YQ.F.

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

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SOLICITUD

PATENTE DE INVENCION

21. **EXPEDIENTE No.** 04-109920

54. **TITULO** COMPOSICION VETERINARIA PARA ANIMALES PEQUEÑOS

51. **CLASIFICACION INTERNACIONAL**

71. **SOLICITANTE** NORBROOK LABORATORIES LIMITED

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C.C. 438.019 de Usaquén

22. **BOGOTA, D.C.,**

(FORMA P-10)

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FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **NORBROOK LABORATORIES LIMITED**
sociedad constituida y existente bajo las leyes del Reino Unido.

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Domicilio: Newry, County Down BT35 6JP,
Reino Unido

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

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Número 438.019 T.P 31.929

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5 PCT (86)

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6 Título (54)

COMPOSICIÓN VETERINARIA PARA ANIMALES PEQUEÑOS

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SI☒ NO☐	GB	2 de Abril de 2002	0207529.9

9 Comprobante de pago No.: 04-85.331 **Fecha:** Noviembre 2/2004

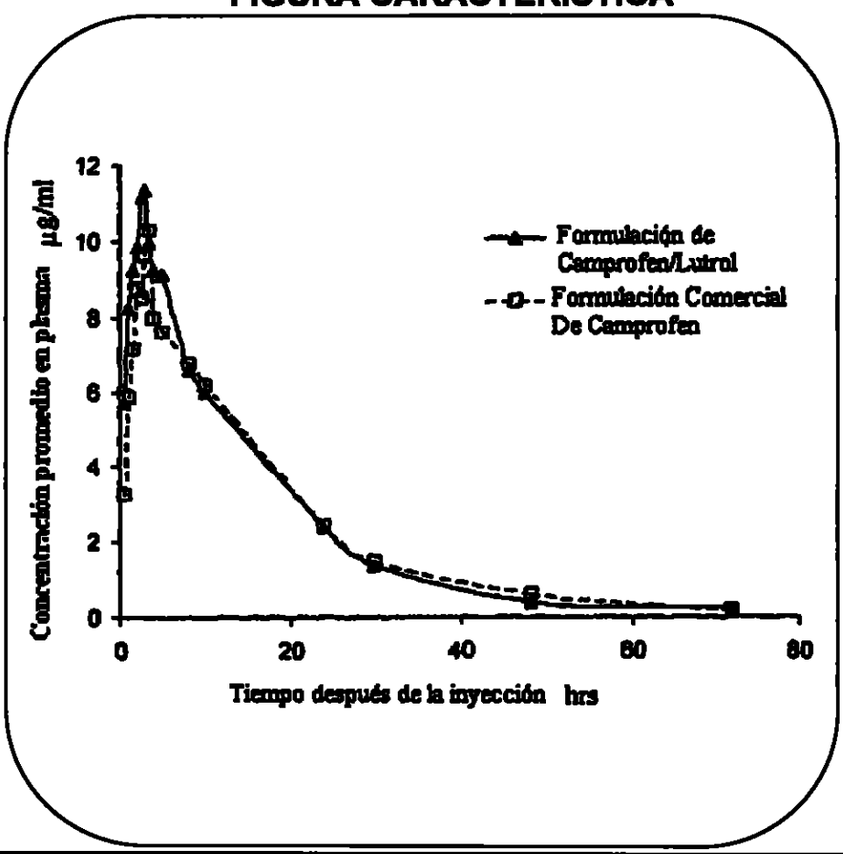
10

Anex s:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 422.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [x] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] Otros

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

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(71) Applicant *(for all designated States except US)*: NORBROOK LABORATORIES LIMITED [GB/GB]; Station Works, Newry, County Down BT35 6JP (GB).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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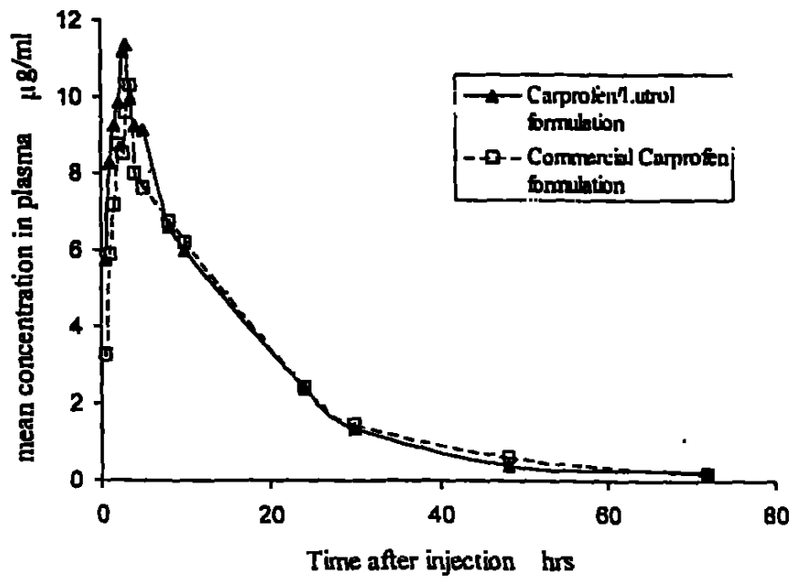
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INJECTABLE VETERINARY COMPOSITION FOR SMALL ANIMALS



(57) Abstract: An injectable aqueous composition for veterinary use containing a non-steroidal anti-inflammatory compound in an amount of from about 0.25 to 30% (w/v) together with a physiologically acceptable oxygenated polymeric surfactant in an amount of from about 0.5 to 20% (w/v).

WO 03/082340 A1

Injectable Veterinary Composition for Small Animals

This invention relates to the use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly the formulation of such drugs in solutions suitable for injection, especially for use in veterinary medicine for the purposes of treating small animals, such as companion animals.

Background of the Invention

Non-steroidal anti-inflammatory drugs find wide application in the treatment of inflammatory conditions and the alleviation of pain in veterinary and human medicine. Such drugs are often characterised by the presence of a carboxylic acid function or derivative thereof. Examples of such non-steroidal anti-inflammatories include carprofen, ibuprofen, ketoprofen, benoxaprofen, naproxen, sulindac, zomepirac, fenclofenac alcofenac, ibufenac, flunixin and indomethacin. The administration of such compounds parenterally can present the difficulty of local irritation and induce haemolytic side effects.

In EP-A-0 280 887, Ferro and Steffen teach the formulation of NSAIDs, by utilising salts of cholanic acid and certain lipids to form mixed micelles in aqueous systems. These compositions have reduced side effects, in comparison with conventional formulations, when administered by injection to dogs.

Objects of the Invention

It is an object of the present invention to provide novel pharmaceutical preparations of non-steroidal anti-inflammatory drugs suitable for injection. It is a further object of the invention to provide such preparations adapted for the provision of analgesia in small animals, especially companion animals.

Summary of the Invention

It has been surprisingly found that NSAIDs, preferably carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a salt thereof, most preferably carprofen in the form of its arginine or lysine salt, can be readily formulated in aqueous systems by the use of certain pharmaceutically acceptable synthetic polymer agents to the effect that the problems of local irritancy and haemolysis associated with conventional formulations of these drugs are avoided or at least greatly reduced.

understood by those skilled in the art that a useful lower range of from about 0.25% (w/v) may be employed where small volume changes in delivery volume are not significant, e.g. in treating felines with a non-steroidal anti-inflammatory compound such as carprofen.

Arginine may be present in an amount from about 1% to 20% (w/v).

The poloxamers are generally present in an amount of from about 2 to 12% (w/v). Moreover an organic solvent can be also present with the poloxamer, generally in the range of about 0.5 to 20% (w/v), in which case the poloxamers can be present in an amount from 1% to 12% (w/v).

A poloxamer generally confirms to the formula $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$, wherein x, y and z are variables which are independently and selectively controllable. The values of x, y and z are respectively whole numbers in the range 2 to 128 and represent target values which will vary slightly according to commercial sources. An example of a preferred poloxamer is $HO(CH_2CH_2O)_{75}(CCH_3HCH_2O)_{30}(CH_2CH_2)_{75}H$.

The present invention provides an aqueous injectable composition comprising carprofen or a physiologically acceptable salt thereof in an amount of from at least 0.25%, preferably 0.5% to 30% (w/v), a polymeric species selected from the group of polyoxypropylene/polyoxyethylene block co-polymers in the amount of from 0.5% to 20% (w/v), a preservative and water sufficient for injection.

According to the invention there is also provided a method of producing a room-temperature stable injectable aqueous composition for veterinary use comprising bringing together carprofen or a physiologically acceptable salt and a poloxamer, and adding sufficient water for injection. Additionally preservatives may also be included. Preferably the poloxamer is $HO(CH_2CH_2O)_{75}(CCH_3HCH_2O)_{30}(CH_2CH_2)_{75}H$.

Furthermore the invention also relates to the use of polyoxypropylene/polyoxyethylene block co-polymers for the manufacture of locally tolerable aqueous injection solutions of non-steroidal compounds.

Example 4

Carprofen 5.0% w/v

L-Arginine EP 3% w/v

Lutrol F68 (poloxamer 188, NF EP) 12% w/v

Propylene Glycol 20% w/v

Water for injection *ad* 100% w/v

Example 5

Carprofen 5.0% w/v

L-Arginine EP 3% w/v

Lutrol F68 (poloxamer 188, NF EP) 3.5% w/v

Propylene Glycol 20% w/v

Water for injection *ad* 100% w/v

Example 6

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F68 (poloxamer 188, NF EP) 5% w/v

Propylene Glycol 20% w/v

Water for injection *ad* 100% w/v

Example 7

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F68 (poloxamer 188, NF EP) 5% w/v

Water for injection *ad* 100% w/v

Example 8

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F68 (poloxamer 188, NF EP) 7% w/v

Propylene Glycol 20% w/v

Water for injection *ad* 100% w/v

Example 14

Carprofen 5.0% w/v

L-Arginine EP 3.3% w/v

Lutrol F68 (poloxamer 188, NF EP) 5% w/v

Benzyl Alcohol 1% w/v

Water for injection *ad* 100% w/v

Example 15

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F68 (poloxamer 188, NF EP) 5% w/v

Benzyl Alcohol 1% w/v

SFS 0.25% w/v

Water for injection *ad* 100% w/v

Example 16

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F68 (poloxamer 188, NF EP) 5% w/v

Benzyl Alcohol 1% w/v

SFS 0.1% w/v

Water for injection *ad* 100% w/v

Example 17

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F68 (poloxamer 188, NF EP) 5% w/v

Benzyl Alcohol 1% w/v

SFS 0.4% w/v

Water for injection *ad* 100% w/v

A comparison was made with the prior art formulation (derived from EP 0 280 887) that uses about 26% (w/v), of cholanic acid and lecithin, in a similar strength carprofen formulation. This formulation demonstrates bioequivalence to the aforesaid cholanic acid/lipid formulations but utilises only 5% (w/v) of the inventive polymeric surfactant additive. Thus compositions of the present invention can substantially reduce the burden of auxiliary ingredients injected into the subject on treatment. These formulations have also been found to have low side effects, with no injection site reactions such as swelling, hardness, softness, heat, redness or pain being observed during studies involving dogs.

A further benefit of compositions according to the invention is that of room temperature stability. A trial lot of the formulation given in the example has been studied over a period of eleven months at ambient temperatures without loss of potency being observed. The trial lot was assayed as containing 5.16% carprofen on manufacture, 5.10% after seven months, and 5.26% after eleven months, these apparent differences being accounted for by slight moisture loss. Currently available formulations typically require controlled chilled storage at 2-8 C, i.e. refrigeration, cool room, or chiller cabinet storage.

A study was undertaken with a view to evaluating the mean levels of carprofen found in dogs following the administration of a dose of approximately 4 mg/kg of a composition according to the Example in comparison with results obtained by administration of a commercially available product of comparable strength.

The results of the pharmacokinetic study are tabulated below and shown graphically in Figure 1. The Table compares the mean plasma concentrations of carprofen found in dogs after subcutaneous injection of carprofen at a dose of approximately 4mg/kg using a commercially available formulation, and using the formulation given in the Example. Statistical analysis of these results confirmed bioequivalence in accordance with European Guidelines (Volume 8 of EMEA/CVMP/016-00/Final).

CLAIMS

1. An injectable aqueous composition for veterinary use containing a non-steroidal anti-inflammatory compound in an amount of from about 0.5 to 30% (w/v) together with a physiologically acceptable oxygenated polymeric surfactant in an amount of from about 0.5 to 20% (w/v).

2. An injectable aqueous composition according to Claim 1 wherein the non-steroidal anti-inflammatory compound is selected from the group consisting of carprofen, ibuprofen, ketoprofen, benoxaprofen, naproxen, sulindac, zomepirac, fenclofenac, alcofenac, ibufenac, flunixin and indomethacin.

3. An injectable aqueous composition according to Claim 2 wherein the non-steroidal anti-inflammatory compound is carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt thereof.

4. An injectable aqueous composition according to Claim 3 wherein the carprofen salt is in the form of an arginine salt.

5. An injectable aqueous composition according to Claim 3 wherein the carprofen salt is in the form of a lysine salt.

6. An injectable aqueous composition according to any one of Claims 1 to 3 wherein the non-steroidal anti-inflammatory is present in an amount of from about 2.5 to 7.5% (w/v).

7. An injectable aqueous composition according to any one of Claims 1 to 3 wherein the non-steroidal anti-inflammatory is present in an amount of from about 2.5 to 5% (w/v).

8. An injectable aqueous composition according to any one of Claims 1-7 comprising arginine in an amount of from about 1 to 20% (w/v).

selected from the group of polyoxypropylene/polyoxyethylene block co-polymers in the amount of from 0.5% to 20% (w/v), a preservative and water sufficient for injection.

19. A method of producing a room-temperature stable injectable aqueous composition for veterinary use comprising bringing together an effective amount of carprofen or a physiologically acceptable salt thereof and a poloxamer, and adding sufficient water for injection.

20. A method according to Claim 19 wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is about 75, y is about 30 and z is about 75.

21. A method of producing an injectable aqueous composition according to Claims 19 or 20 wherein said method further comprises the inclusion of a preservative.

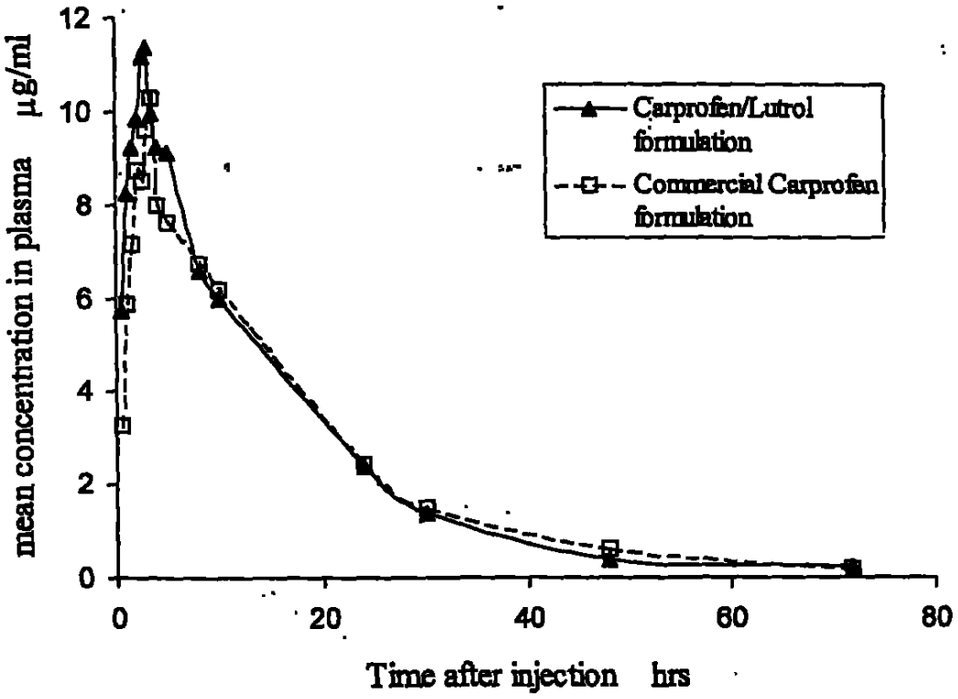
22. An injectable aqueous composition for veterinary use according to any one of the Examples 1 to 19 hereinbefore.

23. A method of producing an injectable aqueous composition substantially as described in the Example 1.

24. The use of polyoxypropylene/polyoxyethylene block co-polymers for the manufacture of locally tolerable aqueous injection solutions of non-steroidal compounds.

12

Figure 1


mean concentration in plasma µg/ml
12
10
8
6
4
2
0
0
20
40
60
80
Time after injection hrs
Carprofen/Lutrol formulation
Commercial Carprofen formulation

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/01404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/10

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)
WPI Data, PAJ, EPO-Internal, 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.
X Y	EP 0 955 063 A (BASF AKTIENGESELLSCHAFT) 10 November 1999 (1999-11-10) claims 1,3 page 2, line 46 - line 48 page 4, line 16 - line 32 page 5; examples 15,16	1,2,6,7, 9-15, 22-24 3-5,8, 16-20
X	US 5 283 067 A (LEO GELLER; ET AL.) 1 February 1994 (1994-02-01) claim 1 column 2, line 65 -column 3, line 11 column 5; example 4	1,6,7, 9-11, 22-24

-/--

[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

"E" earlier document 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
2 September 2003	10/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 03/01404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 955063 A	10-11-1999	EP 0955063 A1	10-11-1999
US 5283067 A	01-02-1994	CH 673395 A5	15-03-1990
		AT 18588 A ,B	15-09-1993
		AU 612343 B2	11-07-1991
		AU 1110288 A	04-08-1988
		BE 1000442 A4	06-12-1988
		CA 1305058 C	14-07-1992
		DE 3802357 A1	11-08-1988
		DK 45588 A	31-07-1988
		ES 2008420 A6	16-07-1989
		FI 880368 A	31-07-1988
		FR 2611498 A1	09-09-1988
		GB 2201089 A ,B	24-08-1988
		GR 88100041 A	16-12-1988
		IE 60453 B1	13-07-1994
		IT 1224241 B	26-09-1990
		JP 63192716 A	10-08-1988
		LU 87115 A1	08-03-1989
		NL 8800231 A	16-08-1988
		NO 880403 A	01-08-1988
		NZ 223343 A	27-03-1990
		PH 23652 A	27-09-1989
		PT 86644 A ,B	01-02-1988
		SE 8800228 A	31-07-1988
		YU 15488 A1	31-10-1989
		ZA 8800638 A	25-10-1989
CH 663788 A	15-01-1988	CH 663788 A5	15-01-1988

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
32/64087WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 03/ 01404	31/03/2003	02/04/2002

Applicant

NORBROOK LABORATORIES LIMITED

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 03/01404

16

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 955063	A	10-11-1999	EP	0955063 A1	10-11-1999
US 5283067	A	01-02-1994	CH	673395 A5	15-03-1990
			AT	18588 A ,B	15-09-1993
			AU	612343 B2	11-07-1991
			AU	1110288 A	04-08-1988
			BE	1000442 A4	06-12-1988
			CA	1305058 C	14-07-1992
			DE	3802357 A1	11-08-1988
			DK	45588 A	31-07-1988
			ES	2008420 A6	16-07-1989
			FI	880368 A	31-07-1988
			FR	2611498 A1	09-09-1988
			GB	2201089 A ,B	24-08-1988
			GR	88100041 A	16-12-1988
			IE	60453 B1	13-07-1994
			IT	1224241 B	26-09-1990
			JP	63192716 A	10-08-1988
			LU	87115 A1	08-03-1989
			NL	8800231 A	16-08-1988
			NO	880403 A	01-08-1988
			NZ	223343 A	27-03-1990
			PH	23652 A	27-09-1989
			PT	86644 A ,B	01-02-1988
			SE	8800228 A	31-07-1988
			YU	15488 A1	31-10-1989
			ZA	8800638 A	25-10-1989
CH 663788	A	15-01-1988	CH	663788 A5	15-01-1988

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/01404

12

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CH 663 788 A (F. HOFFMANN-LA ROCHE & CO.) 15 January 1988 (1988-01-15) claims 1,2 page 2, left-hand column, line 30 - line 34 page 2, right-hand column, line 29 - line 36 page 3, right-hand column; example 4D	3-5,8, 16-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

6

18

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 32/64087WO

Box No. I TITLE OF INVENTION

Injectable Veterinary Composition for Small Animals

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Norbrook Laboratories Limited
Station Works
Newry
BT35 6JP
County Down, Northern Ireland

Telephone No. 028 302 64435

Facsimile No. 028 302 61721

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BLAKELY, William
79 Chapel Road
Killeavy, Newry
County Down BT35 8JZ
Northern Ireland

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Fitzpatricks
4 West Regent Street
Glasgow
G2 1RS
United Kingdom

Telephone No. 0141 306 9000

Facsimile No. 0141 306 9090

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

19

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CROMIE, Lillian
65 Old Warrenpoint Road
Newry, County Down
BT34 2PN
Northern Ireland

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

This person is applicant for the purposes of:
☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DUFFY, Sean
3 New Road
Silverbridge
Newry, County Down
BT35 9PG, Northern Ireland

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

This person is applicant for the purposes of:
☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GM Gambia	☒ NZ New Zealand
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman
☒ AL Albania	☒ HU Hungary	☒ PH Philippines
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland
☒ AT Austria	☒ IL Israel	☒ PT Portugal
☒ AU Australia	☒ IN India	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ JP Japan	
☒ BB Barbados	☒ KE Kenya	☒ SC Seychelles
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SD Sudan
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SE Sweden
☒ BY Belarus		☒ SG Singapore
☒ BZ Belize	☒ KR Republic of Korea	☒ SK Slovakia
☒ CA Canada	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CN China	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CO Colombia	☒ LR Liberia	☒ TN Tunisia
☒ CR Costa Rica	☒ LS Lesotho	☒ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LU Luxembourg	
☒ DE Germany	☒ LV Latvia	☒ TZ United Republic of Tanzania
☒ DK Denmark	☒ MA Morocco	☒ UA Ukraine
☒ DM Dominica	☒ MD Republic of Moldova	☒ UG Uganda
☒ DZ Algeria		☒ US United States of America
☒ EC Ecuador	☒ MG Madagascar	
☒ EE Estonia	☒ MK The former Yugoslav Republic of Macedonia	☒ UZ Uzbekistan
☒ ES Spain		☒ VC Saint Vincent and the Grenadines
☒ FI Finland	☒ MN Mongolia	☒ VN Viet Nam
☒ GB United Kingdom	☒ MW Malawi	☒ YU Yugoslavia
☒ GD Grenada	☒ MX Mexico	☒ ZA South Africa
☒ GE Georgia	☒ MZ Mozambique	☒ ZM Zambia
☒ GH Ghana	☒ NO Norway	☒ ZW Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ NI Nicaragua	☐	☐
☐	☐	☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 02/04/02 02 April 2002	0207529.9	United Kingdom		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the International search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / European Patent Office

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐	Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	

Sheet No. 5

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets)	:	5
description (excluding sequence listings and/or tables related thereto)	:	10
claims	:	3
abstract	:	1
drawings	:	1
Sub-total number of sheets	:	20
sequence listings	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form: see (c) below)		
Total number of sheets	:	20

(b) ☐ only in computer readable form (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*: — Number of items

1. ☐ fee calculation sheet :
2. ☐ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☐ copy of general power of attorney; reference number, if any: ..... :
5. ☐ statement explaining lack of signature :
6. ☐ priority document(s) identified in Box No. VI as item(s): ..... :
7. ☐ translation of international application into *(language)*: ..... :
8. ☐ separate indications concerning deposited microorganism or other biological material :
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :
   - (ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :
   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*
    - (i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application) :
    - (ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*) :
    - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :
11. ☒ other *(specify)*: Patents Form 23/77 ..... : 1

Figure of the drawings which should accompany the abstract: 1	**Language of filing of the international application:** English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Eric Ede
for Fitzpatricks
(Agent for the Applicant) Date: 28 March 2003

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

23

From the RECEIVING OFFICE

To:
Fitzpatricks
4 West Regent Street
Glasgow

G2 1RS

6N
EE

DP 10/04/03

PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing (day/month/year)	09 APR 2003

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
32/64087WO	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2003/001404	31/03/2003	02/04/2002

Applicant
Norbrook Laboratories Limited et al

Title of the invention
Injectable Veterinary Composition for Small Animals

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

☒ was transmitted to the International Bureau on 8 April 2003

☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

☐ because the necessary national security clearance has not yet been obtained.

☐ because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office	Authorized officer
The Patent Office Cardiff Road, Newport South Wales NP10 8QQ	Phil Jones
Facsimile No.	Telephone No. 01633 814930

Form PCT/RO/105 (July 1992)

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/_____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 32/43/64087WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB03/01404	31 March 2003 (31/03/03)	2 April 2002 (02/04/02)

Title of invention: Injectable Veterinary Composition for Small Animals

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Norbrook Laboratories Limited
Station Works
Newry
BT35 6JP
County Down, Northern Ireland

Telephone No.: 028 302 64435
Facsimile No.: 028 302 61721
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality: United Kingdom
State *(that is, country)* of residence: United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BLAKELY, William
79 Chapel Road
Killeavy, Newry
County Down BT35 8JZ
Northern Ireland

State *(that is, country)* of nationality: United Kingdom
State *(that is, country)* of residence: United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CROMIE, Lillian
65 Old Warrenpoint Road
Newry, County Down
BT34 2PN
Northern Ireland

State *(that is, country)* of nationality: United Kingdom
State *(that is, country)* of residence: United Kingdom

☐ Further applicants are indicated on a continuation sheet.

Sheet No. 2.

International application No.
PCT/GB03/01404

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DUFFY, Sean
3 New Road
Silverbridge
Newry, County Down
BT35 9PG
Northern Ireland

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
United Kingdom	United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/GB03/01404

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Fitzpatricks
4 West Regent Street
Glasgow G2 1RS
United Kingdom

Telephone No.
+141 306 9000

Facsimile No.
+141 306 9090

Teleprinter No.

Agent's registration No. with the Office

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description
[X] as originally filed
[ ] as amended under Article 34

the claims
[X] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings
[X] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Sheet No. 4.

International application No.
PCT/GB03/01404

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	1 sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Eric Ede
for FITZPATRICKS
(Agents for the Applicants)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

The International Bureau of WIPO
34 chemin des Colombettes
PO Box 18
Geneva 20
CH-1211
SWITZERLAND

VIA FACSIMILE - 5 PAGES
FAX NO. 0041 22 733 5428
CONFIRMATION BY MAIL

Our Reference	Your Reference	Date
32/64087WO		10 November 2003

Dear Sirs

International (PCT) Patent Application No. PCT/GB03/01404
Injectable Veterinary Composition for Small Animals
in the name of Norbrook Laboratories Limited

We refer to the communication dated 10th September 2003 notifying the applicant of the outcome of the International Search.

Please find enclosed herewith amended claims 1-21 to replace those currently on file. The claims have been amended to restrict them to a physiologically active salt of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) and a poloxamer wherein said injectable aqueous composition is stable at room temperature. Where originally there were 24 claims after amendment there are now 21. Claim 1 was amended and claims 2 and 3 were cancelled to be replaced by new claim 2 and previous claim 14 became new claim 3. Claims 6, 7, 9, 17 have been amended in line with claim 1 above. Claims 10, 14 (now 3) and 24 were cancelled. All other claims were renumbered and their dependencies amended where necessary to take account of the cancelled claims.

EP0955063 (D1) describes the use of an aqueous composition for subcutaneously or intramuscularly administering drug formulations. The composition comprises a combination of a polyoxyethylene-polyoxypropylene (Copolymer (A)) with a weight average molecular weight of 8000 to 20000; and a polyoxyethylene-polyoxypropylene (Copolymer (B)) with a weight average molecular weight of 4000 to 8000. The composition is described as being useful for the subcutaneous or intramuscular administration of various agents with the advantage being stated that the composition is liquid at room temperature but when administered forms a depot gel, allowing controlled release of the pharmaceutical compounds.

D1 also states that the use of poloxamer is well known to be useful in the manufacture of pharmaceutical preparations but these compounds in solution may also be stabilised by the presence [illegible] see page 2

lines 46 to 48 of D1. In summary D1 teaches the combined use of both Copolymer A and Copolymer B for the production of improved pharmaceutical preparations with sol-gel transitional properties, in relation to temperature dependent viscosity and penetration resistance, page 4 lines 16 to 18, examples 1 to 16 and figures 1-4 of D1.

The amended claims set enclosed herewith is both novel and inventive over D1, as D1 does not refer to any advantage of increased room temperature stability of a sol-gel type of pharmaceutical preparation by the inclusion of poloxamers in the disclosed manner. The only reference in D1 to temperature is that the sol-gel transitional temperature is between 20 and 40°C, which facilitates sustained release of the drug being administered at body temperature, see page 5 lines 54 to 57.

US5283067 (D2) describes a dry formulation obtainable by lyophilisation, which is suitable for the preparation of a stable, aqueous suspension for the parenteral administration of a diclofenac salt. The dry formulation contains a pharmaceutically acceptable and micronised salt of diclofenac and optional pharmaceutically acceptable adjuvants. It also indicates that poloxamers are useful wetting agents or surfactants for the re-suspension of lyophilised diclofenac based pharmaceutical preparations for parenteral or intramuscular injection, see column 2 line 65 to column 3 line 11. Lyophilisation of such preparations allows for storage of these preparations at room temperature. When required for use are they re-suspended in the desired buffer.

The amended claims set enclosed herewith is both novel and inventive over D2 as D2 does not refer to poloxamers as being useful for the long-term stabilisation of pharmaceutical preparations at room temperature, nor does it refer to poloxamers as being useful in the reduction of inflammation upon injection of Carprofen or any other NSAID.

Finally CH663788 (D3) describes new salts of carprofen namely 6-chloro-α-methylcarbazol-2 acid with a basic α-amino acid, either L-Lysine or L-Arginine, but preferably L-Lysine. The advantages of the salts described in this document are indicated as being that NSAID is rendered more soluble and suitable for parenteral administration (Claims 1 to 6 and page 2 lines 41 to 48) as well as having 40% more bio-availability in blood plasma when compared to injection of Carprofen alone in solution, page 2 lines 10 to 16. D3 comments on the suitability of carrier molecules like gelatine, starch, magnesium stereate and polyalkylene glycols for facilitating the administration of the NSAID in a pharmaceutical preparation, page 2, column 2 and lines 29 to 36. It also teaches use of a poloxamer as a suppository base for the administration of Carprofen-Lysitiate.

However, importantly D3 neither describes nor teaches in any way, the usefulness of poloxamers in solution and how they might increase the room temperature stability of pharmaceutical preparations containing Carprofen or salts thereof. Thus again the amended claims set is both novel and inventive over the teachings of D3.

Accordingly we believe that the enclosed amended claims1-21 are both novel and inventive over all the cited art either alone or in combination.

Yours faithfully
FITZPATRICKS

Enc: Claims 1 to 21

Amendment under Article 19(1) PCT

CLAIMS

1. An injectable aqueous composition for veterinary use containing a physiologically active salt of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) in an amount of from about 0.5 to 30% (w/v) together with a poloxamer in an amount of from about 0.5 to 20% (w/v) and said injectable aqueous composition being stable at room temperature.

2. An injectable aqueous composition according to Claim 1 wherein said composition is room temperature stable for a minimum of 11 months.

3. An injectable aqueous composition according to Claims 1 or 2 wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH2CH2)_zH$ wherein x is about 75, y is about 30 and z is about 75 or x is 98, y is 67 and z is 98.

4. An injectable aqueous composition according to Claim 1 wherein the carprofen salt is in the form of an arginine salt.

5. An injectable aqueous composition according to Claim 1 wherein the carprofen salt is in the form of a lysine salt.

6. An injectable aqueous composition according to any one of Claims 1 to 5 wherein the carprofen is present in an amount of from about 2.5 to 7.5% (w/v).

7. An injectable aqueous composition according to any one of Claims 1 to 5 wherein the carprofen is present in an amount of from about 2.5 to 5% (w/v).

8. An injectable aqueous composition according to any one of Claims 1-7 comprising arginine in an amount of from about 1 to 20% (w/v).

9. An injectable aqueous composition for veterinary use containing a physiologically active salt of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid).

in an amount of from at least about 0.25% (w/v) together with a poloxmer in an amount from about 0.5 to 20% (w/v).

10. An injectable aqueous composition according to Claim 9 wherein the poloxamers are present in an amount of from about 2 to 12% (w/v).

11. An injectable aqueous composition according to Claim 9 wherein an organic solvent is present with the poloxamer.

12. An injectable aqueous composition according to Claim 11 wherein the organic solvent is present in the range of 0.5 to 20% (w/v).

13. An injectable aqueous composition according to Claims 11 or 12 wherein the poloxamers are present in an amount of from 1% to 12% (w/v).

14. An injectable aqueous composition for veterinary use containing from about 0.25% to 30% (w/v) of carprofen arginine salt together with a poloxamer in an amount from about 0.5 to 20% (w/v).

15. An injectable aqueous composition for veterinary use according to claim 14 comprising arginine in an amount of from 1 to 20% (w/v).

16. An aqueous injectable composition comprising carprofen or a physiologically acceptable salt thereof in an amount of from 0.25% to 30% (w/v), a polymeric species selected from the group of polyoxypropylene/polyoxyethylene block co-polymers in the amount of from 0.5% to 20% (w/v), a preservative and water sufficient for injection.

17. A method of producing a room-temperature stable injectable aqueous composition for veterinary use comprising bringing together an effective amount of carprofen or a physiologically acceptable salt thereof and a poloxamer, and adding sufficient water for injection.

18. A method according to Claim 17 wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is about 75, y is about 30 and z is about 75.

19. A method of producing an injectable aqueous composition according to Claims 17 or 18 wherein said method further comprises the inclusion of a preservative.

20. An injectable aqueous composition for veterinary use according to any one of the Examples 1 to 19 hereinbefore.

21. A method of producing an injectable aqueous composition substantially as described in the Example 1.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
GRANDE BRETAGNE

13 NOV 2003 INTL

FF

Registered letter

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing (day/month/year)	10-11-2003
Applicant's or agent's file reference: 32/43/64087WO	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB 03/01404	31/03/2003	02/04/2002

Applicant

NORBROOK LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

31/10/2003

2. This date of receipt is:

- [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] ***(If applicable)*** This notification confirms the information given by telephone, facsimile transmission or in person on:

_____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	[illegible] Tel. (+49-89) 2399-8139

Form PCT/IPEA/402 (July 1998) P20452 (05/11/2003)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING THE FILING OF AMENDMENTS OF THE CLAIMS

(PCT Administrative Instructions, Section 417)

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
United Kingdom

Date of mailing (day/month/year) 13 November 2003 (13.11.03)	
Applicant's or agent's file reference 32/64087WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB03/01404	**International filing date (day/month/year)** 31 March 2003 (31.03.03)
Applicant NORBROOK LABORATORIES LIMITED et al	

1. The applicant is hereby notified that amendments to the claims under Article 19 were received by the International Bureau on:

   10 November 2003 (10.11.03)

2. This date is within the time limit under Rule 46.1.

   Consequently, the international publication of the international application will contain the amended claims according to Rule 48.2(f), (h) and (i).

3. The applicant is reminded that the international application (description, claims and drawings) may be amended during the international preliminary examination under Chapter II, according to Article 34, and in any case, before each of the designated Offices, according to Article 28 and Rule 52, or before each of the elected Offices, according to Article 41 and Rule 78.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 338.87.40

Authorised officer

Carine SEVILANO

Telephone No. (41-22) 338 8264

35

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
GRANDE BRETAGNE

FF

OP 16/01

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	13/01/2004
Applicant's or agent's file reference: 32/43/64087WO	REPLY DUE: within 1 / 00 months/days from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB03/01404	31/03/2003	02/04/2002

International Patent Classification (IPC) or both national classification and IPC

A61K47/10

Applicant

NORBROOK LABORATORIES LIMITED et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02/08/2004

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828

I. Basis of the opinion

1. The basis of this written opinion is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references).

2. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

PATENT COOPERATION TREATY

FITZPATRICK 32
2004 JAN 14 INTL
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ACKD 19 29/01

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
United Kingdom

Date of mailing (day/month/year) 13 January 2004 (13.01.2004)	
Applicant's or agent's file reference 32/64087WO	**IMPORTANT INFORMATION**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2003/001404	31 March 2003 (31.03.2003)	02 April 2002 (02.04.2002)

Applicant
NORBROOK LABORATORIES LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PT,RO,SE,
   SI,SK,TR
   National :BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,
   EE,ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,
   MG,MK,MW,MX,MZ,NI,NZ,OM,PH,PT,SC,SD,SE,SG,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,
   VC,VN,YU,ZA,ZM,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 38(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer:

Telephone No. (41-22) 338 9254

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
GRANDE BRETAGNE

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	16.03.2004
Applicant's or agent's file reference: 32/64087/00	REPLY DUE: within 2 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/01404	31.03.2003	02.04.2002

International Patent Classification (IPC) or both national classification and IPC
A61K47/10, A61K47/10

Applicant
NORBROOK LABORATORIES LIMITED et al.

1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is:

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Formalities officer (incl. extension of time limits)
Hutterer, G
Telephone No. +49 89 2399-8066

I. **Basis of the opinion**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-21 filed with telefax on 22.01.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-21

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-21 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 1-21 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-21
Industrial applicability (IA)	Claims	

2. Citations and explanations

   see separate sheet

SECTION III .....

1. According to the wording of Article 6 PCT the **claims** shall define the matter for which protection is sought, they must be clear and concise and shall be fully supported by the description.

   Independent product claims 1, 9, 14, 16 and 20 as well as independent method claims 17 and 21 do not meet the requirements of Article 6 PCT with respect to conciseness.

   Although the above claims have been drafted as separate independent claims, they appear to relate effectively within each category to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness.

   Moreover, lack of clarity of the claims as a whole arises by such a wording of claims, since the plurality of independent claims in each category makes it difficult to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

2. Furthermore, an objection could also be based on Article 5 in combination with Article 6 PCT in that respect that the applicant, whilst claiming all ways of achieving the desired result of the claimed subject-matters has provided support and disclosure for only a small number of definite ways, eg claiming a product comprising carprofen in almost any concentration (see present claim 9) and any poloxamer whilst showing in the Examples only embodiments comprising carprofen in one concentration and applying only Lutrol^{R} F68 as the poloxamer. Which means that the subject-matter is neither supported nor disclosed over its whole breadth.

SECTION V. .....

A preliminary evaluation of the requirements of Article 33 PCT is possible despite the deficiencies as mentioned under SECTION III., above.

1. Reference is made to the following documents:

D1: EP-A-0 955 063
D2: CH-A-663 788
D3: US-A-5 283 067

2. The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matters of the independent product claims 1, 9, 14, 16 and 20; and independent method claims 17 and 21 do not involve an inventive step (Rule 65(1)(2) PCT).

The presently claimed product, ie the aqueous composition comprises in certain amounts

- carprofen

and

- a poloxamer.

Such products differ from products disclosed in eg D1 only by the fact that the compound carprofen has not explicitly been mentioned. However, D1 clearly stated that anti-inflammatory compounds can advantageously be used in combination with poloxamers to arrive at products solving to same problem, ie the provision of injectable aqueous compositions, as presently defined. Carprofen is well known to the person skilled in the art as being such a compound and its substitution in the products according to D1 must be considered obvious, this the more, as eg D2 suggests its usability for anti-inflammatory purposes. The person skilled in the art gets furthermore the information from D3 that injectable aqueous compositions comprising poloxamers and anti-inflammatory agents can successfully be prepared to solve exactly the same problem. The claimed subject-matter lacks therefore an inventive step.

It is noted that the Comparative Examples as presented in the description on page 8, fall under the wording of present independent product claims.

Essentially, the dependent claims specify certain carprofen salts which are known from D2, or define the poloxamer which can be taken from eg D1, and indicate that further components can be present. To arrive at these embodiments the person skilled in the art can take corresponding information from D1, thus any inventive step must also be denied for the dependent claims.

3. The amendments filed with the International Bureau under Article 19(1) [illegible]

probably subject-matter which extends beyond the content of the application as filed, contrary to Article 19(2) PCT. Neither the functional statement relating to claim 2 nor the x/y/z values of 98/67/98 as defined in claims 3 and 18 could not be found in the originally filed documents.

4. Claims 20 and 21 comprise references to the description, ie to Examples. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

5. Taking into account the above, it is not at present apparent which part of the application could serve as a basis for a new claim which would satisfy the criteria set forth in Article 33(1) PCT. Should the applicant nevertheless regard some particular matter as suitable an independent claim including such particular matter should be filed taking account of Rule 6.3(b) PCT. The applicant should also indicate in the letter of reply the difference vis-à-vis the state of the art and the significance thereof.

In order to expedite the proceedings relating to the present application it is however considered necessary to determine whether the requirements of inventive step are satisfied in the light of the cited documents D1 - D3 and the general knowledge of the person skilled in the art. Reference is made to the PCT Preliminary Examination Guidelines, Chapter IV, item 8 (particularly with respect to the evaluation of an inventive step).

It should be noted that any argument given with respect to an inventive step can only be considered if reflected by technical features in the wording of the independent claim(s).

Functional features in a product claim are not suited to replace technical features in order to establish improved capabilities of the product per se. If a subject-matter shows different properties or different capabilities then such effects must be attributable to some specific technical features which have not been considered in the prior art.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the [illegible]

the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

The applicant is requested to file amendments by way of replacement pages. He should also take into account the requirements of Rule 66.8 PCT.

Possibly, a specific new embodiment of subject-matter already disclosed might provide unexpected advantages or surprising effects over the pertinent prior art. If so, the applicant should give convincing arguments or should furnish evidence, most preferably by filing test results as a comparison with the closest prior art (eg D1).

To meet the requirements of Rule 5.1(a)(ii) PCT, the documents D1 - D3 should be identified in the description and the relevant background art disclosed therein should be discussed.

The description must be brought into conformity with amended claims; care should be taken during revision, especially of the introductory portion including any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed, Article 34(2)(b) PCT.

In order to expedite proceedings and in view of the short time available under PCT procedures, the applicant should ensure that in the reply it is dealt with all issues raised in this written opinion. According to Rule 66.4 PCT the International Preliminary Examination Authority is entitled to issue only one preliminary opinion.

KJ

Fitzpatricks

chartered patent attorneys
trade mark attorneys

European Patent Office
Erhardtstrasse 27
Munich
D-80298
GERMANY

VIA FACSIMILE – 5 PAGES
FAX NO. 00 49 89 2399 4465
CONFIRMATION BY MAIL

Our Reference	Your Reference	Date
32/64087WO		16 June 2004

Dear Sirs

International (PCT) Patent Application No. PCT/GB2003/001404
Injectable Veterinary Composition for Small Animals
in the name of Norbrook Laboratories Limited

I refer to the written opinion mailed 16 March 2004, and acknowledge the extension of time for submitting a reply as confirmed by the Communication mailed 18 May, 2004. I now submit the Applicant's observations in reply together with proposals for adjusting the claims.

The Examiner has commented on the number of independent claims, and Applicant is prepared to limit the number of independent claims according to the proposed set enclosed herewith. Furthermore, the proposed claims clearly indicate the amounts of Carprofen or Carprofen salt and poloxamer, and the Comparative Examples are not claimed.

The Examiner has referred to three prior art documents and I propose to adopt the same alphanumeric code in discussion of each hereinbelow.

D1 (EP 0955063)

D1 is primarily concerned with an aqueous delivery medium suited for subcutaneous or intramuscular delivery of a pharmaceutically active agent or cosmetic, providing thereby a slow release of said agent, but the D1 inventor of that delivery medium has shown no particular focus on any specific drug, and a long list of pharmaceuticals of differing character is indicated.

Amongst many active pharmaceuticals contemplated for potential use in the proposed "depot" gel-type compositions, there is mentioned the class of analgesics/anti-rheumatics, including Ibuprofen and Tramadol. However, as acknowledged by the Examiner already, Carprofen is not mentioned.

No pharmaceutical formulation examples are given in D1 to demonstrate the efficacy of the proposed delivery medium, and in the absence of any specific teaching, a person of appropriate skill in this art

would have to conduct research to develop means for directly solubilising Carprofen in water and obtaining a room-temperature stable injectable aqueous formulation thereof. It is recalled here that D1 contemplates use of organic solvents in the first instance to dissolve insoluble ingredients (c.f. [0016] D1).

Since D1 is concerned with a slow-release formulation which in a physiological environment e.g. as in intramuscular injection as described in D1, is a gel-depot type of composition, this reference is remote from the injection solutions described in this application. A formulation of the D1 type cannot be used intravenously due to the likelihood of venous/capillary blockage or embolism. Therefore, D1 is not a suitable starting point for addressing the problems observed in Carprofen formulation, e.g. requiring auxiliaries such as in EP- A-0 280 887, with the resulting problems of side effects.

Thus the invention disclosed by the Applicant is not described nor contemplated in D1 and, we respectfully submit that the amended claims define patentable subject matter over D1.

D2 (CH 663 788)

I can agree that Carprofen is specifically discussed in this German language document, and its use together with an essential amino acid, e.g. L-Lysine or L-Arginine, to produce a salt such as Carprofen-L-lysinate is mentioned. It is also noted that parenteral pharmaceutical compositions using an inert carrier are described. However, it should be remarked that in each of the worked examples Carprofen is introduced as an alcoholic solution (methanol or methylene chloride/methanol) as part of the formulation preparation process. When looking at the actual product, one may consider Example 4d) which does not provide an aqueous solution formulation but does provide a suppository containing Carprofen.lysinate in a non-ionic surfactant based on polyethylene glycol and a poloxamer. With the benefit of hindsight, the Examiner considers that D2 seems to suggest Norbrook's invention is lacking in inventive step. However, this is certainly an incorrect view because, D2 is not a reference relating to delivery solutions of Carprofen or salts, but describing first how to make certain salts, and then use of those salts for making solid unit dose forms. The problem is a different one from that considered by Norbrook and the solution quite different. Therefore, the Norbrook invention is not described therein, nor suggested thereby.

D3 (US 5 283 067)

This reference contemplates a freeze-dried formulation suitable for the preparation of a stable, aqueous suspension for the parenteral administration of an NSAID, particularly one characterised by an acetic acid group (rather than the propionic group characteristic of Carprofen or Ketoprofen). Therefore, the teaching of W3 is entirely on the issue of a particular dry formulation that may be prepared for use as a stable aqueous suspension for parenteral administration. This is generally recognised as involving a mechanism of absorption when the dose is administered by subcutaneous, intracutaneous, and intramuscular injection. This may be contrasted with injection into a fluid of distribution for which the current invention is suitable.

Furthermore, even combining D3 with D2 does not lead directly to the invention made by Norbrook. Firstly the disclosures are not complementary, one relates to solid dosage forms, and the other to dry formulations, the latter intended for later make-up to injectable form. If D3 actually taught stable injection solutions, it would be illogical to prepare the dry formulation. Moreover, the D3 reference relates to injectable suspensions, whereas Norbrook provides an injectable solution.

Therefore, the Examiner is respectfully requested to re-consider the references in the light of the foregoing submissions and the amendments made to the claims.

The following points are also submitted. The stability of the injectable solution of the invention was discussed in comparison with the prior art on page 9 of the original disclosure. However, claim 2 is withdrawn at this time without prejudice. The Examiner has also commented on the Examples used to illustrate the invention, but the Applicant is not obliged to do more than describe the invention and illustrate it with reference to worked examples. Other poloxamers are commercially available and still further poloxamers could be specially prepared. The specification discusses poloxamers, especially values for x, y, z, on page 3, and points to a preferred poloxamer. The following example is also within the scope of the invention as contemplated by the Applicant.

The poloxamer is Lutrol F127 (Poloxamer 407):

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F127 (Poloxamer 407) 5% w/v

Benzyl Alcohol 1% w/v

SFS 0.25% w/v

Water for Injection ad 100% w/v

This is illustrative of a formulation using a poloxamer where x = 98, y = 67, and z = 98.

The amended claim 1 is based on the original statements concerning NSAIDs on page 2, and especially with respect to Carprofen or a salt thereof on page 3, lines 16 to 20, and the poloxamer ranges are derived from the same page but particularly taking account of the examples (e.g. Example 3 lower limit). The presence of a preservative is clearly optional as per page 3 line 24, and the Examples given, and having regard to the original claims 1, 3, 10, 11. The Examiner has commented on the presence of "omnibus claims". These claims are permissible in several of the designated states and are retained for the relevant national phases. Such claims are not permissible under e.g. EPC, and will be deleted upon entry to the national phase where appropriate.

Amendment of the description, e.g. to adjust the statements summarising the invention and to acknowledge prior art, is deferred until the relevant national phase.

Since the Applicant has addressed all the points raised in the written opinion, I submit that the file is now in a condition for issue of a favourable IPER having regard to the amended claims now submitted, and the submissions herein on cited art.

Yours faithfully
for Fitzpatricks (Agents for Applicant)

Eric Ede
Authorised Representative
European Patent Attorney

Encs: Amended Claims 1 to 16

CLAIMS

1. A room-temperature stable injectable solution for veterinary use comprising from 0.5 to 30% (w/v) of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 2.4% to 12% (w/v) of a poloxamer, and water *q.s.* for injection.

2. An injectable aqueous solution according to Claim 1, wherein the Carprofen salt is in the form of an arginine salt.

3. An injectable aqueous solution according to Claim 1, wherein the carprofen salt is in the form of a lysine salt.

4. An injectable aqueous solution according to any one of Claims 1 to 3, wherein Carprofen is present in an amount of from 2.5 to 7.5% (w/v).

5. An injectable aqueous solution according to any one of Claims 1 to 3, wherein Carprofen is present in an amount of from 2.5 to 5% (w/v).

6. An injectable aqueous solution according to any one of Claims 1-5, comprising arginine in an amount of from 1 to 20% (w/v).

7. An injectable aqueous solution according to Claim 1, wherein an organic solvent is present with the poloxamer.

8. An injectable aqueous solution according to Claim 7, wherein the organic solvent is present in the range of 0.5 to 20% (w/v).

9. An injectable aqueous solution according to Claim 1, wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is 75, y is 30 and z is 75.

10. An injectable aqueous solution for veterinary use according to Claim 1, where the solution is to be employed in treating felines, wherein the lower limit of the range of Carprofen is 0.25% (w/v).

11. An injectable aqueous solution for veterinary use according to Claim 10, comprising arginine in an amount of from 1 to 20% (w/v).

12. A method of producing a room-temperature stable injectable aqueous solution for veterinary use comprising bringing together Carprofen or a physiologically acceptable salt thereof, a poloxamer, and adding sufficient water for injection, to provide a solution containing from 0.5 to 30% (w/v) of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 2.4% to 12% (w/v) of poloxamer.

13. A method according to Claim 12, wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is 75, y is 30 and z is 75.

14. A method of producing an injectable aqueous solution according to Claim 12 or Claim 13, wherein said method further comprises the inclusion of a preservative.

15. An injectable aqueous solution for veterinary use according to any one of the Examples 1 to 19 hereinbefore.

16. A method of producing an injectable aqueous solution substantially as described in the Example 1.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
UNITED KINGDOM

Date of mailing *(day/month/year)*	10/09/2003
Applicant's or agent's file reference 32/64087WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB 03/01404	International filing date *(day/month/year)* 31/03/2003
Applicant NORBROOK LABORATORIES LIMITED	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Petronella Vaassen-Elsackers

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

IDCID: <XSISA220NOENP4_1 >

NOTES T FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

OCID: <XSISA220NOENP4 1 >

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
ROYAUME-UNI

Date of mailing *(day/month/year)* 09 October 2003 (09.10.03)	
Applicant's or agent's file reference 32/64087WO	IMPORTANT NOTICE

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB03/01404	31 March 2003 (31.03.03)	02 April 2002 (02.04.02)

Applicant
NORBROOK LABORATORIES LIMITED

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 09 October 2003 (09.10.03) under No. 03/082340

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's sole responsibility to monitor all these time limits.

   The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.(41-22) 740.14.35

Authorized officer
Judith Zahra

Telephone No.(41-22) 338.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU 2003 INTL

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
United Kingdom

GN
EE
RECD IP 07/05/03

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
17 April 2003 (17.04.03)	
Applicant's or agent's file reference	**International application No.**
32/64087WO	PCT/GB03/01404

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

NORBROOK LABORATORIES LIMITED (for all designated States except US)
BLAKELY, William et al (for US)

International filing date	:	31 March 2003 (31.03.03)
Priority date(s) claimed	:	02 April 2002 (02.04.02)
Date of receipt of the record copy by the International Bureau	:	14 April 2003 (14.04.03)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PT,RO,SE,SI,SK,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,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,MA,MD,MG,MK,MN,MW,MX,MZ,NI,NO,NZ,OM,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the International application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase - see updated Important Information (as of April 2002)
- [ ] confirmation of precautionary designations (if applicable)
- [ ] requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer:

P. Porsteri

Telephone No. (41-22) 338 9548

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office where a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19928, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at http://www.wipo.int/pct/en/index.html.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date (this time limit may not be extended). If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. The Notice of confirmation and payment must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of International publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

JB

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

6N E 9/6

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
United Kingdom

DP 09/06/03

Date of mailing (day/month/year) 22 May 2003 (22.05.03)	
Applicant's or agent's file reference 32/64087WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB03/01404	International filing date (day/month/year) 31 March 2003 (31.03.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 02 April 2002 (02.04.02)
Applicant NORBROOK LABORATORIES LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
02 April 2002 (02.04.02)	0207529.9	GB	16 May 2003 (16.05.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer José APRAIZ
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8153

Form PCT/IB/304 (July 1998)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FITZPATRICKS
4 West Regent Street
Glasgow G2 1RS
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03.08.2004
Applicant's or agent's file reference 32/43/64087WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/01404	31.03.2003	02.04.2002

Applicant
NORBROOK LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hutterer, G Tel. +49 89 2399-1066

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 32/43/84087WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/01404	International filing date *(day/month/year)* 31.03.2003	Priority date *(day/month/year)* 02.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K47/10		
Applicant NORBROOK LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.10.2003	03.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Rauter, A. Telephone No. +49 89 2399-8645

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01404

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-16 filed with telefax on 16.06.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 10 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION I. .....

item 5.
With letter dated 16.06.04, the applicant filed a set of claims which comprises subject-matter which is considered to go beyond the disclosure as filed. The feature in question relates to the lower limit of 2,4% of the range according to which the poloxamer is to be applied according to independent claims 1 and 12.

The applicant referred with respect to original disclosure of the said technical feature in particular to Example 3 of present description which shows the use of a poloxamer in an amount of 2,4%. Although the originally claimed percentage range of 0,5 - 20% (w/v) of the poloxamer comprises the now specified one, however, the value has been taken out of a composition comprising further components and no clear indication is available that a generalisation as now made in the independent claims is justified.

SECTION III. .....

item 1.
The specific embodiment of claim 10 specifies the lower limit of the Carprofen as being lower than that of the independent claim 1 to which it refers. Thus the requirements of clarity according to Article 6 PCT are not fulfilled.

SECTION V. .....

For the present evaluation of the requirements of Article 33 PCT (see SECTION I., item 5), the percentage range of the poloxamer to be applied in the injectable solution is that specified in the originally filed independent claim 1, *ie* 0,5 - 20% (w/v).

1. Reference is made to the following documents:

   D1: EP-A-0 955 063
   D2: CH-A-663 788
   D3: US-A-5 283 067

2. The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matters of the independent product claims 1, 12, ...

do not involve an inventive step (Rule 65(1)(2) PCT).

The claimed product, ie the aqueous injectable solution comprises in certain amounts

- Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid)

and

- a poloxamer.

Such a solution differs from solutions disclosed in D1 (see *eg* claim 1; paragraphs [0021] and [0024]) only by the fact that the compound Carprofen has not explicitly been mentioned. However, D1 clearly stated that anti-inflammatory compounds can advantageously be used in combination with poloxamers to arrive at injectable solutions solving to same problem, *ie* to provide anti-inflammatory drugs suitable for injection. Carprofen is well known to the person skilled in the art as being such a compound and its substitution in the solutions according to D1 must be considered obvious, this the more, as *eg* D2 (see *eg* claim 6) suggests its usability for anti-inflammatory purposes. The person skilled in the art gets furthermore the information from D3 (see *eg* claim 1; Example 4) that injectable aqueous solutions comprising poloxamers and anti-inflammatory agents can successfully be prepared to solve the said problem.

The reasoning is valid mutatis mutandis for independent method claim 12 and for the embodiments claimed in claims 15 and 16 referring to Examples described in the description.

The claimed subject-matter lacks therefore an inventive step.

It is noted that the Comparative Examples as presented in the description on page 8, fall under the wording of present independent product claims, thus any surprising effect derived by the specified injectable solution cannot be seen.

Essentially, the dependent claims specify certain Carprofen salts which are known from D2, or define the poloxamer which can be taken from *eg* D1, and indicate that further components can be present. To arrive at these embodiments the person skilled in the art can take corresponding information from D1, thus any inventive step must also be denied for the dependent claims.

The applicant provided during the international preliminary examinati...

arguments with respect to certain disclosure of documents D1 - D3, however, as there is also disclosure available as specified above, a different view with respect to the requirements of the PCT cannot be given.

3. Claims 15 and 16 comprise references to the description, ie to Examples. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

22. OCT. 2004 21:07 FITZPATRICKS NO. 3519 P. 2

CLAIMS

1. A room-temperature stable injectable solution for veterinary use comprising from 0.5 to 30% (w/v) of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 2.4% to 12% (w/v) of a poloxamer, and water *q.s.* for injection.

2. An injectable aqueous solution according to Claim 1, wherein the Carprofen salt is in the form of an arginine salt.

3. An injectable aqueous solution according to Claim 1, wherein the carprofen salt is in the form of a lysine salt.

4. An injectable aqueous solution according to any one of Claims 1 to 3, wherein Carprofen is present in an amount of from 2.5 to 7.5% (w/v).

5. An injectable aqueous solution according to any one of Claims 1 to 3, wherein Carprofen is present in an amount of from 2.5 to 5% (w/v).

6. An injectable aqueous solution according to any one of Claims 1-5, comprising arginine in an amount of from 1 to 20% (w/v).

7. An injectable aqueous solution according to Claim 1, wherein an organic solvent is present with the poloxamer.

8. An injectable aqueous solution according to Claim 7, wherein the organic solvent is present in the range of 0.5 to 20% (w/v).

9. An injectable aqueous solution according to Claim 1, wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is 75, y is 30 and z is 75.

10. An injectable aqueous solution for veterinary use according to Claim 1, where the solution is to be employed in treating felines, wherein the lower limit of the range of Carprofen is 0.25% (w/v).

11. An injectable aqueous solution for veterinary use according to Claim 10, comprising arginine in an amount of from 1 to 20% (w/v).

12. A method of producing a room-temperature stable injectable aqueous solution for veterinary use comprising bringing together Carprofen or a physiologically acceptable salt thereof, a poloxamer, and adding sufficient water for injection, to provide a solution containing from 0.5 to 30% (w/v) of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 2.4% to 12% (w/v) of poloxamer.

13. A method according to Claim 12, wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is 75, y is 30 and z is 75.

14. A method of producing an injectable aqueous solution according to Claim 12 or Claim 13, wherein said method further comprises the inclusion of a preservative.

15. An injectable aqueous solution for veterinary use according to any one of the Examples 1 to 19 hereinbefore.

16. A method of producing an injectable aqueous solution substantially as described in the Example 1.

Traducción

67

TRATADO DE C PERACIÓN DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

Referencia del expediente del agente o solicitante 32/43/64067WO	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA/416)
Solicitud internacional No. PCT/GB03/01404	Fecha de presentación internacional (*día/mes/año*) 31.03.2003	Fecha de prioridad (*día/mes/año*) 02.04.2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K 47/10		
Solicitante NORBROOK LABORATORIES LIMITED et al.		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este **INFORME** consta de una total de 7 hojas, incluyendo la portada

   ☒ Este informe también se acompaña de **ANEXOS**, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este Informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

   Estos anexos constan de un total de 2 hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

   I ☒ Fundamentos del Informe

   II ☐ Prioridad

   III ☒ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

   IV ☐ Carencia de unidad de la invención

   V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

   VI ☐ Ciertos documentos citados

   VII ☐ Ciertos defectos de la solicitud internacional

   VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda	Fecha de terminación de este reporte
31.10.2003	03.08.2004
Nombre y dirección de correo de la autoridad encargada del examen preliminar Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Rauter, A Teléfono No. +49 89 2399-8645

Formato PCT/IPEA/409 (portada) (Enero 2004)

I. Base del Informe

1. Respecto a los **elementos** de la solicitud internacional (*Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17)):*

La descripción, Páginas

1-10 como se presentaron originalmente

Las reivindicaciones, Números

1 – 16 presentadas junto con el telefax del 16.06.2003.

Los dibujos, Páginas

1/1 como se presentaron originalmente

2. Respecto al **lenguaje**, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier **secuencia de nucleótido y/o amino ácidos** divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

☐ la descripción, páginas _____,
☐ las reivindicaciones, Nos. _____,
☐ los dibujos, página _____.

5. ☒ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).**

(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe.)

Ver hoja separada

6. Observaciones adicionales, si es necesario

III. No-establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad industrial.

1. La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo (que no sea obvia), o que sea aplicable industrialmente no ha sido examinada con respecto a:

☐ la solicitud internacional completa
☐ las reivindicaciones Nos. _____,

Porque

☐ la solicitud internacional, o las mencionadas reivindicaciones Nos. _____ se relacionan con los siguientes objetos, los cuales no requieren examen preliminar internacional *(especifique):*

☒ la descripción, las reivindicaciones o los dibujos *(indique los elementos particulares abajo)* o las mencionadas reivindicaciones Nos. 10 son demasiado confusas que no se puede formar ninguna opinión significativa *(especifique):*

Ver hoja separada

☐ la descripción, o las mencionadas reivindicaciones Nos. _____ no están adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.

☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos. _____

2. No se pudo realizar un examen preliminar internacional significativo debido a fallas en el listado de nucleótidos y/o aminoácidos para dar cumplimiento con los estándares del Anexo C de las Instrucciones Administrativas:

☐ El formato escrito no ha sido suministrado o no cumple con los estándares.

☐ El formato de lectura por computador no ha sido suministrado o no cumple con los estándades.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	1-16	SI
	Reivindicaciones		NO
Nivel inventivo (NI)	Reivindicaciones		SI
	Reivindicaciones	1-16	NO
Aplicación industrial (AI)	Reivindicaciones	1-16	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

Ver hoja separada

SECCIÓN I. .....

Ítem 5.

Con carta del 16.06.04, el solicitante radicó un capítulo reivindicatorio que comprende un objeto que es considerado como que va más allá de lo revelado cuando se solicitó. La característica en cuestión se relaciona con el límite inferior de 2.4% del rango de acuerdo con el cual el poloxámero debe ser aplicado de acuerdo con las reivindicaciones independientes 1 y 12.

El solicitante se refiere a la divulgación original de dicha característica técnica en particular al Ejemplo 3 de la presente descripción que muestra el uso de un poloxámeo en una cantidad del 2,4%. A pesar de que el porcentaje originalmente reivindicado de 0.5-20% (p/v) del poloxámero comprende el que ahora se especifica, el valor ha sido tomado de una composición que comprende otros componentes adicionales y hay ninguna indicación clara de que una generalización como la que se hace ahora en las reivindicaciones independientes esté justificada.

SECCIÓN III. .....

Ítem 1.

La inclusión específica de la reivindicación 10 especifica el límite inferior del Carpofen como menor al de la reivindicación independiente 1 a la que se refiere. Así no se cumple con el requerimiento de claridad de acuerdo con el Artículo 6 del PCT.

SECCIÓN V. .....

Para la presente evaluación de los requerimientos del Artículo 33 del PCT (Ver SCCIÓN I., ítem 5), el rango de porcentaje del poloxamero que debe ser aplicado en la solución inyectable es el especificado en la reivindicación independiente 1, es decir 0.5 – 20% (p/v).

1. Se hace referencia a los siguientes documentos:

   D1: EP-A-0 955 063
   D2: CH-A-663 788
   D3: US-A-5 283 067

2. La presente solicitud no cumple con los criterios establecidos en el Artículo 33(3) del PCT debido a que el objeto de las reivindicaciones independientes 1, 12, 15 y 16 no alcanza el nivel inventivo (Regla 65(1)(2) PCT).

El producto reivindicado, es decir la solución inyectable comprende ciertas cantidades de

- Carprofen (ácido 6-cloro-α-metil-carbazol-2-acético), y
- Un poloxámero.

Dicha solución difiere de las soluciones divulgadas en D1 (ver por ejemplo, reivindicación 1, *párrafos* [0021] y [0024]) solo en el hecho de que el compuesto Carprofen no ha sido explícitamente mencionado. Sin embargo, D1 claramente afirma que los compuestos antiinflamatorios pueden ser usados ventajosamente en combinación con poloxámeros para llegar a soluciones inyectables que resuelven el mismo problema, es decir, el de proporcionar fármacos antiflamatorios adecuados para inyección. El Carprofen es bien conocido para una persona versada en el arte como un compuesto de esta clase y su sustitución en las soluciones de acuerdo con D1 debe ser considerada obvia, es más, como en por ejemplo D2 (ver reivindicación 6) se sugiere su utilización para propósitos antiinflamatorios. La persona versada en el arte tiene mayor información a partir de D3 (ver reivindicación 1; Ejemplo 4), en donde las soluciones inyectables acuosas comprenden poloxámeros y agentes antiinflamatorios que pueden ser preparados exitosamente para resolver dicho problema.

Este razonamiento es válido mutatis mutandis para el método de la reivindicación independiente 12 y para las inclusiones reclamadas en las reivindicaciones 15 y 16 que se refieren a los ejemplos definidos en la descripción.

El objeto reivindicado no alcanza de esta forma el nivel inventivo.

Se nota que los Ejemplos comparativos como se presentan en la descripción en la página 8, caen dentro de la redacción de las presentes reivindicaciones independientes de producto, así no puede observase ningún efecto sorprendente derivado de la presente composición inyectable especificada.

Esencialmente, las reivindicaciones dependientes especifican ciertas sales de Carprofen que son conocidas a partir de D2, o definen al poloxámero que puede ser tomado del documento D1, e indican que otros componentes pueden estar presentes. Para llegar a estas inclusiones una persona versada en la materia puede tomar la información correspondiente de D1, así el nivel inventivo debe ser también negado para las reivindicaciones dependientes.

El solicitante, durante el procedimiento del examen preliminar internacional, proporcionó argumentos con respecto a ciertas revelaciones hechas por los documentos D1 - D3, sin embargo, como existen también divulgaciones como las especificadas arriba, no puede darse un punto de vista diferente con respecto a los requerimientos del PCT.

3. Las reivindicaciones 15 y 16 comprenden referencias a la descripción, es decir a los Ejemplos. De acuerdo con la regla 6.2(a) del PCT, las reivindicaciones no deben contener dichas referencias a excepción de que sea estrictamente necesario, el cual no es el caso aquí.

REIVINDICACIONES

1. Una composición acuosa inyectable para uso veterinario estable a temperatura ambiente que 0.5 a 30% (p/v) de Carprofeno (ácido 6-cloro-α-metil-carbazol-2-acético) o una sal fisiológicamente aceptable de Carprofeno, y desde 2.4% a 12% (p/v) de un poloxámero, y agua en cantidad suficiente para inyección.

2. Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde la sal de carprofeno está en la forma de una sal de arginina.

3. Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde la sal carprofeno está en la forma de una sal de lisina.

4. Una composición acuosa inyectable de conformidad con cualquiera de las reivindicaciones 1 a 3, en donde el carprofeno está presente en una cantidad de aproximadamente 2.5 a 7.5% (p/v).

5. Una composición acuosa inyectable de conformidad con cualquiera de las reivindicaciones 1 a 3, en donde el carprofeno está presente en una cantidad de aproximadamente 2.5 a 5% (p/v).

6. Una composición acuosa inyectable de conformidad con cualquiera de las reivindicaciones 1 a 5, que comprende arginina en una cantidad de aproximadamente 1 a 20% (p/v).

7. Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde un solvente orgánico está presente con el poloxámero.

8. Una composición acuosa inyectable de conformidad con la reivindicación 7, en donde el solvente orgánico está presente en la escala de 0.5 a 20% (p/v).

9. Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde el poloxámero es $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ en donde x es 75, y es 30 y z es 75.

10. Una composición acuosa inyectable para uso veterinario de conformidad con la reivindicación1, en donde la solución se emplea en el tratamiento de felino, en donde el límite inferior del rango de Carprofeno es 0.25% (p/v).

HOJA MODIFICADA

11. Una composición acuosa inyectable para uso veterinario de conformidad con la reivindicación 10, que comprende arginina en una cantidad de 1 a 20% (p/v).

12. Un método para producir una composición acuosa inyectable estable a temperatura ambiente para uso veterinario, que comprende poner juntos una cantidad efectiva de carprofeno o una sal fisiológicamente aceptable del mismo y un poloxámero, y añadir suficiente agua para inyección para proporcionar una solución que contiene 0.5 a 30% (p/v) de Carprofeno (ácido 6-cloro-α-metil-carbazol-2-acético) o una sal fisiológicamente aceptable de Carprofeno, y desde 2.4% a 12% (p/v) de un poloxámero

13. Un método de conformidad con la reivindicación 12, en donde el poloxámero es $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ en donde x es 75, y es 30 y z es 75.

14. Un método para producir una composición acuosa inyectable de conformidad con las reivindicación 12, en donde el método comprende además la inclusión de un conservador.

15. Una composición acuosa inyectable para uso veterinario de conformidad con cualquiera de los Ejemplos 1 a 19 que anteceden.

16. Un método para producir una composición acuosa inyectable substancialmente como se describe en el Ejemplo 1.

COLO 14456-841-002-7
PRP/WPC14456/ID-000005

HOJA MODIFICADA

COMPOSICIÓN VETERINARIA INYECTABLE PARA ANIMALES PEQUEÑOS

Esta invención se relaciona con el uso de drogas antiinflamatorias, no esteroides (NSAIDs), particularmente la formulación de dichas drogas en soluciones apropiadas para inyección, espacialmente para uso en medicina veterinaria con los propósitos de tratar animales pequeños, tales como animales compañeros.

Antecedentes de la Invención

Las drogas antiinflamatorias no esteroides encuentran amplia aplicación en el tratamiento de condiciones inflamatorias y el alivio de dolor en medicina veterinaria y humana. Estas drogas se caracterizan frecuentemente por la presencia de una función de ácido carboxílico o derivado del mismo. Los ejemplos de dichos antiinflamatorios no esteroides incluyen caprofeno, ibuprofeno, cetoprofeno, benoxaprofeno, naproxeno, sulindaco, zomepirac, fenclofenaco, alcofenaco, ibufenaco, flunixina e indometacina. La administración de dichos compuestos parenteralmente puede presentar la dificultad de irritación local e inducir efectos hemolíticos laterales.

En EP-A-0 280 887, Ferro y Steffen enseñan la formulación de NSAIDs, utilizando sales de ácido colánico y ciertos lípidos para formar micelios mixtos en sistemas acuoso. Estas composiciones tienen efectos laterales reducidos, en comparación con formulaciones convencionales,

cuando se administran mediante inyección a perros.

Objetos de la Invención

Un objeto de la presente invención es proporcionar preparaciones farmacéuticas novedosas de drogas antiinflamatorias, no esteroides, apropiadas para inyección. Un objeto adicional de la invención es proporcionar dichas preparaciones adaptadas para la provisión de analgesia en animales pequeños, especialmente animales mascota.

Compendio de la Invención

Se ha encontrado sorprendentemente que NSAIDs (de preferencia carprofeno (ácido 6-cloro-alfa-metil-carbazol-2-acético) o una sal del mismo, más preferentemente carprofeno en la forma de su sal de arginina o lisina, se puede formular fácilmente en sistemas acuosas mediante el uso de ciertos agentes de polímero sintético farmacéuticamente aceptables al efecto que los problemas de irritación local y hemolisis asociados con formulaciones convencionales de estas drogas se eviten o cuando menos se reducen grandemente.

Consecuentemente, los objetos antes mencionados se pueden lograr mediante esta invención que proporciona una composición acuosa inyectable para uso veterinario que contiene una cantidad efectiva de un compuesto antiinflamatorio no esteroide junto con un agente tensioactivo poliméricos oxigenado, fisiológicamente aceptable.

Un beneficio técnico adicional en comparación con formulaciones que utilizan el método de solubilización de ácido colánico/lípido del ramo anterior se logra también mediante la presente invención que ofrece estabilidad mejorada a temperatura ambiente.

Copolímeros de bloque de polioxipropileno/ polioxietileno (poloxámeros) o derivados de los mismos son los agentes poliméricos preferidos utilizados para los propósitos de la invención como se ilustra en los siguientes ejemplos para una composición que contiene carprofeno o sales fisiológicamente aceptables del mismo como el ingrediente activo. Dicha solución es especialmente útil en medicina veterinaria para una variedad de propósitos analgésicos, antipiréticos y antiinflamatorios tales como del tratamiento de dolor musco-esquelético y visceral en caballos, colores pre y post operativo en gatos y perros y de inflamación aguda asociada con enfermedad respiratoria.

La cantidad de NSAID que se puede acomodar en las soluciones de inyección de la presente invención puede variar dentro de límites amplios, por ejemplo de 0.5 a 30% (p/v), dependiendo de la dosis requerida para tratamiento efectivo del sujeto. La cantidad de poloxámero también puede variar a través de límites amplios, por ejemplo 0.5a 20% (p/v), el límite superior para una formación data siendo determinado por consideraciones de viscosidad. En uso normal, la

solución se puede administrar fácilmente mediante jeringa hipodérmica convencional.

La presente invención proporciona otros medios para formular MSAIDs en solución acuosa, en una forma que es apropiada para administración parenteral a animales o humanos, especialmente animales mascota tales como gatos y perros. Las composiciones de la presente invención proporcionan formulaciones más sencillas que aquellas de EP 0 280 887, sin el requerimiento de lípidos y ácidos colánicos. Una particularidad adicional de estas formulaciones más sencillas es que permanecen estables, sin precipitación anticipada ni turbidez y se pueden almacenar a temperatura ambiente, contrastando con la formulación de ácido colánico/lípido que típicamente requiere almacenamiento refrigerado (2-8°C).

El compuesto antiinflamatorio no esteroide puede estar presente en una cantidad de aproximadamente 2.5 a 7.5% (p/v) o más, de preferencia 2.5 a 5% (p/v). Sin embargo, se entenderá por aquellos expertos en el ramo que una escala inferior útil de alrededor de 0.25% (p/v) se puede emplear cuando cambios de volumen pequeños en volumen de entre no son significativos, v.gr., al tratar felinos con un compuesto antiinflamatorio no esteroide tal como carprofeno.

La arginina puede estar presente en una cantidad de aproximadamente 1% a 20% (p/v).

Los poloxámeros generalmente están presentes en una cantidad de aproximadamente 2 a 12% (p/v). Además, un solvente orgánico también puede estar presente con el poloxámero, generalmente en la escala de aproximadamente 0.5 a 20% (p/v), en cuyo caso los poloxámeros pueden estar presentes en una cantidad de 1% a 12% (p/v).

Un poloxámero generalmente se confirma a la fórmula $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$, en donde x, y, y z son variables que son independiente y selectivamente controlables. Los valores de x, y, y z son respectivamente números enteros en la escala de 2 a 128 y representan valores de blanco que variarán ligeramente de conformidad con fuentes comerciales. Un ejemplo de un poloxámero preferido es $HO(CH_2CH_2O)_{75}(CCH_3HCH_2O)_{30}(CH_2CH_2)_{75}H$.

La presente invención proporciona una composición inyectable acuosa que comprende carprofeno o una sal fisiológicamente aceptable del mismo en una cantidad de cuando menos 0.25%, de preferencia 0.5% a 30% (p/v), una especie polimérica seleccionada a partir del grupo de copolímeros de bloque de polioxipropileno/polioxietileno en una cantidad de 0.5% a 20% (p/v), un conservador y suficiente agua para inyección.

De conformidad con la invención, también se proporciona un método para producir una composición acuosa inyectable, estable a temperatura ambiente para uso

veterinario, que comprende poner juntos carprofeno o una sal fisiológicamente aceptable y un poloxámero, y añadir suficiente agua para inyección. Adicionalmente, también se pueden incluir conservadores. De preferencia el poloxámero es $HO(CH_2CH_2O)_{75}(CCH_3HCH_2O)_{30}(CH_2CH_2)_{75}H$.

Además, la invención también se relaciona con el uso de copolímeros de bloque de polioxipropileno/polioxietileno para la fabricación de soluciones de inyección acuosas localmente tolerables de compuestos no esteroides.

Modo de Funcionamiento de la Invención

La invención se describirá ahora adicionalmente por vía de ejemplo ilustrativo con referencia a la Figura que se acompaña, que representa datos que muestran los niveles promedio de carprofeno encontrados en el plasma sanguíneo de perros después de la administración de una formulación de la invención.

Ejemplos

Ejemplo 1

Una formulación apropiada de carprofeno, en esta modalidad provista como su sal de arginina, se puede hacer poniendo juntos, siguiendo procedimientos convencionales de la industria, los siguientes ingredientes para formar una mezcla que se lleva a volumen de inyección mediante la adición de una cantidad apropiada de agua para inyección:

82

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF, EP), 5.0% p/v

Nipagin M (BP, EP, USP/NF) 0.15% p/v (conservador)

Agua para inyección a 100% p/v

Otros ejemplos de formulaciones apropiadas incluyen:

Ejemplo 2

Carprofeno 5.05 p/v

L-Arginina EP 3% p/v

Lutrol F68 (poloxámero 188, NF EP) 10% p/v

Propilenglicol 20% p/v

Agua para inyección a 100% p/v

Ejemplo 3

Carprofeno 5.0% p/v

L-Arginina EP 3% p/v

Lutrol F68 (poloxámero 188, NF EP) 2.4% p/v

Propilenglicol 20% p/v

Agua para inyección a 100% p/v

Ejemplo 4

Carprofeno 5.0% p/v

L-Arginina EP 3% p/v

Lutrol F68 (poloxámero 188, NF EP) 12% p/v

Propilenglicol 20% p/v

Agua para inyección a 100% p/v

83

Ejemplo 5

Carprofeno 5.0% p/v

L-Arginina EP 3% p/v

Lutrol F68 (poloxámero 188, NF EP) 3.5% p/v

Propilenglicol 20% p/v

Agua para inyección a 1005 p/v

Ejemplo 6

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188,k NF EP) 5% p/v

Propilenglicol 20% p/v

Agua para inyección a 100% p/v

Ejemplo 7

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Agua para inyección a 100% p/v

Ejemplo 8

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 7% p/v

Propilenglicol 20% p/v

Agua para inyección a 100% p/v

Ejemplo 9

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

Agua para inyección a 100% p/v

Ejemplo 10

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 6% p/v

Agua para inyección a 100% p/v

Ejemplo 11

Carprofeno 5.0% p/v

L-Arginina EP 3% p/v

Lutrol F68 (poloxámero 188 NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

Agua para inyección a 100% p/v

Ejemplo 12

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 0.3% p/v

Agua para inyección a 100% p/v

Ejemplo 13

Carprofeno 5.0% p/v

L-Arginina EP 2.7% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

Agua para inyección a 100% p/v

Ejemplo 14

Carprofeno 5.0% p/v

L-Arginina EP 3.3% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

Agua para Inyección a 100% p/v

Ejemplo 15

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

SFS 0.25% p/v

Agua para inyección a 100% p/v

Ejemplo 16

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

SFS 0.1% p/v

Agua para inyección a 100% p/v

Ejemplo 17

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

SFS 0.4% p/v

Agua para inyección a 100% p/v

Ejemplo 18

Carprofeno 5.0% p/v

L-Arginina EP 2.5% p/v

Lutrol F68 (poloxámero 188, NF EP) 5% p/v

Alcohol de Bencilo 1% p/v

SFS 0.25% p/v

Agua para inyección a 100% p/v

Ejemplo 19

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 3% p/v

Alcohol de Bencilo 1% p/v

SFS 0.25% p/v

Agua para inyección a 100% p/v

Los ejemplos de formulaciones que fallaron en lograr objetivos comerciales satisfactorios se muestran abajo:

Ejemplo Comparativo 1

Carprofeno 5.0% p/v

L-Arginina EP 3% p/v

Lutrol F68 (poloxámero 188, NF EP) 20% p/v

87

Propilenglicol 20% p/v

Agua para inyección a 100% p/v

Ejemplo Comparativo 2

Carprofeno 5.0% p/v

L-Arginina EP 3.1% p/v

Lutrol F68 (poloxámero 188, NF EP) 2% p/v

Alcohol de Bencilo 1% p/v

SFS 0.25% p/v

Agua para inyección a 100% p/v

Se hizo una comparación con la formulación del ramo anterior (derivada de EP 0 280 887) que utiliza aproximadamente 26% (p/v) de ácido colánico y lecitina, de una formulación de carprofeno de resistencia similar. Esta formulación demuestra bioequivalencia a las formulaciones de ácido colánico/lípico antes mencionadas pero utiliza solamente 5% (p/v) del aditivo de agente tensioactivo polimérico de la invención. De esta manera, las composiciones de la presente invención pueden reducir substancialmente la carga de ingredientes auxiliares inyectados al sujeto en tratamiento. Estas formulaciones también se han encontrado que tienen bajos efectos laterales, sin reacciones de sitio de inyección tales como hinchamiento, dureza, suavidad, calor, calidad de rojo, o dolor siendo observadas durante estudios que involucran perros.

Un beneficio adicional de composiciones de

conformidad con la invención es aquel de estabilidad a temperatura ambiente. Un lote de prueba de la formulación dada en el ejemplo se estudió durante un período de once meses a temperaturas ambientales sin pérdida de potencia siendo observada. El lote de prueba se ensayo como conteniendo 5.16% de carprofeno durante la fabricación, 5.10% después de siete meses, y 5.26% después de once meses, estas diferentes aparentes siendo consideradas mediante ligera pérdida de humedad. Las formulaciones actualmente disponibles de manera típica requieren almacenamiento enfriado controlado a 2-8°C, es decir, almacenamiento en refrigeración, habitación fría, o gabinete enfriador.

Se hizo un estudio con vistas a evaluar los niveles promedio de carprofeno encontrados en perros después de la administración de una dosis de aproximadamente 4 mg/kg de una composición de conformidad con el Ejemplo en comparación con los resultados obtenidos por administración de un producto comercialmente disponible de resistencia comparable.

Los resultados del estudio farmacocinético se tabulan abajo y se muestran de manera gráfica en la Figura 1. El Cuadro compara las concentraciones de plasma medias de carprofeno encontradas en perros después de inyección subcutánea de carprofeno a una dosis de aproximadamente 4 mg/kg usando una formulación comercialmente disponible, y usando la formulación proporcionada en el Ejemplo. El

análisis estadístico de estos resultados confirmó la bioequivalentcia de conformidad con European Guidelines (Volumen 8 de EMEA/CMPM/016-00/Final).

Cuadro 1

Tiempo después Inyección (horas	Formulación de Carprofeno/ Lutrol (ug/ml)	Formulación de Carprofeno Comercialmente disponible (ug/ml)
0.5	5.73	3.27
1	8.24	5.86
1.5	9.24	7.16
2	9.85	8.76
2.5	11.18	8.53
3	11.36	9.63
3.5	9.94	10.29
4	9.23	7.99
5	9.12	7.6
8	6.57	6.75
10	5.98	6.18
24	2.39	2.41
30	1.37	1.48
48	0.39	0.6
72	0.23	0.18

90

REIVINDICACIONES

1.- Una composición acuosa inyectable para uso veterinario que contiene una sal fisiológicamente activa de Carprofeno (ácido 6-cloro-α-metil-carbazol-2-acético) en una cantidad de aproximadamente 0.5 a 305 (p/v) junto con un poloxámero en una cantidad de alrededor de 0.5 a 20% (p/v) y la composición acuosa inyectable siendo estable a temperatura ambiente.

2.- Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde la composición es estable a temperatura ambiente durante un mínimo de 11 meses.

3.- Una composición acuosa inyectable de conformidad con las reivindicaciones 1 o 2, en donde el poloxámero es $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH2CH2)_zH$ en donde x es aproximadamente 75, y es alrededor de 30 y z es aproximadamente 98, y es 67 y z es 98.

4.- Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde la sal de carprofeno está en la forma de una sal de arginina.

5.- Una composición acuosa inyectable de conformidad con la reivindicación 1, en donde la sal carprofeno está en la forma de una sal de lisina.

6.- Una composición acuosa inyectable de conformidad con cualquiera de las reivindicaciones 1 a 5, en

donde el carprofeno está presente en una cantidad de aproximadamente 2.5 a 7.5% (p/v).

7.- Una composición acuosa inyectable de conformidad con cualquiera de las reivindicaciones 1 a 5, en donde el carprofeno está presente en una cantidad de aproximadamente 2.5 a 5% (p/v.

8.- Una composición acuosa inyectable de conformidad con cualquiera de las reivindicaciones 1 a 7, que comprende arginina en una cantidad de aproximadamente 1 a 20% (p/v).

9.- Una composición acuosa inyectable para uso veterinario que contiene una sal fisiológicamente activa de Carprofeno (ácido 6-cloro-α-metil-carbazol-2-acético), en una cantidad de cuando menos aproximadamente 0.25% (p/v) junto con un poloxámero en una cantidad de alrededor de 0.5 a 20% (p/v).

10.- Una composición acuosa inyectable de conformidad con la reivindicación 9, en donde los poloxámeros están presentes en una cantidad de aproximadamente 2 a 12% (p/v).

11.- Una composición acuosa inyectable de conformidad con la reivindicación 9, en donde un solvente orgánico está presente con el poloxámero.

12.- Una composición acuosa inyectable de conformidad con la reivindicación 11, en donde el solvente }

92

orgánico está presente en la escala de 0.5 a 20% (p/v).

13.- Una composición acuosa inyectable de conformidad con las reivindicaciones 11 o 12, en donde los poloxámeros están presentes en una cantidad de 1% a 12% (p/v).

14.- Una composición acuosa inyectable para uso veterinario que contiene aproximadamente 0.25% a 30% (p/v) de sal de arginina de carprofeno junto con un poloxámero en una cantidad de aproximadamente 0.5 a 20% (p/v).

15.- Una composición acuosa inyectable para uso veterinario de conformidad con la reivindicación 14, que comprende arginina en una cantidad de 1 a 20% (p/v).

16.- Una composición acuosa inyectable que comprende carprofeno o una sal fisiológicamente aceptable del mismo en una cantidad de 0.25% a 30% (p/v), una especie polimérica seleccionada del grupo de copolímeros de bloque de polioxipropileno/polioxietileno en la cantidad de 0.5% a 20% (p/v), un conservador y agua suficiente para inyección.

17.- Un método para producir una composición acuosa inyectable estable a temperatura ambiente para uso veterinario, que comprende poner juntos una cantidad efectiva de carprofeno o una sal fisiológicamente aceptable del mismo y un poloxámero, y añadir suficiente agua para inyección.

18.- Un método de conformidad con la reivindicación 17, en donde el poloxámero es

$HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$, en donde x es aproximadamente 75, y es alrededor de 30 y z es aproximadamente 75.

19.- Un método para producir una composición acuosa inyectable de conformidad con las reivindicaciones 17 o 18, en donde el método comprende además la inclusión de un conservador.

20.- Una composición acuosa inyectable para uso veterinario de conformidad con cualquiera de los Ejemplos 1 a 19 que anteceden.

21.- Un método para producir una composición acuosa inyectable substancialmente como se describe en el Ejemplo 1.

94

RESUMEN DE LA INVENCIÓN

Una composición acuosa inyectable para uso veterinario que contiene un compuesto antiinflamatorio y no esteroide en una cantidad de aproximadamente 0.25 a 30% (p/v) junto con un agente tensioactivo poliméricos oxigenado, fisiológicamente aceptable, en una cantidad de alrededor de 0.5 a 20%, (p/v).

[redacted]

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

95

Item	Expediente No	04109926 No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO	1	✓
10	OTROS:		

Observaciones: arte final

[redacted]

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04109926 00000000 Folios: 96
Fecha (AMD): 2004-11-02 16:50:32
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 35,331
FECHA : NOVIEMBRE 2 DE 2004

96

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32759693	02/11/2004	421,143,500.00

***** C O N C E P T O *****

CANT.	REMISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo 14956-841-002-7

97

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04109926 00000000 Folios: 96
Fecha (AMD): 2004-11-02 16:50:32
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	( )
Indicación de que se solicita la concesión de una patente.	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
Descripción de la invención.	( )	( )
Dibujos de ser estos pertinentes. X	( )	( )
Comprobante de pago de las tasas establecidas.		
COMPLETA ( )	INCOMPLETA ( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	( )
Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable: Claudia M. Nieva

Fecha:

Industria y Comercio
SUPERINTENDENCIA

2020

Bogotá D C

Doctor(a)
EMILIO FERRRERO
Apoderado(a)
NORBROCCK LABORATORIES LIMITED 16878

REFERENCIA:	Radicación N°	**04-109926**
	Solicitud internacional	**PCT/GB03/01404**
	Fecha inicio fase nacional	**2004-11-04** 02
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
26 NOV. 2004
202063

3 DIC 2004.