Revised: April 2005 (2nd version, revisions associated with the amendment of the Pharmaceutical Affairs Law)

Standard Commodity Classification No. of Japan
872325

– H_2-receptor antagonist –

Gaster® Injection 10 mg
Gaster® Injection 20 mg

< Famotidine Injection>

Designated drug, Prescription drug
(Caution-Use only pursuant to the prescription of a physician, etc.)

Storage
Store at room temperature.

Expiration date
Refer to the indication on the package.

	10 mg	20 mg
Approval No.	21700AMZ00145	21700AMZ00146
Date of listing in the NHI reimbursement price	July 2005	
Date of initial marketing in Japan	**July 2005**	

CONTRAINDICATIONS (GASTER Injection is contraindicated in the following patients.)
Patients with known hypersensitivity to this drug or any of its components

■ DESCRIPTION

Brand name		GASTER® Injection 10mg	GASTER® Injection 20mg
Content per ampule	Active ingredient	(JP) Famotidine 10mg (1 mL)	(JP) Famotidine 20mg (2 mL)
	Inactive ingredient	Nicotinamide 50mg, ascorbic acid 1mg, lactic acid, isotonizing agent, pH adjuster	Nicotinamide 100mg, ascorbic acid 2mg, lactic acid, isotonizing agent, pH adjuster
Color		Colorless to light yellow clear	
pH		5.8-6.2	
Osmotic pressure ratio		1.6-1.8	

Container: Colorless ampule

■ INDICATIONS

Inhibition of upper gastrointestinal hemorrhage (associated with peptic ulcers, acute stress-induced ulcers and hemorrhagic gastritis), Zollinger-Ellison syndrome and upper gastrointestinal hemorrhage induced by invasive stress (related to extensive surgical procedures which require postoperative intensive care, or to cases where intensive care is required due to cerebrovascular disease, brain trauma, multiple organ failure or extensive burns), preanesthetic administration.

■ DOSAGE AND ADMINISTRATION

- **Inhibition of upper gastrointestinal hemorrhage (associated with peptic ulcers, acute stress-induced ulcers and hemorrhagic gastritis), Zollinger-Ellison syndrome and upper gastrointestinal hemorrhage induced by invasive stress (related to extensive surgical procedures which require postoperative intensive care, or to cases where intensive care is required due to cerebrovascular disease, brain trauma, multiple organ failure or extensive burns):**
  The recommended adult dosage is 20mg of famotidine diluted with 20mL of physiological saline (JP) or glucose injection (JP), slowly administered intravenously twice daily (every 12h) or infused intravenously after it is mixed with infusion fluid.
  Otherwise, 20mg of famotidine is administered intramuscularly twice daily (every 12h).
  The dosage may be adjusted depending on the patient's age and symptoms.
  Generally, in upper gastrointestinal hemorrhage or in Zollinger-Ellison syndrome, the onset of effects is observed within 1 week. Patients should be switched to oral therapy after oral administration can be tolerated.
  For inhibition of upper gastrointestinal hemorrhage induced by invasive stress (related to extensive surgical procedures which require postoperative intensive care, or to cases where intensive care is required due to cerebrovascular disease, brain trauma, multiple organ failure or extensive burns), administration should be continued for a sufficient period of the intensive care (for about 3 days for postoperative invasive stress, and for about 7 days for other kinds of invasive stress).
- **Preanesthetic administration:**
  The recommended adult dosage is 20mg of famotidine administered intramuscularly at 1h before anesthesia.
  The same dose may be diluted with 20mL of physiological saline (JP) or glucose injection (JP) and slowly administered intravenously at 1h before anesthesia.

< Precautions >

Administration to patients with renal dysfunction[1)]
This product is known to be excreted substantially by the kidneys in the form of unchanged drug. Therefore, administration of this product to patients with renal dysfunction results in an increase in blood concentration of unchanged drug and a decrease in urinary excretion. The following dosage is therefore recommended in patients with renal dysfunction:

<In the case of a patient whose regular dose is 20mg twice daily>

Creatinine clearance (mL/min)	Recommended dosage
Ccr ≥ 60	20mg, twice daily
60 > Ccr > 30	20mg, once daily or 10mg, twice daily
30 ≥ Ccr	10mg, once every two days or 5mg, once daily
Dialysis patient	10mg, once daily after dialysis or 5mg, once daily

■ PRECAUTIONS

1. Careful Administration (GASTER Injection should be administered with care in the following patients.)

(1) Patients with known hypersensitivity to drugs

(2) Patients with renal disorders [As a high level of drug concentration in the blood may persist, it is advisable to take measures such as reductions of the dose or a prolongation of the adminictration interval.]

(3) Patients with cardiac disorders [This product may cause cardiovascular adverse reactions.]

(4) Patients with hepatic disorders [Symptoms may be aggravated.]

(5) Elderly patients [See "Use in the Elderly"]

2. Important Precautions

(1) For “inhibition of upper gastrointestinal hemorrhage induced by invasive stress”, use this product only **when stress-induced ulcers may develop** due to extensive surgical procedures which require postoperative intensive care, or in patients who require intensive care due to cerebrovascular diseases, brain trauma, multiple organ failure or extensive burns. Burns with a Burn Index of 10 or greater are defined as extensive burns.

(2) Patients should be observed carefully during treatment**,** and **the minimum required dose** (**administration should be for about 3 days for postoperative invasive stress, and for about 7 days for other indications**) **should be used** according to symptoms. If response is not evident, other treatments should be implemented. Careful observation is essential to detect **any changes in hematological, hepatic or renal parameters, etc.**.

3. Drug Interactions

[Precautions for Coadministration] (GASTER Injection should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Azole antifungal agents Itraconazole	This product may decrease blood concentrations of these drugs.	The inhibitory action of this product on gastric acid secretion decreases the rate of oral absorption of these drugs [2,3].

4. Adverse Reactions

Adverse reactions (including abnormalities in clinical laboratory tests) with this product were observed in 360 (1.8%) of 20,137 (including both oral and intravenous administration routes) in clinical trails until approval and drug-use result surveys (excluding preanesthetic administration, invasive stress, and intramuscular administration for upper gastrointestinal hemorrhage). The major adverse reactions were constipation and a decrease in leukocytes.

(at the time of approval of orally disintegrating tablets)

- For indications for preanesthetic administration, adverse reactions such as pain and induration at the injection site were observed in 3 cases (5 events, 0.2%) of 3,332 cases (including intravenous injection and intramuscular injection), in clinical trails until approval and drug-use result surveys.

(at the end of the GASTER for Injection reexamination)

- In clinical studies for invasive stress (35 cases administered in intramuscular injection and 483 cases administered in intravenous injection) and upper gastrointestinal hemorrhage (33 cases administered in intramuscular injection), adverse reactions were not observed.

(at the time of additional indications for GASTER for Injection were approved)

(1) Clinically significant adverse reactions

1) Shock or anaphylactoid reactions (< 0.1%): Since symptoms of shock or anaphylactoid reactions, such as dyspnea, generalized erythema, vascular edema (facial edema, pharyngeal edema, etc.), and urticaria may occur, patients should be observed carefully. If such reactions are observed during treatment, discontinue treatment immediately and institute appropriate measures.

2) Pancytopenia, agranulocytosis, aplastic anemia, and hemolytic anemia (Incidence unknown): Since pancytopenia, agranulocytosis, aplastic anemia, and hemolytic anemia may occur (initial symptoms: generalized fatigue, weakness, subcutaneous or submucosal hemorrhage, fever, etc.), periodic hematology tests should be conducted. If such reactions are observed, discontinue treatment immediately and institute appropriate measures.

3) Mucocutaneo-ocular syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome) (Incidence unknown): Since mucocutaneo-ocular syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell's syndrome) may occur, patients should be observed carefully. If such reactions are observed during treatment, discontinue treatment immediately and institute appropriate measures.

4) **Hepatic dysfunction and jaundice** (Incidence unknown): Since elevation of AST (GOT), ALT (GPT), etc., and jaundice may occur, patients should be observed carefully. If such reactions are observed during treatment, discontinue treatment immediately and institute appropriate measures.

5) **Rhabdomyolysis** (Incidence unknown): Rhabdomyolysis may occur. If hyperkalaemia, myoglobinuria, marked increase of muscle-specific enzyme levels in serum, and myalgia are observed during treatment, discontinue treatment immediately and institute appropriate measures.

6) **Prolonged QT interval, ventricular tachycardia (including Torsades de Pointes), and ventricular fibrillation** (Incidence unknown): Since prolongation of the QT interval, ventricular tachycardia (including Torsades de Pointes), and ventricular fibrillation may occur, patients should be observed carefully. If such reactions are observed during treatment, appropriate measures such as drug discontinuation should be taken.
This symptom is especially likely to occur in patients with cardiac disorders such as myocardial infarction, valvular disease, and cardiomyopathy, therefore the patient's condition must be closely monitored after drug administration.

7) **Impaired consciousness and convulsions** (Incidence unknown): Since impaired consciousness or generalized convulsions (clonic, spastic, myoclonic) may occur, patients should be observed carefully. If such reactions are observed during treatment, appropriate measures such as drug discontinuation should be taken.
Since this symptom is especially likely to occur in renal disorder patients, caution should be taken.

8) **Interstitial nephritis and acute renal failure** (Incidence unknown): Interstitial nephritis or acute renal failure may occur. If fever, eruption, or abnormal renal function (increased BUN or increased creatinine) develops at an early stage, discontinue treatment immediately and institute appropriate measures.

9) **Interstitial pneumonia** (Incidence unknown): Interstitial pneumonia accompanied by fever, cough, dyspnea, or chest X-ray abnormalities may occur. If such reactions are observed during treatment, discontinue treatment and appropriate measures such as coadministration of corticosteroid should be taken.

(2) Clinically significant adverse reactions (Analog)

Asystolia: It has been reported that asystolia may occur with other H_2-receptor antagonists.

(3) Other adverse reactions

	5% > ≥0.1%	**< 0.1%**	**Incidence unknown**[note2)]
Hypersensitivity note1)		Rash/ Eruption, Urticaria (Erythema), Facial edema	
Hematologic note1)	Leukocytes decreased	Platelets decreased, Eosinophil increased	
Gastrointestinal	Constipation	Diarrhea/ Loose stools, Thirst, Nausea/ Vomiting, Feeling of enlarged abdomen, Appetite decreased, Stomatitis, etc.	
Cardiovascular		Blood pressure increased,Facial hot flushes,Tinnitus	Bradycardia, Tachycardia, Atrioventricular block
Hepatic	AST (GOT) increased, ALT (GPT) increased, ALP increased	Total bilirubin increased, LDH increased	Abnormalities in hepatic function, Jaundice
Nervous system/ Psychiatric		Generalized fatigue, Enervation,Headache, Sleepiness,Insomnia	Reversible confusion, Depression, Convulsion, Disorder in consciousness
Endocrine Note1)		Menstrual irregularity, Gynecomastia	

Note1) If such a reactions are observed during treatment, this product should be discontinued.
Note2) Data based on spontaneous reports.

5. Use in the Elderly

This product should be administered with care such as starting at lower doses and prolongation of the administration intervals. [This product is mainly excreted by the kidneys. Elderly patients are more likely to have renal hypofunction, and high blood concentrations may persist.]

6. Use during Pregnancy, Delivery or Lactation

(1) This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established.]

(2) Nursing mothers should avoid breast feeding during treatment. [It has been reported that this product excrete in breast milk.]

7. Pediatric Use

The safety of this product in pronatises, newborns, sucklings, infants, and children has not been established. [Insufficient clinical experience.]

8. Precautions concerning Use

(1) For intramuscular administration:

To prevent damage to tissues or nerves on intramuscular injection, the following cautions should be paid.

1) Intramuscular injection should be restricted to conditions in which this route is absolutely necessary. The duration of intramuscular therapy should be kept to the absolute minimum. Avoid repeated injection at the same site. Special attention must be paid to newborns, pronatises, infants, and children.
2) Do not inject at innervated sites.
3) If insertion of the injection needle evokes intense pain, or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.
4) Intramuscular administration may cause pain or induration at the injection site.

(2) Precaution in preparation:

The ampule of this product is a one-point-cut type. It is recommended that the cut point of the ampule be wiped clean with an alcohol swab before cutting.

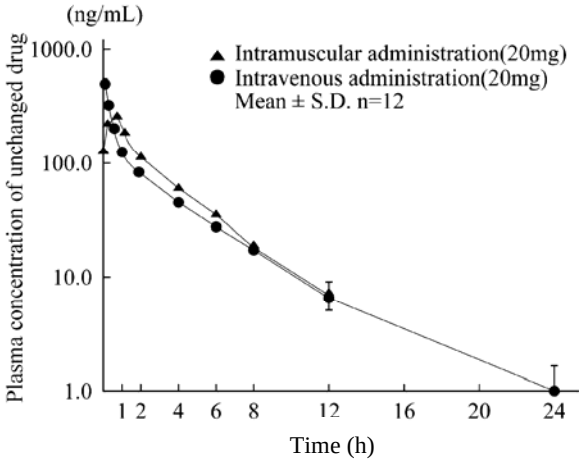
9. Other Precautions

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[4)]

When 20mg GASTER for Injection are administered intramuscularly to humans, the plasma concentration reaches maximum at 30min after administration. The half-life is 2 to 3h after both intramuscular and intravenous administration.



<Pharmacokinetic parameters in clinical dosage>

	Dosage (mg)	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng·h/mL)
Intravenous administration	20	—	—	2.45	771
Intramuscular administration	20	0.411	265	2.66	686

2. Metabolism[4,5)]

The only metabolite found in urine when administerd to humans is S-oxide.The percentage of the S-oxide form in the total amount excreted into urine is 2.2% to 11.0% for intramuscular administration, and 5.2% to 11.3% for intravenous administration.

3. Excretion[4,5)]

The excretion rate of unchanged drug in the urine to 24h after administration is 71.0% to 89.6% for intramuscular administration, and 57.8% to 96.4% for intravenous administration.

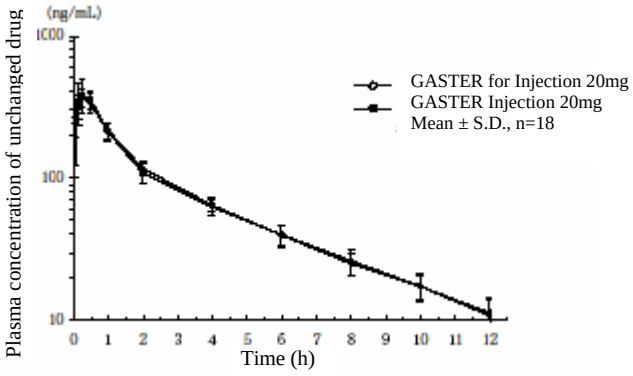
4. Pharmacokinetics in patients with renal dysfunction[1)]

<Parameters when GASTER for Injection 20mg is administered intravenously>

Mean Ccr values (mL/min/1.48m^2)		$t_{1/2}$ (h)	AUC (ng·h/mL)	C_{tot} (mL/min)
98.9	n=7	2.59	857	412
73.8	n=9	2.92	909	381
49.2	n=5	4.72	1424	242
10.3	n=10	12.07	4503	84

5. Bioequivalence after intramuscular administration[6)]

When GASTER Injection and GASTER for Injection are administered to humans intramuscularly, the data showed that both formulations are bioequivalent.



■ CLINICAL STUDIES

1. Clinical efficacy

(1) Upper gastrointestinal hemorrhage and Zollinger-Ellison syndrome

An outline of the results from a total of 229 cases, including an open study (53 cases), a dose-determination study (84 cases) and a double-blind comparative studies (59 cases) with intravenous administration, and an open study (33 cases) with intramuscular administration are shown below [7-10)].

Upper gastrointestinal hemorrhage	**Hemostatic effects** Intravenous administration of this product showed hemostatics effect in 91.2% of cases (165 out of 181) and the usefulness of the product was confirmed in a double blind comparative study. In the dose-determination and double-blind comparative studies, hemostasis was achieved in 91.0% of cases

	(91 out of 100) when 20mg of this product was intravenously administered twice daily, and the rate of hemostasis within 36h of administration was 66.0% (66 out of 100). The rate of hemostasis within 3 days was 84.0% (84 out of 100). With intramuscular administration, hemostasis and usefulness were similar to those noted with intravenous administration. **Hemostatic maintenance effects** Hemostasis was maintained with oral administration (20mg twice daily) after hemostasis was achieved with intravenous administration.
Zollinger-Ellison syndrome	In an open study with 6 patients (5 administered p.o. and 1 administered i.v.), hemostasis was achieved in 5 patients (4 administered p.o. and 1 administered i.v.).

(2) Inhibition of upper gastrointestinal hemorrhage induced by invasive stress (related to extensive surgical procedures which require postoperative intensive care, or to cases where intensive care is required due to cerebrovascular disease, brain trauma, multiple organ failure or extensive burns)

An outline of the results from a total of 519 cases, including an open study (85 cases), a dose-determination study (189 cases) and a double-blind comparative studies (209 cases) with intravenous administration, and an open study (36 cases) with intramuscular administration are shown below [11-19].

Inhibition of upper gastrointestinal hemorrhage induced by invasive stress	In clinical studies to suppress gastric acid secretion due to invasive stress (related to extensive surgical procedures which require postoperative intensive care, or to cases where intensive care is required due to cerebrovascular disease, brain trauma, multiple organ failure or extensive burns), intravenous administration of 20mg of this product twice daily resulted in an effective rate of 77.4% (250 out of 323). Usefulness was confirmed by a double-blind comparative studies. In the open study with intramuscular administration, the effective rate and usefulness were similar to those noted with intravenous administration.

(3) Preanesthetic administration

An outline of the results obtained from a total of 315 cases, including an open study (23 cases), a non-blind comparative studies (79 cases) and a double-blind comparative studies (132 cases) with intramuscular administration, and a non-blind comparative studies (81 cases) with intravenous administration are shown below [20-22].

Preanesthetic administration	In clinical studies, including a double-blind comparative studies, 20mg of this product was intramuscularly or intravenously administered to prevent aspiration pneumonia developing as a result of anesthesia. In each case there was a significant decrease in gastric secretion levels and an elevation in the pH of the gastric juice. The effective rate was 80.1% (241 out of 301). Usefulness was confirmed by a double-blind comparative study.

■ PHARMACOLOGY

1. Effects on humans

(1) Inhibition of gastric acid and pepsin secretion

1) Basic secretion and secretion in response to various stimulants

Basic secretion and secretion in response to various stimulants were inhibited at 2h after oral administration of 20mg of this product to healthy adults and to patients with peptic ulcers. Gastric acid secretion was reduced by 71.6% to 99.6% and pepsin secretion was reduced by 29.5% to 96.9%.

	Reduction in gastric acid secretion (%)	Reduction in pepsin secretion (%)
Basic secretion[23]	98.0	71.0
Tetragastrin (4μg/kg, intramuscular injections) stimulated secretion[24]	94.7	75.1
Betazole (1mg/kg, intramuscular injections) stimulated secretion[24]	99.6	96.9
Insulin (0.2IU/kg, intravenous injections) stimulated secretion[25]	71.6	29.5
Food stimulated secretion[26]	98.9	—

Basic secretion, tetragastrin-stimulated secretion and betazole-stimulated secretion were inhibited after intravenous administration of 20mg of this product [26,27].

2) Nocturnal secretion[28]

Seven hour secretion of gastric acid and pepsin (from 23:00 to 6:00) in healthy adults and in patients with peptic ulcers was reduced by 91.8% and 71.8%, respectively, after oral administration of 20mg of this product.

3) 24h secretion/gastric pH[29]

Gastric secretion in healthy adults was inhibited for 12h or greater (from 20:00) by oral administration of 20mg of this product, and the reduction in gastric acid secretion was 93.8%. The gastric pH was 4 or greater at 1h after administration, and ranged from 5 to 6 during the 12h period.

4) Blood concentration and the inhibitory effect on gastric acid secretion[30]

Positive correlations were observed between blood concentrations of this product and its inhibitory effect on gastric acid secretion. The blood concentration which inhibited gastric acid secretion by 50% was 13ng/mL.

(2) Effect on gastric mucosal blood flow[31]

Increased gastric mucosal blood flow was observed after intravenous administration of 0.1 to 0.2mg/kg to healthy adults.

(3) Effect on gastric mucous secretion[32]

No effect was observed on the concentration of mucus in the gastric juice in patients with duodenal ulcers.

(4) Effect on gastric emptying[33]

Oral administration of 20mg of this product to patients with gastric or duodenal ulcers had no effect on gastric emptying.

(5) Effect on hepatic hemodynamics[34)]

Intravenous administration of 20mg of this product had no effect on hepatic blood flow or on portal blood flow in healthy adults.

(6) Effect on blood gastrin levels[35)]

No effect on blood gastrin levels was observed in patients with gastric or duodenal ulcers treated with 20mg twice a day orally for 1 to 2 months.

(7) Effect on blood prolactin, etc.[36)]

Intravenous administration of 20mg or oral administration of 20mg twice daily for 4 weeks of this product showed no effect on blood prolactin, gonadotropic hormone, or sex hormone levels in healthy adults or in patients with peptic ulcers.

2. Effects on animals

(1) Histamine H_2-receptor antagonistic effect[37,38)]

The antagonistic effects of this product on histamine H_2-receptors, measured by indices which include the heart rate in an isolated guinea pig's atrium, the contraction of an isolated rat's uterus, and gastric secretion in dogs, were 10 to 148 times stronger than those of cimetidine.

(2) Inhibition of gastric acid secretion[39-41)]

The inhibitory effects of this product on gastric acid secretion induced by histamine stimulation in dogs were about 40 times more potent and about 1.3 to 1.5 times longer in duration of action than that of cimetidine.

Also, the effects of this product on gastric secretion induced by various invasive stresses in rats were similar or slightly stronger than those of pirenzepine hydrochloride, and more potent than those of cimetidine or ranitidine hydrochloride.

(3) Effects on gastric mucous secretion[40)]

There was significant inhibition of the decrease in glycoprotein in gastric mucosa induced by stress in rats.

(4) Effects on experimental ulcers[42, 43)]

This product shows a more potent suppressive effect than cimetidine on gastric ulcers induced by indomethacin, aspirin, prednisolone, stress and pyloric ligation, and on duodenal ulcers induced by cysteamine and mepirizole. Moreover, repeated administration accelerated the healing of gastric ulcers induced by acetic acid, and duodenal ulcers induced by mepirizole, and these effects were stronger than those of cimetidine.

(5) Effects on gastric hemorrhage[40)]

This product showed a suppressive effect on gastric hemorrhage induced in rats by exsanguination and histamine administration.

3. Mechanism of action

This product inhibits upper gastrointestinal hemorrhage and prevents aspiration pneumonia by suppressing gastric acid secretion by means of blockade of histamine H_2-receptors in the parietal cells of the gastric mucosa.

■ PHYSICOCHEMISTRY

Nonproprietary name:

Famotidine

Chemical name:

N-(1-Amino-3-{[2-(diaminomethyleneamino)-1, 3-thiazol-4-yl]methylsulfanyl}propylidene)sulfamide

Molecular formula:

$C_8H_{15}N_7O_2S_3$

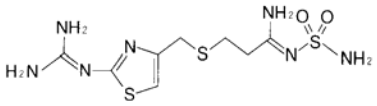
Molecular weight:

337.45

Melting point:

About 164 °C (decomposition)

Structural formula:



Description:

Famotidine is a white to yellowish white crystal. It is freely soluble in acetic acid (100), slightly soluble in ethanol (95), very slightly soluble in water. It is soluble in 0.5 mol/L hydrochloric acid test solution. It is gradually colored by light.

■ PACKAGING

GASTER® Injection 10 mg:

Boxes of 5 ampules

GASTER® Injection 20 mg:

Boxes of 5 ampules, 50 ampules

■ REFERENCES

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REQUEST FOR LITERATURE OR INQUIRY ABOUT PRODUCT SHOULD BE MADE TO:

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