

**AUSTRALIAN PRODUCT INFORMATION**  
**BILISCPIN® FOR INFUSION (Meglumine iotroxate)**

**1 NAME OF THE MEDICINE**

Meglumine iotroxate

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 1 mL Biliscopin for infusion contains 0.105 g meglumine iotroxate.

For the full list of excipients, see Section 6.1 List of excipients.

**3 PHARMACEUTICAL FORM**

Biliscopin for infusion is a radiocontrast medium for cholangiography and cholecystography.

**4 CLINICAL PARTICULARS**

**4.1 THERAPEUTIC INDICATIONS**

Biliscopin for infusion is indicated for radiological examination of the hepatic and biliary ducts and gallbladder when examination by oral technique is unsuccessful or inappropriate.

**4.2 DOSE AND METHOD OF ADMINISTRATION**

General information

Contrast media should not be used in case of occurrence of particulate matter or defective container. The infusion bottle should not be attached to the infusion set until immediately before the examination. Contrast medium solution not used in one examination session must be discarded.

Dietary suggestions

In cholegraphy the diagnostic yield can be increased by ensuring that the bowels are empty of faecal matter and gas by avoiding stimulation of the gall bladder. Patients should therefore be put on a minimum, low-residue, non-gas forming diet 24 hours before the examination. Easily digestible foods and clear liquids, e.g. tea without milk, fruit juice or clear fat-free soup can be given. The patient should not be given eggs, rusks, fruit, pulpy goods, paste or milk products. If a laxative is prescribed, it should be taken about 20 hours before the examination.

Patient should fast on the day of the examination, which is best carried out in the morning. After administration of Biliscopin for infusion, the patient should not eat or smoke until the examination is complete, but is allowed to drink water or weak tea if thirsty.

Hydration

Adequate hydration must be assured before and after contrast medium administration. Disorders of the water and electrolyte balance must be corrected before the examination.

Anxiety

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions. These patients may be given a sedative.

Pre-testing

Sensitivity testing using a small test dose of contrast medium is not recommended as it has no predictive value. Furthermore, sensitivity testing itself has occasionally led to serious and even fatal hypersensitivity reactions.

## Dosage

One bottle (100 mL) of Biliscopin for infusion (1 mL=20 drops).

Infusion time	Rate of infusion
30 mins	1 drop/1sec
45 mins	1 drop/1½ secs
60 mins	1 drop/2 secs

Note: The probability of adverse reactions increases with increasing doses, and, therefore, the minimum dose consistent with diagnostic need should be used.

Infusion time: not less than 30 minutes, the tolerance will increase with longer infusion times.

The infusion should always be started at a low rate and then increased to the final, higher rate after 3- 5 minutes. This technique reduces heterotopic excretion and improves the tolerance.

## Administration of the contrast medium

Biliscopin for infusion is administered with the patient lying down.

It is advisable to keep the patient under observation at least between the end of administration and the taking of films.

Warming the infusion bottle to body temperature helps eliminate the sensation of cold which is sometimes experienced by sensitive patients at the start of the infusion.

The duration of administration should never be less than the values given under "Dosage", since the tolerance will otherwise be reduced. It is therefore advisable to choose a longer time, particularly as this is often accompanied by a better diagnostic yield.

## Exposure times

With Biliscopin for infusion optimal visualisation depends, amongst other factors, on the duration of infusion.

Infusion time	Exposure time after end of infusion
30 mins	30 - 90 mins
45 mins	30 - 75 mins
60 mins	15 - 60 mins

Contrast delineation which cannot be detected using the normal technique can frequently be detected by tomography or zonography.

## Testing the gallbladder reflex

For testing the reflex of the gallbladder, the best time to take the picture is about 30-45 minutes after the fatty meal. If the pictures are taken at about 30 minutes, they will be optimal for the common bile duct because the gallbladder starts to empty at this time; if taken at about 45 minutes, the gallbladder can be visualised in its state of maximum contraction.

## Tissue tolerance to paravasation

Inadvertent paravenous administration of Biliscopin for infusion can cause pain, but experience has shown that it is not followed by serious tissue reactions. Field block with a local anaesthetic helps to relieve the pain. For more extensive paravasation, it is recommended that a hyaluronidase preparation be injected into the affected area to hasten absorption.

### 4.3 CONTRAINDICATIONS

Severe cardiovascular insufficiency, particularly right ventricular failure or cardiac decompensation, hypersensitivity to iodine-containing contrast media, thyrotoxicosis, severe functional disturbance of the liver or of the kidneys, monoclonal IgM gammopathy, e.g. macroglobulinaemia (Waldenstrom's disease), myelomatosis, Dubin-Johnson syndrome. Children below 14 years. Pregnancy (see Section 4.6 Fertility, Pregnancy and Lactation below).

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### Hydration

Adequate hydration must be assured before and after contrast medium administration. Disorders of the water and electrolyte balance must be corrected before the examination.

#### Hypersensitivity

Occasionally, allergy-like hypersensitivity reactions have been observed after use of X-ray contrast media such as Biliscopin (see Section 4.8 Adverse Effects). These reactions are usually manifest as non-serious respiratory or cutaneous symptoms, as mild respiratory distress, reddening of the skin (erythema), urticaria, itching or facial oedema. Serious events such as angioedema, subglottic oedema, bronchospasm and allergic shock are possible. Generally these reactions occur within one hour after administration of contrast media. However, in rare cases delayed reactions may occur (after hours to days).

Patients with hypersensitivity or a previous reaction to iodinated contrast media are at increased risk of having a severe reaction.

Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to iodine or to radiographic media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions and premedication with antihistamines and/or glucocorticoids may be considered.

Patients with bronchial asthma are at special risk of having bronchospasms or a hypersensitivity reaction.

There is an increased risk of severe reactions in individuals with heart failure and coronary artery disease.

Hypersensitivity reactions can be aggravated in patients on beta-blockers, particularly in people with bronchial asthma. Moreover, it should be considered that patients on beta-blockers may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.

If hypersensitivity reactions occur (see Section 4.8 Adverse Effects), administration of the contrast medium must be discontinued immediately and - if necessary - specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for intravenous contrast medium administration. To permit immediate countermeasures to be taken in emergencies, appropriate drugs, an endotracheal tube and a respirator should be ready at hand.

#### Individual hypersensitivity

With Biliscopin for infusion, as with any contrast medium, the possibility that there are some patients who will prove hypersensitive to the substance must be considered. If marked side effects or suspected allergic reactions occur during infusion, and do not disappear or even get worse when the infusion is briefly interrupted, it is probable that the patient has such a hypersensitivity and the investigation must be abandoned. However, the cannula should be

left in the blood vessel for some time in order to maintain access for therapeutic measures. Even relatively minor symptoms such as itching of the skin, sneezing, violent yawns, tickling in the throat, hoarseness, or attacks of coughing may be early signs of a severe reaction (including shock) and therefore merit careful attention.

### Thyroid dysfunction

The small amount of free inorganic iodide from iodinated contrast media might interfere with thyroid function. Therefore, the need for examination merits particularly careful consideration in patients with latent hyperthyroidism or goiter.

Since iodine-containing contrast agents may alter the results of thyroid function tests, such tests, if indicated, should be performed prior to the administration of this preparation. The capacity of the thyroid tissue to take up iodine will be reduced for about eight to ten weeks or more by iodinated biliary X-ray contrast media.

Patients with hyperthyroidism are at risk (although not at acute risk) in the period following administration of intravenous cholegraphic agents, because the high protein-affinity of these agents may also affect proteins of the thyroid gland and hence exacerbate the disease.

In neonates, especially preterm infants, who have been exposed to Biliscopin, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function, as an exposure to excess iodine may cause hypothyroidism, possibly requiring treatment.

### Renal failure

Temporary renal failure may occur in very rare cases. Preventive measures against acute renal failure following contrast medium administration include:

Identification of high-risk patients, e.g. patients with: a history of renal disease, pre-existing renal insufficiency, previous renal failure after contrast medium administration, diabetes mellitus with nephropathy, volume depletion, multiple myeloma, age greater than 60 years, advanced vascular disease, paraproteinemia, severe and chronic hypertension, gout, patients receiving large or repeated doses.

Most cholecystographic agents exert a uricosuric effect and thereby an increased risk of renal damage in hyperuricaemic patients.

In the presence of severe advanced liver disease a greater amount of Biliscopin may be diverted to the kidneys for excretion. In such patients renal function should be assessed before and a few days after cholecystography.

### **Use in hepatic impairment**

In case of impaired hepatic function, the risk of renal failure is increased if the recommended dosages and infusion times are not considered.

Administration of urographic agents should be postponed in patients with known or suspected hepatic or biliary disease who have recently undergone cholecystography.

### Metformin therapy

The use of renally or partially renally excreted intravascular X-ray contrast media can lead to transient impairment of kidney function. This may result in lactic acidosis in patients taking biguanides.

As a precaution, biguanides should be stopped 48 hours before until at least 48 hours after contrast medium administration and reinstated only after normal renal function has been regained.

### Phaeochromocytoma

Patients with pheochromocytoma may develop a severe (occasionally uncontrollable) hypertensive crisis following intravascular contrast medium use. Premedication with alpha-receptor blockers is recommended.

The administration of radio-opaque materials to patients known or suspected of having phaeochromocytoma should only take place when the physician deems that the possible benefits outweigh the considered risks and then only with extreme caution while keeping the volume of drug to an absolute minimum. Blood pressure should be assessed throughout the procedure and measures for treating hypertensive crises should be readily available.

### Anxiety

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium related reactions. These patients may be given a sedative.

### Very poor state of health

The need for examination merits particularly careful consideration in patients with a very poor general state of health. Contrast media have been shown to promote the phenomenon of sickling in individuals who are homozygous for sickle-cell disease.

X-ray examination with contrast media should be employed in severely ill patients, or in patients whose general condition is very poor, only if considered absolutely necessary. Special caution is required in patients with marked hypertension.

This also applies to patients with an allergic disposition, e.g. bronchial asthma, since experience has shown that these patients are prone to exhibit hypersensitivity reactions to drugs.

Some radiologists give an antihistamine or corticoid prophylactically in these cases. However, because of the possibility of precipitation, contrast medium and prophylactic agents must not be administered as a mixed solution. Particular caution should be exercised in allergic patients who had previously tolerated injectable iodine-containing contrast media without any complication, since they may have become sensitized to these substances in the meantime.

The possibility of thrombosis or other complications due to mechanical trauma of the intravenous procedure should be borne in mind.

Although not an absolute contraindication to use, any history of sensitivity to iodine *per se* or to any contrast agent, calls for extreme caution in administration.

The recommended dose of Biliscopin should not be exceeded.

Serious and even fatal reactions have been associated with the administration of radio-opaque media. It is of the utmost importance that a course of action be planned in advance for the immediate treatment of serious reactions and that adequate and appropriate facilities be available to deal with these.

Caution should be exercised in patients with coronary artery disease. Blood pressure should be monitored following administration of Biliscopin to these patients.

The use of intravenous biliary contrast media in patients with monoclonal IgM gammopathy, e.g. macroglobulinaemia (Waldenstrom's disease), leads to gelatinous changes in the blood which can have serious consequences.

It is theoretically conceivable, if not yet confirmed by relevant reports, that the risks attending *i.v* cholegraphy are increased in multiple myeloma. The decision to perform *i.v* cholegraphy in the presence of multiple myeloma should therefore only be made after very careful consideration of the circumstances.

### **Paediatric use**

Safety and effectiveness in children below the age of 14 years has not been established.

In neonates, especially preterm infants, who have been exposed to Biliscopin, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function, as an exposure to excess iodine may cause hypothyroidism, possibly requiring treatment. See also Section 4.4 Special Warnings and Precautions for Use, subsection 'Thyroid dysfunction'.

### **Use in the elderly**

No data available

### **Effects on laboratory tests**

#### Interference with diagnostic tests

Thyroid function can increase for some time after the examination with biliary contrast media.

The capacity of the thyroid gland to take up iodine will be reduced for about 8-10 weeks by iodinated biliary X-ray contrast media.

The drug may interfere with some chemical determinations made on urine specimens; therefore urine specimens should be collected before administration of the drug or two or three days afterwards.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

- Concomitant administration of pethidine may produce spasms of the sphincter of Oddi.
- Adverse reactions are believed to be more common in women taking oral contraceptives. Antihistamines or corticoids should not be administered for prophylaxis as a mixed injection, as precipitation may occur.
- Hypersensitivity reactions can be aggravated in patients on beta-blockers.
- The prevalence of delayed reactions (eg fever, rash, flu-like symptoms, joint pain and pruritus) to contrast media is higher in patients who have received interleukin.
- Diabetic nephropathy may predispose to renal impairment following intravascular contrast medium administration. This may precipitate lactic acidosis in patients who are taking biguanides. As a precaution, biguanides should be stopped 48 hours prior to the contrast medium examination and reinstated only after adequate renal function has been regained.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

No data available.

### **Use in pregnancy**

X-ray examinations should if possible be avoided during pregnancy. Safety for use in pregnancy in humans has not been established. Biliscopin is embryotoxic in rabbits.

Most authorities consider elective contrast radiography of the abdomen contraindicated during pregnancy. Biliscopin for infusion may be used in pregnant women only if in the judgement of the treating clinician such use is deemed essential to the patient's welfare

and the expected benefits outweigh any potential risks to the patient or the fetus.

Caution should be exercised when using Biliscopin in pregnant women. See also Section 4.4 Special Warnings and Precautions for Use, subsection 'Thyroid dysfunction', and Paediatric Use.

### **Use in lactation**

It is not known whether Biliscopin is excreted in milk; most cholecystographic media are so excreted. In the newborn they can cause significant hyperbilirubinaemia, specifically during the first eight weeks of life. Alternative arrangements for feeding the infant should, therefore, be made. See also Section 4.4 Special Warnings and Precautions for Use, subsection 'Thyroid dysfunction', and Paediatric Use.

## **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

As with all iodinated contrast media, in rare cases there is a possibility of delayed reactions following contrast medium administration that could impair the ability to drive and use machines.

## **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

In order to give an approximate indication of incidence the following definitions apply when the words "common", "uncommon" and "rare" appear in the text:

- common: incidence  $\geq$  1: 100
- uncommon: incidence  $<$  1: 100, but  $\geq$  1: 1000
- rare: incidence  $<$  1: 1000, but  $\geq$  1: 10000
- very rare: incidence  $<$  1: 10000

Side effects in association with the use of iodinated intravascular contrast media are usually mild to moderate and transient in nature. However, severe and life-threatening reactions as well as deaths have been reported.

### Anaphylactoid reactions/hypersensitivity

Violent yawns, tickling in the throat, hoarseness, asthma, oedema of the glottis and swollen eyelids. Angioedema, conjunctivitis, coughing, pruritus, rhinitis, sneezing and urticaria have been reported commonly. These reactions, which can occur irrespective of the amount administered and the mode of administration, may be the first signs of incipient state of shock. Severe reactions can occur in the form of a circulatory reaction accompanied by peripheral vasodilatation and subsequent hypotension, reflex tachycardia, dyspnoea, agitation, confusion and cyanosis possibly leading to unconsciousness and shock. Administration of the contrast medium must be discontinued immediately and - if necessary - specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for the administration of the contrast medium. To permit immediate countermeasures to be taken in emergencies, appropriate drugs, an endotracheal tube and a ventilator should be ready to hand. (See Section 4.4 Special Warnings and Precautions for Use).

Effects on the liver and kidneys are dose-related and may take some days to manifest themselves. In view of the above possibility, special caution must be exercised in patients with pre-existing hepatic or renal disease.

Delayed contrast medium reactions are rare.

### Cardiovascular disorders

Ventricular fibrillation and collapse. Clinically relevant transient disturbance in heart rate, blood pressure, cardiac rhythm or function and cardiac arrest are uncommon.

### Cerebrovascular disorders

Even state epilepticus. Transient neurological complications such as: dizziness, headache, agitation or confusion, amnesia, disturbed speech, vision, and hearing; convulsions, tremor, photophobia, coma, and somnolence are uncommon.

### Respiratory disorders

Transient disturbance in respiratory rate, dyspnoea, respiratory distress and coughing are common. Bronchospasm and laryngeal spasm occur uncommonly.

Respiratory arrest and pulmonary oedema are very rare reactions.

### Gastrointestinal disorders

Nausea, vomiting and abdominal pain are common reactions.

Diarrhoea occurs very rarely.

### Hepato-biliary disorders

A transient elevation of liver values in blood serum (e.g. ALT (GPT), AST (GOT), GGT, LDH, ALP, bilirubin) may occur especially in patients with pre-existing hepato-biliary disorders.

### Skin disorders

Itching of the skin, angioedema, flush, erythema, urticaria, pruritus and exanthema have been commonly observed.

### Renal disorders

Temporary renal failure may occur in very rare cases.

### General disorders and administration site conditions

Restlessness, flushing, salivation, and pressure in the upper abdomen. A general feeling of warmth and headache have been reported as being common. Malaise, chills or sweating and vasovagal reactions are rare.

In very rare cases alterations in body temperature are possible.

Extravasation of Biliscopin gives rise to local pain and oedema, and in rare cases also to more severe tissue reactions.

### Toxic effects on liver or kidneys

Rises in liver function tests, jaundice, pale stools, dark urine, centrilobular necrosis of the liver, azotaemia, casts in the urine, uricosuria.

### Other reactions

Precipitation of Bence-Jones protein (myelomatosis patients), acute pancreatitis, precipitation of proteins associated with Waldenstrom's disease.

## **Adverse drug reactions from post-marketing spontaneous reports**

### Endocrine disorders

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported with unknown frequency following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism.



## **Life-threatening reactions**

These may be:

Circulatory insufficiency and collapse, ventricular fibrillation, asthma, fever, blanching, weakness, gagging and a feeling of suffocation, gasping, itching, other kinds of skin eruption, oedema, and lacrimation.

The greater the infusion rate of Biliscopin for infusion, the higher is the incidence of commonplace side effects, such as unpleasant sensations of taste, nausea, vomiting, erythema, a sensation of pain or sensations of heat. These side effects are rare if the recommended rate of administration is adhered to. If they do occur they can usually be ameliorated quite rapidly by reducing the rate of infusion still further or by allowing a brief pause in the procedure. Too rapid an administration may put the patient's life at risk - particularly if he has previous manifest or latent cardiovascular damage or if his general condition is poor.

### **Reporting Suspected Adverse Effects**

Reporting suspected adverse reactions after registration 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 at <http://www.tga.gov.au/reporting-problems>.

## **4.9 OVERDOSE**

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: iodinated X-ray contrast media.

ATC code: V08AC02

#### **Mechanism of action**

No data available

#### **Clinical trials**

No data available

### **5.2 PHARMACOKINETIC PROPERTIES**

#### **Distribution**

*In vitro* meglumine iotroxate binds to plasma proteins to the extent of 60-90% depending on concentration.

#### **Excretion**

Following intravenous administration Biliscopin is rapidly excreted, mainly by the liver into the bile. Visualisation of the hepatic and common bile ducts and the gallbladder can, therefore, be achieved. Visualisation of the biliary ducts is usually possible 30-60 minutes after completion of administration.

### **5.3 PRECLINICAL SAFETY DATA**

In animals it crosses the placental barrier.

#### ***Genotoxicity***

No data available

#### ***Carcinogenicity***

No data available

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Biliscopin for infusion contains sodium calciumedetate, sodium bicarbonate and sodium chloride in aqueous solution.

### **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

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Infusion bottle of 100 mL containing 105 mg of iotroxate meglumine/mL, boxed to protect from light and X-rays.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

Infusion bottle of 100 mL

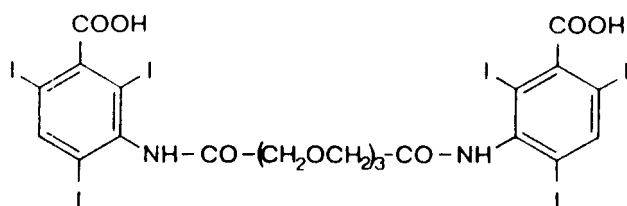
### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

### **6.7 PHYSICOCHEMICAL PROPERTIES**

Each 1 mL Biliscopin for infusion contains 0.105 g meglumine iotroxate (3,3'-(3,6,9-trioxaundecanedioyl-diimino) -bis-(2,4,6-triiodobenzoic acid), N-methylglucamine salt) along with small amounts of sodium calciumedetate, sodium bicarbonate and sodium chloride in aqueous solution. The solution is clear, colourless to faintly yellowish and odourless. It should be protected from light.

## Chemical structure



## Physico-chemical properties

Molecular formula C<sub>22</sub>H<sub>18</sub>I<sub>6</sub>N<sub>2</sub>O<sub>9</sub>

Molecular weight 1215.83

Iodine content per bottle of 100 mL: 5g

Iodine concentration: 5% w/v

Meglumine iotroxate content per bottle of 100 mL: 10.5g

Meglumine iotroxate concentration: 10.5% w/v

Osmotic pressure at 37°C: 0.69-0.77 mPa

## CAS number

CAS No. 72704-51-9

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

## 8 SPONSOR

Bayer Australia Ltd  
ABN 22 000 138 714  
875 Pacific Highway  
PYMBLE NSW 2073

[www.bayer.com.au](http://www.bayer.com.au)

## 9 DATE OF FIRST APPROVAL

July 1995

## 10 DATE OF REVISION

14 June 2018

### Summary table of changes

<b>Section changed</b>	<b>Summary of new information</b>
All sections	Reformatted into the SmPC format.
4.4	Addition of warning to monitor thyroid function as excess iodine may cause neonatal hypothyroidism.
4.6	Addition of a Use in paediatrics section to include a recommendation to monitor thyroid function, as an exposure to excess iodine may cause hypothyroidism.
4.8	Addition of details of reports of adverse drug reactions indicative of hypothyroidism following iodinated contrast media administration.
6.2	Addition of instruction that this medicinal product should not be mixed with other medicinal products.
6.3	Addition of the registered shelf life.