SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Blumyne 40 mg/5 mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 8 mg of indigo carmine (indigotin).
Each 5 mL ampoule contains 40 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 : 25-30 mOsmol/L

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Blumyne is indicated 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 1 ampoule of 5 mL by slow intravenous injection.
A second ampoule may be injected 20 to 30 minutes after the first injection if necessary.

Paediatric population

The safety and efficacy of Blumyne in children has not been established (see section 4.4).

Patients with renal impairment

Blumyne may be administered in patients with a clearance of creatinine ≥ 10 mL/min.

However, Blumyne 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 the medicinal product.
Considering the dark blue colour of Blumyne, filtration is recommended during intravenous administration (for example, a filter of 0.45 µm, with a filtering surface of at least 2.8 cm^2, composed of a 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.

Paediatric population
The efficacy and safety of Blumyne in children has not been established.

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 Blumyne 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 suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to abstain from indigo carmine administration 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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, 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 Blumyne were as well evaluated in a randomized intra-patient controlled, blind to dose of Blumyne, 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 Blumyne 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 Blumyne dose for visualization of urinary flow from the ureteral orifices. The 2.5 mL dose is not approved (see section 6.5).
Both 5 mL and 2.5 mL dose indigo carmine injections were statistically significantly superior versus saline injection in providing visualization of urine efflux. Exploratory analyses showed no statistically significant difference between the 2 doses of indigo carmine in all efficacy variables. Indigo carmine was safe and well tolerated. No adverse events were assessed as related to indigo carmine.

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 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

3 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
22, Rue Marc Donadille
13013 Marseille
France

8. MARKETING AUTHORISATION NUMBER(S)

PL 40051/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01/03/2024
Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

10/07/2024