

**Revised: April 2005 (11th version;

Revision according to the revised Pharmaceutical Affairs Law)

*Revised: May 2004

Standard Commodity Classification No. of Japan

872325

- H₂-RECEPTOR ANTAGONIST-**STOGAR[®] Tablet 5**
STOGAR[®] Tablet 10

< lafutidine tablet >

Designated drug

Storage : Store at room temperature in a closed container.
See "PRECAUTIONS FOR HANDLING".
Expiration date: indicated on the outer package.







	STOGAR[®] Tablets 5	STOGAR[®] Tablets 10
Approval No.	21200AMZ00027000	21200AMZ00028000
Date of listing in the NHI reimbursement price	April 2000	
Date of initial marketing in Japan	April 2000	

CONTRAINDICATIONS (STOGAR is contraindicated in the following patients.)

Patients with a history of drug hypersensitivity to any of the ingredients in the product.

DESCRIPTION

- STOGAR tablet 5 contains 5mg of lafutidine in each tablet.
- STOGAR tablet 10 contains 10mg of lafutidine in each tablet.
- STOGAR tablet is film coated and has no odor or slight peculiar odor.

Brand name	STOGAR [®] Tablets 5	STOGAR [®] Tablets 10
Identification code	FZ11	FZ12
Appearance		
		
		
Diameter	5.6mm	6.1mm
Thickness	2.6mm	2.7mm
*Weight	65.6mg	80.6mg

- STOGAR contains the following inactive ingredients: lactose, microcrystalline cellulose, corn starch, light anhydrous silicic acid, croscarmellose sodium, hydroxypropylcellulose, talc, magnesium stearate, hydroxypropyl methylcellulose 2910, macrogol 6000, titanium oxide, and carnauba wax as inactive ingredients.

INDICATIONS

- Gastric ulcers, duodenal ulcers and stomal ulcers.

- Gastric mucosal lesions (erosion, hemorrhage, redness or edema) associated with acute gastritis and acute exacerbation of chronic gastritis.
- Preanesthetic medication.

DOSAGE AND ADMINISTRATION● **Gastric ulcers, duodenal ulcers and stomal ulcers**

For adults, the usual dosage is 10mg as lafutidine orally administered twice a day, once after breakfast and once after the evening meal or before sleeping. The dose may be adjusted according to the patient's age and symptoms.

● **Gastric mucosal lesions (erosion, hemorrhage, redness or edema) associated with acute gastritis and acute exacerbation of chronic gastritis**

For adults, the usual dosage is 10mg as lafutidine orally administered once a day, once after the evening meal or before sleeping. The dose may be adjusted according to the patient's age and symptoms.

● **Preanesthetic medication**

For adults, the usual dosage is 10mg as lafutidine orally administered twice, once before sleeping on the day before operation and once 2 hours before introduction of anesthetic on the day of operation.

Precautions Related to Dosage and Administration

In dialytic patients (not during dialysis), it is reported that their maximum blood concentration of lafutidine increase twice as high as that of normal adults. Therefore, the administration should be started carefully with lower dosage.

PRECAUTIONS

1. **Careful Administration (STOGAR should be administered with care in the following patients.)**

- 1) Patients with a history of drug hypersensitivity
- 2) Patients with impaired hepatic function [Symptoms may be exacerbated.]
- 3) Patients with impaired renal function [Symptoms may be exacerbated.]
- 4) Patients on dialysis [Increase in blood concentration of lafutidine is reported](See "Pharmacokinetics" section)
- 5) The elderly (See "Use in the Elderly" section.)

2. Important Precautions

Patients should be carefully observed during treatment, and the minimum required dose should be used according to symptoms. If response is not evident, other treatments should be implemented. Careful observation should be made for any changes in **hematological, hepatic or renal parameters**, and for changes in other factors.

3. Adverse Reactions

Adverse reactions (including abnormal changes in laboratory tests) were observed in 32 (2.5%) of the 1,287 patients evaluated at the time of approval. The main adverse reactions were constipation in 3 patients (0.2%). Abnormal changes in laboratory tests were observed in 22 patients.

1) Clinically Significant Adverse Reactions

(1) **Shock, anaphylactic reactions:** Shock and anaphylactic reactions may appear, therefore patients should be carefully observed. If any abnormality such as pallor facial, blood pressure decreased, redness generalized, or breathing difficult is seen, this drug should be discontinued and appropriate measures should be taken.

(2) **Hepatic function disorder** (unknown frequency#), **jaundice** (unknown frequency#)

Hepatic function disorder involving increased AST(GOT), ALT(GPT) or gamma-GTP, or jaundice may appear.

Therefore patients should be carefully observed. If any abnormality is seen, this drug should be discontinued, and appropriate measures should be taken.

(3) **Agranulocytosis** (unknown frequency#), **thrombocytopenia** (unknown frequency#)

Agranulocytosis (initial symptom: sore throat, general malaise, fever, etc.) or thrombocytopenia may occur. If any abnormality is observed, this drug should be discontinued and appropriate measures should be taken.

2) Clinically Significant Adverse Reactions (Analog)

It has been reported that **pancytopenia, aplastic anemia, interstitial nephritis, oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), rhabdomyolysis, heart block (atrioventricular block etc.), and asystolia** may occur with other H₂-receptor antagonists.

3) Other Adverse Reactions

The following adverse reactions may occur. If abnormal signs are observed, appropriate measures should be taken including reduction in the dose and discontinuation of the drug.

	0.1% ≤ < 5%	< 0.1%	Unknown frequency#
Hyper-sensitivity			Rash, urticaria, pruritus
Hematological	Increase in leukocytes	Increase in eosinophil, Decrease in leukocytes, red blood cells, and hematocrit	Haemoglobin decreased
Hepatic	Elevation of ALT(GOT), AST(GPT), Al-p, gamma-GT, and total bilirubin	Elevation of LDH and TTT	
Renal	Urinary protein abnormal	Elevation of BUN	
Psychoneurologic		Headache, Insomnia, Sleepiness	Reversible confusion, Hallucination, Consciousness disturbed, Dizziness
Cardiovascular		Heart pounding, Feeling of warmth, Feeling of hot flushes	
Gastro-intestinal	Constipation	Diarrhea, Hard stool	Nausea/ Vomiting, Abdomen enlarged feeling of, Anorexia
Others	Elevation of serum uric acid and Cl	Menstruation delayed, Na increased, K decreased	Gynaecomastia, Oedema, Malaise

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It has been reported that convulsions may occur with other H₂-receptor antagonists.

#Unknown frequency because obtained from post-marketing spontaneous reports.

4. Use in the Elderly

Normally, because physiological function is deteriorated in the elderly, it is advisable to take such measures as a reduction in the dose and a prolongation of the administration interval under careful supervision.

5. Use during Pregnancy, Delivery or Lactation

(1) The safety of lafutidine in pregnant women has not been established. Therefore, the administration of lafutidine to pregnant women or women who may possibly be pregnant should be strictly limited to occasions where the therapeutic benefits outweigh the possible risks associated with the treatment.

(2) Animal studies (in rats) have shown that lafutidine is excreted in breast milk. Therefore, the mothers should be advised to discontinue breast feeding during treatment.

6. Pediatric Use

The safety of this drug in children has not been established (no clinical experience).

7. Precautions concerning Use

Cautions in dispensing: Patients should be advised to press the tablet out of the press-through package (PTP) before taking it. [A case has been reported where a patient

mistakenly ingested a small angular piece of the PTP sheet, which lodged in the esophageal mucosa and caused perforation and subsequent mediastinitis.]

8. Other Precautions

Since treatment with this product may mask the symptoms of gastric cancer, administration should be made after confirming the tumor is not malignant.

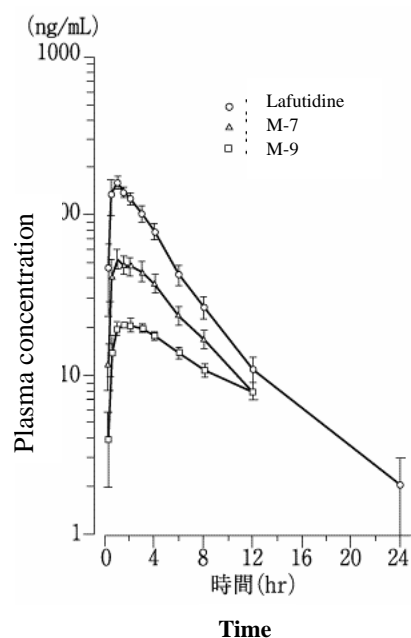
PHARMACOKINETICS

1. Blood concentration:

When 10mg of lafutidine is orally administered to normal adult males, fasting plasma concentration of unchanged drug changed as in the following figure¹⁾:

Tmax (hr)	Cmax (ng/mL)	T1/2 (hr)		AUC _{0-24hr} (ng·hr/mL)
		α	β	
0.8±0.1	174±20	1.55±0.61	3.30±0.39	793±85

(n=6, Mean±S.D.)



2. Metabolism and excretion:

Within 24 hours after peroral administration of lafutidine 10mg in 6 normal adult males, the excretion rates of unchanged drug, metabolite M-4(oxidative elimination of piperidine ring), M-7(oxidation of piperidine ring), and M-9(sulfonylation) in the urine are $10.9\pm 1.5\%$, $1.7\pm 0.2\%$, $7.5\pm 0.8\%$, and $0.3\pm 0.1\%$ respectively. Total excretion rate in the urine is approximately 20% of the given dosage¹⁾. It has been reported that CYP3A4 is mainly (CYP2D6 is partially) associated with the metabolism of lafutidine (in vitro). Unless reaching 3 microgram/mL, no saturation of binding to proteins is observed (binding rate to human serum proteins : $88.0\pm 1.2\%$) (in vitro).

3. Blood concentration in the elderly and patients on dialysis

Among the elderly, there was no difference in pharmacokinetics parameters between those with normal renal function(Ccr average 88.0 ± 9.4 mL/min) and those with deteriorating renal function (Ccr $20\sim 60$ mL/min, average 45.2

± 7.8 mL/min). In dialytic patients during not undergoing dialysis, the Cmax and the T_{1/2} values were doubled, and the AUC was tripled compared with those in normal adults. Lafutidine was cleared 7~18 % by blood dialysis.

		Tmax (hr)	Cmax (ng/mL)	T1/2 (hr)	AUC (ng·hr/mL)
Normal Adults (n=6) (control)		0.8±0.1	174±20	3.30±0.39	793±85
The elderly (n=5)	Normal renal function	1.0±0.2	195±17	3.05±0.19	869±65
	deteriorating renal function	1.1±0.2	196±23	2.93±0.21	853±113
The patients on dialysis (n=6)	During dialysis	2.6±0.5	226±36	4.57±0.2* (n=4)	853±128*
	Not during dialysis	0.8±0.1	336±40	6.71±0.30 (4.37±0.45)*	2278±306 (1264±133)*

(Lafutidine 10mg, mean±S.D.)

Each parameter on the table was calculated from the following plasma concentration transition; Patients on dialysis while undergoing dialysis : 0-6 hour. The others : 0-24 hour.

* For the comparison to the parameters during dialysis (0-6 hour), the parameters calculated from 0-6 hour data during not undergoing dialysis showed in parenthesis.

The elderly who have deteriorating renal function: Ccr=20, 34, 54, 58, 60 mL/min (n=5)

CLINICAL STUDIES²⁾⁻¹⁵⁾

	General improvement rate *	Improvement rate of subjective/objective symptom *	Cure/improvement rate by endoscopic judgment
Gastric ulcer	93.0% (211/227)	97.3% (213/219)	76.2% (173/227)
Duodenal ulcer	96.8% (121/125)	99.2% (130/131)	88.8% (111/125)
Stomal ulcer	84.6% (11/13)	100% (11/11)	84.6% (11/13)
Gastric mucosal lesions in acute and chronic gastritis	88.4% (152/172)	89.5% (162/181)	84.2% (144/171)
Preanesthetic medication	Total inhibitory effect on gastric juice and gastric acid secretion (pH ≥ 2.5) was 99.4 % (178/179).		

"Significantly improved" and "moderately improved" were combined.

PHARMACOLOGY

1. Effects on humans

1) Basic gastric acid secretion and secretion in response to various stimulants

Basic secretion¹⁶⁾ and secretion in response to such stimulants as tetragastrin and betazole hydrochloride¹⁷⁾ at 2 hour after oral administration of 10mg of lafutidine to

healthy adults were inhibited by 95.1%, 84.0%, 98.3% respectively. Pepsin secretion were inhibited by 69.2%, 46.0% and 86.8% respectively.

2) Nocturnal gastric acid secretion

Seven hour secretion of gastric acid and pepsin (from 23:00 to 6:00) in healthy adults was reduced by 95.6% and 57.9%, respectively, after oral administration of 10mg of lafutidine¹⁸⁾.

3) 24 hour gastric pH monitor

Gastric pH in healthy adults after oral administration of 10mg of lafutidine before sleep became pH5 or greater at 2 hours after administration and ranged from pH6 to 7 during the 10 hr period. The rate of holding time of pH3 or greater was 75% during 12 hours at night.

Gastric acid secretion was also inhibited during the day by oral administration of 10mg twice a day. The rate of holding time was 67.8% at night and 60.2% at daytime during 12 hours¹⁹⁾.

2. Effects on animals

1) Inhibition of gastric acid secretion

The inhibitory effect on gastric acid secretion 4 hours after administration of lafutidine in the duodenum with the pylorus ligated, was 0.1 times more potent than that of famotidine and 2.3 times more potent than that of cimetidine (in rats). However, the inhibitory effect of lafutidine in response to various stimulants lasted longer than that of famotidine and cimetidine (in rats and dogs)²⁰⁾.

2) H₂-receptor antagonistic effect

The antagonistic effects of lafutidine on specific binding of tiotidine to H₂-receptor in cerebral cortex membrane of guinea pig was 1.9 times stronger than that of famotidine and 85.5 times stronger than that of cimetidine (*in vitro*)²¹⁾.

3) Effect on acute gastric mucosal lesions

Lafutidine showed protective effect on gastric mucosal damage induced by various necrotic substances (ammonia, hydrochloric acid-ethanol, ethanol, hydrochloric acid, hydrochloric acid-taurocholic acid), especially on the damage induced by ammonia (in rats)²²⁾.

4) Effect on acute / chronic ulcers

Lafutidine not only suppressed the occurrence of acute gastric ulcers (water immersion restraint stress, indomethacin, ligated pylorus aspirin, histamine) and acute duodenal ulcers (mepirizole, diethyldithiocarbamate)²³⁾, but also accelerated the healing and suppressed the recurrence of chronic ulcers (acetic acid ulcers²⁴⁾, burning ulcers²⁵⁾ (in rats).

5) Effect on gastritis

Lafutidine showed an accelerating effect on recovering of gastritis induced by ammonia and taurocholic acid (in rats)²⁶⁾.

6) Effect on gastric mucosal blood flow

Gradually increased gastric mucosal blood flow was observed after administration in stomach (in rats)²⁷⁾.

7) Effect on gastric mucus

Lafutidine accelerated gastric mucus production in organ culture of gastric mucosa in rats (*in vitro*)²⁸⁾. Peroral administration of lafutidine also increased the amount of mucin in gastric mucosa gel²⁹⁾, and repeated administration of lafutidine showed increasing tendency of the gel layer in the pyloric gland region (rats)³⁰⁾.

8) Effect on gastric mucosa restitution

Repairing process of gastric mucosa damaged by ammonia solution was examined by covering rate of alcian blue stained cells. Lafutidine increased the rate 30 minutes after the induction of injury, showing acceleration of restitution by migration of epithelial cells (rats)³¹⁾.

9) Mechanism of action

Lafutidine is a H₂-receptor antagonist with persistent effect on suppression of gastric acid secretion. It also protect gastric mucosa, accelerate mucosa reconstitution, increase gastric mucosal blood flow and gastric mucus, via capsaicin-sensitive nerve found in the gastric mucosa.

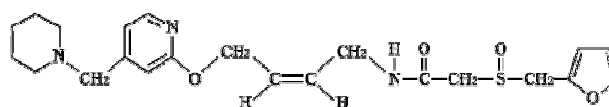
PHYSICOCHEMISTRY

Nonproprietary name: Lafutidine

Chemical name:

(±)-2-(Furfurylsulfinyl)-N-[4-[4-(piperidinomethyl)-2-pyridyl]oxy-(Z)-2-butenyl]acetamide

Structural formula:



Molecular formula: C₂₂H₂₉N₃O₄S

Molecular weight: 431.56

Description:

Lafutidine is yellowish white crystalline powder with slight peculiar odor. It is freely soluble in acetic acid, slightly soluble in methanol, slightly insoluble in ethanol (99.5), very slightly soluble in diethyl ether and practically insoluble in water. Methanol solution of lafutidine (1->100) does not show optical activity.

Melting point: 96-99 °C

Partition coefficient: log P : -3.36(pH 2)
log P : 0.39(pH 6)
log P : 2.37 (pH 10)

(n-octanol/Britton-Robinson Buffer(20±1 °C))

PRECAUTIONS FOR HANDLING

Caution: Slight pigmentation is noted under the condition of repeated exposure to 500 Lux fluorescent light for 8 hours followed by shielding for 16 hours at 30 degrees Celsius

with relative humidity of 75%. Therefore this product should be stored carefully after being unsealed.

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PACKAGING

- STOGAR® Tablet 5 Press through packages:
Boxes of 100tab (10 tab x 10)
Boxes of 1000tab (10 tab x 100)
- STOGAR® Tablet 10 Press through packages:
Boxes of 100tab (10 tab x 10)
Boxes of 1,000tab (10 tab x 100)
Boxes of 1,400tab (14 tab x 100)
Bottle 500 tablets

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