

Revised: February 2012 (14th version) D10

Standard Commodity Classification No. of Japan
873399

- 5-HT₂blocker -**ANPLAG[®] Tablets 50mg****ANPLAG[®] Tablets 100mg**

< The Japanese Pharmacopoeia Sarpogrelate Hydrochloride tablets >

ANPLAG[®] Fine granules 10%

< The Japanese Pharmacopoeia Sarpogrelate Hydrochloride fine granules >

Storage
Store at room temperature.

Expiration date
Do not use after the expiration date indicated on the package and the label.

	Tablets 50 mg	Tablets 100 mg	Fine granules 10%
Approval No.	20500AMZ 00340	20500AMZ 00341	21100AMZ 00174
Date of listing in the NHI reimbursement price	August 1993	August 1993	May 1999
Date of initial marketing in Japan	October 1993	October 1993	May 1999
International birth date	July 1993		
Date of latest reexamination	August 2002		

CONTRAINDICATIONS (ANPLAG is contraindicated in the following patients.)

- (1) Patients with haemorrhage (Haemophilia, capillary fragility, gastrointestinal ulceration, urinary tract haemorrhage, haemoptysis, vitreous haemorrhage) [Haemorrhage may be aggravated.]
- (2) Pregnant women and women who may be possibly pregnant. (See "Use during Pregnancy, Delivery or Lactation" section.)

Description / Dosage form	White / Fine Granules
---------------------------	-----------------------

INDICATIONS

Improvement of ischemic symptoms including ulcer, pain and feeling of coldness, associated with chronic arterial occlusion

DOSAGE AND ADMINISTRATION

The usual dosage for adult patients is 100 mg of sarpogrelate hydrochloride, administered after meal three times a day. The dosage may be adjusted according to the patient's age and symptoms.

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

- (1) Patients during menstrual period [Haemorrhage may be aggravated.]
- (2) Patients with bleeding tendency and haemorrhagic diathesis [Bleeding tendency may be aggravated.]
- (3) Patients receiving anticoagulants (warfarin, etc.) or antiplatelets (aspirin, ticlopidine hydrochloride, cilostazol, etc.) [Bleeding tendency may be aggravated.]
- (4) Patients with severe renal impairment [This product excretion may be impaired.]

2. Important Precautions

It is recommended that laboratory tests should be carried out regularly during administration.

DESCRIPTION

	Tablets 50mg	Tablets 100mg
Active ingredient (per tablet)	Sarpogrelate hydrochloride (JP) 50mg	Sarpogrelate hydrochloride (JP) 100mg
Inactive ingredient	Cellulose, carmellose, hydroxypropylcellulose, anhydrous silicic acid, citric acid hydrate, magnesium stearate, hypromellose, titanium oxide, macrogol 6000, talc	
Description / Dosage form	White / Film-coated tablets	White / Film-coated tablets
Appearance	  	  
Size	Diameter (mm) 6.6 Thickness (mm) 3.0 Weight (mg) 90	Diameter (mm) 7.7 Thickness (mm) 4.1 Weight (mg) 178

	Fine granules 10%
Active ingredient (per g)	Salpogrelate hydrochloride (JP) 100mg
Inactive ingredient	White soft sugar, hydroxypropylcellulose, citric acid hydrate, hypromellose, ethylcellulose, cetanol, sodium lauryl sulfate, aminoalkylmethacrylatecopolymer E, triacetin, talc, calcium stearate, saccharin sodium

3. Drug Interactions

Precautions for coadministration (ANPLAG should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Anticoagulants (warfarin, etc.)	Bleeding tendency may be aggravated.	The effects of drugs may be intensified mutually.
Antiplatelets (aspirin, ticlopidine hydrochloride, cilostazol, etc.)		

4. Adverse Reactions

Out of 4,807 patients treated, 151 adverse reactions to this product were observed in 107 patients (2.23%). The main adverse reactions were nausea in 12 patients (0.25%), heartburn in 10 patients (0.21%), abdominal pain in 9 patients (0.19%), etc. (at the time of completion of reexamination).

(1) Clinically significant adverse reactions

- Cerebral haemorrhage, gastrointestinal haemorrhage** (incidence <0.1%): The patient should be carefully observed, since cerebral haemorrhage and gastrointestinal haemorrhage including haematemesis and melaena may occur. If any abnormalities are observed, this product should be discontinued and appropriate measures should be taken.
- Thrombocytopenia** (incidence unknown): The patient should be carefully observed, since thrombocytopenia may occur. If any abnormalities are observed, this product should be discontinued and appropriate measures should be taken.
- Hepatic function disorder, jaundice** (incidence unknown): The patient should be carefully observed, since hepatic function disorder and jaundice with increased AST (GOT), ALT (GPT), Al-P, γ -GTP and LDH, may occur. If any abnormalities are observed, this product should be discontinued and appropriate measures should be taken.
- Agranulocytosis** (incidence unknown): The patient should be carefully observed, since agranulocytosis may occur. If any abnormalities are observed, this product should be discontinued and appropriate measures should be taken.

(2) Other adverse reactions

Incidence Type	5%> ≥0.1%	<0.1%	Incidence unknown
Hypersensitivity ^{note 1)}	Rash, redness	Papular rash, pruritus	Erythema, urticaria
Hepatic ^{note 2)}	Hepatic function disorder (increased bilirubin, increased AST(GOT), increased ALT(GPT), in-		

	creased Al-P, increased γ -GTP, increased LDH, etc.)		
Haemorrhagic tendency ^{note 2)}	Haemorrhage (Epistaxis, subcutaneous haemorrhage, etc.)		
Gastrointestinal	Nausea, heartburn, abdominal pain, constipation	Foreign body feeling of oesophagus, anorexia, enlarged feeling of abdomen, diarrhea	Vomiting, stomatitis
Cardiovascular	Palpitation	Breath shortness, chest pain, hot flushes	
Psychoneurologic	Headache	Sleepiness, taste abnormality, dizziness	
Renal	Proteinuria, urinary occult blood positive, increased BUN, increased creatinine		
Haematologic	Anaemia	Decreased platelet count	Decreased white blood cell count
Others	Increased blood triglycerides, increased serum cholesterol, decreased serum albumin, urinary sugar, abnormal urinary sediment	Increased weight, oedema, malaise, decreased serum calcium	Numbness, pyrexia, pharynx pain, pharynx discomfort, sensation of pharynx burning

Note

- In the event of such symptoms, administration should be discontinued.
- The patient should be carefully monitored for abnormal haemorrhage.
Administration should be discontinued, and appropriate therapeutic measures should be taken, if abnormalities are observed.

5. Use in the Elderly

ANPLAG should be carefully administered such as the initial dose reduced to e.g. 150 mg/day to elderly patients, whose conditions should be closely monitored. [The elevated blood concentrations of this drug may persist, since elderly patients often have reduced physiological function such as renal and hepatic function etc. in general.]

6. Use during Pregnancy, Delivery or Lactation

- (1) ANPLAG should not be used in pregnant women and in women who may possibly be pregnant. [Animal studies have shown increased incidence of embryo-fetus mortality and decrease of neonatal survival rate in rats.]
- (2) Use of this product in lactating women is not recommended. If administration of this product is judged to be essential, breast-feeding should be discontinued during administration. [An animal study (in rats) has shown that this product is excreted in breast milk.]

7. Pediatric Use

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

8. Precautions concerning Use

- (1) Precautions regarding dispensing:

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the PTP sheet prior to use. [It was reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

- (2) Precautions in taking fine granules:

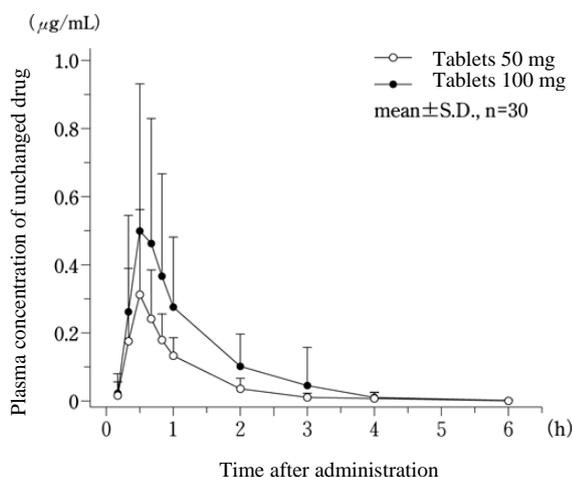
Instruct the patient to take ANPLAG Fine granules promptly, after unsealing. [The granules may be congealed if they improperly preserved.]

Instruct the patient to swallow the granules immediately. [If the granules are held in the mouth for long time, they will leave bitter taste.]

PHARMACOKINETICS

1. Absorption¹⁾

The plasma concentrations and pharmacokinetic parameters of unchanged drug after a single oral administration of an ANPLAG Tablets 50 mg or an ANPLAG Tablets 100mg to healthy male subjects (n=30) in fasting state are shown in the following figure and table, respectively.



	Tablet 50 mg	Tablet 100mg
Cmax (µg/mL)	0.3636±0.2488	0.7218±0.4041
tmax (h)	0.689±0.321	0.889±0.651
t _{1/2} (h)	0.753±0.149	0.753±0.169
AUC _{0-∞} (µg·h/mL)	0.2908±0.1199	0.5958±0.2665

(Mean±S.D., n=30)

2. Metabolism and excretion²⁾

After a single oral administration of sarpogrelate hydrochloride at a dose of 100 mg to healthy adults, no unchanged drug was detected in either urine or feces up to 24 hours after administration. The total excretion rate in urine and feces up to 24 hours after administration were 44.5% and 4.2%, respectively.

(For reference)

Absorption, distribution, metabolism and excretion in animals³⁾

When ¹⁴C- sarpogrelate hydrochloride was orally administered to rats, the tissue concentrations of radioactivity reached maximum at 15-30 minutes after the administration in the most of the tissues. The concentrations of radioactivity in the liver, kidney and lung were higher than that in the plasma. The concentration of radioactivity in each tissue rapidly declined. Excretion rates in urine and feces up to 96 hours after administration were 30-40% and 60-70%, respectively.

3. Metabolizing enzyme

This product is deesterified, and then its metabolite is further metabolized by multiple cytochrome P450 isoforms (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4).

CLINICAL STUDIES⁴⁻¹⁰⁾

In 194 patients with chronic arterial occlusion in clinical studies (including a double-blind comparative study), various ischemic symptoms associated with peripheral circulatory failure such as ulcer, pain, and feeling of coldness were evaluated, and the rate of usefulness is shown in the following table.

Disease	“Useful” or better	“Slightly useful” or better
Chronic arterial occlusion	125 patients / 194 patients (64.4 %)	170 patients / 194 patients (87.6 %)

PHARMACOLOGY

1. Mechanism of action¹¹⁻¹⁴⁾

Sarpogrelate hydrochloride has a specific antagonistic effect to 5-HT₂ serotonin receptor in platelets and vascular smooth muscle, which shows an anti-platelet effect and the inhibitory effect on vasoconstriction.

2. Inhibitory effect of platelet aggregation

- (1) ANPLAG with oral administration inhibited platelet aggregation induced by concomitant serotonin and collagen in healthy adults and patients with chronic arterial occlusion (*ex vivo* study).^{4, 15)}

- (2) Sarpogrelate hydrochloride inhibited the collagen-induced platelet aggregation and the secondary platelet aggregation induced by ADP or epinephrine in an *in vitro* study.¹¹⁾

Sarpogrelate hydrochloride inhibited the collagen-induced platelet aggregation enhanced by serotonin.¹¹⁾

3. Antithrombotic action

- (1) Sarpogrelate hydrochloride inhibited the progression of lesions in experimental model of peripheral arterial obstructive disease (lauric acid injection-induced peripheral artery occlusion in rats).¹⁶⁾

- (2) Sarpogrelate hydrochloride inhibited the thrombus formation in experimental thrombosis model (arterial thrombus formation induced by vascular endothelial injury in mice and arterial thrombus formation in polyethylene tubing implanted in rats).¹⁷⁾

4. Inhibitory effect on vasoconstriction¹²⁾

Sarpogrelate hydrochloride inhibited the serotonin-induced contraction of rat vascular smooth muscle (*in vitro*). In addition, sarpogrelate hydrochloride also inhibited the contraction of vascular smooth muscle resulted from platelet aggregation.

5. Improvement of microcirculation

ANPLAG increased transcutaneous tissue oxygen pressure and skin surface temperature in patients with chronic arterial occlusion.¹⁸⁾

Sarpogrelate hydrochloride improved the disturbances of circulation in a rat model of collateral circulation disorder.¹⁹⁾

PHYSICOCHEMISTRY

Nonproprietary name:

Sarpogrelate Hydrochloride (JAN)

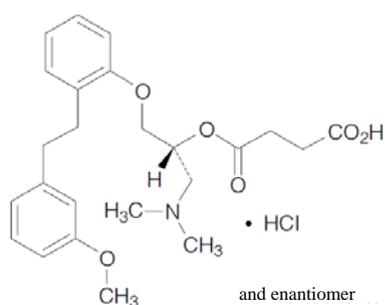
Chemical name:

(2-*RS*)-1-Dimethylamino-3-{2-[2-(3-methoxyphenyl)ethyl]phenoxy}propan-2-yl hydrogen succinate monohydrochloride

Molecular formula: C₂₄H₃₁NO₆•HCl

Molecular weight: 465.97

Structural formula:



Description: Sarpogrelate hydrochloride occurs as white crystalline powder.

It is slightly soluble in water or ethanol (99.5).

It dissolves in 0.01mol/L hydrochloric acid T.S.

A solution of Sarpogrelate Hydrochloride (1 in 100) shows no optical rotation.

PACKAGING

Anplag Tablets 50 mg:

Boxes of 100 (10 tablets×10) and 1,000 (10 tablets×100) in press-through packages

Bottles of 500

Anplag Tablets 100 mg:

Boxes of 100 (10 tablets×10), 500 (10 tablets×50) and 630 (21 tablets×30) in press-through packages

Bottles of 500

Anplag Fine granules 10%:

Boxes of 90 (1 g×90) sachets and 300 (1g×300) sachets

REFERENCES

- 1) Mitsubishi Tanabe Pharma Corporation: Report on the pharmacology of ANPLAG Tablets 50mg, 100mg (internal report)
- 2) Komatsu, T. et al.: Drug Metab. Pharmacokinet. 1991;**6**(3):353-375
- 3) Komatsu, T. et al.: Drug Metab. Pharmacokinet. 1991;**6**(3):377-398
- 4) Yamaguchi, H. et al.: J. Clin. Ther. Med. 1991; **7**(6):1235-1241
- 5) Furukawa, K. et al.: J. Clin. Ther. Med. 1991; **7**(6):1193-1204
- 6) Furukawa, K. et al.: J. Clin. Ther. Med. 1991; **7**(6):1205-1226
- 7) Furukawa, K. et al.: J. Clin. Ther. Med. 1991; **7**(8):1747-1770
- 8) Yamaguchi, H. et al.: J. Clin. Ther. Med. 1991; **7**(8):1771-1782
- 9) Hoshino, S. et al.: Jpn. Pharmacol. Ther. 1998; **26**(1):47-59
- 10) Esato, K. et al.: Jpn. Pharmacol. Ther. 1998; **26**(1):61-74
- 11) Hara, H. et al.: Thromb. Haemostas. 1991; **65**(4):415-420
- 12) Hara, H. et al.: Jpn. Pharmacol. Ther. 1991; **19**(S):611-618
- 13) Dobashi, H. et al.: J. Pharmacobio-Dyn. 1991; **14**:461-466
- 14) Maruyama, K. et al.: J. Pharmacobio-Dyn. 1991; **14**:177-181
- 15) Isogai, Y. et al.: J. Clin. Ther. Med. 1991; **7**(6):1227-1233
- 16) Hara, H. et al.: Arzneimittel. Forsch. 1991; **41**(6):616-620
- 17) Hara, H. et al.: Thromb. Haemostas. 1991;**66**(4): 484-488
- 18) Ito, K. et al.: J. Clin. Ther. Med. 1991; **7**(6):1243-1251
- 19) Mitsubishi Tanabe Pharma Corporation: Report on the pharmacokinetics of sarpogrelate hydrochloride (internal report)

REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Information Department
Pharmacovigilance & Quality Assurance Division
Mitsubishi Tanabe Pharma Corporation
2-6-18, Kitahama, Chuo-ku, Osaka 541-8505, Japan

Manufactured and Distributed by :

Mitsubishi Tanabe Pharma Corporation
2-6-18, Kitahama, Chuo-ku, Osaka 541-8505, Japan