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Standard Commodity Classification No. of Japan
874299

- ANTINEOPLASTIC AGENT AND AGENT FOR TREATING LYMPHANGIOMA -

PICIBANIL® Injection 0.2KE
PICIBANIL® Injection 0.5KE
PICIBANIL® Injection 1KE
PICIBANIL® Injection 5KE

Biological products, Powerful drug, Prescription-only drug*1

Storage
Store at temperatures ≤10°C and avoid freezing.

Expiration date
Use before the expiration date specified on the package.

Brand name	PICIBANIL			
	0.2KE	0.5KE	1KE	5KE
Approval No.	21800AMX 10780	21800AMX 10781	21800AMX 10782	21800AMX 10783
Date of listing in the NHI reimbursement price	December 2006			
Date of initial marketing in Japan	October 1975			
Date of latest reevaluation	December 1989			
Date of latest approval of indications	January 1995			
Date of reexamination results	October 2008			

Caution – The injection should be used promptly after reconstitution.

*1: Caution - Use only pursuant to the prescription or directions of a physician, etc.

CONTRAINDICATIONS (PICIBANIL® is contraindicated in the following patients.)

- (1) Patients with a history of shock caused by this product.
- (2) Patients with a history of shock caused by benzylpenicillin [This product contains benzylpenicillin.]

RELATIVE CONTRAINDICATIONS (As a general rule, PICIBANIL® is contraindicated in the following patients. If the use of PICIBANIL® is considered essential, it should be administered with care.)

Patients with a history of hypersensitivity to this product or other penicillin antibiotics [This product contains benzylpenicillin.]

DESCRIPTION

In each vial

Brand name			PICIBANIL			
			0.2KE	0.5KE	1KE	5KE
Ingre- dient/ con- tent	Active ingre- dient	Lyophi- lized powder *2 (mg)	0.56	1.4	2.8	14

		Dried bacterial cells (mg)	0.02 (equivalent to 0.2KE)	0.05 (equivalent to 0.5KE)	0.1 (equivalent to 1KE)	0.5 (equivalent to 5KE)
	Inactive ingredient	Mag- nesium sulfate hy- drate (mg)	0.02	0.05	0.10	0.48
		DL-me thio- nine (mg)	0.04	0.10	0.20	1.00
		Maltose hydrate (mg)	17.69	17.23	8.37	1.34
		Ben- zylpeni- cillin potas- sium (unit)	540	1,350	2,690	13,470
		Potassium dihydrogen phosphate Sodium hydroxide Sodium chloride				

Dosage form	Lyophilized injection (colorless, transparent vial)
Color, description	White to whitish lyophilized powder or solid mass
pH*3	6.0-7.5
Osmotic pressure ratio*3	Approx. 1

Suspension diluent per ampule: 2 mL of isotonic sodium chloride solution, JP

*2: Lyophilized powder of *Streptococcus pyogenes* (A group, type 3) Su strain cells treated with penicillin. As components of culture medium in the manufacturing process, Todd Hewitt Broth (derived from bovine heart, bovine skeletal muscle, bovine bone marrow, bovine fat tissue, bovine connective tissue, and bovine milk, and from porcine heart, porcine pancreas and porcine stomach), bovine meat (derived from bovine skeletal muscle), Peptone N powder (bovine milk treated with porcine pancreatin [an enzyme derived from porcine pancreas]), and skim milk (derived from bovine milk) are used.

*3: After suspension in the accompanying diluent (the osmotic pressure in relation to isotonic sodium chloride solution)

INDICATIONS

- o Prolongation of survival time in patients with gastric cancer (postoperative cases) or primary lung cancer in combination with chemotherapy.
- o Reduction of cancerous pleural effusion or ascites in patients with gastrointestinal cancer or lung cancer.
- o Head and neck cancer (maxillary cancer, laryngeal cancer, pharyngeal cancer, and tongue cancer) and thyroid cancer that are non-responsive to other drugs.
- o Lymphangioma

DOSAGE AND ADMINISTRATION

- o Prolongation of survival time in patients with gastric cancer (postoperative cases) or primary lung cancer in combination with chemotherapy

In combination with chemotherapy, this product should be suspended in the accompanying isotonic sodium chloride solution, and administered intramuscularly, subcutaneously or intradermally. The usual initial dosage is 0.2-0.5KE once a day or once every other day. While monitoring the patient's condition, the dosage is gradually increased to 2-5KE over a two to three-week period. The maintenance dosage is 2-5KE once or twice a week.

- o Reduction of cancerous pleural effusion or ascites in patients with gastrointestinal cancer or lung cancer

After suspending this product in the accompanying isotonic sodium chloride solution, 5-10KE is generally administered into the serous cavity once or twice a week.

- o Head and neck cancer (maxillary cancer, laryngeal cancer, pharyngeal cancer, and tongue cancer) and thyroid cancer that are resistant to other drugs

After suspending this product in the accompanying isotonic sodium chloride solution, 5-10KE is generally injected into a tumor or the marginal area of a tumor once a day or once every several days. However, this product should not be administered by more than one route to the same patient on the same day.

o Lymphangioma

This product is suspended in isotonic sodium chloride solution to prepare 0.05-0.1KE/mL solutions. As a general rule, an amount of suspended solution equal to the amount of aspirated fluid collected from lymphangioma is injected locally. The maximum dosage is 2KE/injection, and the dosage may be adjusted depending on the patient's age and symptoms.

<Precautions Related to DOSAGE AND ADMINISTRATION >

Sensitivity toward this product (including the development of fever) varies from one patient to the next. Therefore, it is advisable to start treatment with a low dose and gradually increase the dose while monitoring the patient's condition, even in the case of "Reduction of cancerous pleural effusion or ascites in patients with gastrointestinal cancer or lung cancer" or "Head and neck cancer (maxillary cancer, laryngeal cancer, pharyngeal cancer, and tongue cancer) and thyroid cancer that are non-responsive to other drugs" above.

PRECAUTIONS

1. Careful Administration (PICIBANIL® should be administered with care in the following patients.)

- (1) Patients with cardiac or renal diseases [Animal toxicology studies showed hemolytic streptococcal infection-like findings (e.g., cardiac and renal impairments, or amyloidosis) after long-term high-dose administration of this product.]
- (2) Patients with a history of hypersensitivity to cephem antibiotics.
- (3) Patients with a personal or familial predisposition to allergic reactions such as bronchial asthma, rash or urticaria.

2. Important Precautions

- (1) Since there is no way to predict exactly the onset of **shock or anaphylactoid symptoms** that may be caused by the product, the following measures should be taken.
 - 1) Patients should be carefully interviewed for their medical history before the administration. Because the product contains benzylpenicillin, it is especially important to confirm whether they have a history of allergy to antibiotic agents, etc.
 - 2) Facilities for emergency care should be available to ensure that patients can be treated immediately after the onset of shock.
 - 3) Patients should be placed at rest and closely monitored from the beginning through the end of the administration. Special caution should be taken immediately after the beginning of the administration.

- 4) When the product is restarted after a drug-free period, it should be carefully administered with a low starting dose.
- (2) Since the product, which consists of live bacteria that cannot grow in any culture media, is to be administered wholly and repeatedly to living bodies, sufficient caution should be taken for adverse reactions.

3. Adverse Reactions

Malignant tumor: 13,092 adverse reactions to this product were reported in 8,312 (31.9%) of 26,027 patients treated. The major adverse reactions were fever with 6,019 events (23.1%), injection site pain with 2,893 events (11.1%), injection site redness (induration, swelling, etc.) with 1,198 events (4.6%), general malaise with 848 events (3.3%), anorexia with 789 events (3.0%), etc. (At the completion of reporting of adverse reaction incidence: March 1982.)

Lymphangioma: 1,049 adverse reactions to this product were reported in 333 (94.6%) of 352 patients treated. The major adverse reactions were fever with 303 events (86.1%), injection site swelling with 279 events (79.3%), injection site redness with 210 events (59.7%), increased CRP with 80 events (22.7%), increased WBC with 64 events (18.2%), injection site pain with 18 events (5.1%), etc. (At end of reexamination, October 2008)

1) Clinically significant adverse reactions

- 1) Shock, anaphylactoid symptoms:** Since shock or anaphylactoid symptoms may occur, patients should be closely monitored. If any abnormalities are observed, the administration of this product should be discontinued and appropriate measures taken.
- 2) Interstitial pneumonia:** Since interstitial pneumonia may occur or may be exacerbated, patients should be closely monitored. If abnormalities such as fever, cough, dyspnea and abnormal chest X-ray findings, are observed, the administration of this product should be discontinued and appropriate measures (e.g., administration of adrenal corticosteroid) taken.
- 3) Acute renal failure:** Since acute renal failure may occur, patients should be closely monitored. If abnormalities such as increased BUN or creatinine, or decreased urinary output are observed, the administration of this product should be discontinued and appropriate measures should be taken.

2) Other adverse reactions

If the following adverse reactions are observed, appropriate measures such as dosage reduction or discontinuation should be taken.

	Incidence unknown	≥5%	<5%
Hypersensitivity ^{*4}	Purpura		Pruritus, rash
Local reactions		Swelling ^{*6} , redness ^{*7} , pain	Induration, feeling of warmth
Hematologic		Increased WBC ^{*8}	Increased platelets, anemia

Hepatic ^{*5}			Increased AST (GOT), increased ALT (GPT), increased ALP
Gastrointestinal			Anorexia, nausea/vomiting, diarrhea
Renal	Increased BUN, increased creatinine, decreased urinary output		Proteinuria
Other		Fever ^{*9} , increased CRP ^{*10}	General malaise, headache, increased CK (CPK), arthralgia

*4: If adverse reactions occur, the administration of this product should be discontinued.

*5: If these abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

*6: 79.3% (lymphangioma)

*7: 59.7% (lymphangioma)

*8: 18.2% (lymphangioma)

*9: 23.1% (malignant tumor), 86.1% (lymphangioma)

*10: 22.7% (lymphangioma)

4. Use in the Elderly

Since the elderly have reduced physiological function, the dosage should be adjusted with care.

5. Use during Pregnancy, Delivery or Lactation

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.]

6. Precautions concerning Use

(1) Precautions regarding preparation

The suspension diluent is supplied in one-point-cut ampules. The cut point of the ampule should be wiped with an alcohol swab before opening.

(2) Precautions regarding administration

1) Intramuscular or subcutaneous administration may cause pain, redness or induration at the injection site. If repeated injection is required, the site of injection should be changed.

2) When administering this product into lymphangiomas, the following cautions should be taken:

- The patient's clinical condition should be carefully monitored after administration because local reactions such as swelling, and occurrence of fever, increased WBC, etc. have been frequently noted.
- The dose should be minimized and the patient carefully observed since post-injection local swelling may cause a compression of the trachea or stridor (especially injection into the neck).

(3) Precaution in intramuscular administration

For intramuscular injection, pay attention to the following in order to avoid the adverse effects of the injection on tissues, nerves, etc:

- 1) Do not inject at innervated sites.
- 2) 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.
- 3) Intramuscular injection to infants and children should be limited to the minimum required.

7. Other Precautions

Delayed shock occurring up to several hours after high-dose administration by intralesional or intracavity injection has been reported.

CLINICAL STUDIES

1. Prolongation of survival time in combination with chemotherapy

1) Gastric cancer (postoperative cases)¹⁾

A randomized comparative study was conducted on 46 patients with gastric cancer who underwent non-curative resection. When compared to the group of patients who only received chemotherapy, the prolongation of survival time was confirmed in the group of patients treated with chemotherapy and intramuscular administration of this product (the initial dosage was 0.2KE, and the dosage was increased to 2KE over a four-week period. Then, 2KE of this product was administered once a week) (figure 1).

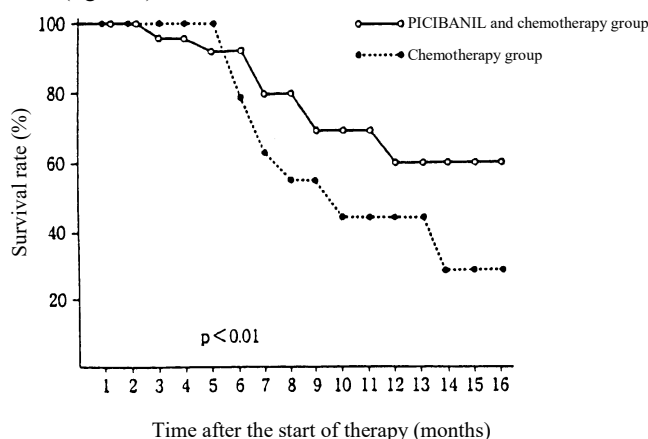


Figure 1. Survival curves for patients with gastric cancer who underwent non-curative resection

2) Primary lung cancer

A randomized comparative study was conducted on 311 patients with operable lung cancer. When compared to the group of patients who only received chemotherapy, the prolongation of survival time was confirmed in the group of patients treated with chemotherapy and intramuscular administration of this product (the initial dosage was 0.2KE, and the dosage was increased gradually to 2KE. The maintenance dosage is 2KE once a week) (figure 2)²⁾.

Also, a randomized comparative study was conducted on 73 patients with inoperable lung cancer. When compared to the group of patients who only received chemotherapy, the prolongation of survival time was confirmed in the group of patients treated with chemotherapy and intramuscular/subcutaneous administration of this product (the initial dosage was 0.2KE, and the dosage was increased gradually. The maintenance dosage was 2KE³⁾.

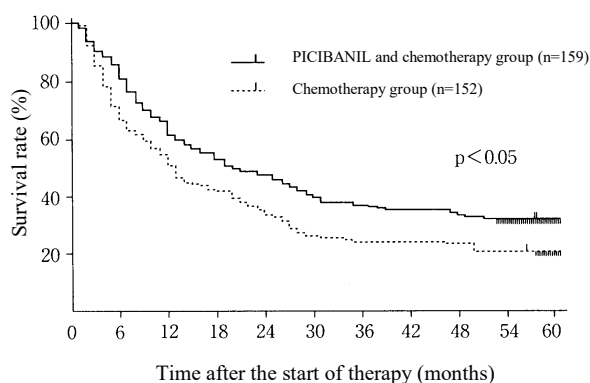


Figure 2. Survival curves for patients with operable lung cancer

2. Reduction of cancerous pleural effusion or ascites

- (1) This product was administered intraperitoneally to 134 patients with ascites caused by the progression or recurrence of gastrointestinal cancer. Ascites disappeared in 76 patients (56.7%) and was reduced in 8 patients (6.0%)⁴⁾.
- (2) This product was administered intrapleurally to 25 patients with pleural effusion caused by the progression of lung cancer with or without chemotherapy. Pleural effusion disappeared in 17 patients (68.0%) and was reduced in 6 patients (24.0%)⁵⁾.

3. Head and neck cancer and thyroid cancer that are non-responsive to other drugs⁶⁾

This product was effective in treating 52 patients with various head and neck cancer and 10 patients with thyroid cancer when 5KE for the initial administration and then 10KE as a maintenance dosage was administered two or three times a week into a tumor or the margin of a tumor.

Cancer	Number of patients assessed	Response rate
Head and neck cancer	52	17.3%
Thyroid cancer	10	20.0%

4. Lymphangioma⁷⁾

This product was effective in treating patients with lymphangioma, when 0.5 KE/10 mL or 1.0 KE/10 mL (maximum 20 mL) was administered locally into lymphangiomas.

Assessment period	Number of patients assessed	Response rate
Two months after administration	53	75.5%

Six months after administration	48	85.4%
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PHARMACOLOGY

1. Effect on experimentally induced tumors

(1) Effect on autologous tumors

In experiments using mice with spontaneously induced tumors⁸⁾ or methylcholanthrene-induced tumors⁹⁾, the intratumor/intramuscular administration of this product suppressed tumorous proliferation.

(2) Effect on isogenic tumors

In experiments using mice¹⁰⁾ and rats¹¹⁾ with isogenic tumors, the intraperitoneal administration of this product prolonged survival time and shrank tumors. Furthermore, in a study using guinea pigs¹²⁾ with isogenic tumors, the intratumor administration of this product shrank tumors.

(3) Effect of PICIBANIL[®] in combination with chemotherapy¹³⁾

The coadministration of this product and fluorouracil (antineoplastic agent) to mice with L1210 tumors prolonged survival time when compared to administration of fluorouracil alone.

2. Mechanism of action

(1) Effect on tumor cells¹⁴⁾

This product has been shown to directly suppress the proliferation of tumor cells.

(2) Effect on biophylaxis

The administration of this product increased neutrophils, macrophages and lymphocytes (humans¹⁵⁾); activated neutrophils (rats¹⁶⁾), macrophages (humans¹⁵⁾) and NK cells (humans¹⁷⁾); and caused the induction of CTL cells (rats¹⁸⁾). Furthermore, the administration of this product induced the production of various cytokines, such as IL-1, IL-2 (mice¹⁹⁾), IL-8 (humans²⁰⁾), IL-12 (mice²¹⁾), IFN- γ (mice²²⁾), TNF- α (humans²⁰⁾), G-CSF (humans²⁰⁾) and GM-CSF (humans²⁰⁾), that are involved in the proliferation and activation of the above-mentioned cells, thus suggesting that the antitumor effect of this product is manifested through various types of host biophylaxis activated by the product.

(3) Mechanism of action in lymphangioma^{23,24)}

The local administration of this product into lymphangioma causes an inflammatory response, which induces the production of cytokines such as TNF (cytokines promote the induction of macrophages, etc., involved in inflammation as well as increasing the permeability of endothelial cells). This series of events accelerates the excretion of lymph, thus reducing the size of lymphatic vascular lumen (humans).

PHYSICOCHEMISTRY

Description:

White to whitish hygroscopic lyophilized powder or solid mass with a slight distinctive odor. When this product is diluted and mixed with

isotonic sodium chloride solution, the resulting solution turns turbid or slightly turbid.

PACKAGING

0.2KE:

Boxes of 5 vials

0.5KE:

Boxes of 5 vials

1KE:

Boxes of 1 and 5 vials

5KE:

Boxes of 1 and 5 vials

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**REQUESTS FOR LITERATURE SHOULD BE
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BRAND NAMES IN OTHER COUNTRIES

Picibanil (Korea, Taiwan, China)