Elaszym® tablets

PRECAUTIONS and ADVERSE REACTIONS

Precautions

(1) Adverse Reactions

(rarely: <0.1%; infrequently: 0.1% - <5%; no specific designation: ≥5% or frequency unknown)

1) Hypersensitivity: Rash and itching may infrequently occur. If such symptoms are observed, appropriate measures such as suspension of administration should be taken.

2) Gastrointestinal: Diarrhoea, gastric disorder, anorexia, and nausea may infrequently occur. Constipation, feeling of enlarged abdomen, and stomach discomfort may rarely occur.

#(2) Cautions in Use

Delivery of the drug:

It is directed that the drug packed in PTP sheet should be taken out from the sheet before use (it has been reported that the sharp edge of mistakenly swallowed PTP sheet stuck and perforated into esophageal mucosa, resulting in severe complications such as mediastinitis).

#Revised in 1996

•Attention should be paid to revision of precautions.

Adverse reactions

Adverse reactions were reported before and after the approval as follows. Symptoms with the mark * are adverse reactions which have not been described in "Precautions".

(Investigation period: from August 4, 1975, to August 31, 1984)

(Data as of in March, 1985)

	Before approval	After approval	Total
Number of institutions	38	1,129	1,167
Number of patients	691	9,441	10,132
Number of patients with adverse reactions	7	87	94
Number of adverse reactions	7	103	110
Incidence of patients with adverse reactions (%)	1.01	0.92	0.93

Adverse reaction	Number of adverse reactions (%)

	Before approval	After approval	Total
[Skin]	2 (0.29)	25 (0.26)	27 (0.27)
Itching	2 (0.29)	10 (0.11)	12 (0.12)
Rash	—	15 (0.16)	15 (0 15)
[Gastrointestinal]	5 (0 72)	72 (0.76)	77 (0.76)
Anorexia	1 (0.14)	17 (0.18)	18 (0.18)
Gastro-Intestinal disorder	1 (0 14)	9 (0.10)	10 (0.10)
Abdomen Enlarged Feeling of	1 (0.14)	7 (0.07)	8 (0.08)
Stomach discomfort	—	9 (0.10)	9 (0 09)
*Epigastric pain	—	2 (0.02)	2 (0 02)
Nausea	—	11 (0 12)	11 (0.11)
*Vomiting	—	1 (0.01)	1 (0.01)
Diarrhoea	2 (0.29)	11 (0.12)	13 (0 13)
Constipation	—	5 (0.05)	5 (0.05)
[Hepatic]	—	1 (0.01)	1 (0.01)
*Hepatic Function Abnormal	—	1 (0.01)	1 (0.01)
[Others]	—	5 (0.05)	5 (0.05)
*Feeling of hot flashes	—	2 (0.02)	2 (0.02)
*Numbness	—	2 (0.02)	2 (0.02)
*Face oedema	—	1 (0.01)	1 (0.01)

• See page 1 for "Precautions".

PRODUCT OUTLINE

Elastase, a main ingredient of Elaszym, was discovered in the human pancreas in 1949 as an important enzyme responsible for the metabolism of elastic fibers in blood vessels.

It has been reported that pancreatic elastase activity is markedly lower in patients with arteriosclerosis and the elderly than in healthy and young people.

In rabbits and rats, it has been demonstrated that elastase improves abnormalities in serum lipids by physiologically regulating the metabolism of lipoprotein and transmigration of lipid components.

Moreover, in atherosclerotic lesions experimentally induced by hyperlipemia in rabbits, it inhibits deposition of fats on arterial walls as well as degeneration of elastin and hyperplasia of collagen in arterial walls.

In double-blinded clinical studies, Elaszym has been shown to improve hyperlipemia.

• See page 1 for "Precautions".

INDICATIONS

Hyperlipemia

DOSAGE AND ADMINISTRATION

The usual adult dosage is 3 tablets daily, which is orally administered before meal in three divided doses. The dosage may be increased to 6 tablets daily if the desired effect has not been achieved. The dosage should be adjusted depending on the patient's age and symptoms.

COMPOSITION

Elaszym is a white enteric coated tablet, and contains 1,800 elastase units (hereafter abbreviated as EL.U.) of elastase ES per tablet. It contains tocopherol as additive.

DESCRIPTION

1. Product description

Product name	Dosage form / Identification code	Appearance			Description
		Front	Back	Side	
Elaszym tablets	enteric coated tablet				White
		Diameter (mm) 6.8	Weight (mg) 127	Thickness (mm) 3.9	

2. Physical properties of the active ingredient:
   Elastase ES is an enzyme obtained from the porcine pancreas, and degrades elastin as well as casein, fibrin, and denatured collagen.

Nonproprietary name: Elastase ES
Trivial name: Pancreatopeptidase E

Physical and chemical properties:

Elastase ES is a gray to light brown powder with a characteristic odor and little taste. One gram of elastase ES is soluble with slight opacity in 20 to 80 ml of sodium hydroxide solution while it is practically insoluble in water, methanol, ethanol, ether, chloroform and hexane.

STORAGE AND HANDLING

Caution: This product is a designated drug.
Storage: Store at room temperature. Keep it from moisture after opening (moisture may reduce the content).
Expiration date: Use before the expiration date indicated on the package or the label.

According to the 111th bulletin (March 29, 1994) by the Ministry of Health and Welfare, doses for up to thirty days may be prescribed at once for hyperlipemia, the indication of this drug.

~~Approval number: (57AM) 1037~~
Approval date: September 8, 1982

• See page 1 for "Precautions".

What is elastase?

Elastase is the generic name of all enzymes involved in the metabolism of the elastic fiber, elastin. It was discovered by Balo and Banga in the human pancreas in 1949, as metabolic enzyme for human elastic fiber elastin. Elastase is widely distributed in the body, and classified into pancreas-derived, leukocyte-derived, platelet-derived, smooth-muscle-cell-derived, and macrophage-derived ones, according to the origin. It varies in molecular weight, physical properties, and elastin-degrading activity and degradation site, depending on the origin.

With porcine pancreatic elastase I as a major ingredient, Elaszym was introduced in 1981.

Origin	Porcine pancreas	Human pancreas		Human leukocyte	Human platelet	Human aorta	Porcine aorta	Simian alveolus macrophage
Molecular weight	I 25,900	I 33,000	II 26,600	34,400	26,000	22,300	23,000	—
Relative ratio of degrading activity for insoluble elastin	100	50	42	40	—	10.9	12	100

Maekubo, H: Drugs of the Future, 11, 402 (1986)

Stereo-structure of porcine pancreatic elastase I

• See page 1 for "Precautions".

Elaszym consistently improves serum lipid abnormalities associated with hypertension and diabetes

In 666 patients with hyperlipemia whose roentgenogram showed calcified arteries of the lower limbs or who had hypertension or diabetes as an underlying disease, Elaszym was administered at doses ranging from 5,400 to 10,800 EL.U./day for 6 months or more to evaluate its effect on abnormalities of serum lipids. Total cholesterol significantly decreased 3, 6, 9, and 12 months after the start of the treatment, and a similar result was found even in the abnormally high total cholesterol group (≥250 mg/dL). In addition, another similar result was also found in neutral fat.

There was a marked improvement in HDL-cholesterol in the low HDL-cholesterol group (<40 mg/dL).

Adverse reactions were reported in 11 of 666 patients (1.7%), and most were gastrointestinal disorder, itching, and rash (redness).

Total Cholesterol

before administration | 3 months | 6 months | 9 months | 12 months

Total cholesterol (≥250 mg/dL)

before administration | 3 months | 6 months | 9 months | 12 months

Neutral fat

before administration | 3 months | 6 months | 9 months | 12 months

Neutral fat (≥150 mg/dL)

before administration | 3 months | 6 months | 9 months | 12 months

HDL-cholesterol (<40 mg/dL)

before administration | 3 months | 6 months | 9 months | 12 months

Goto, Y. et al· The Japanese Journal of Clinical and Experimental Medicine, 62 (9), 230 (1985)

[Reference request number: ELA-0419]

• See page 1 for "Precautions".

Elaszym consistently improves serum lipid abnormalities associated with ischemic cardiac disease and hypertension

In 276 patients with hyperlipemia who had ischemic cardiac disease or hypertension as an underlying disease, Elaszym was administered at a dose of 10,800 EL.U./day for 2 to 39 months (mean, 23.1 ± 7.9 months) to evaluate its effect on abnormalities of serum lipids.

Total cholesterol significantly decreased 3, 6, 9, 12, 15, 18, 21, 24, 25 and more months after the start of the treatment, and a similar result was found even in the abnormally high total cholesterol group (≥230 mg/dL), resulting in a mean decrease of 9.4% in 273 patients analyzed. In addition, a similar result was also found in neutral fat, resulting in the mean decrease of 16.3% in 272 patients analyzed.

HDL-cholesterol significantly increased 3, 6, 9, 18, 24, 25 and more months after the start of the treatment in the low HDL-cholesterol group (<45 mg/dL), resulting in a mean increase of 4.4 mg/dL in 135 patients analyzed.

There was no severe adverse reaction, or no change in other laboratory parameters.

Total cholesterol

pretreatment 3 6 9 12 15 18 21 24 25 - longer

Neutral fat

pretreatment 3 6 9 12 15 18 21 24 25 - longer

HDL-cholesterol

pretreatment 3 6 9 12 15 18 21 24 25 - longer

Iimura, I. et al: The Japanese Journal of Clinical and Experimental Medicine, 67 (10), 229 (1990)

[Reference request number: ELA-0602]

• See page 1 for "Precautions".

Elaszym improves serum lipid abnormalities in hypertensive patient receiving antihypertensive diuretics or β-blockers

In 167 hypertensive patients receiving antihypertensive diuretics or β-blockers, Elaszym was administered at a dose of 10,800 EL.U./day for 3 to 25 months to evaluate its effect on abnormalities of serum lipids.

Total cholesterol significantly decreased 3, 6, 9, 12, 15, 18, 21, 24, 25 and more months after the start of the treatment. A similar result was also found in neutral fat.

HDL-cholesterol, tended to increase ($P<0.1$) 21 and 25 months after the start of the treatment, and significant by increased ($P<0.05$) at the final evaluation.

No severe adverse reactions, or changes were observed in other laboratory parameters.

Total cholesterol

Neutral fat

pretreatment 3 6 9 12 15 18 21 24 25 - longer

pretreatment 3 6 9 12 15 18 21 24 25 - longer

Iimura, I. et al: The Japanese Journal of Clinical and Experimental Medicine, 67 (10), 229 (1990)
[Reference request number: ELA-0602]

• See page 1 for "Precautions".

Elaszym is highly effective against hyperlipemia IIb, III, IV

Of 336 patients with hyperlipemia, which was classifiable in 141 patients according to the WHO's criteria, Elaszym was administered at doses ranging from 5,400 to 10,800 EL.U./day for 3 months or more to evaluate its effect on the changes in LDL-cholesterol and VLDL-cholesterol by the type of hyperlipemia. LDL-cholesterol significantly decreased in hyperlipemia IIa and IIb, and VLDL-cholesterol in hyperlipemia III and IV, with an overall higher rate of improvement in hyperlipemia IIb, III and, IV.

Adverse reactions were reported in 13 of 336 patients (3.89%), and most were anorexia, cutaneous pruritus, and gastric discomfort.

LDL-cholesterol changes in different types

preadministration

postadministration

(paired t-test)

VLDL-cholesterol changes in different types

preadministration

postadministration

(paired t-test)

Arakawa, M. et al: The Japanese Journal of Clinical and Experimental Medicine, 62 (3), 237 (1985)
[Reference request number: ELA-0367]

• See page 1 for "Precautions".

Relations between Elaszym and arterial function in hyperlipemia and arteriosclerosis

Pulse wave velocity and Elaszym

Pulse wave velocity (PWV) is known to be one of the most effective diagnostic means for physical properties of the aorta (degree of sclerosis).

Of 184 patients with arteriosclerotic diseases, 126 and 58 patients were randomized to the Elaszym-treated group (10,800 EL.U./day) and the untreated group, respectively, to evaluate the change in PWV over 14 years. While PWV increased over the time in the untreated group, such increase was controlled (with preserved elasticity) in the Elaszym-treated group.

The changes of PWV in Elaszym-treated group and untreated group

	N	Coefficient for regression
Healthy adult group	259	0.072/year
Untreated group	58	0.192/year
Elaszym-treated group	126	0.048/year

Hasegawa, M: Japanese Journal of Geriatrics (modified), 32, 344 (1995)
[Reference request number: ELA-0624]
Hasegawa, M: Second Chinese western medical association
- The international symposium of arteriosclerosis, thrombosis, and primary prevention. (1994)

• See page 1 for "Precautions".

Carotid sclerosis index (β) and Elaszym

Carotid sclerosis index (β) is considered to be an effective index to indicate the degree of carotid sclerosis. It is expressed as the rate of change in internal pressure required to enlarge the vascular diameter per unit, and a higher value suggests more advanced carotid sclerosis.

Of 910 patients with arteriosclerotic diseases including hyperlipemia (hypertension, ischemic cardiac diseases, etc.), 198 and 712 patients were randomized to the Elaszym-treated group (10,800 EL.U./day) and the untreated group, respectively, to evaluate β change over several years. A similar evaluation was also performed in 422 healthy adults (with no arteriosclerotic diseases) as the controls for comparison.

While β increased during 8 to 14 years in the untreated group, such increase was controlled at lower levels in the Elaszym-treated group than in the control group.

The time-course change of Δβ

Untreated group
Healthy adult group
Elaszym-treated group

Hasegawa, M: The Journal of Japanese College of Angiology, 35 (6), 349 (1995)
[Reference request number: ELA-0623]

• See page 1 for "Precautions".

B mode ultrasonic tomography of carotid arteries and Elaszym

Ultrasonic tomography of carotid arteries is a diagnostic means for the properties of vascular walls by applying ultrasonic waves through the cervical surface, and globally known as an increasingly authorized index.

Of 120 patients with hyperlipemia accompanied by carotid lesions, 52 and 68 patients were randomized to the Elaszym-treated group (10,800 EL.U./day) and the untreated group, respectively, to evaluate the change in maximum hyperplasia of carotid walls (MAX-IMCT) over about 2 years.

While MAX-IMCT significantly increased in the untreated group, such increase was controlled with the mean tending to decrease in the Elaszym-treated group. There was a significant difference in MAX-IMCT change between the two groups, and the progress of arteriosclerotic lesions was significantly controlled in the Elaszym-treated group.

b: MAX-IMCT

vascular surface   vascular lumen   vascular wall

MAX-IMCT

Preobservation   Postobservation
Untreated group
(n=68)

Preobservation   Postobservation
Elaszym-treated group
(n=52)

Handa, N: The Journal of Japanese College of Angilogy, 35 (6), 365 (1995)
[Reference request number: ELA-0625]

• See page 1 for "Precautions".

Pharmacokinetics of exogenous elastase (Elaszym®)

Porcine pancreatic elastase is distributed into blood after orally administered to humans

It has been demonstrated that porcine pancreatic elastase is distributed to blood after orally administered to humans. In 12 healthy adults ranging 20 to 80 years, the blood concentrations of elastase were determined by ELISA after a single oral administration of the daily dose of Elaszym tablets (6 tablets, 10,800 EL.U.)*. The maximum blood concentrations (0.88 ± 0.41 ng/mL) were seen 10 to 14 hours after administration, with a half-life of 19.4 hours.

* A single dose of 10,800 EL.U. does not meet the dosage and administration approved. The dosage and administration approved is as follows: "The usual adult dosage is 3 tablets (5,400 EL.U.) daily, which is orally administered before meal in three divided doses. The dosage may be increased to 6 tablets (10,800 EL.U.) daily if the desired effect has not been achieved. The dosage should be adjusted depending on the patient's age and symptoms".

The blood concenrtation changes of porcine pancreatic elastase after oral administration to humans

Kouno, T: Clin. Chem Enzym. Comms, 4, 123 (1991)
[Reference request number: ELA-0605]

How elastase exists in serum and lymph (humans)

Porcine pancreatic elastase is classified into serine protease. In general, serine protease, if active, is bound to the protease inhibitor α_1-macroglobulin and α_1-proteinase inhibitor in the blood, and migrates in flowing blood and lymph before metabolized in the liver.

In humans, elastase is bound to α_1-macroglobulin and α_1-proteinase inhibitor at a ratio of 4 : 1.

antigen-antibody binding site

active site

α_1PI: α_1-proteinase inhibitor
α_1M: α_1-macroglobulin
E: elastase

Ogawa, M: The Japanese Journal of Clinical Medicine, 39, 2642 (1981)

Absorption, distribution, and metabolism of elastase (rats, dogs)

In the rat jejunum ligated at both ends, immunocytochemical observation of enteral absorption of Elaszym has demonstrated that the enzyme is enterally absorbed without being degraded to components of lower molecular weight[1]. When the blood concentrations of elastase were determined by means of enzyme immunological assay after 20 Elaszym tablets (36,000 EL.U.*) were orally administered to each dog, the blood concentrations gradually declined after reaching the maximum (0.56 ng/mL) 10 hours after administration. Meanwhile, the area under the blood concentration-time curve (AUC) increased dose-dependently. After absorbed, Elaszym is bound to α_1-macroglobulin and α_1-antitrypsin in the serum, and widely distributed in all tissues before metabolized mainly in the liver[2) 3) 4)].

*Equivalent to 3 to 6 times as much as the therapeutic dose

1) Tsujii, T: Histochemistry, 81, 427(1984)
2) Katayama, K. et al: Biochim. Biophys. Acta, 336, 165 (1974)
3) Katayama, K. et al: Biochim. Biophys. Acta, 336, 178 (1974)
4) Katayama, K et al: Biochim. Biophys. Acta, 336, 191 (1974)

Porcine pancreatic elastase is enterally absorbed without being degraded or losing its activity (rats)

In rats, it has been demonstrated that elastase injected into the intestine is absorbed from the jejunal mucosa without being degraded to components of lower molecular weight (photo). ^{131}I-labeled elastase injected into the intestine is partially absorbed as a macromolecule while retaining its reactivity to antibody, and is bound to α_1-macroglobulin and α_2-proteinase inhibitor in the serum; this indicates that elastase is absorbed while retaining its activity. It has been shown that 60% of the dose is absorbed into the lymphatic system, and 40% into the portal system.

Tsujii, T:Histochemistry, 81, 427 (1984)
[Reference request number: ELA-0388]

Porcine pancreatic elastase bound to α_1-proteinase inhibitor exhibits its activity after it migrates to tissues (rats)

It has been reported that after porcine pancreatic elastase bound to α_1-proteinase inhibitor, which has a longer half-life than that bound to α_1-macroglobulin, when intravenously administered to rats, was incorporated into endothelial cells of arteries and migrated to elastic laminae, which were finally decomposed as the image shows (as).

vl: vascular lumen
en: endothelial cell of blood vessel
ei: elastic internal lamina
jc: junction of endothelial cell
as: decomposed (?)
sm: smooth muscle cell

Tsujii, T :Histochemistry, 88, 443 (1988)
[Reference request number: ELA-0533]

Elastase activates lipoprotein lipase (LPL) involved in the catabolism of chylomicron and LDL in the metabolic pathway of lipoprotein, as well as hepatic lipase (HTGL) involved in the catabolism of intermediate IDL to LDL.

It also activates lecithin-cholesterol acyltransferases (LCAT) that esterifies cholesterol derived from peripheral tissues and increases HDL. In addition, it stimulates the catabolism of bile acids in liver.

In conclusion, elastase stimulates the metabolism of lipoprotein and improves abnormal metabolism of serum lipids and lipoprotein by activating the enzyme system involved in the metabolism of lipoprotein.

bile acid
stimulates cholesterol catabolism in liver
liver
chylomicron remnant
intestine
chylomicron
enhances lipoprotein lipase activity
enhances HTGL activity
peripheral cell
enhances lecithin-cholesterol acyltransferase activity
peripheral cell
HTGL: hepatic triacylglycerol lipase

Elastase enhances lipoprotein lipase activity (*in vitro*)

Post heparin plasma (PHP) was prepared by intravenously administering heparin (500 U/kg) to rabbits. To the normal rabbit plasma, low concentrations of elastase (0, 1.45, 2.90, and 14.5 ng/mL as final concentration) was added and incubated at 37°C for 5 minutes before addition of elastatinal to inactivate elastase; then, PHP were added.

Lipoprotein lipase activity in plasma was increased, indicating that elastase indirectly stimulates lipoprotein lipase activity.

Effect of elastase on lipoprotein lipase activity

Lipoprotein lipase

Elastase concentration

Koide, J et al: The Journal of Japanese Atherosclerosis Society, 12 (6), 1529 (1985)
[Reference request number: ELA-0384]

Elastase enhances HTGL activity (*in vitro*)

Elastase was orally administered to rats at doses of 20 and 40 mg/kg/day for 10 days to determine lipase activity in sliced liver (hepatic triacylglycerol lipase activity: HTGL). Elastase increased HTGL activity dose-dependently.

Effect of elastase on HTGL activity

Ueki, H: Study report of Japanese industrial science institution, 7, 40 (1994)

Elastase improves serum lipid abnormalities in rabbits loaded with high-fat diets

In rabbits, hyperlipemia was induced by feeding with diets containing 1% cholesterol for 18 weeks. At the same time, elastase was intramuscularly administered at a dose of 10 mg/kg/day to evaluate its effect on serum lipids (total cholesterol) and the change in serum elastase-like activity.

Serum total cholesterol markedly increased in the fat-diet group while it tended to be controlled in the elastase-treated group. Serum elastase-like activity was higher in the elastase-treated group than that in the fat-diet and control groups, and the activity was highly inhibited by elastatinal, the specific elastase inhibitor; this suggests that serum elastase-like activity is closely related to serum lipid abnormalities.

Effect of elastase on serum cholesterol

Okamoto, T: The Journal of Japan Atherosclerosis Society, 14 (5), 1013 (1986)
[Reference request number: ELA-0417]

Serum elastase-like activity:

determined using the synthesized substrate Suc(-Ala-)3pNA.

The changes in serum elastase-like activity

Okamoto, T: The Journal of Japanese Atherosclerosis Society, 14 (3), 775 (1986)
[Reference request number: ELA-0479]

Elastase inhibits proliferation of smooth muscle cells (*in vitro*)

The effect of elastase on proliferation of smooth muscle cells was evaluated *in vitro,* using the uptake of ^{3}H-thymidine as a cell proliferation parameter. After 24-hour incubation of agar containing elastase (1 to 50 mg/mL), proliferation activity was determined. Elastase inhibited cell proliferation dose-dependently. Elastase inactivated by phenyl methyl sulfonyl fluoride (PMSF) failed to inhibit cell proliferation; this indicates that cell proliferation inhibition depends on elastase activity.

In addition, lactate dehydrogenase activity was determined within the similar range of concentration. There was no increase in the activity, indicating no cytotoxicity.

3H-thymidine uptake (cpm/well)

Elastase concentration (ng/mL)

Fukuo, K: Atherosclerosis, 110, 111 (1994)

The effect of elastase on deposition of cholesterol on arterial walls in rabbits with arteriosclerosis induced with high-fat diet

Arteriosclerosis was induced in rabbits by feeding with diets containing 1% cholesterol for 53 weeks. At the same time, elastase was intramuscularly administered at a dose of 10 mg/kg/day.

The cholesterol content of aortic walls markedly increased in the fat-diet group while such increase was significantly controlled in the elastase-treated group ($p<0.01$).

The effect of elastase on the content of cholesterol in arterial walls

Cholesterol/aorta (mg/g)

normal diet group fat diet group fat diet + elastase-treated group

Okamoto, T: The Journal of Japanese Atherosclerosis Society, 14 (5), 1013 (1986)
[Reference request number: ELA-0471]

The effect of elastase on the tunica intima in aorta

The effect of elastase on nuclear muscle in hyperplastic tunica intima

The effect of elastase on cell proliferation and development of arteriosclerotic lesions associated with hyperlipemia and experimentally-induced endothelial disorder (rabbits)

In rabbits, endothelial cells were ablated from the aortic arch to the abdominal aorta, by means of a balloon-tip catheter, and arteriosclerosis was induced by feeding with diet containing 0.2% cholesterol for 6 weeks. Elastase was orally administered at a dose of 540 EL.U./day for 14 weeks to compare the area of aorta-occupying atheroma between the elastase-treated and untreated groups.

In the elastase-treated group, the development of atheroma was significantly controlled with the area of aorta-occupying atheroma of 16.0 ± 5.8%, compared with 27.1 ± 5.4% in the untreated group; this indicates that elastase supresses arteriosclerotic lesions associated with endothelial disorder and hyperlipemia. In addition, smooth-muscle cell proliferation caused by platelet extract containing platelet-derived growth factor tended to be controlled in the hypelipemic serum and plasma of elastase-treated animals.

Group	Area of aorta-occupying atheroma	Grade of area of aorta-occupying atheroma
Fat diet + ballooning group	27.1 ± 5.4%	I, II, III
Fat diet + ballooning + oral elastase group	16.0 ± 5.8%	I, II, III

(%) χ^2-test $p < 0.05$

Grade I (0 - 3%)

Grade II (3 - 20%)

Grade III (20 - 100%)

Mean ± SE

The effect of elastase on proliferation of smooth muscle cells (in vitro)

	Group	Uptake of ^{3}H-thymidine into smooth muscle cells**	Ratio to the control group
Serum*	Normal group	5.29	100
	Fat diet group	7.35	136
	Fat diet + oral elastase group	6.61	125
Plasma*	Normal group	1.03	100
	Fat diet group	2.00	194
	Fat diet + oral elastase group	1.58	153

* Serum and plasma were collected after 2-week feeding.

** Uptake of thymidine was used as cell proliferation parameter.

Saeki, T. et al: Acta Pathol. Jpn., 37 (9), 1423 (1987)

[Reference request number: ELA-0515]

In rabbits, hyperplasia of tunica intima in arteries was induced by inserting a polyethylene tube into the aorta thoracica descendens for 24 hours and injuring the endothelial cells.

Elastase was orally administered at a dose of 1,800 EL.U./day for 12 weeks to compare hyperplasia of the tunica intima and nuclear density in the hyperplastic tunica intima between the elastase-treated and untreated groups 8 and 12 weeks after the start of feeding.

No difference was observed in the mean thickness of hyperplastic tunica intima between the two groups 8 weeks after the start of feeding, but it was significantly lower in the elastase-treated group than the untreated group 12 weeks after the start of feeding ($p<0.05$). In addition, nuclear density of smooth muscle cells in the hyperplastic tunica intima was significantly lower in the elastase-treated group than in the untreated group 8 weeks after the start of feeding ($p<0.05$), and showed a similar tendency 12 weeks after the start of feeding.

Control, untreated group (C)
Elastase-treated group (E)

Asada, Y: The Journal of Japan Atherosclerosis Society, 16 (6), 881 (1988)
[Reference request number: ELA-0555]

The effect of elastase on removal of intercellularly accumulated LDL (in vitro)

Using a smooth muscle cell culture, extracellular matrix (cell matrix) was prepared. Human ^{3}H-labeled LDL was added to it and incubated for 16 hours before addition of low concentrations of elastase, and then incubated for another 4 hours.

After addition of elastase, ^{3}H-LDL bound to the extracellular matrix was released dose-dependently.

The effect of elastase on extracellular matrix-bound LDL

Morisaki, M: The Journal of Japan Atherosclerosis Society, 15 (7), 1419 (1987)
[Reference request number: ELA-0528]

The effect of elastase on degeneration and calcification of elastic fibers in arterial walls in rabbits with hyperlipemia-induced arteriosclerosis

In 38-month old rabbits, arteriosclerosis was induced by loading N_2 gas and noradrenaline, and feeding with diets containing 0.5% cholesterol for 22 weeks. Elastase was orally administered at a dose of 3,600 EL.U./day. Elastic fibers (elastin), were considerably ruptured and decreased in number by approximately 20% in the sclerosis (untreated) group, compared with the healthy group. In the elastase-treated group, no morphological changes or prominent decrease were observed in the fibers: the content was lower just by approximately 3% than in the healthy group. This indicates that elastase inhibits degeneration of elastin and stimulates its production in arteries (the content of aortic elastin was histochemically determined).

Mean ± SE

Healthy group	Sclerosis (untreated) group	Sclerosis + elastase-treated group
52.8 ± 4.3%V (100)	42.3 ± 2.6%V (80.1)	51.4 ± 5.9%V (97.3)

P<0.01

In the elastase-treated group, calcification of elastic fibers in arteries was milder than that in the sclerosis (untreated) group, indicating that elastase has decalcifying effect.

Healthy group	Sclerosis (untreated) group	Sclerosis + elastase-treated group
52.8 ± 4.3%V (100)	42.3 ± 2.6%V (80.1)	51.4 ± 5.9%V (97.3)

Hasegawa, M: The Journal of Japan Atherosclerosis Society, 12 (1), 207 (1984)

[Reference request number: ELA-0283]

TOXICITY STUDY

Acute toxicity

LD_{50} (EL.U./kg)

Species / Route of administration	Rat		Mouse	
	♂	♀	♂	♀
Oral	> 150,000	> 150,000	> 150,000	> 150,000

Subacute toxicity

In dogs orally receiving 900 and 4,500 EL.U./kg/day for 12 weeks, no specifically abnormal findings were observed in clinical signs, hematology, urinalysis, or hystopathology.

Chronic toxicity

In rats orally receiving 2,250, 5,700, 11,250, and 22,500 EL.U./kg/day for 24 weeks, no specifically abnormal findings were observed in clinical signs, hematology, urinalysis, or hystopathology.

Reproductive study

In mice and rats orally receiving 750, 7,500, and 75,000 EL.U./kg/day for 7 days during organogenesis, there was no fetal death, growth inhibition, or teratogenicity, and no effect on neonatal morphological or functional differentiation.

<For reference> Relations between elastase and arteriosclerosis

In 1953, Balo and Banga reported that the pancreatic elastase content was markedly lower in patients with arteriosclerotic diseases.

In Japan, it has been reported that elastase activity in human serum (degrading activity for the synthesized substrate Suc(-Ala-)3pNA (elastase-like activity) and elastin-degrading activity) is reduced with aging.

In addition, Bihari-Verga found that elastase-inhibiting activity was markedly higher in patients with ischemic cardiac diseases, chronic cerebrovascular disorders, and peripheral angiopathy than in healthy adults, suggesting the importance of elastase in arteriosclerosis.

Serum elastase-like activity:
determined using the synthesized substrate Suc(-Ala-)3pNA

Serum elastin-degrading activity changes in different age groups

Elastin-degreading activity

Juvenile (n=25) Adult (n=31) Aged (n=23)

Serum elastase-like activity changes in different age groups

Serum elastase-like activity

Juvenile (n=15) Adult (n=19) Aged (n=23)

Seyama, Y: Clin. Chem, 14, 13 (1983)

Serum elastase inhibiting activity in arteriosclerotic patients

Elastase inhibitory activity

Ischemic cardiac disease Peripheral angiopathy
Chronic cerebrovascular disorder Healthy adults

Bihari-Verga, M: Atherosclerosis, 50, 273 (1984)

<For reference> Actual treatment of hyperlipemia

In recent years, rapid progress has been made in the pathogenetic and pathologic research of arteriosclerosis. This is because the researches have been intensely conducted not only from the aspect of risk factors such as serum lipid abnormalities (e.g., hyperlipemia) and thrombosis, but also from the aspect of metabolism in blood vessels. In Japan, hyperlipemic patients with serum cholesterol exceeding 300 mg/dL account for only approximately 10% of all hyperlipemic patients, extremely lower than in the USA and European countries. Given this fact, therapeutic approaches must be taken to control the function of cells composing blood vessels (e.g., endothelial cells, smooth muscle cells) and to correct abnormal metabolism in blood vessels including extracellular connective tissues (e.g., elastin, collagen) in arteriosclerosis, although it is needless to say that hyperlipemia is an important risk factor.

Among anti-hyperlipemic agents, those approachable to lesions in arterial walls are classified as follows, based on the mechanism of action;

① Control of production of oxidized LDL:

probucol, α-tocopherol

② Control of function of macrophage:

probucol, α-tocopherol

③ Control of proliferation of smooth muscle cells:

ACE inhibitors, certain calcium antagonists, elastase

④ Removal of denatured connective tissues: elastase

⑤ Removal of intercellular lipids: elastase

The treatment of arteriosclerosis has steadily progressed from the control of risk factors to the control of risk factors with normalization of metabolism in arterial walls.

Choice of anti-hyperlipemic agents based on the efficacy

① Mild (cholesterol 220-260 mg/dL, neutral fat 150-300 mg/dL):
pantethine (0.6 g/day), gamma oryzanol(300 mg/day), dextran sulfate sodium (300-600 mg/day), tocopherol nicotinate (300-600 mg/day), elastase (5,400-10,800 EL.U /day), etc.

② Moderate (cholesterol 260-300 mg/dL, neutral fat 300-600 mg/dL):
niceritrol, clinofibrate, simfibrate, etc.

③ Severe (cholesterol ≧ 300 mg/dL):
HMG-CoA reductase inhibitors

Choice of anti-hyperlipemic agents based on the mechanism of action

① Inhibitors for absorption: melinamide(1.5-2.25 g/day)
soysterol(600-1,200 mg/day)

② Inhibitors for synthesis: pravastatin sodium(5-10 mg/day)
clofibrates [clofibrate (1.5 g/day), clinofibrate (600 mg/day), cinfibrate (760-1,500 mg/day), aluminum clofibrate (500 mg/day)]
nicotinic acid [nicomol(600-1,200 mg/day),niceritrol(600 mg/day)]

③ Accelerators for excretion of bile acids:
cholestyramine (8-12 g/day)
probucol (500 mg/day, in case of familial hypercholesterolemia, the dosage may be increased to 1,000 mg/day)

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