

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

*
We SANDOZ LTD. of
CH-4002 Basle,
Switzerland.

LODGED AT SUB-OFFICE

18 DEC 1985

Melbourne

ALLOWED 210.1.90

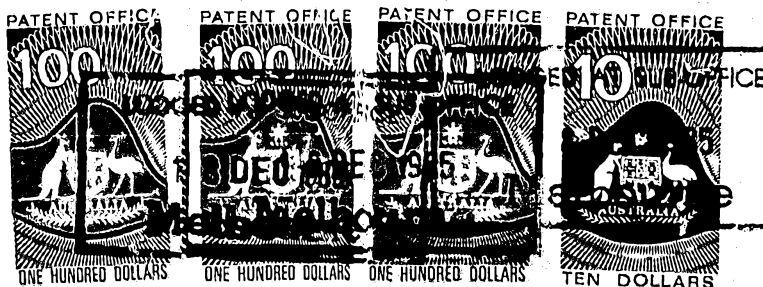
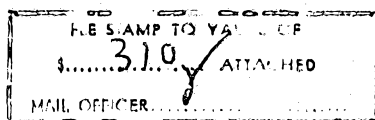
hereby apply for the grant of a Standard Patent for an invention entitled:

~~"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"~~
TREATMENT OF GASTROINTESTINAL DISORDERS

which is described in the accompanying ^{provisional} complete specification.

Details of basic application(s):—

Number	Convention Country	Date
P 3446484.C	Federal Republic of Germany	20th December, 1984
P 3531281.5	Federal Republic of Germany	2nd September, 1985
P 3531282.3	Federal Republic of Germany	2nd September, 1985
1414/85	Switzerland	2nd April, 1985
2667/85	Switzerland	24th June, 1985
3130/85	Switzerland	19th July, 1985
3129/85	Switzerland	19th July, 1985
3383/85	Switzerland	7th August, 1985
3382/85	Switzerland	7th August, 1985



The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 18th day of December 1985

H. M. Rimington

To: THE COMMISSIONER OF PATENTS

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention
entitled: TREATMENT OF GASTROINTESTINAL DISORDERS

Insert title of invention.

Insert full name(s) and address(es)
of declarant(s) being the appli-
cant(s) or person(s) authorized to
sign on behalf of an applicant
company.

KX
We JEAN KRAMER and HANS RUDOLF HAUS, both of
SANDOZ LTD., 35 Lichtstrasse, CH-4002 Basle,
Switzerland

Cross out whichever of paragraphs
1(a) or 1(b) does not apply

1(a) relates to application made
by individual(s)
1(b) relates to application made
by company; insert name of
applicant company.

do solemnly and sincerely declare as follows :-

1. (a) ~~xxxxx~~ the applicant(s) for the patent
We are
or (b) ~~xxxxx~~ authorized by SANDOZ LTD.

Cross out whichever of paragraphs
2(a) or 2(b) does not apply

2(a) relates to application made
by inventor(s)
2(b) relates to application made
by company(s) or person(s) who
are not inventor(s); insert full
name(s) and address(es) of inven-
tors.

the applicant..... for the patent to make this declaration on ^{its} ~~their~~ behalf.

2. (a) ~~xxxxx~~ the inventor(s) of the invention
We are
or (b)

Karl Heinz Buchheit, Breisacherstrasse 22, CH-4057 Basle,
Switzerland; a citizen of the Federal Republic of Germany

~~is~~ the actual inventor..... of the invention and the facts upon which the applicant.....
~~is~~
~~are~~ entitled to make the application are as follows :-

State manner in which applicant(s)
derive title from inventor(s)

The inventor has assigned the invention to the applicant.
The applicant has the consent of Sandoz-Patent-
GMBH to claim priority from the 3 basic German
applications.

Cross out paragraphs 3 and 4
for non-convention applications.
For convention applications,
insert basic country(s) followed
by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ~~was~~ made
in Federal Rep... of Germany..... on the December... 84.....
by SANDOZ-PATENT-GMBH, Humboldtstrasse 3, rrach, Germany;
~~in~~ a German Body Corporate ~~as the~~
~~by~~
in Switzerland..... on the April 2, 1985
by SANDOZ LTD. continuation on separete sheet

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~
the first application..... made in a Convention country in respect of the invention the subject
of the application.

Insert place and date of signature.

Declared at Basle this 27th day of November 1985

Signature of declarant(s) (no
attestation required)

Note: Initial all alterations.

SANDOZ Ltd

duly authorized

DAVIES & COLLISON, MELBOURNE and CANBERRA Officer

duly authorized

in (b) Switzerland, on (c) June 24, 1985
by (d) the said SANDOZ LTD.

in (b) Switzerland on (c) July 19, 1985
by (d) the said SANDOZ LTD.

in (b) Switzerland on (c) July 19, 1985
by (d) the said SANDOZ LTD.

in (b) Switzerland on (c) August 7, 1985
by (d) the said SANDOZ LTD.

in (b) Switzerland on (c) August 7, 1985
by (d) the said SANDOZ LTD.

in (b) Federal Rep. Of Germany on (c) September 2, 1985
by (d) the said SANDOZ-PATENT-GMBH

in (b) Federal Rep. of Germany on (c) September 2, 1985
by (d) the said SANDOZ-PATENT-GMBH

in (b) on (c)
by (d)

(12) PATENT ABRIDGMENT (11) Document No. AU-B-51396/85
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 595172

(54) Title
TREATMENT OF GASTROINTESTINAL DISORDERS

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C07D 451/14 A61K 031/405 A61K 031/435 A61K 031/445

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1414/85	02.04.85	CH SWITZERLAND
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3130/85	19.07.85	CH SWITZERLAND
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(56) Prior Art Documents
, 027837 54255/79 C07D 451/04,451/02,487/04
BE 897117
BE 900425

(57) Claim

1. A method of treating a subject suffering from a serotonin-induced gastro-intestinal disturbance which comprises administering indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1-oct-3-yl ester to a subject in need of such treatment.
6. A method of managing or treating a gastro-intestinal disturbance chosen from the following: diarrhea, spastic colon and irritable bowel syndrome, gastritis, peptic ulcer, biliary dyskinesia, appendicitis, ulcerative colitis, Crohn's disease, carcinoid syndrome, achalasia, hiatus hernia, cardia insufficiency, gastro-oesophageal and gastro-duodenal reflux, stomach hypotonia, pylorus hyperplasia, paralytic ileus and Hirschsprung's disease, which

(11) AU-B-51396/85
(10) 595172

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comprises administering indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester to a subject in need of such treatment.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

Class

Int. Class

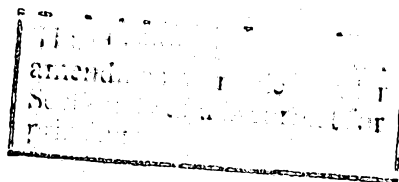
Application Number: 51596/85
Lodged:

Complete Specification Lodged:
Accepted:
Published:

595172

Priority:

Related Art:



Name of Applicant: SANDOZ LTD.

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Actual Inventor(s): Karl Heinz BUCHHEIT

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Complete Specification for the invention entitled:

~~"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"~~

TREATMENT OF GASTROINTESTINAL DISORDERS

The following statement is a full description of this invention,
including the best method of performing it known to us :-



TREATMENT OF GASTROINTESTINAL DISORDERS

The invention relates to treatment of gastrointestinal disorders with esters having serotonin M antagonistic activity (also known as 5-HT₃ antagonism).

5 The essentially antagonistic action against 5-HT of the compound ICS 205-930, indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester, the compound of the invention, (known from Belgian Patent No. 897,117) on the rabbit vagus, rabbit heart and guinea pig ileum has been described (F. Donatsch et al., Br.J.Pharmacol. 1984, 81 34P), and also its topical application to
10 humans as the first 5-HT₃ antagonist. It was stated to be a competitive antagonist of the 5-HT₃ receptors in the guinea pig ileum on the basis of the effect of the compound in counteracting 5-HT induced spasms, these spasms being prolonged and permanent contractions. Moreover, no analysis was disclosed of its action in the
15 guinea pig ileum.

Several drugs e.g. metoclopramide are known for the treatment of gastrointestinal disorders (gut motility disorders). Action has been ascribed to opiates (e.g. loperamide), dopaminergic compounds (e.g.
20 metoclopramide) although for most drugs the mode of action is not well understood (see J.R.Malegelede Scand.J.Gastroenterology, 19, Suppl.96, 1984, pp.115-121). Thus metoclopramide has been shown to have an IC₅₀ of about 170 nM/litre in binding studies for dopamine sites with



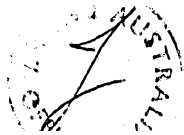
tritiated haloperidol.

European Patent Publication 13138 discloses benzoic acid amides of piperidylamines having an alkylene bridge across ring positions 2 and 6. The compounds are stated to be active inter alia in increasing the
5 intragastric pressure in the rat, in reversing the apomorphine induced delay in gastric emptying in the rat, and inhibiting the apomorphine-induced emetic effect in the rat. The compounds are indicated to be dopamine antagonists and useful in the treatment of impaired
10 dyspepsia, flatulence, esophageal reflux, peptic ulcer and emesis.

The compound of the present invention does not significantly affect apomorphine-induced symptoms. It shows on the other hand a long lasting and potent effect in the treatment of serotonin-induced
15 gastrointestinal disturbances by action on 5-HT₃ receptors. The compound of the invention has thus a different mechanism of action to that stated for those in European Patent Publication 13138 and is well tolerated.

20 Peristaltic movements (Peristalsis) are coordinated contractions and necessary for the proper functioning of the gastrointestinal system. We have now found that activation of 5-HT₃ receptors is involved in provocation of abnormal peristaltic movements and associated gastrointestinal disorders of motility and secretion. Also we have found
25 that serotonin antagonists are useful in decreasing increased peristaltic movements in the intestines and increasing decreased peristaltic movements in the stomach, and are hence indicated for use in the treatment of disorders of gastric motility.

30 We have found that reflexes responsible for different kinds of intestinal reactions such as smooth muscle contractions, secretion by mucosal cells and/or dilation of intestinal blood vessels, a pre-requisite for the secretion of fluids, are stimulated by stimulation of 5-HT₃ receptors located on afferent sensory neurons by 5-HT₃ released on the serosal side and are blocked by 5-HT₃



antagonists.

The action of the compound of the invention is shown in the following tests:-

5 The compound of the invention induces gastric emptying as indicated in standard in vivo tests, e.g. in conscious guinea pigs having stomachs made atonic (i.e. having decreased peristaltic movements) by fasting and wherein the passage of glass spheroids observed by X-ray techniques. The experiment is effected as follows:-

10 Food was withdrawn for 14 hours before the measurement of gastric emptying. The experiment was conducted under low illumination with minimal noise and disturbance, and was carried out only by those experimentors who had daily contact with the guinea pigs and who
15 carried out the initial training to accustom the guinea pigs to handling. Therefore, animals were subject to minimal stress. Measurement of gastric emptying was achieved by X-ray location (50 KV, 30 mA, 0.5 - 0.9 s) using Kodak plates (NS-2T, 13 x 18 cm) of polystyrene-coated barium sulphate spheroids (approximately 30, 1 mm
20 in diameter) which were swallowed by the guinea pigs when placed in the back of the mouth in 0.2 ml of 1% carboxymethylcellulose with 0.05 ml glycerin to initiate prompt and voluntary swallowing. The passage of the spheroids was followed for 3 - 4 h: during this period animals were placed in their normal housing cages and were only removed 5 min
25 prior to X-ray (at 30 - 60 min intervals) when they were placed in an individual perspex holding cage which held the animal comfortably in a stable position: the holding cage was correctly shaped (33 . 15 cm, and 13 cm high) to hold a 450 - 550 g guinea pig between foam - lined sides and an animal trained to entering the cage would do so and remain quiet and unstressed during the X-ray procedure. Gastric
30 emptying was measured as the number of spheroids leaving the stomach.

Six guinea pigs were used at each dose level of drug and responses compared to those of guinea pigs receiving the appropriate vehicle. The significance of differences between drug and control responses

was assessed using the Mann Whitney U test.

The compound of the invention is active at doses of about 0.01 to about 1 mg/kg i.p. in enhancing gastric emptying. The compound was about 50 times more active than metoclopramide.

5

The effect of the compound increasing gastric emptying indicates a increased tonus on the gastrointestinal tract.

The compound of the invention is also indicated for use in inhibiting
10 increased peristaltic movements in the intestines as indicated in the following tests:-

The inhibition of the increase in gastrointestinal motility induced by
15 5-hydroxytryptophan (5-HTP) by the compound of the invention was observed.

Male NMRI mice (18-32 g in weight) were deprived of food 20 hours before the test. Water was not limited. The animals were separated by a barrier from their straw and access to feces. At the beginning of
20 the test the animals were separated in individual single cages and water was removed.

All animals were treated with the test compound or saline. I.p. administration was used. Injection volume was 0.1 ml/10 g. 30 minutes
25 after pre-treatment 5-HTP or saline was administered. Injection volume 0.1 ml/10 g. Dose 3 mg/kg. At the same time charcoal was administered perorally (10% suspension in water; 0.1 ml/10 g). 45 minutes after the start of the experiment the animals were killed. The intestines from the stomach to the rectum were examined. For each animal the transit
30 distance of the front of the charcoal meal along the intestine was measured. The distance was ascertained as a percentage of the whole intestinal length. Groups of at least 3 animals were used.

The compound of the invention inhibits 5-HTP induced motility at doses of about 10 to 100 microg/kg i.p.



ICS 205-930

ED₅₀ i.p.

70 microg/kg

In a further test the compound is shown to inhibit cholera toxic-induced secretory diarrhea which leads to increased peristaltic motility.

5

Method

Male NMRI mice (20-30 g) were deprived of food for 24 hours, but had free access to water. For the duration of the experiment water was subsequently withdrawn. Saline or the test compound were administered intraperitoneally. Four dose levels of each drug were investigated and each dose was given to 5 animals. One hour after pre-treatment with the drug the animals were challenged with 200 micrograms of pure cholera toxin p.o. through a tube to the stomach followed by 2 ml of Tyrode solution. Three hours later the administration of the test compound was repeated. Four hours after the cholera toxin challenge the animals were killed and the content of the whole intestine determined by weighing.

20 Administration protocol

0 hours	Administration of test compound
1 hour	Administration of cholera toxin
3 hours	Repeated addition of test compound
25 4 hours	Sacrifice of animals

The intestinal contents are usually increased under the influence of cholera toxin. This effect was reduced by 50% by the test compound, in particular by 50% at a dose of 100 to 500 micrograms/kg. An increase in the dose of ICS 205-930 did not lead to a reduction in the intestinal contents.

The isolated longitudinal muscle of the guinea pig ileum with its

adhering myenteric plexus is a well established model which permits investigation of the mechanism of action of various neurotransmitters. It does not, however, indicate by itself action of the compound on peristaltic movements.

5 Method

Male guinea pigs (200-400 g) were killed by a blow on the head and exsanguinated. A length of small intestine was removed about 2 cm from the ileo-caecal valve. The mesentery was carefully removed and the
10 ileum was stretched over a glass rod. By stroking tangentially away from the mesenteric attachment with a wad of cotton wool, the longitudinal muscle layer was separated and stripped from the underlying circular muscle. Longitudinal muscle strips, 3 - 4 cm length, were mounted in a 10 ml organ bath containing Tyrode solution
15 at 37°C and bubbled with 5% carbon dioxide in oxygen. The Tyrode solution was of the following composition (mmol/l): NaCl, 137.0; CaCl₂, 1.8; KCl, 2.7; MgCl₂, 1.05; NaHCO₃, 11.9; NaH₂PO₄, 0.4; glucose, 5.6. The strips were placed under a resting tension of 500 mg. Contractions were recorded with a isotonic pendulum lever. After
20 equilibration for 30 min a set concentration of carbachol was applied in 190 min intervals until a consistant reaction was achieved.

Production of the concentration/reaction curve

25 Non-cumulative concentration-response curves for 5-HT were established by adding increasing concentrations of the agonist to the organ bath at intervals of at least 15 min. Preceding experiments showed that the intervals were long enough to avoid tachyphylaxis. Each concentration was left in contact with the tissue for 1 min. Each strip was only
30 used to record two concentration-response curves; the first for 5-HT alone and the second for 5-HT in the presence of a set concentration of antagonist, each strip thus serving as its own control.

Antagonists were allowed to pre-equilibrate for at least 10 min prior to addition of 5-HT. The contractions expressed as percentage of the



maximal response to 5-HT obtained from several preparations were plotted as mean values in order to obtain log-concentration-response curves. Inhibition constants were expressed in the form of pA_2 values which were graphically determined according to conventional methods (Arunlakshana and Schild, 1959, McKay 1978).

- 5 In this test 5-HT elicits a concentration - dependent contractile effect. 5-HT induces its major contractile effects in the longitudinal muscle strip of the guinea pig ileum by releasing substance P from nerve endings within this tissue. Its effect is mediated by two
- 10 different 5-HT receptors. At low concentrations 5-HT activates a neuronal receptor which causes substance P release. The liberated substance P activates neuronal substance P receptors and this causes the release of acetylcholine which subsequently activates muscarinic receptors located on smooth muscle cells and brings about contraction.
- 15 At higher concentrations 5-HT activates a second neuronal receptor which results in release of sufficient quantities of substance P to cause activation of substance P receptors on smooth muscle cells and thereby cause contraction.
- 20 The compound of the invention blocks preferentially the low affinity 5-HT receptors thereby inhibiting 5-HT-induced contractions e.g. at concentrations from about 10^{-7} to about 10^{-9} mol/litre.

	high affinity receptor	low affinity receptor
25 ICS 205-930	$pD'_2 = 5.7$	$pA_2 = 7.9$

- 30 The compound has little affinity for the high affinity 5-HT receptor indicated to be responsible for controlling secretion and motility processes involving acetylcholine release, but has greater affinity for the low affinity serotonin receptor sub-type which is indicated to be involved in pathophysiological abnormal peristaltic movements conditions such as gastroparesis (lack of stomach motility) or diarrhea.

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The compound of the invention preferentially inhibits the 5-HT induced disturbance of the peristaltic reflex without affecting the basal gut reflex activity. This is in contrast to drugs like atropine which paralyse the whole reflex, and metoclopramide which has dopamine antagonist action.

5

The compound of the invention has insignificant action on dopamine binding sites, e.g. having an IC_{50} of 100 mM/litre or more using tritiated haloperidol.

10 Gastrointestinal disorders which result from increased peristaltic movements in the intestinal tract or from decreased peristaltic movements in the stomach are therefore indicated to be treated by blockade of 5-HT₃ neuronal receptors. The compound of the invention is indicated for use in the treatment of gastrointestinal disorders.

15 The compound also inhibits or prevents the action of 5-HT on low affinity 5-HT receptors in the gastrointestinal tract, and therefore is indicated for use in the treatment of disturbances of motility. It is also indicated for use in gastrointestinal disorders where an abnormal increase in the synthesis or liberation of 5-HT from the enterochromaffin cells or neurons taken place without significantly
20 affecting basal secretion or motility. It is also indicated to be well tolerated.

The compound of the invention is therefore indicated for use in the treatment of gastrointestinal disturbances which require antagonism of
25 5-HT₃ receptors.

The compound is indicated for use in the treatment of disorders resulting from increased peristaltic movements in the intestines and intestinal disorders arising from activation of 5-HT₃ receptors,
30 including diarrhea, e.g. secretory diarrhea, bacterial induced diarrhea, choleic diarrhea, traveller's diarrhea and psychogenic diarrhea, spastic colon and irritable bowel syndrome. The compound is also indicated for use in the treatment of disorders due to hypersecretion in the intestines, e.g. as a result of inflammation



such as arising out of gastritis, peptic ulcer, biliary dyskinesia, appendicitis, ulcerative colitis, Crohn's diseases and due to carcinoid syndrome leading to increased 5-HT secretion.

Furthermore, the compound is indicated for use in the treatment of disorders arising from decreased peristaltic movements in the stomach and/or stomach disorders arising from activation of 5-HT₂ receptors, including those arising from decreased gastric emptying, including treatment of oesophageal motility disturbances, achalasia, hiatus hernia, cardia insufficiency, gastro-oesophageal and gastroduodenal reflux, stomach hypotonia and pylorus hyperplasia.

Furthermore, the compound is indicated for use in the treatment of paralytic ileus and Hirschsprung's disease.

For these indications, the exact dosage will, of course, vary depending upon the mode of administration and treatment desired. In general, satisfactory results are obtained in doses about 0.01 to about 10 mg/kg. An indicated daily dosage is from about 5 to 20 mg p.o. of the compound conveniently administered, for example, in divided doses 2 to 4 times a day. If desired, the compound may be administered in a single dose for acute therapy.

The compound of the invention may be administered in similar manner to known standards for use in these indications.

Accordingly the invention provides in one aspect:-

- a) a method of treating a subject suffering from a serotonin-induced gastro-intestinal disturbance which comprises administering indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1-oct-3-yl ester to a subject in need of such treatment,
- b) a method of managing or treating a gastro-intestinal disturbance chosen from the following: diarrhea, spastic colon and irritable bowel syndrome, gastritis, peptic ulcer, biliary dyskinesia,

- appendicitis, ulcerative colitis, Crohn's disease, carcinoid syndrome, achalasia, hiatus hernia, cardia insufficiency, gastro-oesophageal and gastro-duodenal reflux, stomach hypotonia, pylorus
- 5 hyperplasia, paralytic ileus and Hirschsprung's disease, which comprises administering indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester to a subject in need of such treatment,
- 10 c) use of a pharmaceutical composition containing indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester for a method as defined above.
- 15 The compound may be administered in free base form or in pharmaceutically acceptable acid addition salt form or in a quaternary ammonium salt form. Such salts may be prepared in conventional manner and are in general known. They exhibit the same order of activity as the free base
- 20 form and pharmaceutical compositions comprise the compound in free base or pharmaceutically acceptable acid addition salt form or quaternary ammonium salt form in association with pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner.
- 25 The compound is preferred to be administered in the salt form in the above mentioned Belgian patent, e.g. as the hydrochloride.

The compound may be administered by any conventional route, in particular enterally, preferably orally, e.g. in the form of tablets or capsules or parenterally, e.g. in the form of injectable solutions or suspensions.

- 5 Suitable pharmaceutical carriers and diluents for oral administration include polyethylene glycol, polyvinylpyrrolidone, mannitol, lactose etc. granulating agents, and disintegrating agents such as starch and algenic acid, binding agents such as stearic and gelatine, lubricating agents such as magnesium stearate, stearic acid and talc. Suspensions
- 10 may contain conserving agents like ethyl p-hydroxy-benzoate, suspending agents such as methyl-cellulose, tenside etc. For parenteral forms the compositions are preferably buffered, aqueous solutions (pH between 4 and 5).

- 15 The following examples illustrate the invention.



EXAMPLE 1: Tablets for oral administration

Tablets containing the constituents as specified below were produced in conventional manner and are indicated for use in the indications specified above.

5	ICS 205-930 in form of hydrochloride (corresponding to 15 mg free base)	16.9 mg
	Hydroxy-propyl-cellulose	1.2 mg
	Corn Starch	12.0 mg
10	Lactose	92.8 mg
	Silica	0.6 mg
	Magnesium stearate	1.5 mg
15	Tablet weight	125.0 mg

EXAMPLE 2: Injection solution for i.v. administration

20 A composition for injection is made up in conventional manner and is indicated for use at a dose of 10 mg a day.

	A	B	C
ICS 205-930 in form of			
25 hydrochloride	1.13 ¹⁾	2.256 ²⁾	11.282 ³⁾
Acetic acid (99 to 100%)*	1.2	0.6	0.6
Sodium acetate 3.H ₂ O*	1.8	3.18	3.18
Sodium chloride	8	7.5	6.5
Water for injection to	1.0 ml		

- 30
- 1) = 1 mg free base
 - 2) = 2 mg free base,
 - 3) = 10 mg free base

pH value 4.3;

Buffer used* 1/30 molar

EXAMPLE 3: Capsules for oral administration

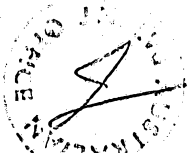
5 mg and 15 mg capsules (A and B respectively) containing the constituents as specified below were produced in conventional manner and are indicated for use in the indications specified above 2 - 4 times a day in the case of A and once a day in the case of B.

	A mg	B mg
ICS 205-930 in the form of hydrochloride	5.641	16.92
10 Lactose 200 mesh	84.929	79.29
Lactose 100 mesh	84.43	79.29
Corn Starch	120.00	120.00
Silica	1.5	1.5
Magnesium stearate	3.0	3.0
15	300 mg	300 mg

Capsules containing other weights can be formulated in conventional manner.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating a subject suffering from a serotonin-induced gastro-intestinal disturbance which comprises administering indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1-oct-3-yl ester to a subject in need of such treatment.
2. A method of claim 1 wherein the disturbance results from increased peristaltic movements of the intestines or an intestinal disorder arising from activation of 5-HT₃ receptors.
3. A method of claim 1 wherein the disturbance is due to hypersecretion in the intestines leading to increased 5-HT secretion.
4. A method of claim 1 wherein the disturbance arises from decreased peristaltic movements in the stomach.
5. A method of claim 1 wherein the disturbance arises from decreased gastric emptying.
6. A method of managing or treating a gastro-intestinal disturbance chosen from the following: diarrhea, spastic colon and irritable bowel syndrome, gastritis, peptic ulcer, biliary dyskinesia, appendicitis, ulcerative colitis, Crohn's disease, carcinoid syndrome, achalasia, hiatus hernia, cardia insufficiency, gastro-oesophageal and gastro-duodenal reflux, stomach hypotonia, pylorus hyperplasia, paralytic ileus and Hirschsprung's disease, which comprises administering indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester to a subject in need of such treatment.
7. A method of claim 6 wherein the disturbance is gastro-oesophageal reflux disorder.
8. A method of claim 6 wherein the disturbance is spastic colon.



9. A method of claim 6 wherein the disturbance is irritable bowel syndrome.
10. A method of claim 6 wherein the disturbance is diarrhea.
11. A method of claim 10 wherein the diarrhea is secretory diarrhea.
12. A method of claim 10 wherein the diarrhea is bacterial induced diarrhea.
13. A method of claim 10 wherein the diarrhea is choleic diarrhea.
14. A method of claim 10 wherein the diarrhea is traveller's diarrhea.
15. A method of claim 10 wherein the diarrhea is psychogenic diarrhea.
16. A method of treating a gastro-intestinal disturbance ^{according to claim 1} substantially as hereinbefore described with reference to any particular example.
17. A method according to any one preceding claim wherein indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester is in the form of the hydrochloride.
- ~~18. A pharmaceutical composition for use in a method according to any one of claims 1 to 17.~~
- ~~19. A package containing a pharmaceutical composition containing indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester in association with instructions for use in a method according to any one of claims 1 to 17.~~
18. Use of a pharmaceutical composition containing indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-[3,2,1]oct-3-yl ester for a method according to any one of claims 1 to 17.

~~21. Use of indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo-
[3,2,1]oct-3-yl ester in the manufacture of a medicament suitable
for use in a method according to any one of claims 1 to 17.~~

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