

## 1. NAME OF THE MEDICINAL PRODUCT

Indigo carmine Provingo 40 mg/5 mL, solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Indigo carmine (indigotine) ..... 40 mg.  
For 5 mL of solution for injection.

Each mL of solution contains 8 mg of indigo carmine (indigotin).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Blue to bluish-purple solution for injection.

pH : 3.0 to 6.5

Osmolarity : 0,025-0,030 Osmol/L

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Indigo carmine Provingo is indicated in adults for the intra-operative detection of suspected ureteral injuries during abdominal and pelvic surgery.

### 4.2 Posology and method of administration

#### Posology

This medicinal product is to be injected by intravenous route. The recommended initial dosage is 5 mL (1 ampoule) by slow intravenous injection.

A second ampoule of 5 mL may be injected 20 to 30 minutes after the first injection if necessary.

#### *Paediatric population*

The safety and efficacy of Indigo carmine Provingo in children has not been established.

#### *Patients with renal impairment*

Indigo carmine Provingo may be administered in patients with a clearance of creatinine  $\geq 10$  mL/min.

However, Indigo carmine Provingo should not be used in patients with a clearance of creatinine  $< 10$  mL/min (see section 4.4).

#### *Patients with hepatic impairment*

The excretion of indigo carmine is mainly renal. There is no data in patients with hepatic impairment, however no dosage adjustment is necessary.

#### *Elderly*

No adjustment is necessary.

#### Method of administration

Slow intravenous injection under monitoring of arterial pressure and heart rate.

#### *Precautions to be taken before administering this medicine*

Since Provingo indigo carmine is an intense blue color, the use of a filter is recommended at the time of intravenous administration (e.g. a 0.45 µm filter, with a filtration area of at least 2.8 cm<sup>2</sup>, in hydrophilic polyethersulfone membrane).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Special warnings

Indigo carmine may cause a transient elevation of blood pressure and reflex bradycardia especially in patients under general anaesthesia or under spinal anaesthesia. Rare idiosyncratic reactions with bradycardia and hypotension have also been reported. It is therefore necessary to monitor heart rate and blood pressure during and a few minutes after the injection.

Intravenous injection should be stopped if the following symptoms occur: bradycardia, tachycardia, hypotension, hypertension, rash or erythema, respiratory symptoms such as dyspnea or bronchospasm.

In patients with a clearance of creatinine < 10 mL/min, the time to onset of indigo carmine in urines may be delayed for several minutes. Therefore, it should not be used in patients with clearance of creatinine < 10 mL/min.

Indigo carmine may interfere with pulse oxymetric methods.

A discolouration of urine may be observed following administration of indigo carmine.

#### Precautions for use

Indigo carmine should be used with caution in case of:

- concomitant use of medicines inducing bradycardia,
- heart rate and conduction disorders,
- high blood pressure,
- low heart rate,
- coronary disorders due to its peripheral vasoconstrictor effect.

The use of indigo carmine should be avoided in patients with:

- uncontrolled heart failure,
- history of allergic reactions,
- hemodynamic instability.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

There are no or limited amount of data from the use of indigo carmine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Indigo carmine Provingo is not recommended during pregnancy and in women of childbearing potential not using contraception.

### Breast-feeding

It is unknown whether indigo carmine or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from indigo carmine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## 4.7 Effects on ability to drive and use machines

Not applicable.

## 4.8 Undesirable effects

The most common adverse reactions of indigo carmine are mainly related to its alpha-adrenergic activity and are of cardiovascular origin.

Other idiosyncratic reactions such as changes in blood pressure or heart rate or anaphylactoid reactions have also been described. Serious adverse reactions of indigo carmine are very rare.

Adverse reactions are listed below by system organ class and frequency, using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Adverse reaction	Frequency
Cardiac disorders	Hypertension (transient)	Very common
	Bradycardia	Very common
	Tachycardia	Very rare
	Hypotension	Very rare
	Atrioventricular block	Very rare
Respiratory, thoracic and mediastinal disorders	Dyspnea	Very rare
	Bronchial hyperreactivity	Very rare
Skin and subcutaneous tissue disorders	Rash	Very rare
	Erythema	Very rare
	Skin discolouration	Very rare
Immune system disorders	Anaphylactoid reaction	Very rare

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## 4.9 Overdose

No case of overdose has been reported in the literature for doses up to 80 mg of indigo carmine administered intravenously.

### Symptoms

An overdose could induce a hypertensive crisis and severe bradycardia.

### Management

In case of overdose, a peripheral vasodilator therapy may be considered.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: diagnostic agents, Tests for renal function and ureteral injuries , ATC code: V04CH02.

Indigo carmine is a dye clinically used for diagnostic purposes. When it is intravenously administered, it causes dark blue discolouration of urine within 4-9 minutes of injection. This intense coloration enables the detection of any lesions of the urinary tract.

Indigo carmine with its alpha-adrenergic properties triggers an increase of peripheral vascular resistance, resulting in moderate and transient increase of blood pressure and a probably reactional moderate decrease of heart rate.

A meta-analysis of published studies was used to evaluate the diagnostic performance of indigo carmine in the detection of ureteral injury in abdominal and pelvic surgery. This meta-analysis showed that the sensitivity and specificity of the test with indigo carmine were high (respectively 89,2% and 99,7%) as well as the impact on the diagnosis process (positive predictive value of 86,7% and negative predictive value of 99,7% in a population with an incidence of ureteral lesions of 2,3%). The likelihood ratio obtained also allow to confirm that the diagnostic test with indigo carmine is useful to confirm both presence (positive likelihood ratio of 285) or absence (negative likelihood ratio of 0,111) of ureteral injury during abdominal and pelvic surgery.

The safety and efficacy of indigo carmine were as well evaluated in a randomized intra-patient controlled, blind to dose of Indigo carmine Provingo, multi-center study in 118 adult patients undergoing urological or gynecological surgical procedures.

Patients were randomized in a 1:1 ratio to receive 2.5 mL or 5 mL of indigo carmine intravenously prior to the end of the surgical procedure. Each patient underwent cystoscopy and received 5 mL of sodium chloride injection 0.9% followed by the randomized indigo carmine dose for visualization of urinary flow from the ureteral orifices. The 2.5 mL dose is not approved (see section 4.2).

Visualisation of urine efflux was significantly better after injection of indigo carmine (at 5 mL and or 2.5 mL doses) than after injection of saline.

### **5.2 Pharmacokinetic properties**

Indigo carmine is largely reversibly bound to protein plasma after IV injection. It is quickly eliminated from the plasma compartment and it is easily and largely eliminated by the kidney. A small amount is excreted in the bile.

Pharmacokinetic profile of indigo carmine was assessed in pharmacokinetic study in healthy volunteers; in this study indigo carmine plasmatic half-life was 12 minutes.

In case of renal function impairment, the average time of excretion can be extended for several minutes.

### **5.3 Preclinical safety data**

Acute toxicity data for indigo carmine are available from rat and mouse studies. In rats, the LD50 (median lethal single dose) is 93 mg/kg by intravenous route while in mice the LD50 is 405 mg/kg by subcutaneous route.

No carcinogenicity study has been conducted by intravenous route with indigotin (indigo carmine). However, long-term studies in rats (oral) and mice (subcutaneous) have not revealed any carcinogenic effects.

In oral dosing studies performed in rats and rabbits, doses of indigo carmine up to 250 mg/kg/day did not produce any teratogenic effects. However oral availability is approximately 3%, so the risk of intravenous administration of indigo carmine during pregnancy cannot be evaluated from the data available.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Water for injections.

Citric acid monohydrate (for pH adjustment).

Sodium citrate (for pH adjustment).

### **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

5 years.

After opening : From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

### **6.4 Special precautions for storage**

Do not refrigerate or freeze.

### **6.5 Nature and contents of container**

5 mL type I brown glass ampoules. Pack of 5 ampoules.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

PROVEPHARM SAS  
22, Rue Marc Donadille  
13013 Marseille  
France

## **8. MARKETING AUTHORISATION NUMBER(S)**

xxxxx/xxxx

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY}

**10. DATE OF REVISION OF THE TEXT**

05/09/2025