Revised: November 2021 (1st version)

Standard Commodity Classification No. of Japan
877225, 87729

Agent for renal function tests
Agent for identification of sentinel lymph nodes

Indigocarmine injection (JP)

Prescription-only drug Note)

INDIGOCARMINE Injection 20 mg "AFP"

Storage: The product should be stored at room temperature.
Expiration date: 3 years.

Note) Caution: Use only pursuant to the prescription of a physician, etc.

Approval No.	22100AMX01014
Date of initial marketing in Japan	September 1951

2. CONTRAINDICATIONS (Indigocarmine is contraindicated in the following patients.)

Patients with a history of hypersensitivity to any of the components of this drug

3. DESCRIPTION

3.1 Composition

Brand name	Active ingredient	Inactive ingredient
INDIGOCARMINE Injection 20 mg "AFP"	Each ampule (content per 5 mL) contains 20 mg (0.4 w/v%) of indigocarmine (JP).	Glacial acetic acid

3.2 Product Description

Brand name	Description	pH (JP)	Osmotic pressure ratio (ratio to physiological saline solution)
INDIGOCARMINE Injection 20 mg "AFP"	Dark blue solution	3.0 – 5.0	ca. 0.1

4. INDICATIONS

- Renal function tests (measurement by split renal function measurement)
- Identification of sentinel lymph nodes in the following diseases:
  Breast cancer, malignant melanoma

5. PRECAUTIONS CONCERNING INDICATIONS

<Identification of sentinel lymph nodes>

Sentinel lymph node biopsy using this drug should only be conducted in cases in whom it is indicated under the supervision of a physician with sufficient knowledge and experience in this test method. When selecting cases, the latest relevant guidelines, etc. should be referred and careful consideration should be given to the indicated tumor sizes and sites, etc.

6. DOSAGE AND ADMINISTRATION

<Renal function tests>

Usually, following intravenous injection of indigocarmine at 20 to 40 mg (5 to 10 mL), the initial excretion time is measured using a cystoscope.

<Identification of sentinel lymph nodes>

For the identification of sentinel lymph nodes in breast cancer, usually administer up to 20 mg (5 mL) of indigocarmine subcutaneously near the malignant tumor or in the areola, in divided doses as appropriate.
For the identification of sentinel lymph nodes in malignant melanoma, usually administer 4 to 12 mg (1 to 3 mL) of indigocarmine to several intradermal locations near the malignant tumor, in divided doses as appropriate.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

<Identification of sentinel lymph nodes>

It is desirable to use this drug in combination with the radioisotope method whenever possible. In such cases, refer to the package insert of the concomitant drug before use.

8. IMPORTANT PRECAUTIONS

<Common to all indications>

8.1 This drug may cause shock. Indications should be carefully selected, and if this test is necessary for diagnosis, subjects should be instructed to rest until the completion of the test after injection and should be closely monitored during use. [See Sections 9.1.1 and 11.1.1.]

<Renal function tests>

8.2 Subjects should be instructed to rest, in positions such as lateral or sitting position until the completion of the test after injection and should be closely monitored.

<Identification of sentinel lymph nodes>

8.3 When conducting sentinel lymph node biopsy, based on existing information, the necessity and limitations, etc. of this test should be thoroughly explained to the patients or their family, and their consent should be obtained before the conduct.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication or History of Diseases, etc.

9.1.1 Patients with allergic predisposition

[See Sections 8.1 and 11.1.1.]

9.1.2 Patients with hypertension

Symptoms may be exacerbated.

9.5 Pregnant Women

This drug should be used in pregnant or possibly pregnant women only if the expected therapeutic benefits outweigh the possible risks.

9.6 Breast-feeding Women

The expected therapeutic benefits and benefits of breast milk nutrition are considered and continuation or discontinuation of breast-feeding should be reviewed.

9.8 Geriatric Use

This drug should be carefully administered while monitoring patients' conditions. Blood pressure elevation and bradycardia, etc. easily occur.

11. ADVERSE REACTIONS

The following adverse reactions may occur. Patients should be closely monitored and if any abnormal findings are observed, appropriate therapeutic measures such as discontinuation of administration should be taken.

11.1 Clinically Significant Adverse Reactions

11.1.1 Shock (incidence unknown)

[See Sections 8.1 and 9.1.1.]

11.2 Other Adverse Reactions

	Incidence unknown
Hypersensitivity	Rash, etc.
Cardiovascular	Blood pressure elevation, bradycardia
Gastrointestinal	Nausea/vomiting

14. PRECAUTIONS CONCERNING USE

<Renal function tests>

14.1 Precautions for Diagnosis

The initial excretion time in healthy adults is 3 to 5 minutes, and if it is within 10 minutes at the latest, it is not considered dysfunction. In patients with renal dysfunction, the initial excretion time is delayed [1].

(Note) In addition to the initial excretion time of the dye, the time to reach the maximum concentration of the dye in urine (normal: 5 to 7 minutes) and the duration of excretion (normal: 90 minutes) are measured in some cases.

15. OTHER PRECAUTIONS

15.1 Information Based on Clinical Use

In foreign countries, it has been reported that elderly patients with a history of bronchial asthma suffered fatal cardiac arrest.

16. PHARMACOKINETICS

16.1 Blood Concentration

16.1.1 Single dose

Immediately after intravenous injection of this drug at 20 mg to healthy adults, plasma concentration reached a peak, followed by a rapid decline, and plasma concentration was almost undetectable 2 to 3 hours after intravenous injection [2].

16.5 Excretion

The initial urinary excretion time in healthy adults is 3 to 5 minutes after intravenous injection, and the concentration reached the maximum in urine at 5 to 7 minutes [3].

Following intravenous injection of ^{35}S-indigocarmine at 1.4 mg/kg (equivalent to the amount used in renal function tests in humans) to rats, 63% of the dose was excreted in urine by 6 hours. Of this amount, 12% was metabolized as isatin-5-sulfonic acid, 6% as 5-sulfoanthranilic acid, and the remaining 45% as unchanged drug. In bile, about 10% of the dose was detected as unchanged drug at 30 minutes after intravenous injection. However, there was no tendency toward increase thereafter [4].

18. PHARMACOLOGY

18.1 Measurement Method

Indigocarmine is a disodium indigotindisulfonate formed by sulfonating indigo.

In a renal function test using indigocarmine, while observing with a cystoscope, the excretion status of indigocarmine from both ureters is monitored, and the affected kidney is identified.

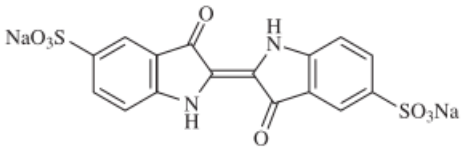
Following injection of this drug into the body, it is rapidly excreted in urine from the kidneys.

In patients with renal dysfunction, excretion of this drug is delayed, and thus, by examining the initial excretion time with a cystoscope after injection, renal function can be estimated. This method can diagnose renal function separately between the left and right kidneys and is suitable for identifying unilateral lesions [1, 5].

19. PHYSICOCHEMISTRY

Nonproprietary name:	Indigocarmine
Chemical name:	Disodium 3,3'-dioxo-[$\Delta^{2,2'}$-biindoline]-5,5'-disulfonate
Molecular formula:	$C_{16}H_8N_2Na_2O_8S_2$
Molecular weight:	466.35

Chemical structural formula:



Description: Indigocarmine occurs as blue to dark blue powder or granules. It is odorless.
It is sparingly soluble in water, and practically insoluble in ethanol (95) or diethyl ether.
It is hygroscopic.
When compressed, it has a coppery luster.

22. PACKAGING

5 mL [10 ampoules (brown)]

23. REFERENCES

1) Inada T. et al.: Sogo-Igaku. 1950; 7 (18): 879-880
2) Ueha T.: The Journal of the Osaka Odontological Society. 1960; 23 (4): 802-813
3) Kosakai N. et al.: Load test. Igaku-Shoin Ltd. 1972; 80
4) Lethco, EJ. et al.: J Pharmacol Exp Ther. 1966; 154 (2): 384-389
5) Thomas, BA. et al.: JAMA. 1917; 69 (21): 1747-1752

24. REFERENCE REQUEST AND CONTACT INFORMATION

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26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Manufactured and Distributed by:

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