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(51) International Patent Classification ⁵ : A61K 31/00, 31/445, 31/245 A61K 31/435, 31/46	A3	(11) International Publication Number: WO 94/00113 (43) International Publication Date: 6 January 1994 (06.01.94)
(21) International Application Number: PCT/GB93/01330 (22) International Filing Date: 24 June 1993 (24.06.93) (30) Priority data: 9213708.2 27 June 1992 (27.06.92) GB 9214399.9 7 July 1992 (07.07.92) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : SANGER, Gareth, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 14 April 1994 (14.04.94)
(54) Title: MEDICAMENTS CONTAINING 5-HT ₄ RECEPTOR ANTAGONISTS		
(57) Abstract A method for the treatment and/or prophylaxis of gastrointestinal disorders associated with upper gut motility and/or emesis in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, and effective and/or prophylactic amount of a 5-HT ₄ receptor antagonist.		

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INTERNATIONAL SEARCH REPORT

International Application No **PCT/GB 93/01330**

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 31/00 A 61 K 31/445 A 61 K 31/245 A 61 K 31/435 A 61 K 31/46		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	FASEB J. vol. 6, no. 4, 1992 page A1560 E.LEUNG ET AL. 'CHARACTERIZATION OF 5-HT4 RECEPTORS IN THE RAT ESOPHAGEAL MUSCULARIS MUCOSAE BY SDZ 205,557' see abstract ---	1-7
X	EUR.J.PHARMACOL. vol. 204, no. 3, 12 November 1991 pages 273 - 280 P.BHANDARI ET AL. 'PRELIMINARY EVIDENCE FOR THE INVOLVEMENT OF THE PUTATIVE 5-HT4 RECEPTOR IN ZACOPRIDE- AND COPPER SULPHATE-INDUCED VOMITING IN THE FERRET' & IBIDEM vol. 211, no. 3, 18 February 1992 page 430 see abstract ---	1-7
¹⁰ 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 "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		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
30-11-1993	18.03.94	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	THEUNS	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X, P	BR.J.PHARMACOL. vol. 107 , October 1992 page 125P M.V.WAIKAR ET AL. 'PROC.SUPPL.OCT.- DAU 6285: A PROBE FOR THE 5-HT ₄ RECEPTOR IN RAT OESOPHAGUS AND MONKEY BLADDER' see abstract ---	1-7
X	EUR.J.PHARMACOL. vol. 211, no. 1 , 28 January 1992 pages 117 - 120 A.P.D.W.FORD ET AL. '5-HYDROXYTRYPTAMINE STIMULATES CYCLIC AMP FORMATION IN THE TUNICA MUSCULARIS MUCOSAE OF THE RAT OESOPHAGUS VIA 5-HT ₄ RECEPTORS' see abstract ---	1-7
X	EP,A,0076530 (JANSSEN PHARMACEUTICA N.V.) 13 April 1983 see page 34, paragraph 1 see page 40, paragraph 3 ---	1-7
X	EUR.J.PHARMACOL. vol. 181, no. 1-2 , 1990 pages 119 - 125 H.W.VAN DEN BRINK ET AL. 'R 50 595, A SELECTIVE NON-COMPETITIVE ANTAGONIST OF CISAPRIDE, BRL 24924 AND 5-HYDROXYTRYPTAMINE ON THE GUINEA-PIG ILEUM' see the whole document ---	1-7
X, P D	WO,A,9303725 (SMITH-KLINE BEECHAM PLC) 4 March 1993 cited in the application see page 2, line 5 - line 9 see page 10, line 20 - line 24 ---	1-7
X, P D	WO,A,9302677 (SMITH-KLINE BEECHAM P.L.C.) 18 February 1993 cited in the application see page 2, line 18 - line 22 see page 9, line 33 - page 10, line 16 ---	1-7
X, P D	WO,A,9305038 (SMITH-KLINE BEECHAM PLC) 18 March 1993 cited in the application see page 2, line 9 - line 13 ---	1-7
X, P D	EP,A,0501322 (GLAXO GROUP LIMITED) 2 September 1992 cited in the application see page 5, line 28 - line 29 ---	1-7
X, P D	WO,A,9305040 (SMITH-KLINE BEECHAM PLC) 18 March 1993 cited in the application see page 5, line 27 - page 6, line 8 --- -/-	1-7

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0309423 (INSTITUTO DE ANGELI S.P.A.) 29 March 1989 see page 2, line 4 - line 15 ---	1-7
X,P	EP,A,0505322 (SANDOZ L.T.D.) 23 September 1992 see page 20, line 38 - line 43 ---	1-7
X,P	FR,A,2674853 (SYNTHELABO) 9 October 1992 see page 20, line 20 - line 36 ---	1-7
X,P	WO,A,9308187 (SMITH-KLINE BEECHAM PLC) 29 April 1993 see page 2, line 10 - line 14 ---	1-7
E	WO,A,9316072 (SMITH-KLINE BEECHAM PLC) 19 August 1993 see page 2, line 10 - line 12 ---	1-7
X	ALIMENT.PHARMACOL.THER. vol. 6, no. 3, June 1992 pages 273 - 289 N.J.TALLEY 'REVIEW ARTICLE: 5-HYDROXYTRYPTAMINE AGONISTS AND ANTAGONISTS IN THE MODULATION OF GASTROINTESTINAL MOTILITY AND SENSATION: CLINICAL IMPLICATIONS' see page 281; table 4 -----	1-7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/01330

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:
Please see attached sheet ../..

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

For further information please see form PCT/ISA/206 sent to you 12.01.1994.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

MEANINGFUL SEARCH NOT POSSIBLE OR INCOMPLETE SEARCH

1. The subject matter of claim 8 violates the requirements of Art. 6 and Rule 6.2 PCT. For that reason, no search was performed for the subject matter of claim 8.
2. The attention of the Applicant is drawn to the fact that an additional separate search was needed for identifying the compounds mentioned in claim 7. Claim 7 consequently lacks ready comprehensibility (Art. 6 PCT).
3. In view of the definition of compounds by means of their pharmacological profile rather than by structural parameters, the search (within the framework of the first subject of the lack of unity objection) was limited to such compound(s) for which a structural identification was possible (Art. 6 PCT; Guidelines B-II, 7, last sentence, and B-III, 3.7).
4. With regard to claims 1-6, the attention of the Applicant is drawn to the fact that the ISA is not in the position to perform experiments in order to identify known compounds having the presently claimed pharmacological utility as 5-HT₄ antagonists, or to assess the 5-HT₃/5-HT₄ antagonism ratio. As a consequence it may very well be that relevant prior art has not been retrieved (Art. 6 PCT).
5. Although claims 1-7 are directed to a method of treatment of the human/animal body (Rule 39.1(iv) PCT) the search has been based on the alleged effects of the compound/composition.
6. FR-A-76530 presumably should read EP-A-0076530.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9301330
SA 75940

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP-A- 0076530	13-04-83	AU-B-	553845	31-07-86
		AU-A-	8892582	14-04-83
		CA-A-	1183847	12-03-85
		US-A-	4962115	09-10-90
		US-A-	5057525	15-10-91
		US-A-	5137896	11-08-92
		SU-A-	1593569	15-09-90

WO-A- 9303725	04-03-93	None		

WO-A- 9302677	18-02-93	AU-A-	2363492	02-03-93

WO-A- 9305038	18-03-93	AU-A-	2491092	05-04-93
		AU-A-	2541892	05-04-93
		WO-A-	9305040	18-03-93
		PT-A-	100854	29-10-93
		PT-A-	100855	30-11-93
		AU-A-	2435092	16-03-93
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		AU-B-	3457293	03-09-93
		WO-A-	9316072	19-08-93
		WO-A-	9324117	09-12-93
		WO-A-	9400113	06-01-94

EP-A- 0501322	02-09-92	AU-B-	645402	13-01-94
		AU-A-	1209492	15-09-92
		WO-A-	9214727	03-09-92

WO-A- 9305040	18-03-93	AU-A-	2491092	05-04-93
		AU-A-	2541892	05-04-93
		WO-A-	9305038	18-03-93
		PT-A-	100854	29-10-93
		PT-A-	100855	30-11-93

EP-A- 0309423	29-03-89	AU-A-	2237888	23-03-89
		JP-A-	1106882	24-04-89
		SU-A-	1676451	07-09-91
		US-A-	5223511	29-06-93

EPO FORM P0079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301330

SA 75940

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0505322	23-09-92	AU-A- 1309292	24-09-92
		JP-A- 5086026	06-04-93
FR-A- 2674853	09-10-92	None	
WO-A- 9308187	29-04-93	AU-A- 2752692	21-05-93
WO-A- 9316072	19-08-93	AU-A- 2541892	05-04-93
		AU-B- 3457293	03-09-93
		CN-A- 1073173	16-06-93
		WO-A- 9305038	18-03-93