Revised: OCT 2009（2nd revised edition） Standard Commodity Classification No. of Japan：87449

Medical Interview Form

Framed based on the criteria of 2008 IF entry guidelines of Japanese Society of Hospital Pharmacists

ProstaglandinD$_2$ and Thromboxane A$_2$ receptor antagonists

Medicine for allergic rhinitis

Baynas tablets 50 mg

Baynas tablets 75 mg

Dosage form	Film-coating tablets
Regulatory classification of formula	Prescription drug（caution-use as directed by physician）
Standard・Content	**Baynas tablets 50 mg**: includes Ramatroban 50 mg **Baynas tablets 75 mg**: includes Ramatroban 75 mg
Common name	**Japanese name**:ラマトロバン（JAN） **Western name**:Ramatroban （JAN，INN）
Manufacture and sales approval date, Listing in NHI reimbursement price, Date of release(for sale)	**Date of Manufacture and sales approval:** March 10 2000 **Date of listing in NHI reimbursement price:** May 02 2000 **Date of release:** May 23 2000 **Nipppon Shinyaku Co. Ltd. Date of release:** July 03 2006
Development and marketing authorization holder (import) and licensed seller	**Manufacturer**:Bayer Yakuhin Ltd. **Sales**: Nippon Shinyaku Co., Ltd
Contact address of medical representative	
Inquiry	Nippon Shinyaku Co., Ltd science department, pharmaceutical information department, medical counsellor TEL 075-321-9064 FAX 075-321-9061 Home page for medical personnel http://www.nippon-shinyaku.co.jp/medicine/medicine_conts/

This IF is revised based on the listings of the package inserts of revision, June 2009。

Please confirm the newest information on the package inserts at http://www.info.pmda.go.jp/ Supply of Information on Drugs and Medical devices website

Summary of guidelines for IF usage -Japanese Society of Hospital Pharmacists

1. The details about framing the Medical Interview Form

The packet inserts of the prescription drugs (abbrev. as packet inserts below) are provided as basic information about the prescribed drug. In medical setting where appropriate information about the drug usage is necessary for the daily work for doctors and healthcare workers like pharmacists there are situations in which the packet insert that carrying more detailed information is necessary.

In medical setting, it is being handled by completing the information by questioning and demanding information additionally about the particular drug to the medical representative of the manufacturer. In this case, the Interview Form was created as information list to obtain the required information comprehensively.

In 1988, the 2nd subcommittee of science, The Japanese Society of Hospital Pharmacists (abbrev. As JSPN below) laid out and determined the IF listing format of the 'Medical Interview Form' (abbrev. as IF below). Thereafter, to meet the changes in the drug information needs of the healthcare workers and patients, the revision of IF Entry Guidelines was conducted by the 3rd subcommittee of science, JSHP in September 1998.

Now after ten years, in September 2008, the new IF Entry Guidelines were determined by the subcommittee of JSHP by regarding the huge changes in pharmaceutical and medical environment for both the manufacturers who produce the medical information and pharmacists in the medical setting who are the users.

2. IF is

Established as 'a guideline determined by the JSHP as comprehensive discrete drug manual with collective information that supplements the information of package inserts and information required for quality management of drug, prescription formulation, compounding medicine, appropriate use of the drug, pharmaceutical patient care and as a scientific document necessary for the daily work of healthcare workers like pharmacists and that inquires the manufactures about the making and provisions of the particular drug for the purpose of the healthcare workers'.

However, the matters related to the Pharmaceutical Affair law and manufacture's classified information, matters that invalidates the manufacturing efforts of the manufacturers and the matters that has to be evaluated, judged and supported by the pharmacist themselves does not become IF. In other words, the IF supported by the manufacturers is the one with preamble recognizing the evaluation, judgement and clinical adaptation by pharmacists along with required supplementation.

IF format

1. The standard is to print in A4 size paper, horizontal writing with font size above 9 points as general rule (excluding charts) and as a one-color print. But when red frames and red letters are used in the package inserts, it is made to support this in digital media.
2. Frame based on the IF Entry Guideline and every item name is listed in Gothic font.
3. The content of Front cover is consolidated, the whole Summary of guidelines for IF usage by JSHP is printed by continuing to the cover page and summarized in 2 pages.

Preparation of IF

1. The IF in general is prepared separately for routes of administration (internal drug, injections and external drug) of the formulation.
2. The items and arrangement used in the IF should be based on the IF Entry Guideline established by JSHP.
3. The necessary information that is in line with the motive of IF to supplement the contents of the package insert is given.
4. The matters related to the manufacturer's classified information, the matters that invalidates the manufacturer's manufacturing efforts and the matters that are to be evaluated, judged and supported by healthcare workers and pharmacists will not be given.
5. With the support in digital media as foundation, the IF framed according to the 'Medical Interview Form Entry Guideline 2008' (abbrev. as 'IF Entry Guideline 2008' below), is used by the pharmacists by printing from digital media (PDF) depending upon the need. Industrial binding is not required.

Publication of IF

1. 'IF Entry Guideline 2008' will be adapted from the products that were approved after April, 2009.
2. The making and provision by 'IF Entry Guideline 2008' is not enforceable for the drug aside from those mentioned above.
3. IF will be revised when revision of caution during usage, the time when the re-examination and re-evaluation results (clinical re-evaluation) are officially announced as well as the expansion of indications are made and when the is contents that ought to be mentioned changes hugely.

Summary of guidelines for IF usage -Japanese Society of Hospital Pharmacists

3.In using the IF

The 'IF Entry Guideline 2008' has provision in digital media through PDF files as its basis, rather than in MR based paper medium which was used widely so far. Pharmacists who uses the information, with principle of using the information by printing from the digital, depending on the IT setting of the medical institution, can also request provision of printing in MR to meet the requirement.

A publishing place has been set up in Supply of Information on Drugs and Medical devices website of Pharmaceutical and Medical Device Agency about the digital medium IF.

The manufacturers follow 'Guidelines for making Medical Interview Form' for the making and providing, but based on the origin of the IF, the increase in usefulness of the IF is necessary as the pharmacists are made to complete the contents about the information insufficient in the medical setting and the information that cannot be entered at the time of making the IF through the manufacturers' MR based Interview.

And regarding the entries related to Caution during usage that are revised occasionally, in the period until the IF is revised, the pharmacists has to provide themselves through the package insert and notice provided by the particular drug's manufacturer or through the Pharmaceutical and Medical Devices Information Distribution services along with confirmation of new package insert on Supply of Information on Drugs and Medical devices website depending up on the usage of IF.

Also, the entries related to 'clinical results' and 'important conditions for selling in foreign country' mentioned from point of securing the safety and proper usage are related to the approval. Hence sufficient attention has to be paid in handling.

4. Points to remember during use

Use the IF as vital source of drug information for the daily work of the Pharmacists. But, because of the regulations by the Pharmaceutical Affairs Law and medical drug promotion code, there is a natural limit in the range of information that can be provided by the manufacturer as drug information. From the fact that IF complies with the entry guidelines of JSHP and is made and provided by the particular drug's manufacturer, it should be recognized that the listing and expressions must comply the constraints.
And there is a need for the manufacturer to use the information with the understanding that IF being a material that supplements the package insert and hereupon also based on the openness on the internet, is made carefully so as not to contradict the advertising regulation of Pharmaceutical Affairs Law.

(September 2008)

Table of Contents

I. Entries related to summary

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1. Development details

TXA_2 is an arachidonic acid metabolite that was discovered as the substance that contracts the rabbit aorta by Piper and Vane in 1969 and was identified and named by Hamberg in 1975. The metabolic pathway of the arachidonic acid is known as the so-called arachidonic acid cascade where within the whole body, when the inflammatory cells like the mast cells, eosinophil granulocyte, basophile, neutrophil and platelets receives various stimuli including antigen stimulation, the arachidonic acid is produced by the action of phospholipase from phospholipid of the cell membrane and further leads to the production of bioactive substances like prostaglandin, leukotrienes and thromboxane from arachidonic acid. Substance that acts in the arachidonic acid cascade is already made commercially available as medical drug and is possibly being developed as a new medical drug. Among these TXA2 displays actions like vascular hyper permeability and its role in allergic rhinitis pathology has become clear in recent years.

This drug is a compound that has strong TXA_2 receptor antagonist action discovered in 1986. Furthermore, optical isomers are present since this drug has 1 asymmetric carbon atom in 3_{rd} carbozole framework. Compared to this drug, Ramatroban is an enantiomer synthesised by the method that does not produce optical isomers with weak pharmacological activities.

This drug is being developed in our country by Bayer Yakuhin Ltd. and is acknowledged for its usefulness against allergic rhinitis.

(Approved: March 2000)

2. Therapeutic and pharmaceutical traits of the product

1. It is the only Prostaglandin D_2 and Thromboxane A_2 receptor antagonist suitable for allergic rhinitis.
2. It improves the symptoms of nasal obstruction.
3. It improves conditions like sneeze and runny nose by controlling the aggravation of hypersensitivity of the nasal mucus membrane.
4. It controls the permeation of eosinophil granulocyte into nasal mucus membrane.
5. The effectiveness [more than 'moderate improvement'] against the allergic rhinitis is 66.7% in clinical study.
6. Out of 4,443 study cases in treatment outcome study and at the time of approval, side effects (including the unusual variations in clinical study value) were observed in 232 cases (5.22%). Main side effects were drowsiness in 25 cases (0.56%), headache and heavy headedness in 22 cases (0.50%), rise in ALT(GPT) in 44 cases (0.99%), rise in AST（GOT）in 38 cases（0.86%）, rise in γ-GT in 36 cases (0.81%).

（At the time of reclaim review）

7. Hepatitis, impairment of liver function and jaundice were reported as the serious side effects.

II. Name related entry

1. **Brand name**

(1) Japanese name

バイナス錠50 mg

バイナス錠75 mg

(2) **Western name**

Baynas 50

Baynas 75

(3) Origin of the name

Bay nas: Bayer's allergic rhinitis medicine

2. General name

(1) Japanese name

ラマトロバン（JAN）

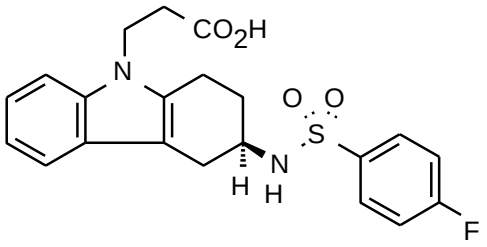
(2) Western name

Ramatroban（JAN，INN）

(3) Stem

Thromboxanea2 Receptor Antagonist, anti-thrombotic agent: -troban

3. **Structural formula and Rational formula**



4. **Molecular formula and Molecular weight**

Molecular formula: $C_{21}H_{21}FN_2O_4S$

Molecular weight: 416.47

5. **Chemical name**

(+)-(3R)-3-(4-fluorobenzenesulfonamido)-1,2,3,4-tetrahydrocarbazole-9-propionic acid (JAN)

6. **Common name, pseudonym, code, number sign**

Company code name: BAY u 3405

7. **CAS registration number**

116649-85-5

1. **Physicochemical properties**

(1) Appearance and characteristics

Ramatroban is an odorless, white colored powder with bitter taste.

(2) Solubility

The solubility of this product related to different types of solvent and pH solutions measured conformed to Japanese pharmacopeia (JP) 13 and 23rd clause of the general rule.

■Solubility of Ramatroban with respect to different solvents (20℃)

Name of the solvent	Notations by JP
Methanol	Soluble
Acetonitrile	Soluble
Ethyl acetate	Soluble
Ethanol (99.5)	Soluble
2-propanol	Slightly soluble
Diethyl ether	Difficult to dissolve
Water	Nearly insoluble
Heptane	Nearly insoluble
Hexane	Nearly insoluble

■Solubility of Ramatroban with respect to different pH solutions (20℃)

pH Solutions	Notations by JP
0.1mol/L HCl solution(pH1)	Nearly insoluble
pH3 buffer solution	Nearly insoluble
pH4 buffer solution	Nearly insoluble
pH5 buffer solution	Nearly insoluble
pH6 buffer solution	Extremely difficult to dissolve
pH7 buffer solution	Difficult To Dissolve
pH8 buffer solution	Difficult To Dissolve
0.1mol/L NaOH solution (pH13)	Slightly Soluble

Every pH buffer solution uses Sörensen buffer solution.

(3) Absorbency

The storage of Ramatroban for a period of 7 days under 25℃ and 75%RH condition in open container, resulted in the absolutely no changes in the weight. Absorbency in the Ramatroban was not observed.

(4) Melting point (decomposition point), boiling point, freezing point

Melting point 149～153℃

(5) Acid base dissociation constant

pKa＝4.0（carboxyl group）

(6) Partition coefficient

■Partition coefficient of Ramatroban (25℃)

pH Solution	Partition coefficient（1-octanol/water）
0.1mol/L HCl solution(pH1)	17,329
pH3 buffer solution	10,397
pH4 buffer solution	5,776
pH5buffer solution	763.6
pH6 buffer solution	109.2
pH7 buffer solution	11.54
pH8 buffer solution	1.261
pH9 buffer solution	0.8420
0.1mol/L NaOH solution (pH13)	0

(7) Other important characteristic values

Specific rotation $[\alpha]_D^{20} = +69 \sim +74^\circ$ (0.1 g of dehydrated matter, methanol, 10 mL, 100 mm)

2. **The stability of the active ingredients under different conditions**

Stability of drug substances

The storage of Ramatroban under conditions of temperature, humidity and light resulted in no changes in all conditions and remained stable.

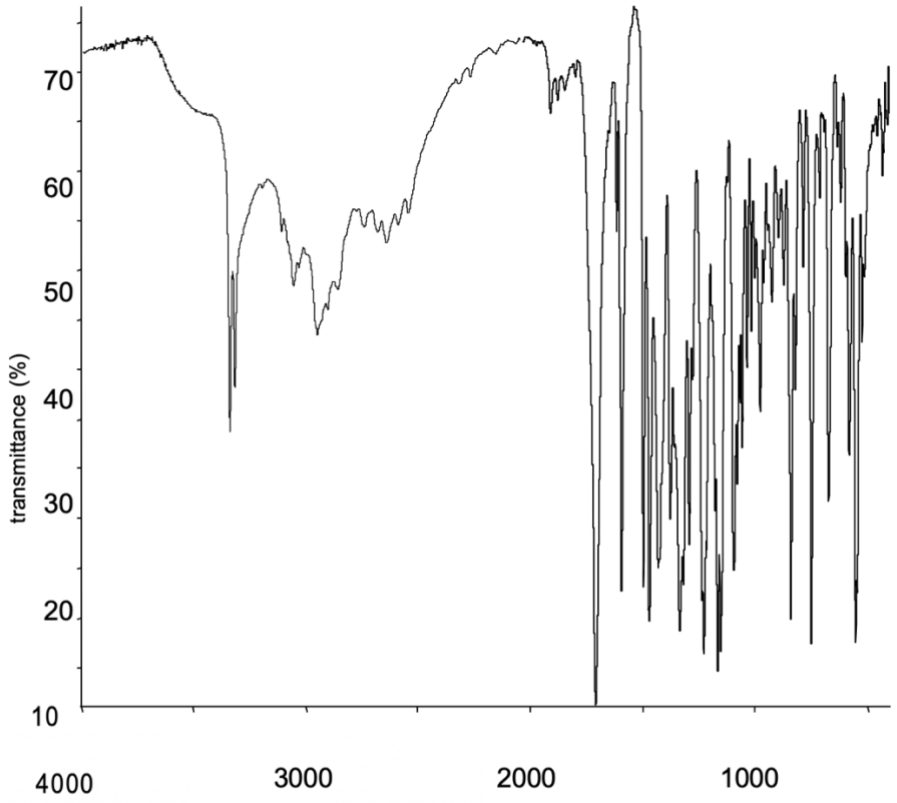
Test entry		Storing condition	Storing container	Test result
Stress testing	Temp.	60℃	Brown glass airtight container	Was stable with no changes observed for a period of 3 months
	Humidity	30℃ 80%RH	Brown glass open container	Was stable with no changes observed for a period of 6 months
	Light	Xenon light (50,000Lx approx.)	Petri dish＋ polyvinyldene film	Was stable with no changes observed for a period of 24 hours
		White fluorescent lamp (1,000Lx approx.)		Was stable with no changes observed for a period of 1200 hours
Long-term storage test		25℃ 60%RH	Brown glass airtight container	Was stable with no changes observed for a period of 60 months
Acceleration test		40℃ 75%RH	Brown glass open container	Was stable with no changes observed for a period of 6 months

3. **Verification test method for active ingredients**

(1) Infra-Red absorption spectrum method (potassium bromide disk method)

Verification method: Reference spectrum method

■Reference spectrum



Infra-red absorption spectrum of Ramatroban

(2) Thin layer chromatography

Operating condition

Absorbent: Thin chromatograph using silica gel (with fluorescent agent）

Eluent: Ethyl acetate/cyclohexane/acetic acid（100）mixture（70:35:1）

Application quantity :Ethyl acetate solution of this product and standard Ramatroban each 5 μL (ramatroban 50 μg equivalent)

Expansion distance: 8 cm approx.

Detection method: Ultra violet rays (dominant wavelength 254 nm）

4. **Method of quantitative determination of the active ingredients**

Liquid chromatography (internal standard method）

Operating condition

Column: Octylsilyl silica gel (5 μm)

Column temperature: 40℃

Moving phase: pH3.0 phosphate buffer solution/acetonitrile mixture (63: 37)

Flow rate: Adjustments are done so that the hold time of the Ramtroban is approximately 8 minutes.

Detector: Ultraviolet absorptiometer（measurement wavelength: 228 nm）
Internal standard solution: p－hydroxy benzoic acid n－hexyl-acetonitrile solution（1→250）

IV. Entries related to Formulation

1. **Dosage form**

(1) Classification, standard and characteristics of dosage form

Dosage form classification: Film-coating tablets

Dosage form	Top surface	Bottom surface	Side	Diameter (mm)	Thickness (mm)	Weight (mg)	Colour Tone
Baynas tablet 50 mg				8.1	3.5	164	White to pale yellow
Baynas tablet 75 mg				9.1	3.8	230	White to pale yellow

(2) Physical properties of dosage form

(3) Identification code

Baynas tablet 50 mg: 127 Baynas tablet 75 mg: 128

(4) pH, osmotic pressure ratio, viscosity, relative density, sterilization principle and stable pH range

Not applicable.

2. **Composition of Dosage Form**

(1) Contents of Active ingredient（Active ingredient）

Baynas tablets 50 mg: 1 tablet contains 50 mg of Ramatroban

Baynas tablets 75 mg: 1 tablet contains 75 mg of Ramatroban

(2) Additives

Lactose hydrate, Hydroxyl propyle-cellose, Magnesium stearate, Hypromellose, Macrogol 4000, Titanium oxide.

(3) Others

Not applicable

3. **Caution related to dispersiveness in suspension and emulsion**

Not applicable

4. **Stability of dosage form under different conditions**

■Stress testing（Temperature, humidity and light）

Baynas tablets 50 mg and 75mg was unstable against temperature and humidity but stable against light. As shown in the table below, after unsealing the aluminium package and keeping it in colourless transparent PTP, it was stable for a period of 6 months at 25℃, 60%RH condition and 1200 hours under white fluorescent lamp (1,000 Lx approx..) respectively.

Baynas tablets 50 mg and 75 mg　Stress testing result

Test entry	Storing condition	Storing container	Storing period	Test result
Temperature	60℃	Brown glass airtight container	1,2,3 months	Minute changes in outer appearance was observed with decrease in dissolution rate. Unstable and increase in the amount of related substance by 0.7～0.8%
Humidity	25℃ 60%RH	Colourless transparent PTP	3,6 months	Stable with only increase in moisture content by 1.2～1.4%was observed.
	30℃ 80%RH	Brown glass open container	0.5,1,2 months	Minute changes observed in outer appearance and moisture content increased by 4% approximately. Unstable and the amount of related substance became 1.5～1.6% and decrease in contents involved in this was observed.
		Colourless transparent PTP	2,4,6 months	Extremely minute changes observed in outer appearance and moisture content increased by 1.8～2.3%. Stable with only increase in amount of related substance by 0.4～0.7%.
Light	Xenon light (50,000Lx approx.)	Petri dish ＋ polyvinyldene film	6,12,24 hours	Stable with no remarkable change observed in all test entry.
	White fluorescent light (1,000Lx approx.)	Colourless transparent PTP	300,600,1200 hours	Stable with no remarkable change observed in all test entry.

■Long term storage test（25℃ 60%RH: Colourless transparent PTP＋Aluminium package）

Baynas tablets 50 mg and 75 mg was stable with no remarkable change observed in all test entry under long term storage test condition for a period of 60 months.

■Acceleration test（40℃ 75%RH: Colourless transparent PTP＋Aluminium package）

Baynas tablets 50 mg and 75 mg was stable with only very minute change in outer appearance and no remarkable change observed under Acceleration test condition for a period of 6 months.

5. **Preparation method and stability after dissolving**

Not applicable

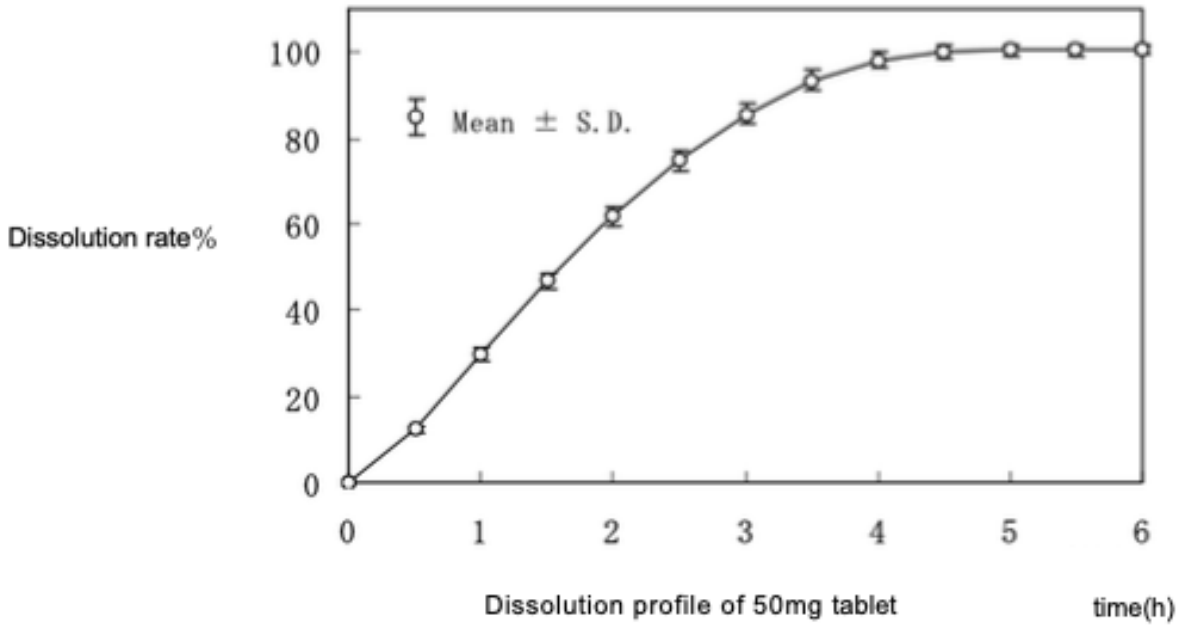
6. **Incompatibility with other drugs (Physicochemical changes)**

No relevant data

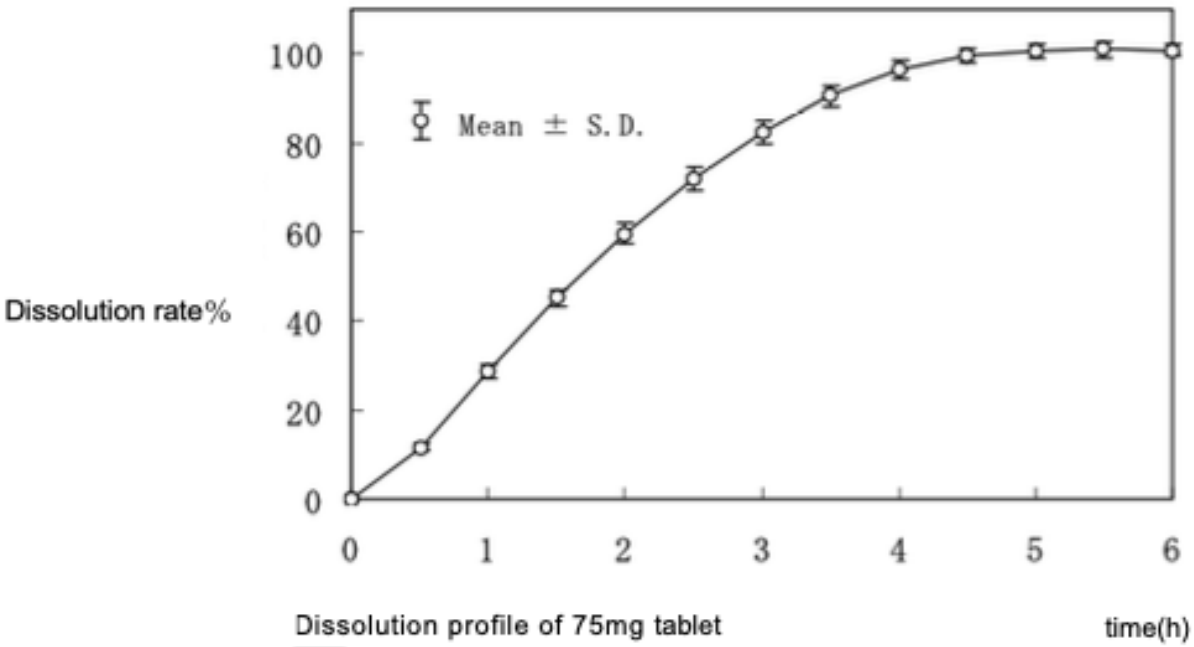
7. **Dissolution behavior**

JP Dissolution test method: 2nd method (paddle method)

Operating condition
Rotation count: 75 turns per minute
Test solution: pH 6.8 Phosphate solution
Measurement wavelength: 284 nm and 340 nm



Dissolution profile of 50mg tablet



Dissolution profile of 75mg tablet

8. **Biological test method**

Not applicable

9. **Verification test method for active ingredients in Dosage form**

Thin layer chromatography
Operating condition
Absorbent: Thin chromatograph using silica gel (with fluorescent agent)
Eluent: Ethyl acetate/cyclohexane/acetic acid (100) mixture (70:35:1)
Application quantity: Ethyl acetate solution of this product and standard Ramatroban each 5 μL (ramatroban50 μg equivalent)
Expansion distance: 8 cm approx.
Detection method: Ultraviolet rays (dominant wavelength 254 nm)

10. **Method of quantitative determination of active ingredients in dosage form**

Examine the amount of Ramtroban in 1 tablet of this product by Content uniformity test accordingly and consider the average value of 10 samples as Content.

Content uniformity test

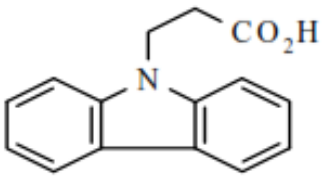
Liquid chromatography

Operating condition
Column: Octylsilyl silica gel (5 μm)
Column temperature:40℃
Moving phase: pH3.0 phosphate buffer solution/acetonitrile mixture (63:37)
Flow rate: Adjustments are done so that the hold time of the Ramtroban is approximately 8 minutes.
Detector: Ultraviolet absorptiometer (measurement wavelength:228 nm)

11. **Titer**

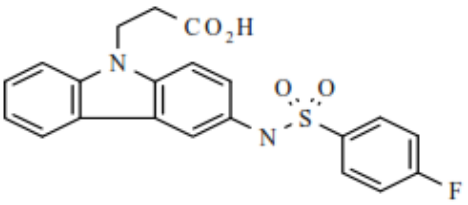
Not applicable

12. Contaminants with possibility of blending



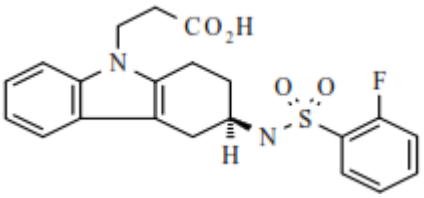
Carbazole-9-propionic acid

(degradation product)



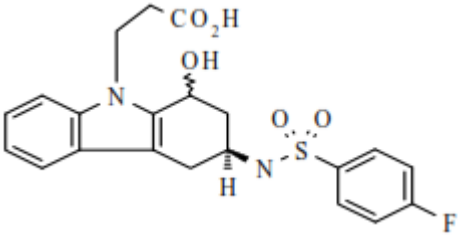
3-(4-fluorobenzenesulfonamide)-Carbazole-9-propionic acid

(by-product residual product and degradation product)



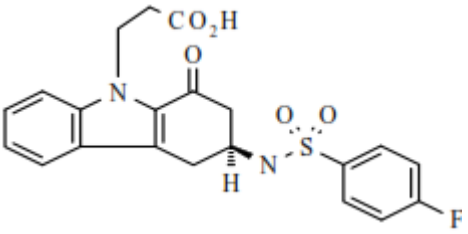
(+)-(3R)-3-(2-fluorobenzene sulfonamide)-1,2,3,4-tetrahydro carbazole-9-propionic acid

(by-product residual product)



(1R,S,3R)-3-(4-fluorobenzene sulfonamide)-1,2,3,4-tetrahydro-1-hydroxycabazole-9-propionic acid

(by-product residual product and degradation product)



(+)-(3R)-3-(4-fluorobenzenesufon amido)-1,2,3,4-tetrahydro-1-oxocarbazole9-propionic acid

(by-product residual product and degradation product)

13. **Information related to the therapeutic cautions required for the container**

Not applicable

14**. Others**

V. Details relevant to treatment

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1. **Efficacy / effect**

Allergic rhinitis.

2. **Usage and dose**

(1) Usage and dose

In general, for adults, one tablet of Ramatroban (75 mg) is to be taken orally twice daily after breakfast and dinner (or before bedtime).

(2) Precautions on usage and dose.

Exercise caution for the elderly, such as starting at a low dose (100 mg/day). (Refer section “Administration of dose to the elderly ").

(Note) The administration of dose to the elderly is as follows:

For the elderly, while observing the patient's condition, carefully administer by starting at a low dose (100 mg/day).
Based on the results of pharmacokinetic screening, the blood concentrations of this drug are estimated to be higher in elderly patients (aged 65 and older) than younger ones. Furthermore, the clinical trials conducted in Japan found that the side effects were observed in 22 of 192 elderly patients (11.46%), and in 64 of 1048 younger patients (6.11%).

Basis for timing of the dosage:

Since the administration interval of this drug was approximately 12 hours, a clinical study was conducted after
breakfast and before bedtime. Considering the pharmacokinetics of this drug are less likely to be affected by diet,
it is advised to be taken after breakfast and after dinner (or at bedtime)

3 . **Clinical results**

(1) Clinical data package (approved since April 2009)

Not applicable

(2) Clinical effect

In the clinical studies including double-blind controlled trials, done on patients with allergic rhinitis, the final overall improvement in the approved dosage and treatment is found in 186 of 279 cases (66.7%), which is considered to be more than "moderate improvement".

(Note) Final overall improvement

After the end of the treatment period (or at the time of discontinuation of treatment), the overall improvement at each evaluation was taken into consideration, and the evaluation was classified as following: marked improvement, moderate improvement, mild improvement, unchanged, and deterioration.

General test [1]

In a general clinical study, 33 patients who have perennial nasal allergy with nasal congestion, were administered 150 mg (in 2 parts) of this drug per day for 4 weeks. The peak flow meter was applied to observe the transition of nasal congestion. As a result, the degree of nasal congestion for which the Nasal Blockage Index was used as an objective index, decreased significantly after administration of the drug [Wilcoxon signed rank test], and proved to be effective against nasal congestion (Tokuji Umino et al, Clinical Medicine, 12, 12, 2593-2611, 1996)[1].

(Note) The approved dosage and administration of this drug are as follows.

The normal dose for adults is 75 mg of Ramatroban to be given orally twice a day after breakfast and dinner (or before bedtime).

(3) Clinical pharmacology test: Tolerability test

(1) Single dose study [2, 3]

A single oral administration on empty stomach of 25 mg, 50 mg, 100 mg, and 150 mg of this drug to 24 healthy men (6 doses each) was well tolerated. In addition, a dose-dependent inhibitory effect on platelet aggregation was confirmed with ex vivo.

(2) Repeated dose study [2, 3]

Administering 75 mg and 100 mg of this drug orally to 12 healthy men twice daily for 9 days after breakfast and dinner (6 doses each; Administered once a day after breakfast on days 1 and 9) was found to be well tolerated. Moreover, during the repeated administration of this drug twice daily, the prominent inhibitory effect on platelet aggregation was found to be maintained with ex vivo of this drug. (Kojiro Yasunag et al, Clinical Medicine, 12, 12, 2523-2539, 1996;[2] Azuma Junichi et al [Clinical Medicine, 13, 3, 511-524 (1997)[3]

(Note) The approved dosage and administration of this drug are as follows.

In general, for adults, 75 mg of Ramatroban is orally administered twice a day after breakfast and dinner (or before bedtime)."

(4) Research study: Dose-response research study [4]

As per envelope method, 50 mg / day, 100 mg / day or 150 mg / day (all in 2 parts) of this drug was orally administered for 59 weeks to 59 patients who have moderate / severe perennial nasal allergy with nasal congestion. The improvement rate (moderate improvement or higher) with regard to the final overall improvement which is the main evaluation criteria, was as high as 72.7% in the 150 mg/day group as against 47.1% in the 50 mg/day group and 46.2% in the 100 mg/day group. The improvement rates (rates above "better") of nasal obstruction were 56.3%, 54.5%, and 90.9%, respectively. High tolerability of the doses suggested the usefulness of this

drug for perennial nasal allergy (Shunkichi Baba et al, Clinical Medicine, 12, 12, 2541-2560, 1996)[4]

(Note: The approved dosage and administration of this drug are as follows.

In general, for adults, 75 mg of ramatroban is orally administered twice a day after breakfast and dinner (or before bedtime).

(5) Verification test

(1) Randomized parallel dose-response study [5]

In order to find the optimum dose for 251 patients with severe perennial nasal allergy and moderate nasal congestion, a double-blind comparative study was conducted wherein three doses of 50 mg/day, 100 mg/day and 150 mg/day (all in 2 parts) were administered for 4 weeks. There was a significant difference in the final overall improvement between the 150 mg/day group and the 50 mg/day group, and between the 150 mg/day group and the 100 mg/day group. A significant correlation of doses was observed among the 3 doses [Cochran-Mantel-Haenszel test (hereinafter abbreviated as C-M-H)]

Furthermore, the improvement rate was significantly higher at 69.8% for 150 mg/day than 40.6% for 50 mg/day and 45.8% for 100 mg/day.

[Fisher's exact test (hereinafter referred to as Fisher)]

With regard to the degree of symptomatic relief, a significant relationship of doses was observed between sneezing and nasal discharge (C-M-H). No significant relationship of doses was observed in the degree of improvement of nasal congestion (C-M-H) as it was found that the improvement rate was 59.7% in the 50 mg/day group, 62.3% in the 100 mg/day group, and 69.8% in the 150 mg/day group. The incidence of subjective side effects was 5.3% (4/76 cases) for 50 mg/day group, 1.3% (1/78 cases) for 100 mg/day group, 3.8% (3/79 cases) for 150 mg/day group. The incidence of abnormal changes of value in the laboratory test was 8.1% (5/62 cases), 7.8% (5/64 cases) 5.9%, and (4/68 cases) respectively. And there was no significant difference in the overall safety level among the three groups. Based on the above results, the optimum dose of this drug for perennial nasal allergy was considered to be 150 mg/day (in 2 parts) (Shunkichi Baba et al, Clinical Medicine, 12, 12, 2561-2591, 1996)[5]

(Note) The approved dosage and administration of this drug are as follows.

In general, for adults, 75 mg of Ramatroban is orally administered twice a day after breakfast and dinner (or before bedtime).

(2) Comparative test-comparison with Terfenadine [6]

Target illness	Usage. Dose
Perennial nasal allergy	Ramatroban group (Oral administration of 150 mg daily): one 75 mg of Ramatroban twice daily, after breakfast and before going to bed.
	Terfenadine group (Oral administration of 120 mg daily): one 60 mg Terfenadine, twice a day, after breakfast and before going to bed.

[6] Baba Shunkichi et al., Otolaryngology Clinic. 87, 1-32, 1996)

A final study confirmed the usefulness of this drug.

(Note) The approved dosage and administration of this drug are as follows.

In general, for adults, 75 mg of Ramatroban is orally administered twice a day after breakfast and dinner (or before bedtime).

(3) Safety test [7, 8, 9]

As long-term administration tests, three tests were conducted in the targeted patients who have perennial nasal allergy with nasal congestion. The dose was 150 mg/day (all in 2 parts) (reduced to 100 mg/day if necessary), and the administration period was 24 weeks. The subjective side effects observed in the long-term treatment evaluation were in 16 cases (8 cases out of 92 cases, 8.7%) The most common matter was gastrointestinal symptoms (many more than 10 cases), followed by skin / cutaneous adnexal symptoms (rash and skin rash only), which accounted to 2 cases. In addition, the abnormal changes in the laboratory tests, considered to be caused by this drug were found in 12 cases (6 out of 92 cases (6.5%)). The main ones were the elevation of AST (GOT) and ALT (GPT), and an overall increase of bilirubin. When the degree of side effects observed in other tests were compared with the details of abnormal changes in the laboratory tests, there was almost no variation, suggesting that the long-term administration was well tolerated. Moreover, even after long-term administration, this drug showed a stable effect and no decrease in its effect was observed.

[7]Tomozushi Takasaka et al, Clinical Medicine, 13, 1, 161-182, 1997

[8]Ryo Ishikawa et al, Clinical Medicine, 13, 1, 183-204,1997

[9]Yoshihiro Ohashi et al, Clinical Medicine, 13, 1, 141-159, 1997

(Note) The approved dosage and administration of this drug are as follows.

In general, for adults, 75 mg of Ramatroban is orally administered twice a day after breakfast and dinner (or before bedtime).

(4) Patients and pathology specific examinations

No applicable data

(6) Therapeutic use

(1) Examination on results of use, examination on results of specific use (special examination), post-manufacturing and sales clinical trial (post-marketing clinical trial)

No applicable data

(2) Summary of tests conducted or details of implemented plans, as conditions of the agreement.

Not applicable

Ⅵ. Pharmacological Items

1. **Pharmacologically related compounds or compound groups**

Prostaglandin D2 and thromboxane A2 receptor antagonist

2. **Pharmacological action**

(1) Site and mechanism of action

Ramatroban binds to the thromboxane A2 (TXA2) receptors of nasal mucosal blood vessels and platelets and has an inhibitory effect on vascular hyperpermeability and inflammatory tumor invasion. Further, it shows an inhibitory effect on migration and degranulation of inflammatory cells by binding to the prostaglandin D2 (PGD2) receptors on inflammatory cells such as eosinophils. Ramatroban exhibits anti-allergic rhinitis action by binding to these two TXA2 and PGD2 receptors.

TXA_2 receptor binding(in vitro)[10,11]

Rabbit and human platelets were used to study the affinity of Ramatroban to TXA2 receptors by conducting substitutive experiments with 3H-SQ29548 and 3H-Ramatroban.
Ramatroban's Ki value of 13 nM for TXA2 receptors of rabbit platelets was approximately 1/8th of Seratrodast's Ki value of 109 nM. That is, Ramatroban's affinity was weaker than Seratodast's affinity. The Ki value of Ramatroban for TXA2 receptors of human platelets was 10 nM, and the specific binding of 3H-Ramatroban was completely replaced by U-46619, which is a TXA2 agonist. Thus, it was suggested that Ramatroban binding to TXA2 receptors is specific and strong.

Platelet-binding specificity of Ramatroban

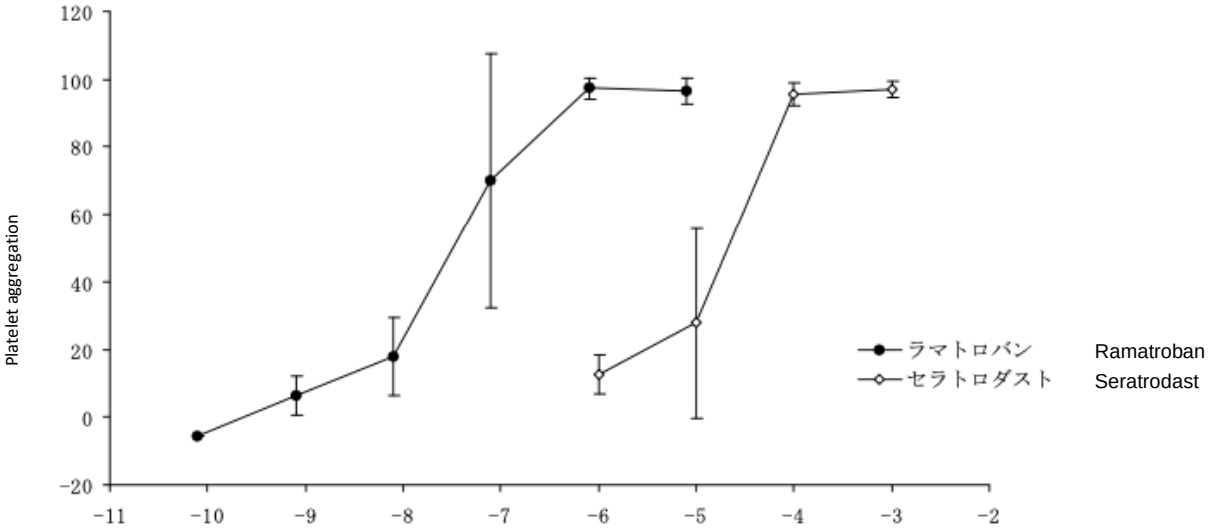
TXA2 receptors [Radioligand]	Test Drug	Ki (nM)	Hill Coefficient	n number
Rabbit platelets [3H-SQ29548]	Ramatroban Seratrodast	13±3 109±22	0.99±0.12 0.93±0.05	3 3
Human platelets Note1) [3H-Ramatroban]	Ramatroban U-46619	10±1 560±243	0.98±0.11 0.78±0.08	5 4

Note 1): Membrane fraction prepared from human platelets was used. Average value ± Standard deviation

1) Antagonist action on TXA_2 receptors in platelets (in vitro) [12]

Inhibitory action of Ramatroban on U-46619-induced in vitro human platelet aggregation response was compared with Seratrodast, which is a TXA2 receptor antagonist.

Inhibitory action (IC50 value approx. $3x10^{-8}$ M) of Ramatroban on U-46619-induced platelet aggregation was effective at the concentration of about 1/1000 that of Seratrodast (IC50 value approx.$3x10^{-5}$ M).



Inhibition action on U-46619-induced in vitro human platelet aggregation
Average value ±Standard deviation n=6

2) Antagonist action on TXA_2 receptors in platelets [13]

The antagonist effect of this drug on TXA2 receptors in blood vessels was studied by using suppression effect against blood vessel constriction as an index.

Ramatroban inhibited the constriction response in rabbit aorta caused by TXA2 analogues cTA2 and U-46619, and the IC50 value was approx. 3 to 4 x 10-7 M. It also showed inhibitory action on U-46619-induced constriction of rat aorta and pig coronary artery. However, Ramatroban did not show an inhibitory action at 7.2x10-5 M on rabbit aorta blood vessel constriction induced by acetylcholine, angiotensin, epinephrine, norepinephrine, histamine, serotonin, and potassium chloride. Therefore, its antagonist action in blood vessels is considered to be specific to TXA2.

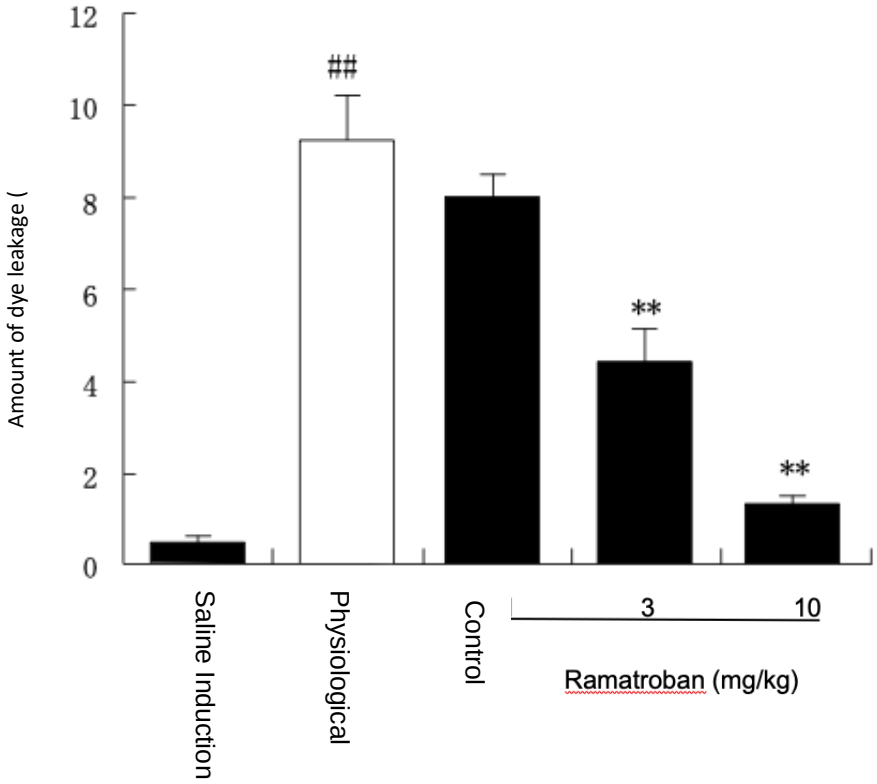
Inhibitory action of Ramatroban on TXA_2 analogues-induced vascular smooth muscle contraction

Tissue	Vasoconstrictor	IC50 (M)
Rabbit aorta	c TxA2 U-46619	3.3x10-7 3.8x10-7
Rat aorta	U-46619	1.3x10-7
Pig coronary artery	U-46619	2.6x10-9

1) Inhibitory action on U-46619-induced vascular hyperpermeability [14]

The effect of Ramatroban on nasal mucosal vascular hyperpermeability induced by perfusing U-46619 (100μg/mL) into the nasal cavity of guinea pigs was studied by using leakage of intravenously injected dye into the perfusate as an index. Ramatroban was orally administered an hour before inducing U-46619.

The perfusion of U-46619 into the nasal cavity significantly increased the amount of dye leaked, therefore, it was confirmed that U-46619 aggravated nasal mucosal vascular hyperpermeability. Ramatroban significantly inhibited the leakage of dye at doses of 3 and 10mg/kg, indicating that it inhibits U-46619-induced nasal mucosal vascular hyperpermeability.



Effect of Ramatroban on U-46619-induced vascular hyperpermeability in nasal mucosa of guinea pigs

Average value ± Standard deviation, n=8

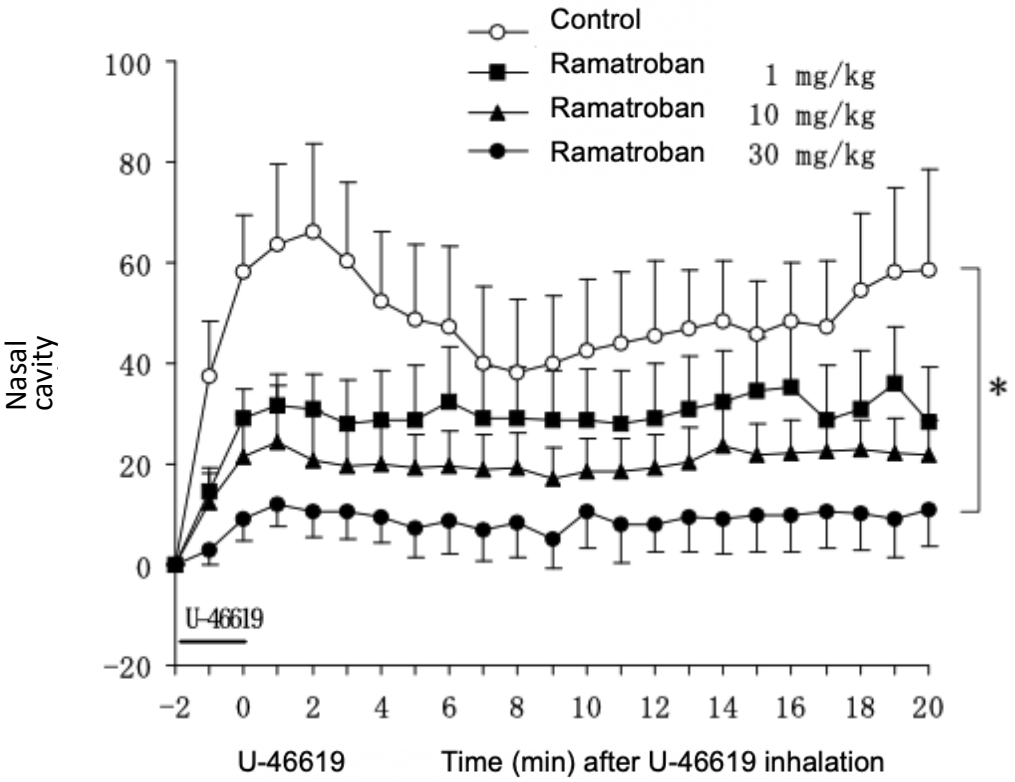
##:p<0.01, significant difference from physiological saline-induced group (Welch's test)

**:p<0.01, significant difference from control group (Dunnett's test)

2) Increased nasal resistance induced by U-46619 14

Modified Konzett-Roessler method to measure the nasal cavity resistance by inserting a cannula in the trachea of guinea pig was used to study the inhibitory effect of Ramatroban on increased nasal cavity resistance induced by inhalation of U-46619 (0.03 %), a TXA2 analogue, into the nasal cavity of guinea pigs. Ramatroban was orally administered 1 hour before U-46619 induction. Inhalation and exposure to U-46619 in guinea pigs' nasal cavity showed a marked increase in nasal cavity resistance. At a dose of 30mg/kg, Ramatroban effectively inhibited the increase in nasal cavity resistance induced by U-46619 as compared to the control group.

Nasal obstruction symptoms of allergic rhinitis are said to be mainly caused by inflammation of mucosal membrane. Since U-46619 aggravates vascular permeability of the nasal mucosa, it is considered that edema was triggered leading to mucosal swelling and causing nasal obstruction.



Effect of Ramatroban on U-46619-induced increased nasal cavity resistance in guinea pigs

Average value ± Standard deviation, n=6

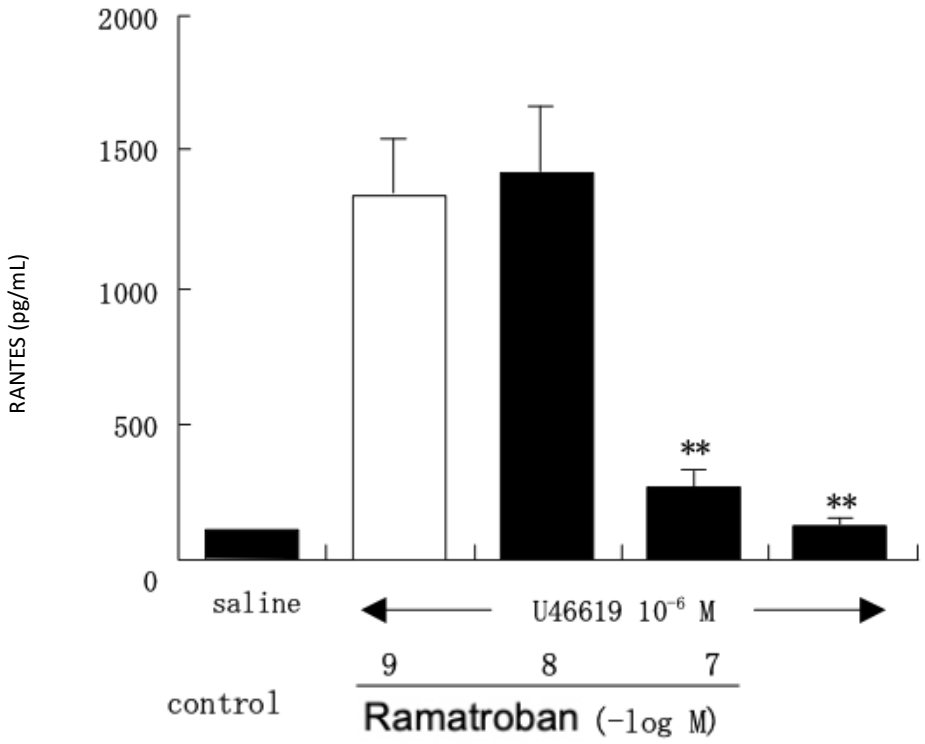
*:p<0.05, significant difference from area under the curve of control group (-2-20min) (Dunnett's test)

3) Inhibitory effect on chemokine (RANTES※) production (in vitro)[28]

※RANTES: regulated upon activation, normal T expressed and presumably secreted

After adding U-46619 to human blood, Ramatroban was added, and RANTES concentration was studied using ELISA method.

Ramatroban significantly inhibited the production of RANTES from 10-8 M, indicating that it has an inhibitory effect on production of chemokine (RANTES) from eosinophil migration.



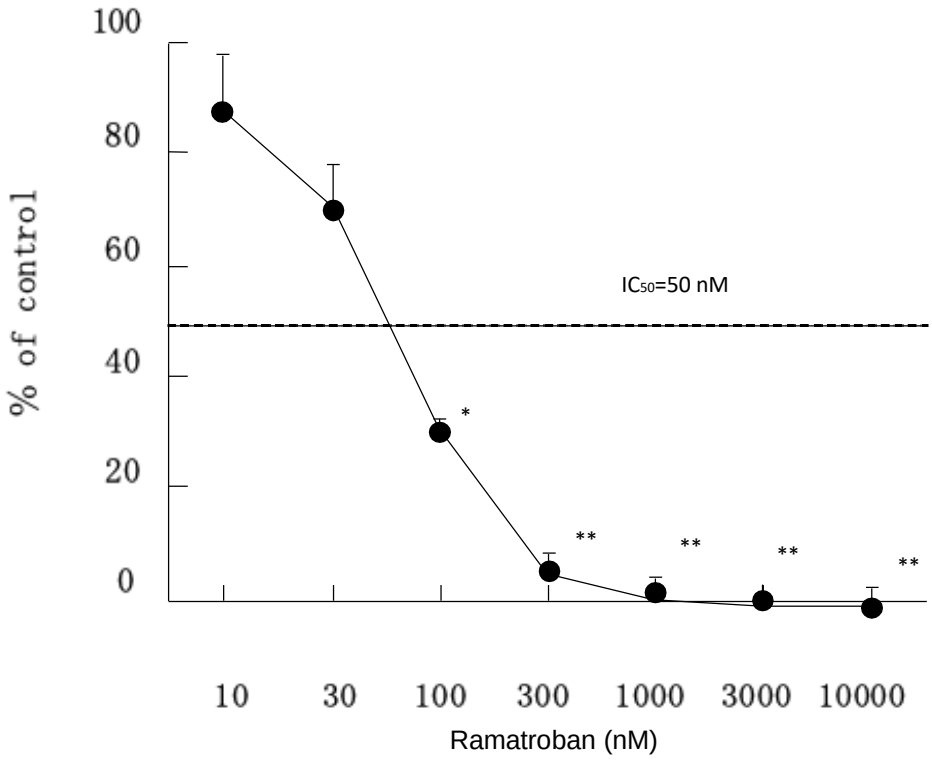
RANTES production by U-46619 and inhibitory effect of Ramatroban

Average value ±Standard deviation n=4

**:p<0.01 significant difference from control group (Dunnett's test)

7) Expression inhibitory action of cell adhesion molecule (ICAM-1 and VCAM-1) (in vitro)28)

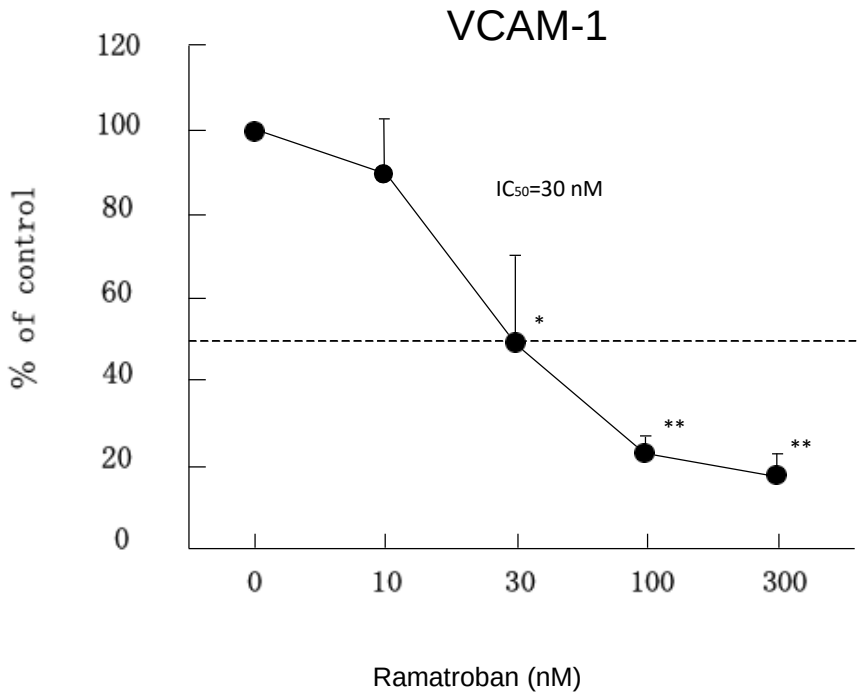
After adding Ramatroban to human microvascular endothelial cells, U-46619 was added and cultured for 20 hours, and the expression rate of adhesion molecules was studied using flow cytometry. Ramatroban inhibited ICAM-1 and VCAM-1 expression at IC50 value of 50 nM and 30 nM, indicating that it has expression inhibitory effect on cell adhesion molecules.



Inhibitory effect of Ramatroban on U-46619-induced ICAM-1 expression

Average value ±Standard deviation n=4

:p<0.05,:p<0.01 significant difference from control group (ANOVA)



Inhibitory effect of Ramatroban on U-46619-induced VCAM-1 expression

Average value ±Standard deviation n=2

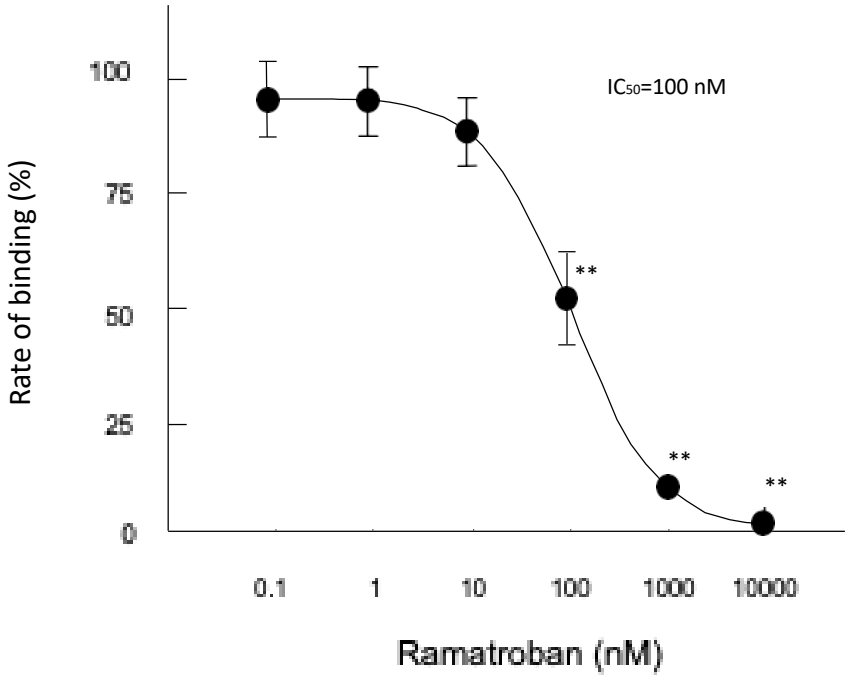
:p<0.05,:p<0.01 significant difference from control group (ANOVA)

8) PGD2 receptor CRTH2* binding inhibitory action (in vitro) 29)

※ CRTH2:chemoattractant receptor-homologous molecule expressed on Th2 cells

Inhibitory performance of Ramatroban in PGD2 binding labelled with 3H was studied using cell line transfected with CRTH2 and highly expressed.

Ramatroban has shown binding inhibitory effect dependent on concentration, indicating its PGD2 receptor CRTH2 antagonist action.



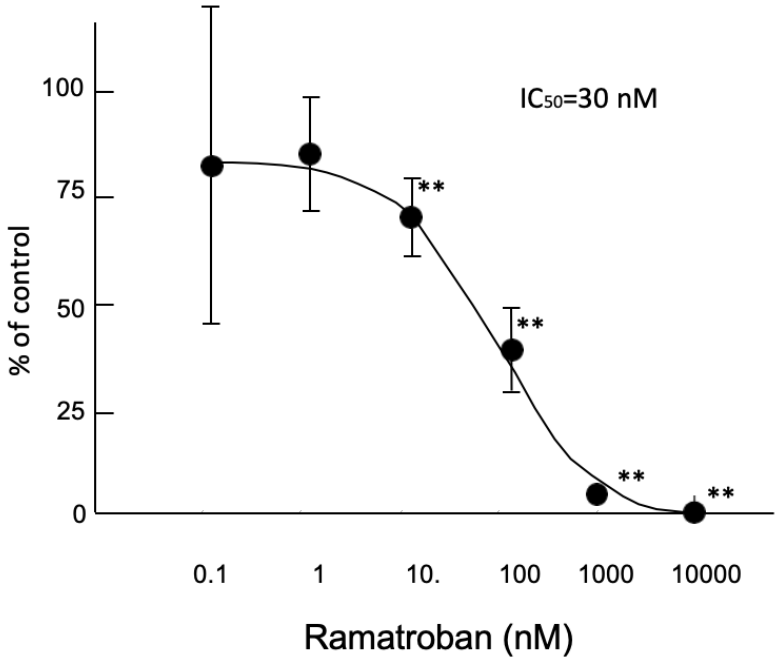
Inhibitory effect of Ramatroban on PGD_2/CRTH2 binding

Average value ±Standard deviation n=7

**:p<0.01(Student's t test)

9) Inhibition effect on intracellular influx of CRTH2 dependent Ca^{2+} (in vitro) 29)

Using cell line transfected with CRTH2 and highly expressed, the effect of Ramatroban pretreatment on Ca^{2+} intracellular influx by PGD2 was studied using fluorescence analysis. Ramatroban showed concentration-dependent inhibitory action. Since degranulation of cells is caused by intracellular influx of Ca^{2+}, it is considered that Ramatroban inhibits cell degranulation by suppressing the intracellular influx of CRTH2-dependent Ca^{2+}.



Inhibitory effect of Ramatroban on intracellular influx of CRTH2-dependent Ca^{2+}

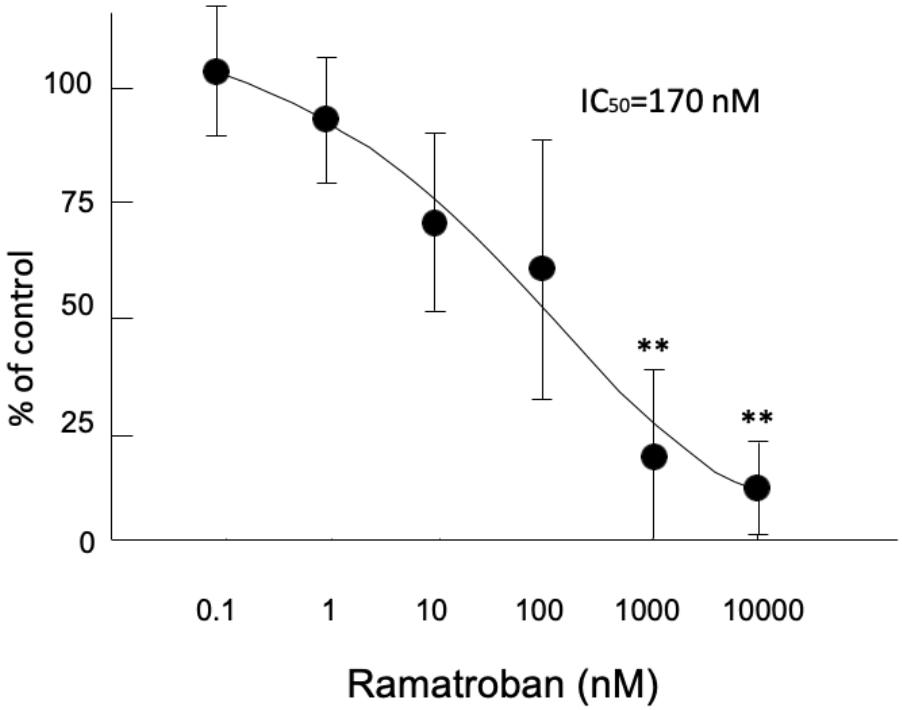
Average value ±Standard deviation n=6

**:p<0.01(Student's t test)

10) Inhibitory action on CRTH2-dependent eosinophil migration (in vitro) 29)

The effect of Ramatroban on human peripheral blood eosinophilotactic activity by PGD2 was studied using Boyden chamber assay.

Ramatroban's concentration-dependent inhibitory action has been confirmed, indicating its inhibitory action on CRTH2-dependent eosinophil migration.



Inhibitory effect of Ramatroban on eosinophil migration due to PGD_2

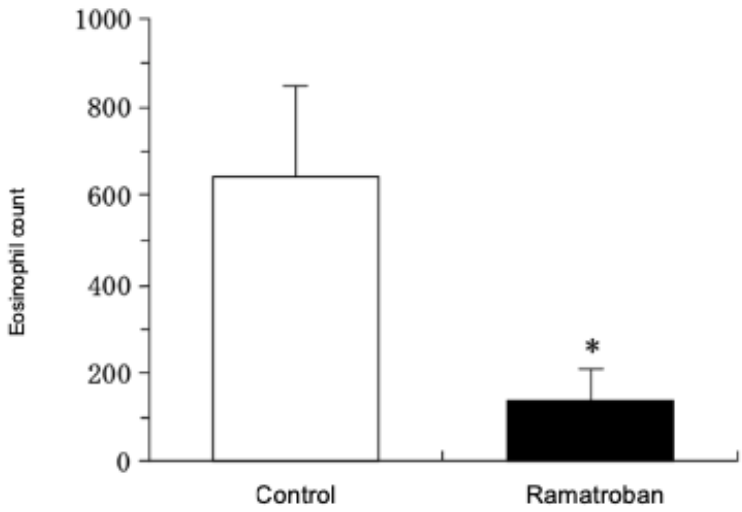
Average value ±Standard deviation n=5

**:p<0.01(Student's t test)

11) Inhibitory action on eosinophil infiltration 15)

In order to study the effect of Ramatroban on eosinophil infiltration of nasal mucosa induced by nasal instillation of antigens in OA-sensitized guinea pigs, 10mg/kg of Ramatroban was orally administered one hour before induction of antigens, and the number of eosinophils inside nasal mucosal tissue was measured after 4 hours.

Ramatroban significantly reduced the number of eosinophils inside antigen-induced mucosal membrane tissue as compared to the control group, indicating its inhibitory effect on eosinophil infiltration.



Effect of Ramatroban on antigen-induced eosinophil infiltration in mucous membrane of antigen-sensitized guinea pigs

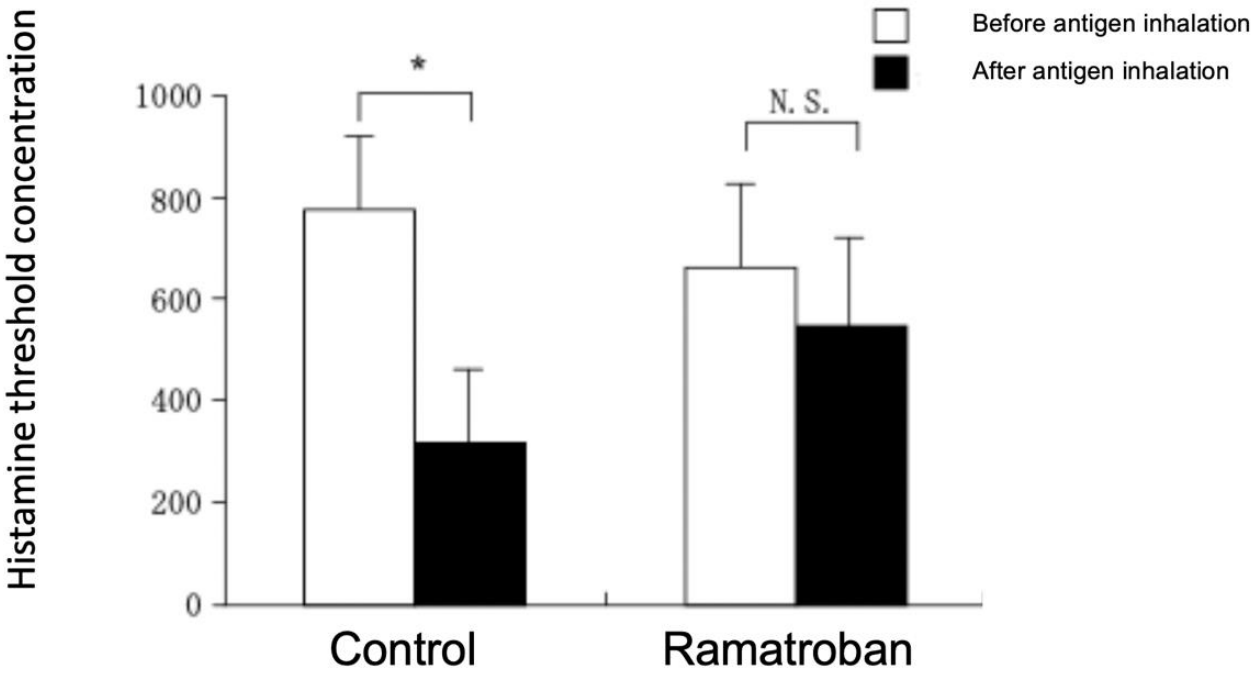
Average value ± Standard deviation, n=8

*:p<0.05 significant difference from control group (Welch's test)

12) Inhibitory action on hypersensitivity of mucous membranes 15)

Ramatroban's inhibitory effect on hypersensitivity of mucous membrane induced by repeated inhalation and exposure to antigens for 7 days was studied in ovalbumin (OA)-sensitized guinea pigs. Hypersensitivity of mucous membrane was evaluated by measuring the reactivity of mucous membrane before and after repeated inhalation of antigens by using threshold concentration of nasal histamine that can induce increased nasal cavity resistance as an index. 15mg/kg of Ramatroban was intraperitoneally administered 30 minutes before each repeated antigen inhalation.

Histamine threshold concentration declined in control group by repeated inhalation of antigens, whereas, in Ramatroban-administered group, the decline in histamine threshold concentration was alleviated, indicating Ramatroban's inhibitory action on hypersensitivity of mucous membrane.



Effect of Ramatroban on histamine hypersensitivity of mucous membranes in antigen-sensitized guinea pigs

Average value ± Standard deviation, n=6

*:p<0.05,(Welch's test)

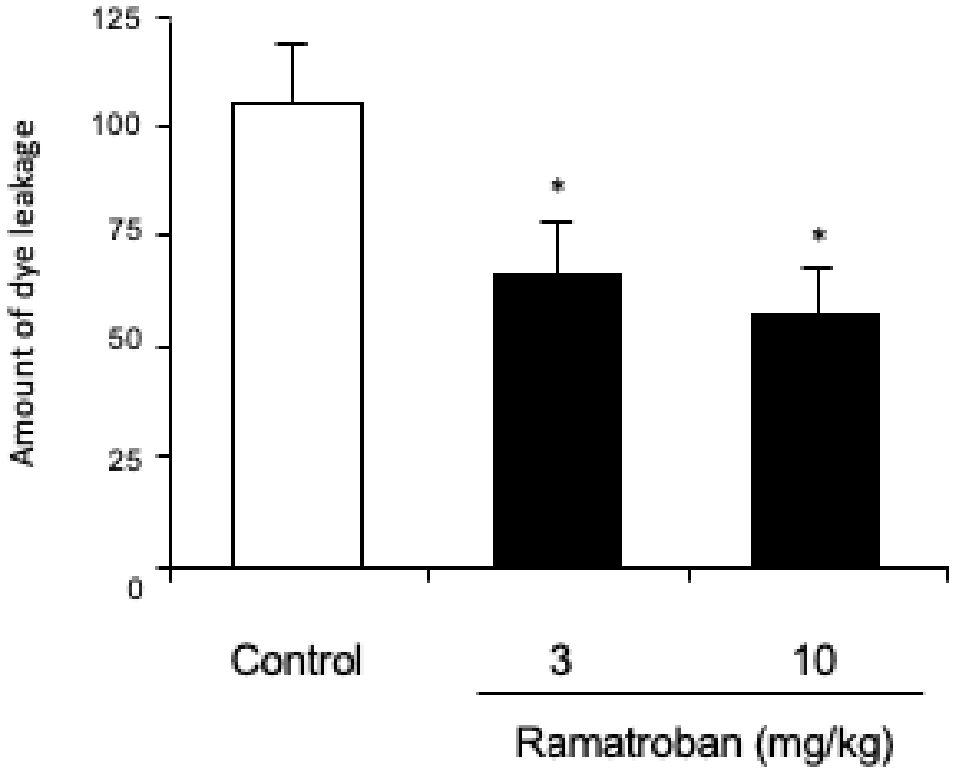
(2) Test results substantiating drug efficacy

1) Anti-allergic rhinitis action

(1) Inhibitory effect on vascular hyperpermeability16)

The effect of Ramatroban on vascular hyperpermeability induced by perfusing antigen solution into the nasal cavity of dinitrophenyl-ascaris-sensitized guinea pigs was studied by using the leakage of intravenously injected dye into the perfusate as an index. Ramatroban was orally administered 1 hour before antigen perfusion.

Ramatroban significantly reduced dye leakage at a dose of 3 mg/kg and above, indicating its inhibitory action on vascular hyperpermeability of mucous membrane.



Effect of Ramatroban on antigen-induced vascular hyperpermeability of mucous membrane in antigen-sensitized guinea pigs

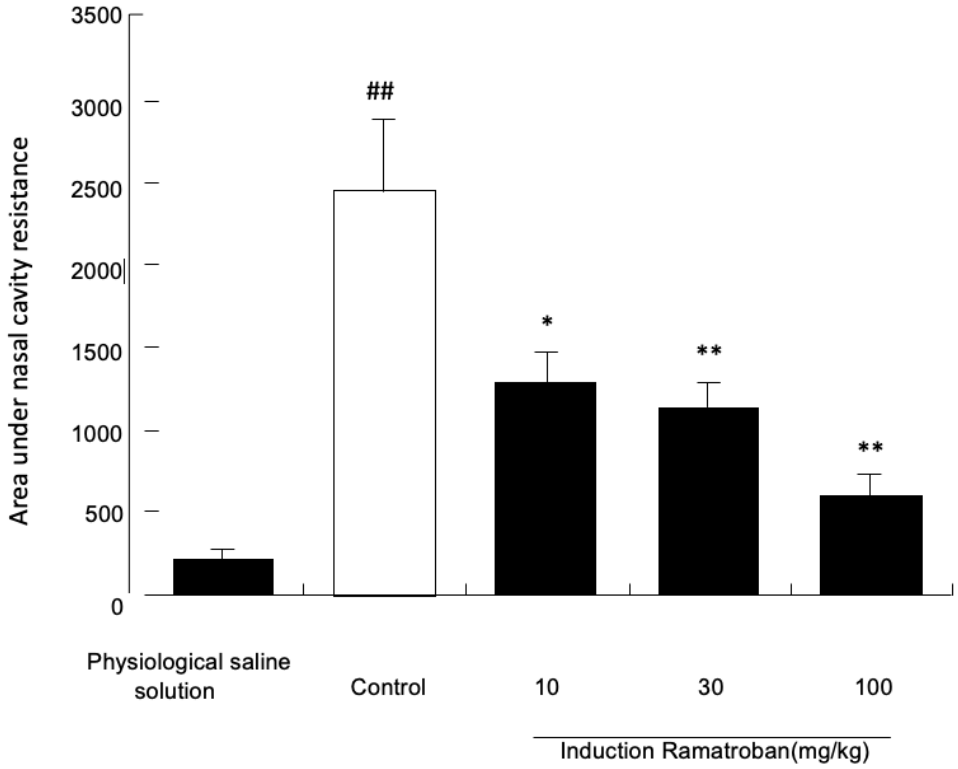
Average value ± Standard deviation, n= 7 to 9

*:p<0.05 significant difference from control group (Dunnett's test) Note 1): Total dye leakage up to 40 minutes from antigen induction.

（2） Inhibitory effect on increased nasal cavity resistance

（i） Model of antigen-induced increased nasal cavity resistance14)

The effect of Ramatroban on increased nasal cavity resistance induced by antigen inhalation was studied in OA-sensitized guinea pigs. The test drug was orally administered 1 hour before antigen induction, and the nasal cavity resistance was measured using modified Konzett-Roessler method. Ramatroban significantly inhibited the increase in antigen-induced nasal cavity resistance at a dose of 10mg/kg and above as compared to the control group, thus indicating its inhibitory action on nasal blockage.



Effect on increase in antigen-induced nasal cavity resistance in antigen-sensitized guinea pigs

Average value ± Standard deviation n=6

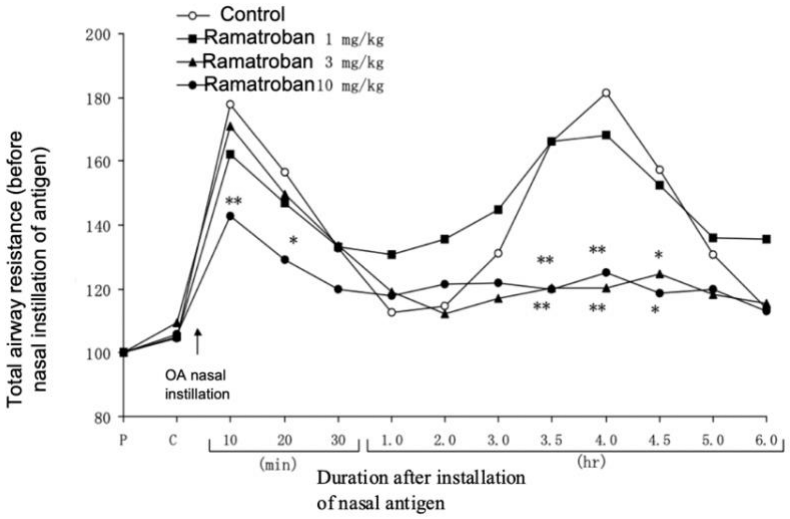
##:p<0.01, significant difference from physiological saline-induced group (Welch's test)

*:p<0.05, **:p<0.01 significant difference from control group (Dunnett's test) Note 1): Based on measured value up to 20 minutes after antigen induction

(ii) Model of biphasic increase in nasal cavity resistance 15),17)

It has been reported that inducing antigens in mucous membrane of patients with allergic rhinitis leads to biphasic nasal obstruction. The effect of Ramatroban on biphasic increase in nasal cavity resistance, that is, increase in nasal cavity resistance immediately after antigen instillation (immediate phase) and re-increase in nasal cavity resistance 4 hours after instillation of antigens (delayed phase) was studied in OA-sensitized guinea pigs as the model of the above phenomenon. The total airway resistance was measured by applying sinusoidal pressure on guinea pigs' body, and by using modified Mead method to calculate the respiratory resistance from the component wave emerging in respiratory airflow. Ramatroban was administered 1 hour after antigen induction. Note that the change in total airway resistance is the sum total of the change in upper airway and lower airway resistance, but in this test, it is considered to be mainly the change in nasal cavity resistance since it was after nasal instillation of antigens.

Ramatroban significantly inhibited the increase in nasal cavity resistance in immediate phase at a dose of 10mg/kg. In delayed phase as well, Ramatroban showed significant inhibitory effect at a dose of 3mg/kg and above



Ramatroban (mg/kg)	Total airway resistance	
	Immediate phase (10min) (%)	Delayed phase (4hr) (%)
Control	177.5±6.1	181.0±13.4
1	162.2±5.6	168.2±4.9
3	171.0±6.4	120.3±3.1**
10	142.8±4.3**	125.2±9.4**

Effect of Ramatroban on antigen-induced biphasic increase in nasal cavity resistance in antigen-sensitized guinea pigs

Average value ± Standard deviation, n=6

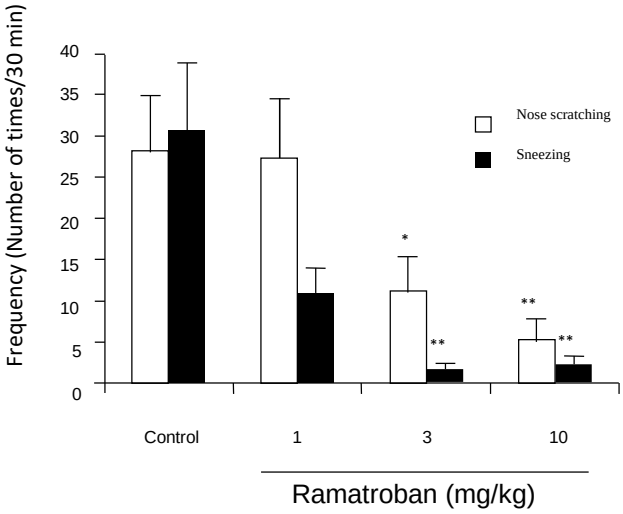
*:p<0.05, significant difference from control group (Dunnett's test)

P:Before nasal instillation, C: Nasal instillation of physiological saline solution

（3） Nasal symptoms expression inhibitory action15)

The effect of Ramatroban on sneezing and nose scratching induced by nasal instillation of antigens in OA-sensitized guinea pigs was studied.

When 3 and 10mg/kg of Ramatroban was orally administered 1 hour before inducing antigens, the number of sneezes and nose scratching reduced significantly as compared to the control group, indicating that the drug inhibits the expression of nasal symptoms.



Effect of Ramatroban on nasal symptoms after inducing antigens in antigen-sensitized guinea pigs

Average value ± Standard deviation, n=12

*:p<0.05, significant difference from control group (Dunnett's test)

(3) Onset and duration of drug action

No applicable data

Ⅶ. Pharmacokinetic Items

1. **Change in blood concentration and measurement technique**

(1) Therapeutically effective blood concentration

No applicable data

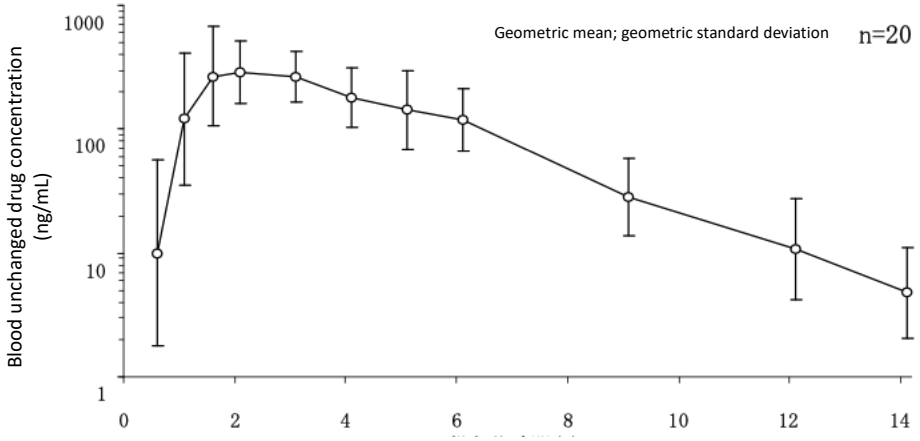
(2) Time to reach maximum blood concentration

See“1. (3) Blood concentration verified in clinical studies”

(3) Blood concentration verified in clinical studies

(1) Blood concentration at single dose in healthy adults18)

The changes in blood unchanged drug concentration and pharmacokinetic parameters after single oral administration of 75 mg of the drug to 20 healthy adult males on empty stomach are shown in the below diagram and table.



Change in blood unchanged drug concentration upon single fasting administration of Ramatroban 75mg tablet to healthy adults

Pharmacokinetic parameters of administration of single fasting dose of Ramatroban tablet 75 mg to healthy adults

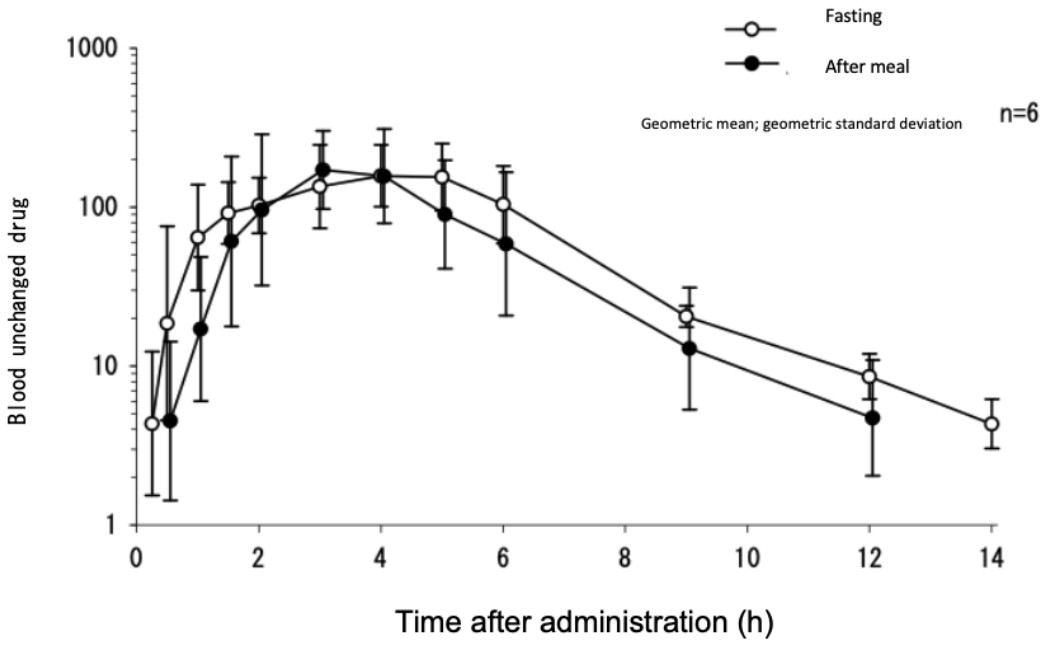
Geometric mean (geometric standard deviation)

Cmax [ng/mL]	tmax [h]	AUC [ng･h/mL]	MRT [h]	t1/2 [h]
418.8 (1.57)	1.83 (1.45)	1517.1 (1.52)	4.39 (1.19)	2.111.77)

Effect of meals

1) Single oral dose of 50 mg of this drug was administered to 6 healthy adult males on empty stomach and 30 minutes after the start of breakfast. When the pharmacokinetic parameters for fasting and postprandial administration were compared by analysis of variance, the postprandial AUC was significantly lower as compared to fasting administration. However, the ratio of AUC of fasting administration to postprandial administration

(postprandial/fasting), is 88.8% on average (90% confidence interval: 81.4% to 96.9%), and the amount of reduction in bioavailability due to meals was considered to be meagre. Thus, the effect of feeding on pharmacokinetics of this drug was not considered clinically problematic.



Change in blood unchanged drug concentration on administration of single dose of Ramatroban tablet 50 mg to healthy adults on empty stomach or after meals.

Pharmacokinetic parameters of administration of single dose of Ramatroban tablet 50mg to healthy adults on empty stomach or after meals

Administration condition	Cmax [ng/mL]	tmax [h]	AUC [ng・h/mL]	MRT [h]	t1/2 [h]
Fasting	209.0 (1.47)	3.3 (1.57)	996.6 (1.28)	4.75 (1.08)	2.17 (1.29)
Postprandial	265.0 (1.32)	2.4 (1.43)	884.8 (1.25)	4.02 (1.36)	1.52 (1.19)
P value (analysis of variance)	0.4594	0.1064	0.0437	0.1745	0.0854

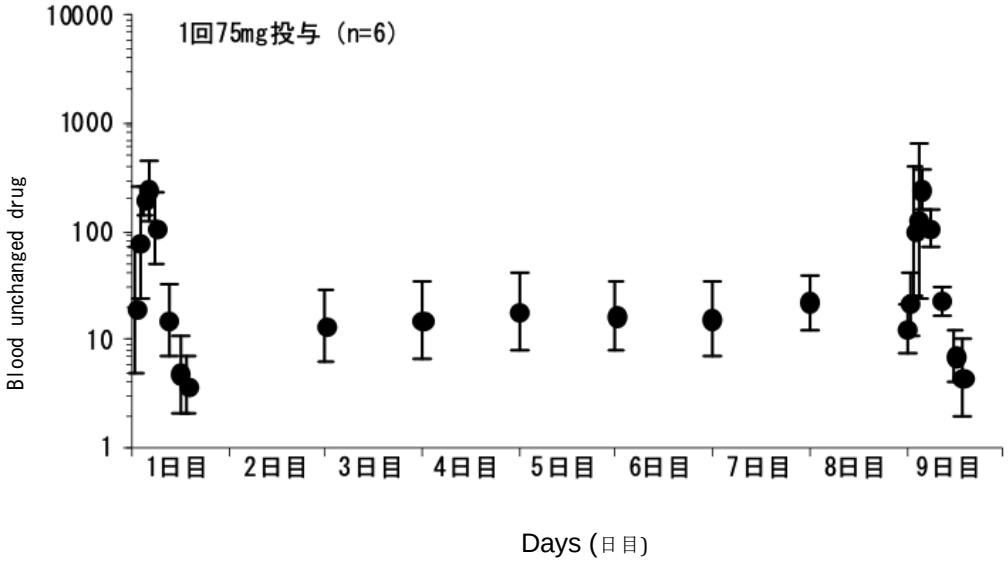
Geometric mean (geometric standard deviation) n=6

Note) The approved indication and dose of this drug is as follows.

“Typically, for adults, Ramatroban 75mg is administered orally twice a day, after breakfast and dinner (or before bedtime)”.

Repeated administration test

The below diagram and table show the change in blood unchanged drug concentration and pharmacokinetic parameters after repeated oral administration of 75mg of this drug twice a day after breakfast and dinner for 9 days (once a day after breakfast on first and ninth day) to 6 healthy adult males. Accumulation due to repeated administration was not seen.



Change in blood unchanged drug concentration after repeated administration of Ramatroban 75mg tablet to healthy adults twice a day for 9 days (once a day on first and ninth day)

Pharmacokinetic parameters after repeated administration of Ramatroban 75mg tablet to healthy adults twice a day for 9 days (once a day on first and ninth day)

Day of Administration	Cmax [ng/mL]	tmax [h]	AUC0-12 [ng･h/mL]	MRT [h]	t1/2 [h]
Day 1	320.9 (1.22)	4.1 (1.25)	1139.1 (1.32)	4.60 (1.14)	2.63 (1.57)
Day 9	302.5 (1.51)	3.2 (1.32)	1142.2 (1.27)	4.63 (1.13)	2.13 (1.51)
Day 9/Day 1	0.94 (1.33)	0.79 (1.61)	1.00 (1.19)	1.01 (1.26)	0.81 (1.29)

Geometric mean (geometric standard deviation), n=6

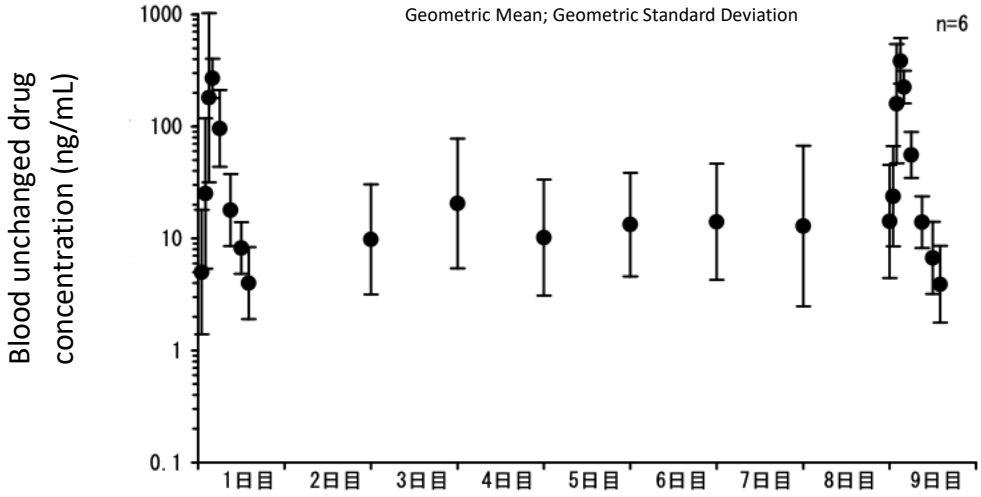
(2) Patient study[19]

As a result of pharmacokinetic study, the predicted systemic clearance in patients with chronic allergic rhinitis was 79.6% of healthy adult males. [See Ⅶ.2.(5)]

(3) Study of elderly population [20]

The below diagram and table show the change in blood unchanged drug concentration and pharmacokinetic parameters after repeated oral administration of 50mg of this drug twice a day after breakfast and dinner for 9 days (once a day after breakfast on first and ninth day) to 6 healthy elderly males. Accumulation due to repeated administration was not seen.

As a result of pharmacokinetic study 19), the systemic clearance in elderly was 78.9% of the non-elderly group (95% confidence interval: 56.4% to 101.4%), which tended to be lower than that in non-elderlies, and it was considered that the blood concentration of this drug in elderlies may be high.



Days (日目)

Changes in blood unchanged drug concentration after repeated administration of 50 mg of this drug twice daily for 9 days (once on days 1 and 9 once daily) to healthy elderly men

Pharmacokinetic parameters of 50 mg of this drug twice daily for 9 days in healthy elderly men

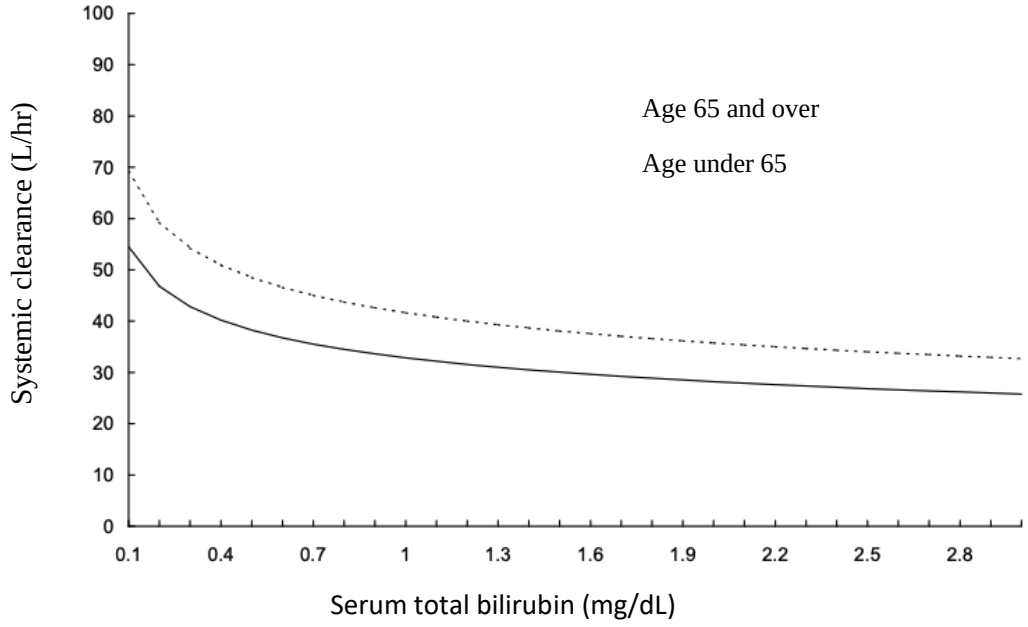
(once on days 1 and 9 once daily)

Administration date	Cmax [ng/mL]	tmax [h]	AUC0-12 [ng·h/mL]	MRT [h]	t1/2 [h]
1 Day 1	404.5 (1.88)	3.1 (1.29)	1188.0 (1.59)	4.61 (1.21)	2.34 (1.25)
9 Day 9	457.9 (1.59)	2.6 (1.23)	1220.3 (1.49)	4.06 (1.14)	2.93 (1.46)
9 Day 9/1	1.13 (1.73)	0.8 (1.20)	1.03 (1.27)	0.88 (1.09)	1.25 (1.51)

(4) Study of cases with declined liver function and declined kidney function 19

As a result of pharmacokinetic study, it was suggested that the higher the total serum bilirubin,

lower the systemic clearance of this drug, and higher its blood concentration. On the other hand, the kidney function test value (BUN, serum creatinine) did not have an impact on the systemic clearance of this drug.



Relationship between systemic clearance and total serum bilirubin estimated from pharmacokinetic screen

(4) Poisonous level

No applicable data

(5) Impact of meals and concomitant drugs

For impact of meals: See “1. (3) Blood concentration verified in clinical studies”

(6) Variable factors for drug disposition identified from population analysis

No applicable data

2. **Pharmacokinetic parameters**

(1) Compartment model

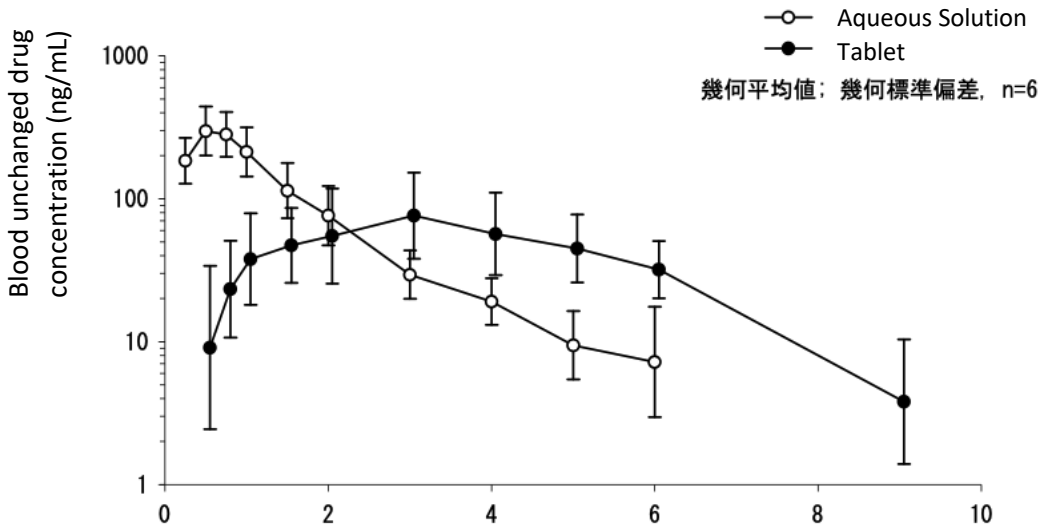
No applicable data

(2) Rate constant

The rate constant was predicted to be 1.220 (95% confidence interval: 0.840 to 1.600). [From pharmacokinetic screening 18]]

(3) Bioavailability

The changes in blood unchanged drug concentration and pharmacokinetic parameters after single oral administration of 25mg of either aqueous solution of Ramatroban or tablet (Ramatroban) to 6 healthy adult males on empty stomach are shown in the below diagram and table. The relative bioavailability of this drug (AUC of administration of Ramatroban tablet/AUC of administration of Ramatroban aqueous solution)
was 80.3% 21



Geometric mean; Geometric standard deviation, n=6

Time after administration (h)

Change in blood unchanged drug concentration upon single fasting dose of Ramatroban aqueous solution or Ramatroban 25mg tablet to healthy adults.

Pharmacokinetic parameters of administration of single fasting dose of Ramatroban aqueous solution or Ramatroban 25mg tablet to healthy adults

Dosage form	Cmax [ng/mL]	tmax [h]	AUC [ng･h/mL]	MRT [h]	t1/2 [h]	Relative bioavailability [%]
Aqueous solution	303.4 (1.44)	0.57 (1.23)	475.3 (1.46)	1.69 (1.17)	1.74 (1.33)	-

Tablet	88.4 (1.66)	3.05 (1.34)	381.6 (1.62)	4.23 (1.23)	1.57 (1.43)	80.3 (1.22)

Geometric mean (geometric standard deviation), n=6

(4) Elimination rate constant

0.33 (calculated from t1/2 after single fasting dose of 75mg of this drug to healthy male adults 18))

(5) Clearance

According to pharmacokinetic study19), the systemic clearance of patients with chronic allergic rhinitis was predicted to be 41.3 L/h (1.4)

[Geometric mean(geometric standard deviation)].

(6) Distribution volume

As per pharmacokinetic study19), the apparent distribution volume was predicted to be 3.420 L/kg (95% confidence interval: 3.089 to 3.75L/kg).

(7) Blood plasma protein coupling rate

The drug has a high coupling capacity with blood plasma protein. For human blood plasma protein,

it is 97 to 98%. It mainly binds with albumin and the binding is reversible

.

3. **Absorption**

No applicable data

Reference Animal data

When Ramatroban was orally administered to rats, dogs, or guinea pigs, Cmax of blood unchanged drug concentration

was observed after 1 to 2 hours of administration. Further, the bioavailability at the time of administration of this

drug in these animals was the highest in dogs (102%), followed by rats (52%), and then guinea pigs (22%).

(1) Site of absorption

The AUC when 14C-Ramatroban was administered intraduodenally to rats was three times as compared to intracolic administration.

It became clear that this drug is mainly absorbed in the small intestine.

Enterohepatic circulation

When the gall collected (0 to 24 hours after administration) from a male rat administered with 5mg/kg of 14C-Ramatroban was intraduodenally administered to another male rat, the excreted urine and gall up to 24 hours after administration contained respectively 1.1% and 15.3% of the dose. In addition, radioactivity equivalent to 0.1% of the dose was found in the carcass excluding the alimentary canal, suggesting that 16.5% of the dose was re-absorbed by enterohepatic circulation.

4. **Distribution**

No applicable data

Reference Animal data (Rats) 22)

The highest radioactivity concentration in internal organs and tissue when 14C-Ramatroban was administered to male rats exceeded the blood plasma radioactivity concentration of liver, kidney, and adipose tissue, but was lower in other internal organs and tissues. Thereafter, most of the radioactivity concentration in organs and tissues disappeared almost in parallel with plasma, but the disappearance from plasma was comparatively slow.

Radioactivity concentration in organs and tissues when single oral dose ^{14}C-Ramatroban was administered to male rats (dose: 4.2mg/kg/day)

Organ/ Tissue	**Radioactivity Concentration (nq eq./g or mL)**					
	1 hour	2 hours	4 hours	48 hours	72 hours	216 hours
Plasma	708 (1.15)	726 (1.12)	196 (1.46)	13.5 (1.30)	2.5 (1.29)	n.d.
	<1.00>	<1.00>	<1.00>	<1.00>	<1.00>	
Blood cells	201 (1.30)	227 (1.34)	51.8 (1.27)	8.8 (1.16)	4.1 (1.26)	4.0 (1.22)
	<0.28>	<0.31>	<0.26>	<0.65>	<1.64>	
Organs	11200 (1.43)	14800 (1.25)	4220 (1.22)	161 (1.48)	46.5 (1.16)	11.0 (1.08)
	<15.82>	<20.39>	<21.53>	<11.93>	<18.60>	
Kidney	4450 (1.24)	3640 (1.14)	894 (2.27)	95.5 (1.34)	23.3(1.32)	11.1 (1.21)
	<6.29>	<5.01>	<4.56>	<7.07>	<9.32>	
Lungs	380 (1.41)	259 (1.08)	94.9 (2.24)	10.3 (1.12)	2.3 (1.22)	1.2 (1.12)
	<0.54>	<0.36>	<0.48>	<0.76>	<0.92>	
Heart	260 (1.48)	219 (1.16)	59.1 (1.27)	5.4 (1.21)	n.d.	n.d.
	<0.37>	<0.30>	<0.30>	<0.40>		
Spleen	108 (1.17)	125 (1.43)	144 (2.38)	6.5 (1.31)	2.2(1.15)	n.d.
	<0.15>	<0.17>	<0.73>	<0.48>	<0.88>	
Skeletal muscle	78.8 (1.46)	76.6 (1.22)	27.0 (1.79)	2.3 (1.27)	n.d.	n.d.
	<0.11>	<0.11>	<0.14>	<0.17>		
Adrenal body	217 (1.17)	182 (1.80)	143 (1.35)	13.9 (1.38)	n.d.	n.d.
	<0.31>	<0.25>	<0.73>	<1.03>		
Salivary glands	151 (1.47)	146 (1.36)	35.9 (1.32)	5.1 (1.27)	n.d.	n.d.
	<0.21>	<0.20>	<0.18>	<0.38>		
Testicle	69.6 (1.19)	77.9 (1.09)	45.5 (1.39)	2.3 (1.49)	0.6 (1.24)	n.d.
	<0.10>	<0.11>	<0.23>	<0.17>	<0.24>	
Vesicular gland	101 (1.85)	132 (2.34)	144 (1.30)	4.3 (1.33)	n.d.	n.d.
	<0.14>	<0.18>	<0.73>	<0.32>		
Brain	18.4 (1.44)	15.5 (1.10)	5.1 (1.21)	1.1 (1.29)	n.d.	n.d.
	<0.03>	<0.02>	<0.03>	<0.08>		
Adipose tissue	123 (1.55)	357 (1.59)	597 (1.38)	10.6 (1.35)	n.d.	n.d.
	<0.17>	<0.49>	<3.05>	<0.79>		
Bones*	181 (1.19)	156 (1.28)	57.9 (1.44)	n.d.	n.d.	n.d.
	<0.26>	<0.21>	<0.30>			
Dermis	168 (1.24)	210 (1.57)	56.1 (1.26)	8.4 (1.14)	3.1 (1.39)	1.4 (1.19)

	<0.24>	<0.29>	<0.29>	<0.62>	<1.24>	

Geometric mean (geometric standard deviation), n=5 < >: Ratio of radioactivity concentration in tissues
to radioactivity concentration in blood plasma (T/P
*Includes bone marrow, n.d.: Below limit of determination

(1) Blood-brain barrier permeability

Even at its highest, the radioactivity concentration in brain tissue was as low as 8% of the radioactivity concentration in blood plasma, indicating that it is difficult for unchanged drug and metabolites to cross the blood brain barrier.

(2) Blood-placenta barrier permeability

The embryonic radioactivity was maximum 1.5% of the radiation dose after oral administration of 14C-Ramatroban to prenatal rats.

(3) Transferability to breast milk

No applicable data

Reference Animal data(Rats) 23)

When ^{14}C-Ramatroban was orally administered to lactating rats at 5mg/kg, although radioactivity was found in breast milk, it disappeared faster than that from blood plasma, and was below the limit of determination in 24 hours after administration.

Radioactivity concentration in breast milk and blood plasma when ^{14}C-Ramatroban was orally administered to lactating rats

Hours (h)	Breast Milk Concentration (μg eq./mL)	Blood Plasma Concentration (μg eq./mL)
1	2.31 (1.38)	0.524 (1.22)
4	1.77 (1.50)	0.159 (1.36)
7	0.579 (1.53)	0.0682 (1.49)
24	n.d.	0.00698 (1.18)

n.d.: Less than limit of determination, geometric mean (geometric standard deviation), n＝ 4 to 5

(4) Transferability to cerebrospinal fluid

No applicable data

(5) Transferability to other tissues

No applicable data

5. **Metabolism**

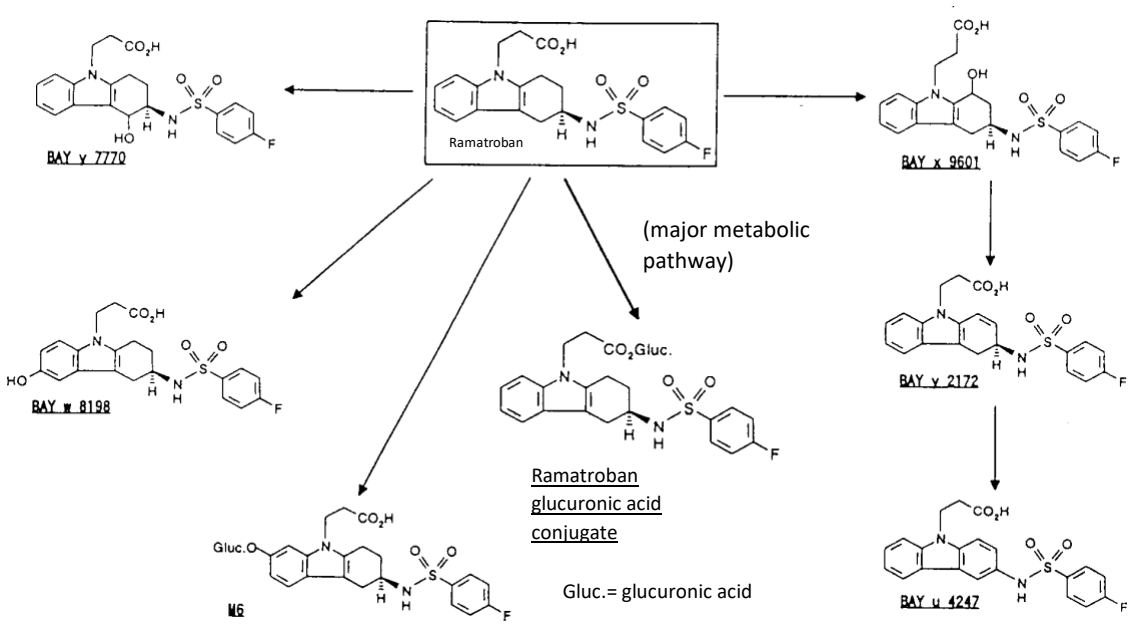
(1) Site of metabolism and metabolic pathway

Site of metabolism: Liver

Major metabolic pathway: Unchanged Acyl glucuronic acid conjugate [22, 24]

It is thought that the major metabolic pathway of this drug in humans is Acyl glucuronic acid conjugate. Further, it is also suggested that hydroxylation is one of the secondary metabolic pathways of this drug.

Secondary metabolic pathway: BAY x 9601, BAY y 7770, M6, BAY u 4247 and BAY w 8198



Putative metabolic pathway in humans

(2) Molecular species of enzymes (such as CYP450) involved in metabolism

Molecular species of enzymes (such as CYP450) contributing to metabolism 25)

The major metabolic pathway of Ramatroban is Acyl glucuronic acid conjugate. Since it partially undergoes oxidative metabolism, the molecular species involved were examined using microsomes from human liver cytochrome P450 (CYP) expression system, and it was found that the molecular species was CYP3A4.

Although this drug inhibited CYP2C9 activity, its inhibition constant (25.1μM) suggests that it is unlikely to act as a human liver CYP inhibitor in the body.

(3) Occurrence of first-pass effect and its rate

No applicable data

(4) Occurrence of metabolite activity and its ratio

No applicable data

(5) Pharmacokinetic parameters of active metabolites

No applicable data

6. **Excretion**

(1) Site and pathway of excretion

The major excretion pathway is considered to be in the feces via biliary excretion.

(2) Rate of excretion

Urinary excretion 26)

The table below shows the urinary excretion rate of each metabolite over 24 hours after administration of the drug against the administered dose after single fasting administration of 50mg or 75mg to healthy adult males

.

The total excretion amount in urine including the unchanged drug and metabolites was as low as 8% of the dosage, and it is considered that this drug is excreted mainly in bile.

Mean cumulative urine excretion rate of Ramatroban unchanged drug and each metabolite 24 hours after administration

Ramatroban	2.37 %#
BAY x 9601	2.86 %
Glucuronic acid conjugate of Ramatroban	1.44 %
BAY w 8198	1.35 %
BAY u 4247	0.06 %
Optical isomer of Ramatroban	n.c.
Total	8.08 %

Arithmetic mean value, n=6, #: n=80

n.c.: not calculated (since the urine concentration was less than limit of determination)

(3) Rate of elimination

No applicable data

7. **Extraction rate due to dialysis, etc.**

No applicable data

Ⅷ. Safety (Precautions for Use) Items

1. **Warnings and reasons**

Not Applicable

2. **Contraindications and reasons (including contraindications in principle)**

Contraindications (do not administer to the following patients)

Patients with a history of hypersensitivity to the components of the drug

3. **Precautions related to efficacy or effect and their reasons**

Not Applicable

4. **Precautions related to indications and dose and their reasons**

Precautions related to usage and dose

For the elderly, be careful with starting with a low dose (100 mg/day) (see "Administration to the elderly")

5. Careful dosage and reasons

Careful dosage (administer carefully to the following patients)
(1) Patients with hemorrhagic tendency [drug may promote bleeding]
(2) Patients during menstrual period [drug may promote bleeding]
(3) Patients with liver disorder [drug may cause liver dysfunction]
(4) Elderly [See "Administration to the Elderly"]

6. **Important basic precautions, their reasons, and measures**

Important basic precautions
When administering this drug to patients with seasonal disorders, it is desirable to start the administration just before the start of peak season and continue till its end.

7. **Interactions**

(1) Contradictions for coadministration and reasons

Not Applicable

(2) Precautions for coadministration and reasons

Use caution (be careful of use)

Drug	Clinical. Presentation/Treatment	Mechanism/Risk Factors
Antiplatelet agents Thrombolytic agents such as Ticlopidine Anticoagulants such as Urokinase Heparin Warfarin, etc.	Coadministration with these drugs may increase the hemorrhagic tendency. Exercise caution such as adequate observation and adjustment of dose.	Since this drug suppresses thrombocytic agglutinativity, using with drugs having similar effects may potentiate the effect.
Salicylic acid-based Aspirin, etc.	According to the interaction study on human plasma protein binding (*in vitro*), salicylic may increase the unbound fraction of the drug by 1.3 to 1.9 times.	It is considered that this drug replaces salicylic acid at the plasma protein binding site, resulting in increased free blood concentration.
Theophylline	Coadministration with theophylline may increase the blood concentration of this drug.	Mechanism unclear

Drug interaction (references, overseas data)
Concomitant use of this drug with theophylline in 12 foreign healthy adults did not lead to changes in the pharmacokinetics of theophylline, however, the blood concentration of this drug increased by two times in

2 cases 27. In addition, when pharmacokinetic study19) was conducted, it was estimated that the systemic clearance of this drug in patients with concomitant use with theophylline will be 61.3% (95% confidence interval: 45.0 to 77.6%) of the patients without concomitant use with theophylline. The unbound fraction of this drug also increased by 1.3 to 1.9 times due to salicylic acid in clinical blood concentration (in vitro).

8. **Adverse reactions**

(1) Overview of adverse reactions

At the time of approval and during use results survey, adverse reactions (including abnormal changes in laboratory test values) were confirmed in 232 cases out of 4,443 cases (5.22%). The main adverse reactions included drowsiness in 25 cases (0.56%), headaches/heaviness in the head in 22 cases (0.50%), increase in ALT (GPT) in 44 cases (0.99%), increase in AST (GOT) in 38 cases (0.86%), and increase in γ-GTP in 36 cases (0.81%).
(at the time of applying for re-examination)

(2) Important adverse reactions and initial symptoms

Serious adverse reactions (less than 0.1%)
Hepatitis, liver dysfunction, jaundice: Liver dysfunction, jaundice with marked elevation in hepatitis, AST(GOT), ALT(GPT), AI-P, γ-GTP, LDH may occur. Hence, perform careful observation, and in case of abnormalities, stop the administration of the drug and take appropriate measures.

(3) Other adverse reactions

	Less than 0.1 to 5%	Less than 0.1%
Hypersensitivity Note 1)	Rash, itching	
Liver Note 1)	Elevated AST(GOT), elevated ALT(GPT), elevated γ-GTP, elevated AI-P, elevated LDH, elevated bilirubin	
Hemorrhagic tendency Note 2	Prolonged APTT, uric blood	Gingival bleeding, nosebleed, subcutaneous bleeding, peliosis, prolonged menses, prolonged prothrombin time
Kidney		Elevated creatine, elevated BUN
Circulatory system	Palpitations	Edema
Digestive system	Nausea, diarrhea, abdominal pain, constipation	Vomiting, indigestion, loss of appetite, mouth ulcers
Blood	Eosinophilia	Hypoglobulia, decrease in hemoglobin Decrease in hematocrit values, hypoleukocytemia
Neuropsychiatric	Drowsiness, headache/heaviness in the head, dizziness	Numbness of the tongue, stiffness of limbs
Other		Dry nose, joint pain, hot flashes, chest tightness Chest abnormality, dysgeusia, fatigue

List of adverse reaction frequency and abnormal laboratory test values by item (at the time of applying for re-examination)

	Investigation Until approval	Use Result survey cumulative total	Total
No of cases evaluated for adverse reaction	1,240	3,203	4,443
No. of cases with adverse reactions	162	70	232
Rate of occurrence of adverse reactions	13.06%	2.19%	5.22%
No. of cases with adverse reaction	303	85	388

Type of adverse reaction	Adverse reaction occurrence rate by type (%)		
Blood and lymphatic system disorders	-	1 (0.03)	1 (0.02)
Iron-deficiency anemia	-	1 (0.03)	1 (0.02)
Heart dysfunction	3 (0.24)	4 (0.12)	7 (0.16)
Palpitations	3 (0.24)	4 (0.12)	7 (0.16)
Gastrointestinal disorders	39 (3.15)	23 (0.72)	62 (1.40)
Stomatitis apthosa	1 (0.08)	-	1 (0.02)
Retching	1 (0.08)	-	1 (0.02)
Nausea	7 (0.56)	4 (0.12)	11 (0.25)
Gastrointestinal disorders	-	1 (0.03)	1 (0.02)
Stomach discomfort	5 (0.40)	4 (0.12)	9 (0.20)
Diarrhea	7 (0.56)	5 (0.16)	12 (0.27)
Hematochezia	-	1 (0.03)	1 (0.02)
Oral hypesthesia	1 (0.08)	-	1 (0.02)
Mouth ulcers	1 (0.08)	-	1 (0.02)
Dry mouth	-	1 (0.03)	1 (0.02)
Gingival hemorrhage	1 (0.08)	1 (0.03)	2 (0.05)
Indigestion	4 (0.32)	-	4 (0.09)
Upper abdominal pain	5 (0.40)	2 (0.06)	7 (0.16)
Cardiac discomfort	1 (0.08)	-	1 (0.02)
Abdominal pain	4 (0.32)	1 (0.03)	5 (0.11)
Abdominal discomfort	1 (0.08)	-	1 (0.02)
Constipation	4 (0.32)	3 (0.09)	7 (0.16)
Vomiting	1 (0.08)	1 (0.03)	2 (0.05)
General disorders and administration site conditions	8 (0.65)	3 (0.09)	11 (0.25)
Discomfort	-	2 (0.06)	2 (0.05)
Chest pain	1 (0.08)	-	1 (0.02)
Chest discomfort	1 (0.08)	-	1 (0.02)
Fatigue	4 (0.32)	-	4 (0.09)
Dry mouth	-	1 (0.03)	1 (0.02)
Feverish	1 (0.08)	-	1 (0.02)
Edema	1 (0.08)	-	1 (0.02)

(continued)

Hepatic-cystic system disorders	-	3 (0.09)	3 (0.07)
Liver dysfunction	-	2 (0.06)	2 (0.05)
Hepatic disorder	-	1 (0.03)	1 (0.02)
Infectious and parasitic diseases	-	1 (0.03)	1 (0.02)
Gastroenteritis	-	1 (0.03)	1 (0.02)
Clinical examination	86 (6.94)	5 (0.16)	91 (2.05)
Enzyme test NEC	32 (2.58)	2 (0.06)	34 (0.77)
Increased blood alkaline phosphatase	19 (1.53)	-	19 (0.43)
Increased blood lactate dehydrogenase	17 (1.37)	2 (0.06)	19 (0.43)
Hematologic test (including blood group test)	21 (1.69)	2 (0.06)	23 (0.52)
Prolonged prothrombin time	2 (0.16)	2 (0.06)	4 (0.09)
Decreased hematocrit	1 (0.08)	-	1 (0.02)
Decrease in hemoglobin	1 (0.08)	-	1 (0.02)
Prolonged activated partial thromboplastin time	6 (0.48)	1 (0.03)	7 (0.16)
Shortened activated partial thromboplastin time	1 (0.08)	-	1 (0.02)
Increase in eosinophils	6 (0.48)	-	6 (0.14)
Decrease in red blood cells	1 (0.08)	-	1 (0.02)
Increase in monocytes	1 (0.08)	-	1 (0.02)
Decrease in white blood cells	3 (0.24)	-	3 (0.07)
Increase in white blood cells	2 (0.16)	-	2 (0.05)
Hepatic-cystic system test	58 (4.68)	2 (0.06)	60 (1.35)
AST(GOT) increase	38 (3.06)	-	38 (0.86)
Increase in ALT(GPT)	43 (3.47)	1 (0.03)	44 (0.99)
Increase in γ-GTP	35 (2.82)	1 (0.03)	36 (0.81)
Increase in blood bilirubin	8 (0.65)	-	8 (0.18)
Lipid test	1 (0.08)	-	1 (0.02)
Decrease in blood cholesterol	1 (0.08)	-	1 (0.02)
Kidney and urinary tract examination	7 (0.56)	3 (0.09)	10 (0.23)
Increase in blood creatinine	1 (0.08)	1 (0.03)	2 (0.05)
Increase in blood urea	2 (0.16)	-	2 (0.05)
Urine blood positivity	5 (0.40)	2 (0.06)	7 (0.16)
Metabolic and nutritional disorders	3 (0.24)	1 (0.03)	4 (0.09)
Sluggishness after meal	3 (0.24)	1 (0.03)	4 (0.09)
Musculoskeletal and connective tissue disorders	2 (0.16)	-	2 (0.05)
Joint pain	1 (0.08)	-	1 (0.02)
Musculoskeletal stiffness	1 (0.08)	-	1 (0.02)

(continued)

Nervous system disorders	29 (2.34)	24 (0.75)	53 (1.19)
Drowsiness	12 (0.97)	13 (0.41)	25 (0.56)
Tremors	-	1 (0.03)	1 (0.02)
Headache	14 (1.13)	8 (0.25)	22 (0.50)
Head discomfort	-	1 (0.03)	1 (0.02)
Lightheadedness	3 (0.24)	2 (0.06)	5 (0.11)
Dysgeusia	3 (0.24)	-	3 (0.07)
Kidney and urinary tract disorders	-	2 (0.06)	2 (0.05)
Chromaturia	-	1 (0.03)	1 (0.02)
Pollakiuria	-	1 (0.03)	1 (0.02)
Reproductive system and breast disorders	1 (0.08)	1 (0.03)	2 (0.05)
Hypermenorrhea	1 (0.08)	1 (0.03)	2 (0.05)
Respiratory, chest, and mediastinal disorders	2 (0.16)	4 (0.12)	6 (0.14)
Dryness in throat	-	1 (0.03)	1 (0.02)
Dry nose	1 (0.08)	-	1 (0.02)
Nosebleed	1 (0.08)	2 (0.06)	3 (0.07)
Asthma	-	1 (0.03)	1 (0.02)
Skin and subcutaneous tissue disorders	14 (1.13)	5 (0.16)	19 (0.43)
Pruritus	3 (0.24)	2 (0.06)	5 (0.11)
Peliosis	2 (0.16)	-	2 (0.05)
Generalized pruritus	1 (0.08)	1 (0.03)	2 (0.05)
Rash	8 (0.65)	3 (0.09)	11 (0.25)
Subcutaneous bleeding	1 (0.08)	-	1 (0.02)

(5) Frequency of adverse reactions by background such as underlying conditions, complications, severity of illness, and surgery

No applicable data

(6) Precautions for drug allergy and method of testing

1. Do not administer the drug to patients with history of hypersensitivity to this drug.
2. Rash and itching may occur. Stop the drug in case of such symptoms.

9. Administration to the Elderly

Administration to the Elderly

When administrating the drug to the elderly, carefully observe their condition and take precautions such as starting from a low dose (100mg/day) [As per the result of pharmacokinetic screening, the blood concentration of this drug in elderly (65 years and above) is estimated to be higher than in non-elderly population. Further, in the clinical

10. Administration to pregnant, parturient, and lactating women

Administration to pregnant, parturient, and lactating women

(1) The drug should be administered to pregnant women or women who may be pregnant only when the therapeutic benefit outweighs the risks. [The safety of this drug in regard to pregnant women has not been established]

(2) It is advisable to avoid administration of the drug to women who are breast-feeding,

11. Administration to infants

Administration to children

Safety of administering the drug to low birth weight babies, newborn babies, infants,

12. Impact on clinical examination results

No applicable data

13. Overdosage

No applicable data

14. Precautions for usage

Precautions for usage

For drug delivery: Give instructions to take the PTP-packed drug after removing the PTP sheet. [It has been reported that in case of accidental ingestion of PTP sheet, the hard, acute part penetrates the esophageal mucosa and further perforates it leading to serious

15. Other precautions

Other precautions
As regards mutagenicity, a positive result was obtained by non-metabolic activation method of the chromosomal abnormality test using cultured cells. However, the result of metabolic activation method of the same test was negative, and moreover, the result was negative when chromosomal abnormality test was conducted using different cultured cells as well as when other mutagenicity tests was performed (A reversion test using bacteria, micronucleus test

16. Other

Ⅸ. Nonclinical Test Items

1. **Pharmacological tests**

(1) Pharmacological tests (See “VI. Pharmacological Items”)

(2) Secondary pharmacodynamics

No applicable data

(3) Safety pharmacology

At an oral dosage of 10mg/kg, Ramatroban showed thrombocytic agglutinativity lowering effect, and bleeding-time prolonging effect at an oral dose of 3mg/kg, however, these are considered to be the effects based on antagonistic action with TXA2 receptors, which is the pharmacological action of this drug. In addition, mild prolongment of anesthesia time, mild increase in sleep depth, mild decrease in excreted potassium, and mild hemolytic action were also observed, but all were only observed at a high dose of 100mg/kg or high concentration of 10-4M, and are not judged to be clinically noteworthy effects.

Test Items		Animal Species	Route of Administration	Dosage (mg/kg)	Test Results
General symptoms and behavior / Central nervous system / Somatic nervous system	1. Effect on general symptoms and behavior (Irwin's multidimensional observation)	Mice	p.o.	10,30,100	No effect
	2. Effect on central nervous system (2. 1. Effect on locomotor activity)	Mice	p.o.	10,30,100	No effect
	(2. 2 Anesthesia enhancing action: Effect on hexobarbital anesthetic Note1))	Mice	p.o.	10,30,100	Mild prolongment of anesthesia, mild increase in sleep depth (100mg/kg)
	(2. 3 Anticonvulsant action: Effect on maximal electroconvulsive Note2)and pentylenetetrazol convulsions Note3))	Mice	p.o.	10,30,100	No effect
	(2. 4 Analgesic action: Hot plate test)	Mice	p.o.	10,30,100	No effect
	(2. 5 Effect on body temperature: Rectal temperature)	Rats	p.o.	10,30,100	No effect
	(2. 6 Effect on spontaneous brain waves)	Rabbits	p.o.	10,30,100	No effect
	(2. 7 Effect on spinal reflex: jaw-tongue reflex)	Anesthetized rats	p.o.	10,30,100	No effect
	(2. 8 Effect on coordination: Balancing ability)	Mice	p.o.	10,30,100	No effect
	(2. 9 Effect on exploratory behavior)	Mice	p.o.	10,30,100	No effect
	(2. 10 Cataleptic agent)	Mice /Rats	p.o.	10,30,100	No effect
	3. Effect on somatic nervous system (3. 1 Effect on myoneural junction: tibial nerve- tibialis anterior)	Anesthetized rats	p.o.	10,30,100	No effect
	(3. 2 Muscle relaxant action: Hanging performance)	Mice	p.o.	10,30,100	No effect
Autonomic nervous system and smooth muscle	4. Effect on autonomic nervous system and smooth muscle (4. 1 Effect on isolated ileum)	Guinea pigs	in vitro	1x10-7, 1x10-6, 1x10-5M	Direct action, acetylcholine/histamine/barium chloride, serotonin contraction: No effect
	(4. 2 Effect on extracted uterus)	Pregnant rats	in vitro	1x10-7, 1x10-6, 1x10-5M	Autonomic movement, oxytocin contraction: No effect
		Non-pregnant rats	in vitro	1x10-7, 1x10-6, 1x10-5M	Autonomic movement, oxytocin contraction: No effect

Test Item		Animal Species	Route of Administration	Dosage (mg/kg)	Test Results
	(4. 3 Effect on isolated sperm duct)	Rats	in vitro	1x10-7, 1x10-6, 1x10-5M	Direct effect, noradrenaline contraction: no effect
	(4. 4 Effect on isolated aorta)	Rabbits	in vitro	1x10-7, 1x10-6, 1x10-5M	Direct effect, phenylephrine contraction: no effect
	(4. 5 Effect on isolated trachea)	Guinea pigs	in vitro	1x10-7, 1x10-6, 1x10-5M	Direct effect, histamine contraction: No effect
Respiratory /Circulatory system / Alimentary system / Water and electrolyte metabolism	5. Effect on respiratory/circulatory system (5. 1 Effect on mean arterial pressure and heart rate)	Anaesthetized dogs	p.o.	10,30,100	No effect
	(5. 2 Effect on breathing movement)	Guinea pigs	p.o.	10,30,100	No effect
	(5. 3 Effect on blood flow to femur)	Anaesthetized dogs	p.o.	10,30,100	No effect
	(5. 4 Effect on electrocardiogram: phase II induction)	Anaesthetized dogs	p.o.	10,30,100	No effect
	6. Effect on alimentary system (6. 1 Effect on intestinal transport property: charcoal method)	Rats	p.o.	30,100,300	No effect
	(6. 2 Effect on gastric mucosa)	Rats	p.o.	30,100,300	No effect
	(6. 3 Effect on histamine-induced gastric acid secretion)	Anesthetized rats	i.d.	10,30,100	No effect
	7. Effect on water and electrolyte metabolism (Urine volume, uric Na+ K+)	Rats	p.o.	10,30,100	Slight decrease in K+ excretion (100mg/kg)
Other	8. Other effects Effect on coagulation/fibrinolytic system and platelets: Effect on thrombin time/thromboplastin time, thromboelastogram, fibrinogen concentration, platelet count and collagen-stimulated platelet aggregation)	Rats	p.o.	10,30,100	Decrease in platelet aggregation activity (≧10mg/kg), Other items: No effect
	(8. 2 Effect on bleeding time)	Rats	p.o.	0.3,1,3	Prolonged bleeding time (3mg/kg)
	(8. 3 Hemolytic action)	Rabbits	in vitro	1x10-6, 1x10-5, 1x10-4M	Mild hemolysis (1x10-4M)

Note 1): 100mg/kg s.c.

(data at the time of approval)

Note 2): 30mA, 40Hz, 0.4sec

Note 3): Measurement of seizure threshold i.v. dosage

4) Other pharmacological tests
No applicable data

2. **Toxicity test**

(1) Single dose toxicity test

Animal Species	Route of Administration	Dosage (mg/kg/day)	Result (mg/kg/day)	
Mice	Oral	1000-5000	LD50 value	♂: 1000-1250 ♀: 1000-1250
Rats	Oral	♂: 1000-5000 ♀: 630-2500		♂: 1000-1250 ♀: 1000-1250
Rabbits	Oral	1000-5000		2500-5000
Dogs	Oral	500, 1000	Approximate lethal dose	Not possible to calculate due to vomiting

(data at the time of approval)

(2) Repeated-dose toxicity study

Animal Species	Route/Period of Administration	Dosage (mg/kg/day)	No Observed Adverse Effect Level (mg/kg/day)
Rats	Oral 13 weeks	10, 30, 100, 200	30
	Oral (mixed with feed) 6 months	200, 1000, 5000 ppm	1000 ppmNote1)
Dogs	Oral 13 weeks	2, 5, 10, 50, 250	10
	Oral, 13 weeks Recovery test	250	Recoverable
	Oral 12 months	3, 10, 30	30 and above

Note1) Average intake per day ♂; 79.9 ♀; 98.1mg/kg

NOAEL was determined to be 30mg/kg/day as per 13-week administration test in rats. Although salivation was observed dose-dependently at a dose of 30mg/kg and above, this was considered to be a secondary effect on salivary glands caused by bitterness of the drug or other physiochemical symptoms and was not judged as toxicity. At doses of 100mg/kg and above, suppression of weight gain and fluctuations in percentage by leukocyte group was observed.

NOAEL was determined to be 10mg/kg/day as per 13-week administration test in dogs. At doses of 50mg/kg and above, increase in bloodALT(GPT) and GLDH was observed. In newly conducted 13-week dosage recovery test on dogs, increase in AI-P and AST(GOT) was also observed in addition to ALT(GPT) and GLDH at a dose of 250mg/kg. However, the increase in these acids returned to normal values during the 4-week recovery period.

In 6-month administration test in rats, the NOAEL was determined to be 1000ppm (average dosage per day: males; 79.9mg/kg, females; 98.1mg/kg). At 5000ppm, suppression of weight gain was seen in males and impact on red blood cells was seen in females. In 12-month administration test in dogs, no toxicologically significant findings were observed at a dose of 30mg/kg/day. Ramatroban concentration in blood after 2 hours of administration of the highest dose of 30mg/kg of this study was 11.9-45.5μg/mL. At the same time, Cmax when Ramatroban 75mg was administered twice a day to healthy male adults was approx. 0.3μg/mL. Therefore, it was judged that a significantly high dose is being administered to study safety in humans.
(data at the time of approval)

(3) Reproductive and developmental toxicity studies

Test Item	Animal Species	Route of Administration	Dosage (mg/kg/day)	No Observed Adverse Effect Level (mg/kg/day)
Pre-pregnancy and early pregnancy administration test	Rats	Oral	10, 30, 100	Male parent animal 30 Female parent animal 100 and above Fetus, offspring 100 and above
Administration test during organogenesis	Rats		20, 60, 180	Mother 60 Fetus, offspring 180 and above
	Rabbits		10, 30, 100	Mother 10 Fetus 100 and above
Administration test during perinatal and lactation period	Rats		30, 100, 200	Mother 200 and above, fetus 200 and above, offspring 100

In pre-pregnancy and early pregnancy administration test in rats, salivation and suppression of weight gain was observed in male parent animal at a dose of 100mg/kg/day. The salivation was considered to be a secondary effect on salivary glands caused by bitterness of the drug or other physiochemical symptoms and was not judged as toxicity. There were no other abnormalities, and the toxicity was determined to be 30mg/kg/day in male parent, 100mg/kg/day and above in female parent, and 100mg/kg/day and above in both fetus and offspring.
In administration test during organogenesis in rats, two tests were conducted independently, one for autopsy of mother at the end of pregnancy and the other for natural childbirth. In both the tests, salivation was observed during administration period at 60mg/kg/day in the mother, and suppression of weight gain was observed at 180mg/kg during the administration period. Further, a decline in feeding amount during administration period was observed at 180mg/kg in the natural birth test. The salivation observed at 60mg/kg/day and above was considered to be a secondary effect on salivary glands caused by bitterness of the drug or other physiochemical symptoms and was not judged as toxicity. There were no abnormalities in the fetus and offspring, and the toxicity was determined to be 60mg/kg/day in the mother and 180mg/kg/day and above in both fetus and offspring.
In administration test during organogenesis in rabbits, suppression of increase in body weight was observed in mother at 30mg/kg/day and above during the administration period. The NOAEL in mother and fetus was determined to be 10mg/kg/day and 100mg/kg/day and above respectively. In administration test during perinatal and lactation period in rats, an increase in number of deaths after implantation was observed in the 200mg/kg group, but there was no other toxicity. Thus, it was concluded that the NOAEL in mother was 200mg/kg/day and above and in fetus and offspring it was 200mg/kg/day and above and 100mg/kg/day and above respectively.

(4) Other specific toxicity

Dependence

Tests were not conducted as there are no factors concerning dependence for this drug.

Antigenicity

Active systemic anaphylaxis (ASA) reaction in guinea pigs, 4-hour and 8-day passive cutaneous anaphylaxis (PCA) reaction in same species, Schultz-Dale (SD) reaction and indirect hemagglutination anaphylaxis (PHA) reaction, as well as, heterogenous rats 24-hour PCA reaction on mice were implemented.
Since Ramatroban was negative in all tests, it was determined that there is no antigenicity.

Mutagenicity

A reversion test on bacteria, chromosomal abnormality test on cultured cells, mouse micronucleus test, additionally, forward mutation assay in

cultured cells and unscheduled DNA synthesis test in cultures cells were implemented.
Ramatroban showed transient and mild induction of structural abnormality in chromosomal abnormality test on Chinese hamster lung fibroblast (CHL) cell line, however, this effect was inactivated by metabolic activation. At the same time, there were no abnormalities observed in other tests including the chromosomal abnormality test on Chinese hamster ovary (CHO) cell line conducted prior to the above test.
Therefore, although Ramatroban showed mild induction of chromosomal abnormality in in vitro tests, it did not show any abnormalities in all other tests including the in vivo mouse micronucleus test. Thus, the possibility of mutagenicity in body is considered to be low.

Carcinogenicity

When carcinogenicity test was conducted on rats and mice, carcinogenicity was not observed in either of the animal species.

Toxicity of analogs, metabolites, and enforced degradation products

The acute toxicity of BAY x 3959 (vice-generative production), BAY x 3509 (decomposition product), BAY u 4247 (vice-generative production, decomposition product, metabolite), BAY x 9601 (vice-generative production, decomposition product, metabolite), BAY u 3406 (optical isomer) and the enforced degradation products of Ramatroban 75mg tablet was studied in mice and rats. As a result, it was determined that there is no toxicity of concern considering the content and clinical dose of these compounds.

Based on the above, it was determined that none of the toxicity findings pose a concern at the clinical dose (3mg/kg/day).

X. Management Items

1. **Regulatory Division**

   Formulation: Baynas Tablet 50mg,
   Baynas Tablet 75mg;
   Prescription Drug Note) Note)
   Caution-Use by prescription of doctors

2. **Validated period or expiry date**

   Expiry date: 3 years

3. **Storage conditions**

   Store in airtight container at room temperature

4. **Precautions for handling the drug**

(1) Handling at pharmacies

This drug is a sustained release film-coated tablet and may have considerable bitter taste when crushed and may also lose the durability of its action; hence, do not crush before use.

(2) Precautions for drug delivery (essentials that must be noted by patients)

See “VIII. 14 Precautions for usage”.

5. **Approval conditions, etc**.

Not Applicable

6. **Packaging**

50mg PTP packaging 100 tablet (10 tablets x 10)

75mg PTP packaging 100tablets (10 tablets x 10),500 tablets(10 tabletsx50),700 tablets(14 tablets x50)

7. **Material of container**

PTP packaging: Polypropylene, aluminum foil

8. **Drugs with identical components/same effects**

Drugs with identical components: None

Drugs with same effect: Fexofenadine, Fexofenadine Hydrochloride, Cetirizine Hydrochloride, Seratrodast

9. **International Date of Creation**

March 31, 2000: Japan

10. **Manufacture and sale approval date**

Manufacture approval date: March 10, 2000

Approval number: Baynas tablet 50mg 21200AMZ00163

Baynas tablet 75mg 21200AMZ00164

11. **Date of listing in the drug price list**

May 2, 2000

12. **Dates and contents of addition of effects, indications, and changes in dose**

Not Applicable

13. **Dates and content of release of re-examination results, re-evaluation results**

No applicable data

14. **Period of re-examination**

March 10, 2000 to March 9, 2006 (End)

15. **Information concerning drugs with restricted administration period**

There are no restrictions related to administration period for this drug.

16. **Codes**

Brand name	HOT No.	MHLW NIH Drug Price Standard Code	Bill medical computer processing system code
Baynas tablet 50mg	113368403	4490021F1025	610443008
Baynas tablet 75mg	113369103	4490021F2021	610443009

17. **Precautions for health insurance benefit**

Not Applicable

XI. Literature

1. **Citation**

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2. **Other references**

XII. **References**

1. **Sales status in major foreign countries**

Not Applicable

3. Clinical support information from overseas

No applicable data

XIII. Remarks