantageously, biodegradable over a set time course, for example a period of 1 to 5 days, by which time the active agents in the formulation are likely to have become exhausted. The material is also chosen so as not to promote too severe a reaction from the surrounding tissue. Examples of suitable materials for the body include gelatin, alginate or collagen. These materials also allow the body flexibility and enable the device to be manufactured by molding or extrusion.

The outer layer may, for example, be made of solid collagen and the inner layer made of sponge-like collagen cross-linked thereto, the sponge-like layer being capable of being impregnated with the pharmaceutical formulation containing the agent to be delivered. In such a situation, the device may be provided to the surgeon for fitment with the formulation already impregnated therein, or it may be wetted with the formulation after fitment, for example by being injected as described earlier.

Alternatively, the agent may be coated onto an internal surface of the body, which surface is just in contact with the blood vessel in use. Alternatively, agent may be dispersed throughout the structure of the body.

It is desirable that the body of the device should have sufficient strength to resist torsional forces. For this purpose, the body may be formed with, for example, an inner layer, e.g. a collagen film, or longitudinal, transverse or helical ribs. Ribs may be provided that subdivide the reservoir into compartments, and to provide additional stability.

As indicated above, VEGF proteins or nucleic acids may be used for the treatment or prevention of intimal hyperplasia arising from any clinical circumstances. For example, it is possible to treat hyperplasia arising after any type of surgical procedure, including angioplasty, for example balloon angioplasty; bypass surgery, such as coronary bypass surgery in which a vein is anastomosed to an artery; other anastomosis procedures, for example anastomosis in the legs; and endarteriectomy, for example carotid artery endarteriectomy. It is also possible to treat intimal hyperplasia associated with arterial damage or hypertension, for example pulmonary artery hypertension. The invention provides for treatment of intimal hyperplasia in any type of blood vessel, e.g. in an artery or vein, preferably an artery.

According to the invention, it is possible to treat or ameliorate established intimal hyperplasia or to prevent intimal hyperplasia from arising. Similarly, it is possible to diminish the likelihood of intimal hyperplasia arising, or to diminish the severity of established intimal hyperlasia or hyperplasia that is likely to arise. Treatment according to the invention may take place before, during, or after a surgical procedure, for example in order to reduce the chance of hyperplasia arising after the procedure.

Preferably, the VEGF nucleic acid or protein is administered with a view to preventing or treating *de novo* stenosis. It can, however, also be used to treat or prevent restenosis.

The proteins or nucleic acids of the invention are preferably delivered in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier. Any suitable pharmaceutical formulation may be used.

For example, suitable formulations may include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, bactericidal antibiotics and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a frozen or freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use.

It should be understood that, in addition to the ingredients particularly mentioned above, formulations of this invention may include other agents conventional in the art

having regard to the type of formulation in question. Of the possible formulations, sterile pyrogen-free aqueous and non-aqueous solutions are preferred.

The proteins, nucleic acids and vectors may be delivered in any suitable dosage, and using any suitable dosage regime. Those of skill in the art will appreciate that the dosage amount and regime may be adapted to ensure optimal treatment of the particular condition to be treated, depending on numerous factors. Some such factors may be the age, sex and clinical condition of the subject to be treated.

For the delivery of naked nucleic acids encoding VEGF or constructs comprising such nucleic acids, typical doses are from 0.1-5000 μg, for example 50-2000 μg, such as 50-100 μg, 100-500 μg or 500-2000 μg per dose. For the delivery of VEGF protein, suitable doses include doses of from 1 to 1000 μg for example from 1 to 10 μg, from 10 to 100 μg, from 100 to 500 μg or from 500 to 1000 μg.

One embodiment of the invention involves the perivascular delivery of liposomally-associated human $VEGF_{165}$ gene to the popliteal artery of patients with severe peripheral vascular disease undergoing above-knee amputation. This may comprise placing a perivascular gene delivery system in the form of a wrap in position around the popliteal artery and sealing with tissue glue.

The agents to be administered, e.g. an aqueous solution of gene polasmid/liposome complexes, is delivered locally to the target tissue by soaking a strip of collagen sheet with the solution immediately before it is applied to the popliteal artery.

The collagen wrap is a strip cut from surgical collagen sheet of 25 mm long and 4-5 mm wide. It is saturated with 2.0 ml of solution of the agent, containing the dose of gene plasmid, and then wrapped around a 25 mm long segment of the popliteal artery. It is then covered completely with two layers of surgical sealant.

CLAIMS

1. A product comprising:

a biodegradable matrix material in a form that can be wrapped around a body part;

an agent that can be delivered to treat a condition *via* the adventitial surface of a body part, the agent being in a form that can be taken up by the matrix material; and

a sealant;

for combined use in the treatment of the condition, by using the sealant to form a seal around the matrix material when impregnated with the agent.

2. A product according to claim 1, wherein the matrix material is impregnated with the agent.

3. A product according to claim 1, wherein the matrix material and the agent are separate.

4. A product according to any preceding claim, wherein the sealant is a glue.

5. A product according to any preceding claim, wherein the matrix material is associated with a cover layer that is at least relatively impermeable.

6. A product comprising:

a two-layer combination of a biodegradable matrix material and a biodegradable cover layer that is at least relatively impermeable, in a form that can be wrapped around a body part; and

an agent as defined in claim 1;

for combined use in the treatment of the condition.

7. A product comprising a two-layer combination as defined in claim 6, wherein the matrix material is impregnated with an agent as defined in claim 1.

8. A product comprising, aseptically packaged, a biodegradable matrix material as defined in claim 1, impregnated with an agent as defined in claim 1.

9. A product according to any preceding claim, wherein the matrix material and any associated cover layer are in the form of a flexible strip.

10. A product according to any preceding claim, wherein the matrix material and optionally also any associated cover layer comprise collagen.

11. A product according to any preceding claim, wherein the matrix material and any associated cover layer are aseptically packaged.

12. A product according to any preceding claim, wherein the body part is conducting.

13. A product according to claim 12, wherein the body part is a nerve or blood vessel.

14. A product according to any preceding claim, wherein the agent stimulates NO or prostacyclin production.

15. A product according to claim 14, for the treatment or prevention of stenosis induced by a surgical procedure or associated with pulmonary artery hypertension.

16. A product according to claim 15, wherein the surgical procedure is angioplasty, coronary bypass surgery, surgical anastomosis or endarteriectomy.

17. A product according to any of claims 14 to 16, for the treatment or prevention of stenosis or restenosis of the blood vessel.

18. A product according to any of claims 14 to 17, wherein the agent is a nitric oxide synthase, an agonist of a receptor to which VEGF binds, or a nucleic acid encoding the synthase or agonist.

19. A product according to any of claims 14 to 18, wherein the agent is a protein having the function of human VEGF, or a nucleic acid encoding the protein.

20. A product according to any preceding claim, wherein the agent is a nucleic acid in association with a viral or non-viral vector.

21. A product according to claim 14, for the treatment of hypertension, e.g. essential hypertension, primary pulmonary hypertension or cor pulmonale.

22. A method for applying a therapeutic agent to an elongate, internal part of a patient's body, which comprises surgical exposure of the body part; application, around the part, of an outer layer; introduction of a pharmaceutical formulation containing the agent into the volume defined between the outer layer and the outer surface of the body part; and closure of the surgical wound.

23. A method for applying a therapeutic agent to an elongate, internal part of a patient's body, which comprises surgical exposure of the body part; application, around the part, of a strip of a matrix material including the agent; covering the matrix material with an outer, sealing layer; and closure of the surgical wound.

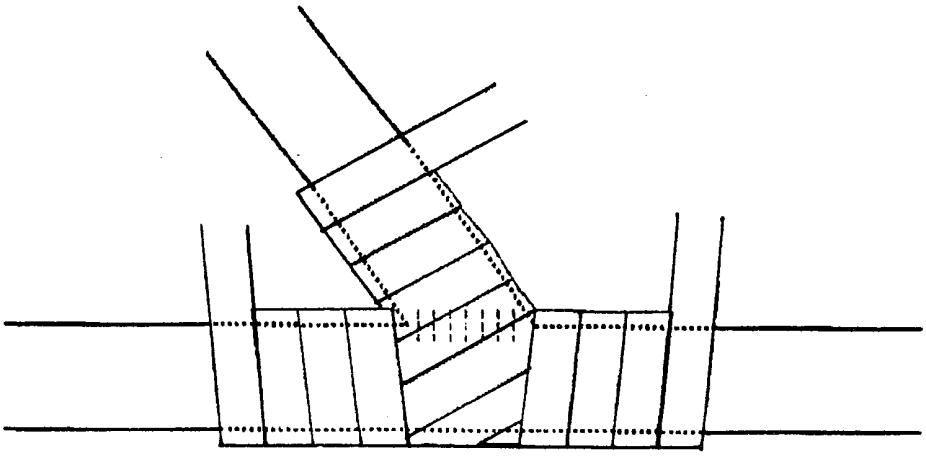

FIGURE 1

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 99/01310

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70 A61K38/44 A61K38/19

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 6 A61K A61L

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SONG C X ET AL: "Controlled release of U-86983 from double-layer biodegradable matrices: effect of additives on release mechanism and kinetics" JOURNAL OF CONTROLLED RELEASE, vol. 45, no. 2, 17 March 1997 (1997-03-17), page 177-192 XP004099366 ISSN: 0168-3659 page 178, "Introduction" page 179, paragraph 3.2 page 14, paragraph 4.6 --- -/--	1,2,5-7, 9,12,13

[X] Further documents are listed in the continuation of box C.

[X] 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

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"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

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"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
29 July 1999	05/08/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

In. :tional Application No
PCT/GB 99/01310

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	VILLA A E ET AL: "LOCAL DELIVERY OF DEXAMETHASONE FOR PREVENTION OF NEOINTIMAL PROLIFERATION IN A RAT MODEL OF BALLOON ANGIOPLASTY" JOURNAL OF CLINICAL INVESTIGATION, vol. 93, no. 3, 1 March 1994 (1994-03-01), pages 1243-1249, XP002043082 ISSN: 0021-9738 abstract pages 1243-4, section "methods" ---	1,2,12, 13,22,23
P,X	WO 98 20027 A (YLAE HERTTUALA SEPPO ;MARTIN JOHN FRANCIS (GB); BARKER STEPHEN GEO) 14 May 1998 (1998-05-14) cited in the application page 1, line 3-7 claims figures page 16, line 1 - page 18, line 5 page 20, line 17 - page 21, line 7 page 25, line 6-21 ---	1-22
X	US 3 797 485 A (URQUHART J) 19 March 1974 (1974-03-19) cited in the application column 1, line 5-17 column 3, line 51-61 column 7, line 22-26 column 9, line 40 - column 10, line 42 examples 8,10 ---	1,4
A	WO 96 38188 A (MASSACHUSETTS INST TECHNOLOGY) 5 December 1996 (1996-12-05) page 4, line 14-24 page 6, line 21-26 page 7, line 1-29 page 9, line 3-9 claims -----	1,2,9, 10,12-17

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01310

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:

Remark: Although claim(s) 22 and 23 is(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

Int tional Application No
PCT/GB 99/01310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820027 A	14-05-1998	AU 4790697 A	29-05-1998
US 3797485 A	19-03-1974	NONE	
WO 9638188 A	05-12-1996	US 5766584 A	16-06-1998
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