

PCTWORLD INTELLECTUAL PROPERTY
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INTERNATIONAL APPLICATION PUBLISHED UNDER

WO 9608238A1

(51) International Patent Classification ⁶ : A61K 31/00, 31/415, 31/31, 9/20, 47/26	A1	(11) International Publication Number: WO 96/08238 (43) International Publication Date: 21 March 1996 (21.03.96)
(21) International Application Number: PCT/EP95/03572 (22) International Filing Date: 12 September 1995 (12.09.95) (30) Priority Data: 9418530.3 14 September 1994 (14.09.94) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BYE, Alan [GB/GB]; Glaxo Research and Development Limited, Greenford Road, Greenford, Middlesex UB6 0HE (GB). EVANS, Jill [GB/GB]; Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). HUCKLE, Paul, Derrick [GB/GB]; Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). LACEY, Laurence, Francis [GB/GB]; Glaxo Research and Development Limited, Greenford Road, Greenford, Middlesex UB6 0NN (GB). RUE, Peter, John [GB/GB]; Gilvus Oak, Park Road, Elsenham, Bishop's Stortford CM22 6DF (GB).		(74) Agents: VOLCKMAN, Janis, Florence et al.; Glaxo Wellcome plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, 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), ARIPO patent (KE, MW, SD, SZ, UG). 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>
(54) Title: USE OF PARACELLULAR ABSORPTION ENHANCERS SUCH AS GLUCOSE FOR ENHANCING THE ABSORPTION OF HISTAMINE H ₂ -ANTAGONISTS (57) Abstract The present invention relates to a method and pharmaceutical compositions for improving the absorption of drug substances, especially histamine H ₂ -receptor antagonists, such as ranitidine, following oral administration.		

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USE OF PARACELLULAR ABSORPTION ENHANCERS SUCH AS GLUCOSE FOR ENHANCING THE ABSORPTION OF HISTAMINE H₂ - ANTAGONISTS

The present invention relates to a method for improving the absorption of drug substances, especially histamine H₂-receptor antagonists, such as ranitidine, following oral administration.

Histamine H₂-receptor antagonists are preferably administered orally and, following oral administration, are absorbed paracellularly (i.e. through the tight junctions between cells of the intestinal mucosa). Although histamine H₂-receptor antagonists are sufficiently well-absorbed following oral administration to effect treatment, enhancement of drug absorption would be advantageous since this would enable lower doses to be effective (enhanced extent of absorption) and would provide more rapid relief from symptoms (enhanced rate of absorption).

It has been reported that certain monosaccharides and amino acids stimulate cytoskeleton contraction to open up paracellular spaces to a sufficient size to pass molecules of a high molecular weight. Thus, Nellans (Nellans, H.N., Adv. Drug Delivery, 1991; 7:339-364) suggested that manipulation of the paracellular pathway could be used to enhance the oral delivery of small peptides and peptidomimetics. However, to date reports of the effects of nutrients such as glucose on intestinal absorption are conflicting and inconclusive. Some in vitro models have suggested that glucose may enhance paracellular absorption. However, Nellans (see above) failed to observe any positive effect on absorption using luminal glucose in vivo suggesting that positive in vitro results may be offset in vivo by secretory water flow such that little or no increase in absorption is observed. However, studies in intact rats with zidovudine (Fleisher, D. et al, Pharm. Res., 7, no. 9, Suppl., S154, 1990) suggest that D-glucose may have a positive effect on paracellular absorption of zidovudine.

There has been no suggestion to date that paracellular absorption enhancers may enhance the absorption of histamine H₂-receptor antagonists or similar drugs.

A method of significantly enhancing the absorption of drug substances, especially histamine H₂-receptor antagonists following oral administration has now been found.

5 Thus, the present invention provides, in one aspect, the use of one or more paracellular absorption enhancers to significantly enhance the absorption of an orally administered drug substance, especially a histamine H₂-receptor antagonist, such as ranitidine, or a physiologically acceptable salt thereof.

10 In a further aspect the invention provides the use of a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof, and one or more paracellular absorption enhancers in the manufacture of medicaments for simultaneous, separate or sequential use in the treatment of gastrointestinal disorders, characterised in that the paracellular absorption enhancer(s)
15 significantly enhances the absorption of the histamine H₂-antagonist.

In a further aspect the invention provides the use of an orally administerable pharmaceutical composition comprising a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof, and one or more paracellular absorption
20 enhancers for the manufacture of medicaments for the treatment of gastrointestinal disorders, characterised in that the paracellular absorption enhancer(s) significantly enhances the absorption of the histamine H₂-antagonist.

25 In a further aspect, the invention provides a method of treatment of gastrointestinal disorders comprising orally administering to a sufferer an effective amount of a pharmaceutical composition comprising a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof and one or more paracellular absorption enhancers, wherein the paracellular absorption
30 enhancer significantly enhances the absorption of the histamine H₂-antagonist.

The term "paracellular absorption enhancer" as used herein encompasses any compound which enhances paracellular absorption. For example, the paracellular absorption enhancers are those which occur naturally in nutrients.
35 Paracellular absorption enhancers include carbohydrates such as monosaccharides, e.g. glucose, galactose, mannose, 3-O-methyl glucose,

xylose, ribose, arabinose, ribulose, fructose and sorbose. The monosaccharides may be employed in either their D- or L- forms. Where the monosaccharide is naturally occurring, the naturally occurring form is preferred.

5 Preferred paracellular absorption enhancers include glucose, e.g. D-glucose. A further preferred group of paracellular absorption enhancers includes galactose, e.g. D-galactose, mannose, e.g. D-mannose, 3-O-methyl glucose, e.g. 3-O-methyl D-glucose, xylose, e.g. D-xylose.

10 It will be appreciated that the paracellular absorption enhancer(s) employed in the instant invention will be of the reversible type i.e. one whose absorption enhancement effect rapidly diminishes when it is no longer present at the site of action. All of the paracellular absorption enhancers specifically mentioned above are of the reversible type.

15

The paracellular absorption enhancers may be used alone or in combination.

20 International Patent Specification No. WO 94/08560 describes chewable ranitidine tablets having inter alia glucose as a chewable base. Chewable tablets according to WO 94/08560 are excluded from the present invention.

25 The term "gastrointestinal disorders" as used herein encompasses a disease or other disorder of the gastrointestinal tract, including for example acid indigestion, overindulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn and meal-induced heartburn, gastritis and dyspepsia, duodenal and gastric ulceration, reflux oesophagitis and Zollinger-Ellison syndrome.

30 It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

35 Histamine H₂-receptor antagonists which may be used in the instant invention include ranitidine, cimetidine, famotidine and nizatidine, and physiologically acceptable salts thereof. A preferred histamine H₂-receptor antagonist for use in the instant invention is ranitidine and physiologically acceptable salts thereof. Such physiologically acceptable salts include salts formed with inorganic or

organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate, citrate, tartrate, fumarate and ascorbate salts. A particularly preferred salt of ranitidine is the hydrochloride.

5 Further ranitidine salts for use in the instant invention are those formed between ranitidine and a complex of bismuth with a carboxylic acid, particularly tartaric acid and, more especially, citric acid. A preferred salt of this class is ranitidine bismuth citrate.

10 It will be appreciated that the paracellular absorption enhancers enhance absorption of the histamine H₂-receptor antagonists following dissociation from their salts.

As mentioned hereinbefore, paracellular absorption enhancers have been found
15 to significantly enhance the absorption of drug substances following oral administration. Surprisingly, both the extent and rate of absorption are enhanced. In the case of histamine H₂-antagonists, the extent and rate of absorption are enhanced with the rate of absorption being increased to an unexpected, surprisingly large degree. Thus, in the case of ranitidine, rates of
20 absorption in human volunteers have been increased by more than 80% compared with appropriate controls.

Thus, according to a further aspect, the present invention provides a method of
25 significantly enhancing the rate of absorption of a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof, by simultaneous, separate or sequential administration of the histamine H₂-receptor antagonist with one or more paracellular absorption enhancers.

The drug substance, e.g. the histamine H₂-receptor antagonist, and one or more
30 paracellular absorption enhancers may be co-administered in the form of separate pharmaceutical compositions for simultaneous and/or sequential use. Preferably, the drug substance, e.g. the histamine H₂-receptor antagonist, and paracellular absorption enhancer(s) are administered as a single pharmaceutical composition for oral use comprising effective amounts of the
35 active ingredients.

Thus, according to a further aspect, the invention provides a pharmaceutical composition for oral use comprising a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof, and one or more paracellular absorption enhancers.

Particularly suitable pharmaceutical compositions according to the instant invention are effervescent tablets or granules, dispersible tablets and liquid syrups or suspensions. Effervescent tablets or granules are particularly preferred.

When the pharmaceutical composition according to the invention is a chewable tablet containing ranitidine, the paracellular absorption enhancer is preferably galactose, mannose, 3-O-methyl glucose, xylose, ribose, arabinose, ribulose, fructose or sorbose.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Suitable methods of formulation are known in the art and include those methods described in UK Patent Specification Nos 2198352 (liquid preparations),

2219940 (effervescent tablets), 2218333 (ranitidine resinate), 2218336 (film-coated tablets), 2229094 (gelatin capsules), 2262445 (pulsed-release formulation), European Patent Specification Nos 349103, 459695, 473431, 523847 and 538034 (chewable tablets), 542364 (controlled-release formulations), International Patent Specification Nos W092/21328 (chewable compositions), WO94/08560 (chewable tablets), W094/05260 (aqueous compositions), WO94/08576 (lipid-coated granules), Canadian Patent Specification No. 2068366 (taste-masked powder), United States Patent Specification Nos 5169864 and 5304571 (aqueous compositions) which patent specifications are incorporated herein by reference. The paracellular absorption enhancer(s) may be incorporated into the above-mentioned formulations according to conventional procedures.

The histamine H₂-receptor antagonist and paracellular absorption enhancer(s) may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the histamine H₂-receptor antagonist and paracellular absorption enhancer(s) may be administered in combination with an antacid, such as calcium carbonate, an analgesic, an antiflatulent, a glucopyranoside, an alginate, a gastrointestinal motility agent, or an antihistamine, or a combination of these. For example, suitable combination formulations are described in International Patent Specification Nos W092/00102, W093/12779 and W093/21932 (combination with antacids), W094/07541 (combination with (s)-ibuprofen salt), WO95/01784 (combination with glucopyranoside), WO95/01792 (combination with antihistamine), WO/01795 (combination with alginate), WO95/01803 (combination with gastrointestinal motility agent), European Patent Specification Nos 426479 (combination with analgesics) and 571217 (combination with antiflatulent) and UK Patent Specification Nos 2105193 (combination with NSAID's) and 2222772 (combination with alginate) which patent specifications are incorporated herein by reference. The paracellular absorption enhancer(s) may be incorporated into the above-mentioned formulations according to conventional procedures.

It will be appreciated that the amount of paracellular absorption enhancer(s) employed in the instant invention is sufficient to provide an absorption enhancing effect.

5 Thus, the ratio of drug substance, e.g. histamine H₂-antagonist, to paracellular absorption enhancer(s) used in the method or compositions according to the invention is in the range of 1:1 to 1:1000 (by weight), e.g. 1:4 to 1:300, such as 1:4 to 1:150, especially 1:80 or 1:40 (by weight).

10 The amount of histamine H₂-receptor antagonist used according to the instant invention is preferably in the range of 10 to 800mg per dosage unit. For example, when ranitidine is employed, the amount of ranitidine in the composition is preferably in the range of 10 to 600mg, more preferably 25 to 300mg, such as 25, 75, 125 or 150mg expressed as the weight of free base.

15 The unit dose (for example contained in one tablet according to the invention) may be administered up to, for example, 12 times a day depending upon the unit dose used, the nature and severity of the conditions being treated, and the age and weight of the patient.

20 Chewable tablets may be prepared using the conventional stages of mixing, granulation, drying, blending, compression and packing.

25 Suitable swallow tablet cores may be prepared in a conventional manner, for example in a similar manner to that described in British Patent Specification No. 2084580 which is incorporated herein by reference. Thus, for example the required quantities of ranitidine or its salt, the paracellular absorption enhancer(s), a lubricant, such as magnesium stearate and optionally a pharmaceutically acceptable disintegrant, such as croscarmellose sodium, are
30 mixed and compressed into tablet cores.

Swallow tablets are conventionally film-coated according to conventional procedures either by aqueous or organic techniques. A preferred film coat is described in British Patent specification No. 2218336 which is incorporated
35 herein by reference.

Effervescent formulations may be prepared in a conventional manner, for example in a similar manner to that described in UK patent specification no. 2219940 which is incorporated herein by reference. Thus, ranitidine or its salt, monoalkali metal citrate, and alkaline carbonate or bicarbonate may, for example, be blended with the paracellular absorption enhancer(s) and suitable excipients and, if desired, granulated. If the manufacturing process includes granulation, this should precede the addition of any flavouring agent(s). Any sweetening agents may be added either before or after granulation. Tablets may be prepared, for example, by compression of the powder blend or granulate, using a lubricant as an aid to tableting.

The following are illustrations of non-limiting examples of pharmaceutical compositions according to the invention. Opaspray white K-1-7000 is a suspension of titanium dioxide and hydroxypropyl cellulose in industrial methylated spirits. Opadry Yellow Y S-1-12606 is a mixture of hydroxypropyl methylcellulose 2910, titanium dioxide, triacetin and iron oxide yellow. Both Opaspray and Opadry are the tradenames of Colorcon Inc., West Point, Philadelphia, USA.

In the following examples, the exemplified paracellular absorption enhancer may be replaced by any of the suitable paracellular or absorption enhancers described herein. Thus, for example, D-glucose may be replaced by D-galactose, mannose, 3-O-methyl glucose or xylose.

Example 1
Chewable Tablet

Ingredient	mg/tablet
Ranitidine HCl	28.0
D-galactose	2268.0
Aspartame	37.5
Povidone	50.0
Peppermint Flavour	41.5
Silica Gel	50.0
Magnesium Stearate	25.0
Isopropyl Alcohol +	qs

+ not present in final product

5 Example 2
Swallow Tablet

Tablet Core	mg/tablet
Ranitidine HCl	28.0
D-glucose	263.75
Croscarmellose Sodium Type A	6.00
Magnesium Stearate	2.25
Target compression weight	300mg

Film Coat	% w/w	Unit amounts (mg/tablet)*
Methylhydroxypropyl Cellulose	4.0	11.3
Opaspray White K-1-7000	3.3	4.7
Isopropyl Alcohol **	26.3	qs
Dichloromethane **	66.4	qs

- 10 * The amount of film coat applied per tablet may be less than that stated, depending on the efficiency of the process.

** Not present in the final product.

15 Example 3
Swallow Tablet

Tablet Core	Unit Amounts (mg/tablet)
Ranitidine HCl	28.000
Microcrystalline Cellulose	92.875
D-xylose	28.0
Magnesium Stearate	1.125
Total Compression Weight	150.00

Film Coat	Unit Amounts (mg/tablet)
Opadry Yellow YS-1-12606	6.75
Purified Water **	42.34

** Removed during processing

5

Example 4

Effervescent Tablet

	(a) mg/ tablet	(b) mg/ tablet	(c) mg/ tablet	(d) mg/ tablet
Ranitidine HCl	168.0	168.0	168.0	84.0
D-glucose	3000.0	3000.0	3000.0	3000.0
Anhydrous Monosodium Citrate	840.0	838.0	935.0	467.5
Sodium Bicarbonate	836.0	834.0	267.0	133.5
Saccharin Sodium	11.0	-	-	-
Aspartame	-	30.0	30.0	15.0
Polyvinylpyrrolidone	40.0	40.0	40.0	20.0
Sodium Benzoate	80.0	60.0	60.0	30.0
Lemon Flavour Powder	25.0	-	-	-
Orange Flavour Powder	-	20.0	qs	qs
Grapefruit Flavour Powder	-	10.0	qs	qs
Pharmaceutical Alcohol For Granulation				

Example 5Effervescent Granules

	(a) mg/sachet	(b) mg/sachet
Ranitidine HCl	168.0	84.0
D-glucose	3000.0	3000.0
Anhydrous Monosodium Citrate	618.72	309.36
Sodium Bicarbonate	615.78	307.89
Aspartame	22.50	11.25
Polyvinylpyrrolidone	52.50	26.25
Orange Flavour Powder	15.0	7.50
Grapefruit Flavour Powder	7.50	3.75
Pharmaceutical Alcohol For Granulation		

5 Example 6Oral Liquid

Amount of ranitidine free base per 10ml	(a) 150mg	(b) 75mg
Ranitidine HCl	1.68g	8.4g
D-glucose	10.0g	10.0g
Ethanol	7.5g	7.5g
Potassium Dihydrogen Orthophosphate	0.095g	0.095g
Disodium Hydrogen Orthophosphate Anhydrous	0.350g	0.350g
Hydroxypropylmethylcellulose	qs	qs
Preservative	qs	qs
Sweetening Agents	qs	qs
Flavour	qs	qs
Purified water BP to	100ml	100ml

Biological Data

- 10 A crossover study in 8 healthy volunteers was carried out to investigate the effects of 0.0, 0.3, 1.0, and 3.0g of D-glucose on the rate and extent of absorption of ranitidine. Volunteers received on separate occasions a solution of ranitidine hydrochloride (75mg) and D-glucose (0.3, 1.0, or 3.0g) dissolved in

50ml of water followed by a further 150ml of tap water. Blood samples for determination of plasma ranitidine concentrations were taken up to 6 hours post dose.

5 A second crossover study in 8 healthy volunteers investigated the effects of 11 and 22g of D-glucose on the rate and extent of ranitidine absorption. This study used a solution of ranitidine hydrochloride (150mg) and D-glucose dissolved in 100ml water. Concentrations up to 10 hours post-dose were measured. The combined results from both studies are summarised below:

Dose of D-glucose (g)	Dose of Ranitidine HCl (mg)	% Increase in	
		Rate of Absorption ^a	Extent of Absorption ^b
0.3	75	16%	7%
1.0	75	19%	11%
3.0	75	**43%	19%
11	150	**70%	14%
22	150	**82%	*17%

10

a measured using partial area under the plasma ranitidine concentration-time curve from zero to 2 hours post dose.

b measured using total area under the curve from zero to the time of last quantifiable plasma ranitidine concentration.

15 * statistically significant $p < 0.05$

** statistically significant $p < 0.01$

Claims

- 5 1. A pharmaceutical composition for oral use comprising a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof, and one or more paracellular absorption enhancers.
2. A composition according to claim 1 wherein the paracellular absorption enhancer is glucose.
- 10 3. A composition according to claim 1 wherein the paracellular absorption enhancer is selected from galactose, mannose, 3-O-methyl glucose, xylose, ribose, arabinose, ribulose, fructose and sorbose.
- 15 4. A composition according to claim 3 wherein the paracellular absorption enhancer is selected from galactose, mannose, 3-O-methyl glucose and xylose.
5. A composition according to any of claims 1 to 4 wherein the histamine H₂-receptor antagonist is ranitidine or a physiologically acceptable salt thereof.
- 20 6. A composition according to claim 5 containing ranitidine hydrochloride.
7. A composition according to claim 5 or 6 containing 25 to 300mg ranitidine expressed as the weight of free base.
- 25 8. The use of a pharmaceutical composition as defined in any of claims 1 to 7 for the manufacture of a medicament for the treatment of gastrointestinal disorders, characterised in that the paracellular absorption enhancer(s) significantly enhances the absorption of the histamine H₂-antagonist.
- 30 9. A method of treatment of gastrointestinal disorders comprising orally administering to a sufferer an effective amount of a pharmaceutical composition as defined in any of claims 1 to 7 wherein the paracellular absorption enhancer significantly enhances the absorption of the histamine H₂-antagonist.
- 35 10. The use of a histamine H₂-receptor antagonist, or a physiologically acceptable salt thereof, and one or more paracellular absorption enhancers in

the manufacture of medicaments for simultaneous, separate or sequential use in the treatment of gastrointestinal disorders, characterised in that the paracellular absorption enhancer(s) significantly enhances the absorption of the histamine H₂-antagonist.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 95/03572

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/00 A61K31/415 A61K31/31 A61K9/20 A61K47/26

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 08560 (GLAXO GROUP LIMITED) 28 April 1994 cited in the application	1,2,5-10
Y	see claims 1-10 ---	3,4
Y	US,A,5 219 563 (STEPHEN J. DOUGLAS ET AL.) 15 June 1993 see column 3, line 3 - line 45 ---	3,4
Y	WO,A,92 04893 (SMITHKLINE BEECHAM CORPORATION) 2 April 1992 see page 3, paragraph 3 see page 4, paragraph 3; examples 1-9 --- -/--	3,4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

17 January 1996

Date of mailing of the international search report

16.02.96

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INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/EP 95/03572

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,Y	J.PHARM.EXP.THER., vol. 274, no. 2, 1995 pages 826-832, G.FRICKER ET AL. 'Enteral absorption of octreotide: Modulation of intestinal permeability by distinct carbohydrates' see abstract ---	3,4
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		DE-A-	3915347	16-11-89
		DK-B-	168934	11-07-94
		FI-B-	92060	15-06-94
		FR-A-	2631232	17-11-89
		GB-A, B	2218333	15-11-89
		GR-B-	1000358	30-06-92
		HK-A-	45094	13-05-94
		IE-B-	60722	10-08-94
		IL-A-	90245	12-04-94
		JP-A-	2111719	24-04-90
		LU-A-	87515	12-06-90
		NL-A-	8901188	01-12-89
		NO-B-	175131	30-05-94
		PT-B-	90523	31-10-94
		SE-A-	8901671	12-11-89
		SG-A-	48194	25-11-94
		RU-C-	2033155	20-04-95
		US-A-	5032393	16-07-91

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		EP-A-	0548238	30-06-93
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