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

<table>
<thead>
<tr>
<th>Active ingredient (per tablet)</th>
<th>Tablets 50mg</th>
<th>Tablets 100mg</th>
<th>Fine granules 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Sarpogrelate hydrochloride (JP)</td>
<td>Sarpogrelate hydrochloride (JP)</td>
<td></td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Cellulose, carmelloose, hydroxypropylocellulose, anhydrous silicic acid, citric acid hydrate, magnesium stearate, hypromellose, titanium oxide, macrogol 6000, talc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description / Dosage form</td>
<td>White / Film-coated tablets</td>
<td>White / Film-coated tablets</td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>50 mg</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>Diameter Thickness (mm)</td>
<td>Weight (mg)</td>
<td>Diameter Thickness (mm)</td>
</tr>
<tr>
<td></td>
<td>6.6</td>
<td>3.0</td>
<td>90</td>
</tr>
<tr>
<td>Description / Dosage form</td>
<td>White / Fine Granules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>August 1993</td>
<td>August 1993</td>
<td>May 1999</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>October 1993</td>
<td>October 1993</td>
<td>May 1999</td>
</tr>
<tr>
<td>International birth date</td>
<td>July 1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of latest reexamination</td>
<td>August 2002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 antplatelets (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.

- 5-HT<sub>2</sub>-blocker -

ANPLAG® Tablets 50mg
ANPLAG® Tablets 100mg
< The Japanese Pharmacopoeia Sarpogrelate Hydrochloride tablets >
ANPLAG® Fine granules 10%
< The Japanese Pharmacopoeia Sarpogrelate Hydrochloride fine granules >
3. Drug Interactions
Precautions for coadministration (ANPLAG should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants (warfarin, etc.)</td>
<td>Bleeding tendency may be aggravated.</td>
<td>The effects of drugs may be intensified mutually.</td>
</tr>
<tr>
<td>Antipllatelets (aspirin, ticlopidine hydrochloride, cilostazol, etc.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
1) 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.
2) 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.
3) 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.
4) 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

<table>
<thead>
<tr>
<th>Incidence Type</th>
<th>Incidence</th>
<th>5%&gt;</th>
<th>0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (note 1)</td>
<td>Rash, redness</td>
<td>Poplar rash, pruritus</td>
<td>Erythema, urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (note 2)</td>
<td>Hepatic function disorder (increased bilirubin, increased AST(GOT), increased ALT(GPT), increased Al-P, increased γ-GTP, increased LDH, etc.)</td>
<td>Haemorrhagic tendency (note 2)</td>
<td>Haemorrhage (Epistaxis, subcutaneous haemorrhage, etc.)</td>
<td>Gastrointestinal</td>
<td>Nausea, heartburn, abdominal pain, constipation</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitation</td>
<td>Breath shortness, chest pain, hot flushes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Headache</td>
<td>Sleepiness, taste abnormality, dizziness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Proteinuria, urinary occult blood positive, increased BUN, increased creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology</td>
<td>Anaemia</td>
<td>Decreased platelet count</td>
<td>Decreased white blood cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Increased blood triglycerides, increased serum cholesterol, decreased serum albumin, urinary sugar, abnormal urinary sediment</td>
<td>Increased weight, oedema, malaise, decreased serum calcium</td>
<td>Numbness, pyrexia, pharynx pain, pharynx discomfort, sensation of pharynx burning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note
1) In the event of such symptoms, administration should be discontinued.
2) 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. Absorption
   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.

<table>
<thead>
<tr>
<th>Tablet 50 mg</th>
<th>Tablet 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.3636±0.2488</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>0.689±0.321</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.753±0.149</td>
</tr>
<tr>
<td>AUC0→∞ (µg•h/mL)</td>
<td>0.2908±0.1199</td>
</tr>
</tbody>
</table>
   (Mean±S.D., n=30)

2. Metabolism and excretion
   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 animals
   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 STUDIES
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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>“Useful” or better</th>
<th>“Slightly useful” or better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic arterial occlusion</td>
<td>125 patients / 194 patients (64.4 %)</td>
<td>170 patients / 194 patients (87.6 %)</td>
</tr>
</tbody>
</table>

PHARMACOLOGY

1. Mechanism of action
   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).
(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 vasoconstriction 12)
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. 16)
Sarpogrelate hydrochloride improved the disturbances of circulation in a rat model of collateral circulation disorder. 19)

PHYSICOCHEMISTRY
Nonproprietary name: Sarpogrelate Hydrochloride (JAN)
Chemical name: (2RS)-1-Dimethylamino-3-({2-[2-(3-methoxyphenyl)ethyl]phenoxy}propan-2-yl hydrogen succinate monohydrochloride
Molecular formula: C_{24}H_{31}NO_{6}•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. Sarpogrelate Hydrochloride shows crystal polymorphism.

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

REFERENCES
1) Mitsubishi Tanabe Pharma Corporation: Report on the pharmacology of ANPLAG Tablets 50mg, 100mg (internal report)
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
3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan

Manufactured and Distributed by:
Mitsubishi Tanabe Pharma Corporation
3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan

This document is an English translation of the Japanese package insert.