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18 September 2008

(54) Title: USE OF AMINOLEVULINIC ACID AND DERIVATIVES THEREOF

(57) Abstract: The invention provides the use of a photosensitiser which is 5- aminolevulinic acid (5-ALA) or a derivative (e.g. an ester) of 5-ALA, or a pharmaceutically acceptable salt thereof, in the manufacture of a composition for use in methods of photodynamic therapy (PDT) on an animal, wherein said PDT comprises: (a) administering to said animal a composition comprising said photosensitiser; and (b) photoactivating said photosensitiser, and wherein side-effects (e.g. pain and/or erythema) of said PDT are prevented or reduced by use of one or more of (i)-(iv): (i) said composition comprises said photosensitiser in a concentration of less than 10 % wt (e.g. 0.5 to 8 %wt), (ii) said composition is administered for less than 2 hours (e.g. 30 minutes to 90 minutes) prior to said photoactivation, (iii) said photoactivation is carried out with a light source having a fluence rate of less than 50 mW/cm<sup>2</sup> (e.g. 5 to 40 mW/cm<sup>2</sup>), (iv) said photoactivation is carried out with sunlight. Preferably, side-effects of PDT are prevented or reduced by using (iii) or (iv) in combination with (i) and/or (ii).

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## INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/221 A61K41/00 A61K31/197 A61P17/10 A61P35/00

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                           | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | <p>SHARFAEI SORAYA ET AL: "Weekly topical application of methyl aminolevulinate followed by light exposure delays the appearance of UV-induced skin tumours in mice."</p> <p>ARCHIVES OF DERMATOLOGICAL RESEARCH JUL 2002, vol. 294, no. 5, July 2002 (2002-07), pages 237-242, XP002485542<br/>ISSN: 0340-3696<br/>the whole document</p> <p style="text-align: center;">-----<br/>-/--</p> | 1-25,<br>27-34        |

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*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.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

24 June 2008

Date of mailing of the international search report

09/07/2008

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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                     | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | MOAN JOHAN ET AL: "Influence of light exposure on the kinetics of protoporphyrin IX formation in normal skin of hairless mice after application of 5-aminolevulinic acid methyl ester."<br>THE JOURNAL OF INVESTIGATIVE DERMATOLOGY<br>NOV 2005,<br>vol. 125, no. 5, November 2005 (2005-11),<br>pages 1039-1044, XP002485543<br>ISSN: 0022-202X<br>the whole document | 1-34                  |
| X         | JUZENIENE ASTA ET AL: "Topical application of 5-aminolevulinic acid and its methylester, hexylester and octylester derivatives: considerations for dosimetry in mouse skin model."<br>PHOTOCHEMISTRY AND PHOTOBIOLOGY SEP 2002,<br>vol. 76, no. 3, September 2002 (2002-09),<br>pages 329-334, XP002485544<br>ISSN: 0031-8655<br>abstract                              | 1-34                  |
| X         | WO 02/10120 A (PHOTOCURE ASA [NO]; GOLDING LOUISE [GB]; KLAVENESS JO [NO]; NILSEN NIL) 7 February 2002 (2002-02-07)<br>the whole document<br>page 40, paragraph 2 - page 45, paragraph 4                                                                                                                                                                               | 1-34                  |
| X         | WO 2006/051269 A (PHOTOCURE ASA [NO]; GOLDING LOUISE [GB]; GODAL ASLAK [NO]; KLAVENESS J) 18 May 2006 (2006-05-18)<br>the whole document<br>examples 3,6,7,10; table 1                                                                                                                                                                                                 | 1-26,<br>28-34        |
| X         | WO 98/30242 A (PHOTOCURE AS [NO]; DZIEGLEWSKA HANNA EVA [GB]; PENG QIAN [NO]; NESLAND) 16 July 1998 (1998-07-16)<br>the whole document<br>page 31, paragraph 6 - page 32, paragraph 1                                                                                                                                                                                  | 1-34                  |
| X         | ITOH Y ET AL: "PHOTODYNAMIC THERAPY FOR ACNE VULGARIS WITH TOPICAL 5-AMINOLEVULINIC ACID"<br>ARCHIVES OF DERMATOLOGY, XX, XX,<br>vol. 136, no. 9,<br>1 September 2000 (2000-09-01), pages<br>1093-1095, XP008038787<br>ISSN: 0003-987X<br>the whole document                                                                                                           | 1-34                  |

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## INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                  | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | POLLOCK B ET AL: "Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action."<br>THE BRITISH JOURNAL OF DERMATOLOGY SEP 2004,<br>vol. 151, no. 3, September 2004 (2004-09),<br>pages 616-622, XP001222029<br>ISSN: 0007-0963<br>the whole document | 1-26,<br>28-34        |
| X         | WIEGELL, STINE REGIN ET AL: "Pain associated with photodynamic therapy using 5-aminolevulinic acid or 5-aminolevulinic acid methylester on tape-stripped normal skin"<br>ARCHIVES OF DERMATOLOGY, 139(9),<br>1173-1177 CODEN: ARDEAC; ISSN: 0003-987X,<br>2003, XP008093462<br>the whole document                                   | 1-26,<br>28-34        |
| X         | WO 03/077911 A (ALLERGAN INC [US])<br>25 September 2003 (2003-09-25)<br>abstract<br>page 25, line 17 - page 28, line 7                                                                                                                                                                                                              | 1-25,<br>27-34        |
| X         | US 2004/048842 A1 (MCMILLAN KATHLEEN [US])<br>11 March 2004 (2004-03-11)<br>abstract; example 2                                                                                                                                                                                                                                     | 1-25,<br>27-34        |
| X         | WO 2005/092838 A (PHOTOCURE ASA [NO];<br>BRAENDEN JON ERIK [NO]; GODAL ASLAK [NO];<br>NILSEN N) 6 October 2005 (2005-10-06)<br>abstract<br>page 18, paragraph 5<br>page 21, paragraph 2 - page 22, paragraph 5                                                                                                                      | 1-34                  |
| X         | TARSTEDT MIKAEL ET AL: "A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp."<br>ACTA DERMATO-VENEREOLOGICA 2005,<br>vol. 85, no. 5, 2005, pages 424-428,<br>XP008093469<br>ISSN: 0001-5555<br>the whole document            | 1-25,<br>27-34        |
| A         | WO 96/28412 A (NORWEGIAN RADIUM HOSPITAL<br>RESE [NO]; DZIEGLEWSKA HANNA EVA [GB];<br>GIERS) 19 September 1996 (1996-09-19)<br>the whole document<br>example 14                                                                                                                                                                     | 1-34                  |
|           | -----<br>-/--<br>-----                                                                                                                                                                                                                                                                                                              |                       |

## INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                      | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | HÖRFELT C ET AL: "Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study."<br>THE BRITISH JOURNAL OF DERMATOLOGY SEP 2006,<br>vol. 155, no. 3, September 2006 (2006-09),<br>pages 608-613, XP002485547<br>ISSN: 0007-0963<br>the whole document<br>----- | 1-34                  |
| A         | CASAS, A. ET AL: "Photosensitization and mechanism of cytotoxicity induced by the use of ALA derivatives in photodynamic therapy"<br>BRITISH JOURNAL OF CANCER , 85(2), 279-284<br>CODEN: BJCAAI; ISSN: 0007-0920, 2001,<br>XP002485548<br>-----                                                                                        | 1                     |

# INTERNATIONAL SEARCH REPORT

International application No.  
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## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 29 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

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

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/000086

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s)                                                                                                                                                                                                                  | Publication<br>date                                                                                                                                                                              |
|-------------------------------------------|----|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| WO 0210120                                | A  | 07-02-2002          | AT 349417 T<br>AU 2749502 A<br>CA 2416307 A1<br>CN 1460099 A<br>CZ 20030260 A3<br>DE 60125555 T2<br>DK 1313695 T3<br>EP 1313695 A1<br>ES 2276844 T3<br>HU 0301427 A2<br>JP 2004505105 T<br>NO 20030398 A<br>NZ 523927 A<br>US 2004106679 A1 | 15-01-2007<br>13-02-2002<br>07-02-2002<br>03-12-2003<br>18-06-2003<br>11-10-2007<br>30-04-2007<br>28-05-2003<br>01-07-2007<br>29-09-2003<br>19-02-2004<br>12-03-2003<br>30-07-2004<br>03-06-2004 |
| WO 2006051269                             | A  | 18-05-2006          | AU 2005303565 A1<br>CA 2586195 A1<br>CN 101056626 A<br>EP 1814534 A1                                                                                                                                                                        | 18-05-2006<br>18-05-2006<br>17-10-2007<br>08-08-2007                                                                                                                                             |
| WO 9830242                                | A  | 16-07-1998          | AU 731042 B2<br>AU 5492698 A<br>BR 9807055 A<br>CA 2275659 A1<br>CN 1243445 A<br>EP 1015030 A2<br>HU 0000057 A2<br>JP 2001501970 T<br>NO 993393 A<br>NZ 336568 A<br>PL 334565 A1<br>RU 2194532 C2<br>US 2002061871 A1                       | 22-03-2001<br>03-08-1998<br>02-05-2000<br>16-07-1998<br>02-02-2000<br>05-07-2000<br>28-10-2000<br>13-02-2001<br>09-09-1999<br>20-12-2002<br>13-03-2000<br>20-12-2002<br>23-05-2002               |
| WO 03077911                               | A  | 25-09-2003          | AU 2003224654 A1<br>US 2003176411 A1                                                                                                                                                                                                        | 29-09-2003<br>18-09-2003                                                                                                                                                                         |
| US 2004048842                             | A1 | 11-03-2004          | AU 2003270536 A1<br>WO 2004024144 A1                                                                                                                                                                                                        | 30-04-2004<br>25-03-2004                                                                                                                                                                         |
| WO 2005092838                             | A  | 06-10-2005          | AU 2005225616 A1<br>CA 2561050 A1<br>CN 1938264 A<br>EP 1727786 A1<br>JP 2007530523 T<br>US 2008064752 A1                                                                                                                                   | 06-10-2005<br>06-10-2005<br>28-03-2007<br>06-12-2006<br>01-11-2007<br>13-03-2008                                                                                                                 |
| WO 9628412                                | A  | 19-09-1996          | AT 202076 T<br>AU 708076 B2<br>AU 4950096 A<br>CN 1178521 A<br>CZ 9702848 A3<br>DE 69613365 D1<br>DE 122006000051 I1<br>DE 69613365 T2<br>EP 0820432 A1<br>ES 2157424 T3<br>HU 9800460 A2                                                   | 15-06-2001<br>29-07-1999<br>02-10-1996<br>08-04-1998<br>18-03-1998<br>19-07-2001<br>04-01-2007<br>02-05-2002<br>28-01-1998<br>16-08-2001<br>28-07-1998                                           |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/000086

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 9628412                                | A                   | JP 3955093 B2              | 08-08-2007          |
|                                           |                     | JP 11501914 T              | 16-02-1999          |
|                                           |                     | LU 90956 A9                | 13-11-2002          |
|                                           |                     | NL 300176 I1               | 02-05-2005          |
|                                           |                     | NL 300207 I1               | 01-12-2005          |
|                                           |                     | NO 974163 A                | 09-09-1997          |
|                                           |                     | NO 2005019 I1              | 26-09-2005          |
|                                           |                     | NO 2005024 I1              | 14-11-2005          |
|                                           |                     | NZ 303251 A                | 27-10-2000          |
|                                           |                     | PT 820432 T                | 28-09-2001          |
|                                           |                     | US 6034267 A               | 07-03-2000          |

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