Specification

TREATING AGENT FOR DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

Technical Field

The present invention relates to a drug or, more particularly, it relates to a treating agent for diarrhea-predominant irritable bowel syndrome or to an agent for improving the symptom of diarrhea of irritable bowel syndrome.

Background Art

Ramosetron is called (-)-(R)-5-[(1-methyl-1H-indol-3-yl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole in its chemical name.

Ramosetron hydrochloride has been sold as an agent for improving the gastrointestinal symptoms (nausea and vomiting) associated with anticancer drug therapy (such as cisplatin) and it is usually administered to adults either orally at 0.1 mg once daily or intravenously at 0.3 mg once daily ("Nasea OD Tablet 0.1 mg", "Nasea Injections 0.3 mg" in JAPAN PHARMACEUTICAL REFERENCE, PRODUCTS and ADMINISTRATION in JAPAN, The Fifth Edition (1999) published by the Japan Medical Products International Trade Association).

In EP-A-381422, there is a disclosure that a series of tetrahydrobenzimidazole derivatives including ramosetron and pharmaceutically acceptable salts thereof has an antagonistic action to $5HT_3$ receptors. On the basis of such an action, there is suggested a possibility of suppression of emesis caused by anti-cancer drugs such as cisplatin and radioactive ray and prevention and treatment of migraine, complex headache, trigeminal neuralgia, anxiety symptom, gastrointestinal motility abnormalities, peptic ulcer, irritable bowel syndrome, etc. and there is a description that usual clinical dose per day for adults is 0.1 to 10 mg by intravenous injection and 0.5 to 50 mg by oral administration which is administered once daily or by dividing into several times.

On the other hand, in WO 99/17755, there is a description that $5HT_3$ receptors are useful for the treatment of female patients suffering from non-constipated irritable bowel syndrome and that the therapeutically effective dose is within a range of 0.01 to 500 mg or, preferably, 0.05 to 50 mg per day. To be more specific, as a result of clinical study where 1 to 8 mg of alosetron were administered twice daily to the patients suffering from non-constipated irritable bowel syndrome, significant improvement was noted in female patients as compared with placebo in relief of pain and discomfort, stool consistency, bowel movement frequency and the proportion of days with urgency treatment while, in male patients, no

significant improvement was noted as compared with placebo except stool consistency.

In addition, in WO 2002/007713, there is a description that, when 1 to 16 mg of $5HT_3$ receptor antagonist are administered three times a day, that is useful for the treatment of irritable bowel syndrome in both male and female patients.

Disclosure of the Invention

The present inventors have carried out intensive investigations for the purpose of creation of novel treating agents for diarrhea-predominant irritable bowel syndrome for which no sufficiently effective treating agent has been available. The present inventors formerly tried clinical study where ramosetron hydrochloride was administered twice daily to patients suffering from irritable bowel syndrome but significant therapeutic effect as compared with placebo was unable to be confirmed.

After that, the present inventors had the idea that the therapeutically effective dose of ramosetron to irritable bowel syndrome might be far lower than 0.1 to 0.3 mg which is a currently adopted dose as an improving agent for the gastrointestinal symptoms associated with anticancer drug therapy. In view of the above, a stable preparation containing very small amount (0.001 to 0.01 mg) of ramosetron hydrochloride was developed and clinical study using such a

preparation was carried out for 12 weeks to male and female patients suffering from diarrhea-predominant irritable bowel syndrome. As a result, a remarkable efficacy has been surprisingly confirmed whereupon the present invention has been achieved.

Thus, the present invention relates to the pharmaceutical composition for therapy of diarrhea-predominant irritable bowel syndrome in male and female patients, containing from 0.001 to 0.05 mg of ramosetron hydrochloride as a daily dose or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt as an active ingredient, or it relates to the pharmaceutical composition for improving diarrhea symptom of irritable bowel syndrome in male and female patients, containing from 0.001 to 0.05 mg of ramosetron hydrochloride as a daily dose or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt as an active ingredient.

Also, the present invention relates to the use of ramosetron hydrochloride in a daily dose of 0.001 to 0.05 mg, or ramosetron or a pharmaceutically acceptable other salt thereof in an equimolar amount for the manufacture of a medicament for the treatment of diarrhea-predominant irritable bowel syndrome in male and female patients or it relates to the use of ramosetron hydrochloride in a daily dose of 0.001

to 0.05 mg, or ramosetron or a pharmaceutically acceptable other salt thereof in an equimolar amount for the manufacture of a medicament for the improvement of diarrhea for male and female patients suffering from irritable bowel syndrome.

Also, this invention relates to the therapeutic method of diarrhea-predominant irritable bowel syndrome in male and female patients, including administering a patient with from 0.001 to 0.05 mg of ramosetron hydrochloride as a daily dose or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt, or it relates to the improving method of diarrhea symptom of irritable bowel syndrome in male and female patients, including administering a patient with from 0.001 to 0.05 mg of ramosetron hydrochloride as a daily dose or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt.

In accordance with the present invention, it is now possible to provide an excellent agent for the treatment of diarrhea-predominant irritable bowel syndrome or an agent for the improvement of diarrhea in irritable bowel syndrome of a diarrhea type regardless of male and female.

As shown in Test Example 1 which will be mentioned later, ramosetron hydrochloride was effective to patients suffering from diarrhea-predominant irritable bowel syndrome regardless of male and female by oral administration of 0.005 mg or 0.01 mg once daily. Since administration of 0.005 mg gave a

significant therapeutic effect being the same as by administration of 0.01 mg, efficacy can be expected even by further one-half of that dose. Subjects of Test Example 1 are Japanese adult patients and there is suggested a possibility that the optimum dose for children will be smaller while it is often that the optimum dose for European and American people is twice as much of that of Japanese. Therefore, although the particularly preferred dose for ramosetron hydrochloride is within a range of 0.002 to 0.02 mg, it is likely that, depending upon the difference in age of the patient and among the races, a daily dose within a range of 0.001 to 0.05 mg is able to treat diarrhea-predominant irritable bowel syndrome or improve diarrhea symptom of irritable bowel syndrome.

In EP-A-381422, there is a description that a clinical dose of tetrahydrobenzimidazole derivative including ramosetron is usually 0.1 mg or more per day and there is neither suggestion nor disclosure that ramosetron hydrochloride shows a therapeutic effect by a daily dose within a range of 0.002 to 0.02 mg. In addition, the present invention is better:

1) than the improving agents containing ramosetron hydrochloride as an effective ingredient and being commercially available at present for the gastrointestinal symptoms associated with anticancer drug therapy in that the therapeutically effective dose is lower by as much as 1/5 to 1/50,

2) than the drugs disclosed in WO 99/17755 in that a sufficient therapeutic effect is achieved regardless of male and female patients and

3) than the drugs disclosed in WO 2002/007713 in that a sufficient therapeutic effect is achieved by administration of dose lower by as much as 1/50 to 1/500 once daily

and such advantages are not predictable from the above-mentioned prior art.

The present invention will now be illustrated in more detail as hereunder.

Ramosetron and pharmaceutically acceptable salts thereof are easily available by a producing process mentioned in EP-A-381422 or by a method similar thereto.

With regard to the pharmaceutically acceptable salt of ramosetron, its specific examples are a salt with mineral acid such as hydrochloric acid, sulfuric acid, phosphoric acid and hydrobromic acid; a salt with organic acid such as acetic acid, oxalic acid, citric acid, maleic acid, malic acid, fumaric acid, tartaric acid and methanesulfonic acid; and a salt with acidic amino acid such as glutamic acid and aspartic acid. Among them, ramosetron hydrochloride which is commercially available is most preferred.

The drug of the present invention is able to be prepared as an oral solid preparation, an oral liquid preparation or

an injection preparation according to conventional methods using organic or inorganic carrier, excipient and other additives suitable for oral or parenteral administration. Preferred ones are those which are able to be administered by a patient himself/herself and are convenient for preservation and carrying and, to be more specific, they are tablets, diluted powder, granules, fine granules, capsules, pills, etc.

In the solid preparation as such, an active substance is mixed with at least one inert diluent such as lactose, mannitol, glucose, microcrystalline cellulose, starch, polyvinylpyrrolidone and magnesium metasilicate aluminate. The composition may contain, by a conventional method, additives other than the inert diluent including a binder such as hydroxypropyl cellulose and hydroxypropyl methyl cellulose; a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, starch and talc; a disintegrating agent such as calcium cellulose glycolate; a stabilizer such as lactose; a dissolving aid such as glutamic acid and aspartic acid; a plasticizer such as Tween 80 and triacetin; and a coloring agent such as titanium oxide and iron sesquioxide. Tablets or pills may be coated, if necessary, with sugar coat or intragastrically soluble or enteric substance such as sucrose, gelatin, agar, pectin, hydroxypropyl cellulose and hydroxypropyl methyl cellulose.

In addition, like the commercially available "Nasea OD

Tablets 0.1 mg", the preparation may be an intraorally disintegrating tablet. For example, the intraorally disintegrating tablet may be prepared according to, for example, US 5,466,464, US 5,576,014, US 6,589,554, WO 2003/009831, WO 2002/092058, etc.

Since the drug of the present invention contains ramosetron of a very low dose, preparations where a stabilization technique of temperature and humidity is applied are particularly preferred.

For example, when a specific compound having a carbonyl group is added, stabilization of ramosetron to temperature and humidity can be achieved. With regard to the specific compound having a carbonyl group, its specific examples are aliphatic carboxylic acid (to be more specific, saturated or unsaturated and linear or branched aliphatic mono-, di- or tri-carboxylic acid or, particularly, aliphatic carboxylic acid having 3 to 36 carbons) or ester thereof, hydroxycarboxylic acid (to be more specific, saturated or unsaturated and linear or branched aliphatic hydroxymono-, di- or tricarboxylic acid or, particularly, hydroxycarboxylic acid having 3 to 36 carbons) or ester thereof, acidic amino acid, enolic acid, aromatic carboxyl compound (to be more specific, aromatic mono-, di- or tri-carboxylic acid which may be substituted with alkyl group or hydroxyl group having 1 to 4 carbon(s) or, particularly, aromatic carboxylic acid having 7 to 20 carbons) or ester

thereof and a macromolecular substance having a carboxyl group and those compounds may be appropriately used either solely or jointly by combining two or more thereof.

Particularly with regard to the specific compound having a carbonyl group, preferred ones are a hydroxycarboxylic acid or ester thereof, a macromolecular compound having a carboxyl group, an aromatic carboxyl compound or ester thereof and an enolic acid; particularly preferred ones are a hydroxycarboxylic acid or ester thereof, a macromolecular substance having a carboxyl group and an aromatic carboxyl compound or ester thereof; and more preferred ones are a hydroxycarboxylic acid or ester thereof and a macromolecular substance having a carboxyl group.

With regard to an aliphatic carboxylic acid, preferred ones are maleic acid, malonic acid, succinic acid and fumaric acid. As the hydroxycarboxylic acid, preferred ones are tartaric acid, malic acid and citric acid and more preferred ones are tartaric acid and citric acid. As the acidic amino acid, preferred ones are glutamic acid and aspartic acid. As the aromatic carboxyl compound, preferred ones are phthalic acid and propyl gallate and more preferred one is propyl gallate. With regard to a macromolecular substance having a carboxyl group, preferred ones are carboxymethyl cellulose and alginic acid and more preferred one is carboxymethyl cellulose. As the enolic acid, preferred ones are ascorbic acid and

erythorbic acid and more preferred one is ascorbic acid.

The above-mentioned carbonyl compound in a form of a hydrate and an anhydride having no water of crystallization such as citric acid hydrate and citric acid anhydride also has been found to achieve a stabilizing effect of the present invention and the invention covers all hydrates, anhydrides and mixtures thereof. With regard to degree of polymerization, molecular weight, etc. of the macromolecular substance, although there is no particular limitation therefor, but a weight-average molecular weight of about 110,000 or about 200,000 is particularly preferred for carboxymethyl cellulose and alginic acid, respectively.

With regard to a compounding amount of a compound for the stabilization of ramosetron or a pharmaceutically acceptable salt thereof, there is no particular limitation so far as it is an amount for achieving the stabilization. It is, for example, 0.01 to 90% by weight, preferably 0.01 to 50% by weight or, more preferably and when its manufacture is also taken into consideration, 0.1 to 10% in the formulation.

Administering amount of ramosetron or a pharmaceutically acceptable salt thereof may be appropriately decided for each case by taking age, race, sex, etc. of the subject to be administered into consideration. In the case of ordinary oral administration of ramosetron hydrochloride, it is about 0.001 to 0.05 mg per day and, most preferably, 0.002 to 0.02 mg per

day for an adult and that is orally administered after a meal once daily.

As discussed above, for certain human patient populations which may include Americans and Europeans for treatment of irritable bowel syndrome including diarrhea-predominant irritable bowel syndrome or to improve diarrhea symptom of irritable bowel syndrome, an optimum daily dose of ramosetron (amounts based on free base form) may be within a range of from 0.0025 mg to 0.05 mg, or more suitably a daily dose within a range of from 0.0025 mg to 0.02 mg or equivalent molar amounts of a pharmaceutically acceptable salt of ramosetron.

As would be understood, references herein to daily dosage amounts of ramosetron or pharmaceutically acceptable thereof designate the total amount of ramosetron or pharmaceutically acceptable salt thereof administered within a 24 hour period, where the total amount may be administered in a single administration (i.e., single daily dose) or multiple administrations (i.e., two or more dosages administered during the 24 hour period where the aggregate amount of the multiple dosages are within the daily dosage amount ranges disclosed herein). As discussed above, a single daily administration may be suitable in at least some protocols. Therapeutic methods of the invention also may include a step of identifying a subject that is need for treatment for irritable bowel

syndrome and/or to relieve or otherwise improve diarrhea symptoms of irritable bowel syndrome. The identification suitably can be in the judgment of a patient or a health professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

A variety of therapeutic regimes may be utilized. For instance, a patient may be treated episodically, e.g. upon experiencing an acute attack of irritable bowel syndrome, ramosetron or a pharmaceutically acceptable salt thereof may be administered in a daily dosage amount as disclosed herein for a period sufficient to alleviate irritable bowel syndrome symptoms such as administration of ramosetron or a pharmaceutically acceptable salt thereof in daily dosage amounts as disclosed herein each day for up to 7 days, 14 days, 21 days, 28 days, 6 weeks, 8 weeks, 12 weeks, 16 weeks or more and then administration terminated until the patient again experiences the onset of irritable bowel syndrome symptoms. Alternatively, a patient may be maintained on a continuous or more prolonged therapy, e.g. an indefinite or prolonged administration (e.g. at least 6, 9, 12 or 15 months) of ramosetron or a pharmaceutically acceptable salt thereof in a daily dosage amount as disclosed herein each day as a prophylactic therapy to avoid or minimize the onset of irritable bowel syndrome symptoms. Other treatment protocols also may be utilized.

Patients with diarrhea-predominant IBS defined by the Rome II Diagnosis Criteria include patients with diarrhea phase of alternating irritable bowel syndrome.(D. A. Drossman, et al., pages 351 to 432, Degnon Associates, McLean, 2000)

Best Mode for Carrying Out the Invention

The present invention will now be illustrated in more detail by way of the following Examples and Test Examples although the present invention is not limited by those Examples, etc.

Example 1

Ramosetron hydrochloride	0.02 part
Lactose	86 parts
Hydroxypropyl cellulose	3 parts
Tartaric acid	1 part
Yellow iron sesquioxide	0.2 part
Titanium oxide	10 parts
Light silicic acid anhydride	0.3 part

Hydroxypropyl cellulose (3 parts), 0.02 part of ramosetron hydrochloride and 1 part of tartaric acid were dissolved in 35 parts of water with stirring using a magnetic stirrer and kneaded with 10 parts of titanium oxide and 0.2 part of yellow iron sesquioxide using a grinding machine, and a spraying liquid (hydroxypropyl cellulose concentration: 8% by weight) was prepared. After that, 86 parts of lactose were

charged in a fluid layer granulator (Flow Coater; manufactured by Freund) and the above spraying liquid was sprayed at a spraying rate of 5 g/minute to conduct a fluid granulation. The granules were dried for 5 minutes at an intake air temperature of 40°C and then mixed with 0.3 part of light silicic acid anhydride to give a diluted powder preparation.

Example 2

Ramosetron hydrochloride	0.0008 part
Mannitol	89 parts
Citric acid anhydride	0.1 part
Maltose	10 part
Red iron sesquioxide	1 part
Magnesium stearate	1 part

Maltose (10 parts), 0.0008 part of ramosetron hydrochloride, 0.1 part of citric acid anhydride and 1 part of red iron sesquioxide were suspended in 67 parts of water with stirring using a magnetic stirrer to prepare a spraying liquid (concentration: 15% by weight). After that, 89 parts of mannitol were charged in a fluidized bed granulator (Flow Coater; manufactured by Freund) and the above spraying liquid was sprayed at a spraying rate of 10 g/minute to conduct a fluid granulation. After the granulation, the granules were dried for 5 minutes at an intake air temperature of 40°C and then mixed with 1 part of magnesium stearate. The mixed powder was

made into tablets using a rotary tableting machine at the rate of 120 mg per tablet to give tablets having about 1 kp of initial hardness. They were preserved for 18 hours at a relative humidity of 75% and then preserved for 4 hours at a relative humidity of 40% to give intraorally disintegrating tablets.

Example 3

The same manufacturing method as in Example 2 was conducted except that the adding amount of citric acid anhydride was changed to 0.2 part to give intraorally disintegrating tablets.

Example 4

The same manufacturing method as in Example 2 was conducted except that the adding amount of citric acid anhydride was changed to 0.5 part to give intraorally disintegrating tablets.

Example 5

Ramosetron hydrochloride	0.0008 part
Mannitol	89 parts
Ascorbic acid	0.2 part
Maltose	10 parts
Red iron sesquioxide	1 part
Magnesium stearate	1 part

Maltose (10 parts), 0.0008 part of ramosetron hydrochloride, 0.2 part of ascorbic acid and 1 part of red iron sesquioxide were suspended in 67 parts of water with stirring using a magnetic stirrer and a spraying liquid (concentration: 15% by weight) was prepared. After that, 89 parts of mannitol were charged in a fluidized bed granulator (Flow Coater; manufactured by Freund) and the above spraying liquid was sprayed at a spraying rate of 10 g/minute to conduct a fluid granulation. After the granulation, the granules were dried for 5 minutes at an intake air temperature of 40°C and then mixed with 1 part of magnesium stearate. The mixed powder was made into tablets using a rotary tableting machine at the rate of 120 mg per tablet to give tablets having about 1 kp of initial hardness. They were preserved at 25°C for 18 hours at a relative humidity of 75% and then preserved at 30°C for 4 hours at a relative humidity of 40% to give intraorally disintegrating tablets.

Example 6

The same manufacturing method as in Example 5 was conducted except that the adding amount of ascorbic acid was changed to 0.5 part to give intraorally disintegrating tablets.

Example 7

Ramosetron hydrochloride	0.0008 part

Mannitol	88 parts
Maltose	10 parts
Yellow iron sesquioxide	1 part
Citric acid anhydride	0.2 part
Magnesium stearate	1 part

Maltose (10 parts), 0.0008 part of ramosetron hydrochloride, 1 part of red iron sesquioxide and 0.2 part of citric acid anhydride were suspended in 67 parts of water with stirring using a magnetic stirrer and a spraying liquid (concentration: 15% by weight) was prepared. After that, 88 parts of mannitol were charged in a fluidized bed granulator (Flow Coater; manufactured by Freund) and the above spraying liquid was sprayed at an intake air temperature of 50°C, a spraying rate of 10 g/minute and a cycle of spray/dry/shaking of 15 seconds/15 seconds/10 seconds to conduct a fluid granulation. After the granulation, the granules were dried for 5 minutes at an intake air temperature of 40°C and then mixed with 1 part of magnesium stearate. The mixed powder was made into tablets using a rotary tableting machine at the rate of 120 mg per tablet to give tablets having about 1 kp of initial hardness. They were preserved at 25°C for 18 hours at a relative humidity of 75% and then preserved at 30°C for 4 hours at a relative humidity of 40% to give intraorally disintegrating tablets.

Example 8

Ramosetron hydrochloride	0.01 part
Avicel	86 parts
Low substituted hydroxypropyl cellulose	10 parts
Citric acid anhydride	0.5 part
Hydroxypropyl cellulose	3 parts
Magnesium stearate	0.5 part

Hydroxypropyl cellulose (3 parts), 0.5 part of citric acid anhydride and 0.01 part of ramosetron hydrochloride were dissolved in 27 parts of water with stirring using a magnetic stirrer to prepare a spraying liquid (concentration of hydroxypropyl cellulose: 10% by weight). After that, 86 parts of Avicel and 10 parts of low-substituted hydroxypropyl cellulose were charged in a fluidized bed granulator (trade name: GPCG-5 manufactured by Powlex) and the above spraying liquid was sprayed at a spraying rate of 100 g/minute to conduct a fluid granulation. After the granulation, the granules were dried at 40°C for 5 minutes and then mixed with 0.5 g of magnesium stearate. The mixed powder was made into tablets using a rotary tableting machine at the rate of 100 mg per tablet to give tablets.

Example 9

Ramosetron hydrochloride	0.1 part

Lactose	77 parts
Corn starch	19 parts
Carboxymethyl cellulose (CMC)	5 parts
Hydroxypropyl cellulose	3 parts
Magnesium stearate	0.3 part

Hydroxypropyl cellulose (3 parts) and 0.1 part of ramosetron hydrochloride were dissolved in 35 parts of water with stirring using a magnetic stirrer to prepare a spraying liquid (concentration of hydroxypropyl cellulose: 8% by weight). After that, 77 parts of lactose, 19 parts of corn starch and 5 parts of CMC were charged in a fluidized bed granulator (trade name: Flow Coater manufactured by Freund) and the above spraying liquid was sprayed at a spraying rate of 10 g/minute to conduct a fluid granulation. After the granulation, the granules were dried at 5 minutes at an intake air temperature of 40°C and then mixed with 0.3 parts of magnesium stearate. The mixed powder was made into tablets using a rotary tableting machine at the rate of 120 mg per tablet to give tablets.

Example 10

Ramosetron hydrochloride	0.0008 part
Mannitol	89 parts
Propyl gallate	5 parts
Maltose	10 parts

Magnesium stearate 1 part

Maltose (10 parts), 0.0008 part of ramosetron hydrochloride and 5 parts of propyl gallate were dissolved in 67 parts of water with stirring using a magnetic stirrer to prepare a spraying liquid (concentration: 15% by weight). After that, 89 parts of mannitol were charged in a fluidized bed granulator (Flow Coater manufactured by Freund) and the above spraying liquid was sprayed to conduct a fluid granulation. After the granulation, the granules were dried at 5 minutes at an intake air temperature of 40°C and then mixed with 1 part of magnesium stearate. The mixed powder was made into tablets using a rotary tableting machine at the rate of 120 mg per tablet to give tablets.

Test Example 1

Clinical study with patients suffering from diarrhea-predominant irritable bowel syndrome

Clinical study was carried out under the following condition using male and female patients suffering from diarrhea-predominant irritable bowel syndrome (IBS) as subjects.

Subjects: Patients suffering from diarrhea-predominant IBS in accordance with the Rome II Diagnosis Criteria (D. A. Drossman, et al., pages 351 to 432, Degnon Associates, McLean, 2000).

Case Number: 418 cases

Test drugs and Administration Methods: Placebo and ramosetron hydrochloride were orally administered for 12 weeks at 0.005 mg or 0.01 mg once daily.

Test Periods: Observation period for one week and treating period for 12 weeks

Observed Items:

1. Main evaluated items

(1) Global assessment of relief of overall IBS symptoms (evaluation by the subjects)

After transition to the treating period, the starting date for administration of the test drug was defined as the first day. Every week, global assessment of relief of overall IBS symptoms was evaluated taking all symptoms by IBS of the subjects into consideration, comparing with their state in the observation period, and this evaluation was recorded in a patient diary. Incidentally, scores for the global assessment of relief of overall IBS symptoms were as follows.

0 = completely relieved

1 = considerably relieved

2 = somewhat relieved

3 = unchanged

4 = worsened

The subjects where the score was 0 or 1 for two weeks or more during the four weeks were made monthly responders and the monthly responder rate per month was calculated separately

for each group of 0.005 mg and 0.01 mg of placebo and ramosetron hydrochloride.

2. Subsidiary evaluation items

(1) Global assessment of relief of abdominal discomfort/pain (evaluation by the subjects)

After transition to the treating period, the starting date for administration of the test drug was defined as the first day. Every week, global assessment of relief of abdominal discomfort/pain by the test drug was evaluated with the state in the observation period and was recorded in a patient diary. Incidentally, scores for the global assessment of relief of abdominal discomfort/pain were as follows.

0 = completely relieved

1 = considerably relieved

2 = somewhat relieved

3 = unchanged

4 = worsened

(2) Global assessment of improvement of abnormal bowel habits (evaluation by the subjects)

After transition to the treating period, the starting date for administration of the test drug was defined as the first day. Every week, global assessment of improvement of abnormal bowel habits was evaluated comparing with the state in the observation period, and was recorded in a patient diary. Incidentally, scores for the global assessment of improvement

of abnormal bowel habits were as follows.

0 = completely relieved

1 = considerably relieved

2 = somewhat relieved

3 = unchanged

4 = worsened

(3) Severity of abdominal discomfort/pain

During the periods of clinical study (both observation period and treating period), the subjects evaluated the severity of abdominal discomfort/pain for each day and wrote in a patient diary. Scores for the severity of abdominal discomfort/pain were as follows.

0 = none

1 = mild

2 = moderate

3 = severe

4 = intolerable

(4) Stool form (appearance)

During the periods of clinical study, the subjects wrote the stool form (appearance) for each day using a score (type) of Bristol's stool form scale in a patient diary. When there were plural defecations within a day or when different stool forms (appearances) were noted in one defecation, only one form (appearance) which was the most representative one on that day (or for which the subject felt most troublesome) was written.

(5) Frequency of bowel movements

During the periods of clinical study, the subjects wrote the frequency of bowel movements for each day in a patient diary.

(6) Urgency

During the periods of clinical study, the subjects wrote whether there was urgency for each day in a patient diary.

(7) Feeling of incomplete bowel movement

During the periods of clinical study, the subjects wrote whether there was feeling of incomplete bowel movement for each day in a patient diary.

With regard to (1) to (3) for the subsidiary evaluation items, they were also subjected to calculations of monthly responder rate the same as those for the main evaluation items.

Results:

With regard to the final monthly responder rate in the global assessment of relief of overall IBS symptoms, it was 26.9% in a placebo group. On the other hand, in the groups of 0.005 mg and 0.01 mg of ramosetron hydrochloride, the monthly responder rates were 42.6% and 43.0%, respectively and were more than 15% than the responder rate in the placebo group. The p values for the groups of 0.005 mg and 0.01 mg to the placebo group were 0.0273 and 0.0264, respectively. With regard to the difference in the responder rates between the placebo group and the ramosetron group for 0.005 mg and 0.01 mg, no difference

was noted between male and female patients.

With regard to the final monthly responder rates in the global assessment of relief of abdominal discomfort/pain and in the global assessment of relief of abnormal bowel habits, the ramosetron hydrochloride group of 0.005 mg and 0.01 mg was also better than the placebo group to an extent of more than 10%.

From the above, the therapeutic effect of 0.005 mg and 0.01 mg of ramosetron hydrochloride to patients suffering from diarrhea-predominant irritable bowel syndrome was confirmed. It was also confirmed that, unlike alosetron disclosed in WO 99/17755, ramosetron hydrochloride was effective for both males and females and that, unlike the drug disclosed in WO 2002/007713, it was effective by administration once daily.

Industrial Applicability

In accordance with the present invention, there can be provided an excellent agent for the treatment of diarrhea-predominant irritable bowel syndrome or an agent for improvement of irritable bowel syndrome being effective for both males and females.

CLAIMS

1. A pharmaceutical composition for the therapy of diarrhea-predominant irritable bowel syndrome in male or female patients, comprising from 0.001 to 0.05 mg of ramosetron hydrochloride as a daily dose, or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt as an active ingredient.

2. A pharmaceutical composition for the therapy of diarrhea-predominant irritable bowel syndrome in male or female patients, comprising from 0.002 to 0.02 mg of ramosetron hydrochloride as a daily dose, or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt as an active ingredient.

3. A pharmaceutical composition for improving diarrhea symptom of irritable bowel syndrome in male or female patients, comprising from 0.001 to 0.05 mg of ramosetron hydrochloride as a daily dose or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt as an active ingredient.

4. A pharmaceutical composition for improving diarrhea symptom of irritable bowel syndrome in male or female patients, comprising from 0.002 to 0.02 mg of ramosetron hydrochloride as a daily dose, or an equivalent molar amount of ramosetron or its pharmaceutically acceptable other salt as an active

ingredient.

5. Use of ramosetron hydrochloride in a daily dose of 0.001 to 0.05 mg, or ramosetron or a pharmaceutically acceptable other salt thereof in an equimolar amount for the manufacture of a medicament for the treatment of diarrhea-predominant irritable bowel syndrome in male or female patients.

6. Use of ramosetron hydrochloride in a daily dose of 0.002 to 0.02 mg, or ramosetron or a pharmaceutically acceptable other salt thereof in an equimolar amount for the manufacture of a medicament for the treatment of diarrhea-predominant irritable bowel syndrome in male or female patients.

7. Use of ramosetron hydrochloride in a daily dose of 0.001 to 0.05 mg, or ramosetron or a pharmaceutically acceptable other salt thereof in an equimolar amount for the manufacture of a medicament for the improvement of diarrhea for male or female patients suffering from irritable bowel syndrome.

8. Use of ramosetron hydrochloride in a daily dose of 0.002 to 0.02 mg, or ramosetron or a pharmaceutically acceptable other salt thereof in an equimolar amount for the manufacture of a medicament for the improvement of diarrhea for male or female patients suffering from irritable bowel syndrome.