PRODUCT MONOGRAPH

# OCTALBIN 5%

Albumin (Human), 50 mg/ml
Solution for Infusion
Prescription Medication

ATC code: B05AA01

Manufactured by:

Octapharma Pharmazeutika Produktionsges m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Manufactured for:

Octapharma Canada, Inc.
308-214 King St W
Toronto, ON M5H 3S6
Canada

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**OCTALBIN 5%**

Albumin (Human) 5%

# PART I: HEALTH PROFESSIONAL INFORMATION

## SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Intravenous infusion | Solution for Infusion<br>Each mL contains 50 mg protein, of which ≥ 96% is human albumin | Sodium, Potassium, N-acetyl-DL-tryptophan, Caprylic acid, Aluminium, Water for injections<br><br>*For a complete listing see* DOSAGE FORMS, COMPOSITION AND PACKAGING *section.* |

## DESCRIPTION

Octalbin 5% is a sterile, liquid preparation of albumin derived from large pools of human plasma. All units of human plasma used in the manufacture of Octalbin 5% is obtained from collection centres that are inspected by national health authorities and audited by Octapharma.
The product is manufactured by the cold ethanol fractionation process followed by ultra- and diafiltration. The manufacturing process includes final container pasteurisation and an additional bulk pasteurisation at 60 ± 0.5°C for 10 – 11 hours. The Octalbin 5% manufacturing process provides a significant viral reduction in *in vitro* studies. These reductions are achieved through a combination of process steps including cold ethanol fractionation and final container pasteurisation.

Octalbin 5% contains no preservative. Octalbin 5% is a clear, slightly viscous liquid; it is almost colorless or slightly yellow or green.

## INDICATIONS AND CLINICAL USE

Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.

The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, according to current therapeutic recommendations.

## CONTRAINDICATIONS

Hypersensitivity to albumin preparations or to any of the excipients.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**
This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering to the patient (see Warnings – General).

### General

Standard measure to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extreme remote risk for transmission of viral diseases. A theoretical transmission of Creutzfeldt-Jakob Disease (CJD), including variant Creutzfeldt-Jakob Disease (vCJD), also is considered remote. No cases of transmission of viral diseases or CJD, including vCJD, have ever been identified for albumin.

Albumin manufactured to European Pharmacopoeia specifications by established processes has a reassuring viral safety record.

The physician should discuss the risks and benefits of the product with the patient, before prescribing or administering to the patient.

If allergic or anaphylactic-type reactions occur, the infusion should be stopped immediately and appropriate treatment instituted. In case of shock, the current medical standards for shock-treatment should be observed.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. In the interest of the patient, it is recommended that, whenever possible, every time that Octalbin 5% (Albumin (Human) 5%) is administered to them, the name and batch number of the product is recorded.

Albumin solutions must not be used in patients at high risk of developing circulatory overload (e.g. congestive cardiac failure, renal insufficiency) or severe deficiency of oxygen carrying capacity (severe anemia).

Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Examples of such conditions are:

- Decompensated cardiac insufficiency
- Hypertension
- Oesophageal varices
- Pulmonary oedema
- Haemorrhagic diathesis
- Severe anaemia
- Renal and post-renal anuria

Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patients circulatory situation. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately.

20-25% Human albumin solutions are relatively low in electrolytes compared to the 4-5% human albumin solutions. When albumin is given, the electrolyte status of the patient should be monitored (see section **DOSAGE AND ADMINISTRATION**) and appropriate steps taken to restore or maintain the electrolyte balance.

If comparatively large volumes are to be replaced, controls of coagulation and haematocrit are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).

**Special Populations**

**Pregnant Women:**
The safety of Octalbin 5% for use in human pregnancy has not been established in controlled clinical trials. While it isn't known if it can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, it should be given to a pregnant woman only if clearly needed.

No animal reproduction studies have been conducted with Octalbin 5%. However, human albumin is a normal constituent of human blood.

**Nursing Women:**
See Pregnant Women above.

**Geriatrics (> 65 years of age):**
No subgroup analysis was performed and therefore no safety or tolerability data regarding a geriatric population can be presented.

**Pediatrics (< 12 years of age):**
Data on the use of Octalbin 5% in children including premature babies are very limited. The

product should only be administered to these individuals if the likely benefits clearly outweigh potential risks.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Adverse reactions for Octalbin 5% are rare. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. In case of severe reactions, the infusion should be stopped and an appropriate treatment should be initiated.

### Clinical Trial Adverse Drug Reactions

Not applicable.

### Less Common Clinical Trial Adverse Drug Reactions (<1%)

Not applicable.

### Abnormal Hematological and Clinical Chemistry Findings

There were no particular issues raised for any laboratory parameters in any of the published studies.

### Post-Market Adverse Drug Reactions

The following adverse reactions have been observed for human albumin during the post-marketing phase. Therefore, these reactions can also be expected for Octalbin 5%.

| System Organ Class | Rare (>1/10,000, <1/1,000) | Very rare (<1/10,000) |
|---|---|---|
| | | |
| *Immune system disorders* | hypersensitivity | anaphylactic shock |
| | | |
| *Psychiatric disorders* | | confusional state |
| | | |
| *Nervous system disorders* | | headache |
| | | |
| *Cardiac disorders* | | tachycardia<br>bradycardia |
| | | |
| *Vascular disorders* | hypotension | hypertension<br>flushing |
| | | |
| *Respiratory, thoracic and mediastinal disorders* | | dyspnoea |
| | | |
| *Gastrointestinal disorders* | | nausea |
| | | |

| System Organ Class | Rare (>1/10,000, <1/1,000) | Very rare (<1/10,000) |
|---|---|---|
| | | |
| *Skin and subcutaneous tissue disorders* | | urticaria<br>angioneurotic edema<br>rash erythematous<br>hyperhidrosis |
| | | |
| *General disorders and administration site conditions* | | pyrexia<br>chills |

## DRUG INTERACTIONS

### Overview
No specific interactions of human albumin with other medicinal products are known.

Human albumin solution must not be mixed with other medicinal products, whole blood and packed red cells.

### Drug-Food Interactions
Interactions with food have not been established.

### Drug-Herb Interactions
Interactions with herbal products have not been established.

### Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

### Drug-Lifestyle Interactions
No effects on ability to drive and use machines have been observed.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations
Human albumin should always be directly administered by the intravenous route.
The concentration of the albumin preparation, dosage and the infusion-rate should be adjusted to the patient's individual requirements.

**Recommended Dose and Dosage Adjustment**

The dose required depends on the size of the patient, the severity of trauma or illness and on continuing fluid and protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required.

If human albumin is to be administered, haemodynamic performance should be monitored regularly; this may include:

-- arterial blood pressure and pulse rate
-- central venous pressure
-- pulmonary artery wedge pressure
-- urine output
-- electrolyte
-- haematocrit/haemoglobin

This product is suitable for premature infants and dialysis patients [1].
The infusion rate should be adjusted according to the individual circumstances and the indication, but should normally not exceed 1 to 2 ml/minute.
In plasma exchange the infusion rate may be higher and should be adjusted to the rate of removal.

**Missed Dose**

Not applicable because Octalbin is administered in a hospital setting by health care professionals.

**Administration**

The solution can be directly administered by the intravenous route.
The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits. This may indicate that the protein is unstable or that the solution has become contaminated.
Once the infusion container has been opened the content should be used immediately. Any unused solution should be disposed of in accordance with local requirements.
Do not use after expiry date given on the label.

**Incompatibilities**

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients. The product should be warmed to room or body temperature before use.

**OVERDOSAGE**

Hypervolaemia may occur if the dosage and rate of infusion are too high. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised central venous pressure and pulmonary oedema, the infusion should be stopped immediately and the patient´s haemodynamic parameters carefully monitored.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Albumin is the predominant product of hepatic protein synthesis and one of the more abundant plasma proteins. Among its multiple physiologic roles that include binding and transport of molecules, free radical scavenging, inhibition of platelet function and antithrombotic effects, and effects on the capillary membrane permeability, human albumin plays an essential part in the generation of colloid-oncotic pressure.

### Pharmacodynamics

Pharmacotherapeutic group: plasma substitutes and plasma protein fractions, ATC code: B05AA01.
Human albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity of the liver.
Physiochemical data:
Human albumin 5% is a mildly hypooncotic solution.
The most important physiological functions of human albumin result from its contribution to oncotic pressure of the blood and transport function. Albumin stabilises circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins.

### Pharmacokinetics

Under normal conditions the total exchangeable albumin pool is 4-5 g/kg body weight of which 40-45% is present intravascularly and 55-60% in the extravascular space. Increased capillary permeability will alter albumin kinetics and abnormal distribution may occur in conditions such as severe burns or septic shock.

Under normal conditions, the average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feed-back regulation. Elimination is predominantly intracellular and due to lysosome proteases.

In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

## STORAGE AND STABILITY

Special precautions for storage:

Store and transport at +2 °C to +25 °C.
Store in the original container in order to protect from light.

Do not use after expiry date.
Do not freeze.
Keep out of the reach of children!

## SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room or body temperature before use.
Do not use non-homogenous solutions, or those which have a deposit.
Solutions which have been frozen should not be used.
Do not begin administration more than four hours after the container has been entered. Partially used vials must be discarded.
Vials which are cracked or have been previously entered or damaged should not be used, as this may have allowed the entry of microorganisms.
The 5% solution contains no preservative.
Any unused product or waste material should be disposed of in accordance with local requirements.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Solution for infusion

Octalbin 5% is human albumin from human plasma source.
Octalbin 5% is a mildly hypooncotic pasteurized solution for intravenous use. It is a clear or slightly opalescent solution containing 5% of protein of which at least 96% is human albumin. Each 100 ml contains 5g of human albumin.

1000 ml solution contain:

| | | |
|---|---|---|
| Sodium | 142.5-157.5 | mmol |
| Potassium | max. 1.0 | mmol |
| N-acetyl-DL-tryptophan | max. 4.2 | mmol |
| Caprylic acid | max. 4.2 | mmol |
| Aluminium | max. 200 | µg |
| Water for injections | ad 1000 | ml |

**Nature and contents of container**
Glass bottles are made of glass quality type II (Ph.Eur.) and are closed with bromobutyl rubber stoppers quality type I (Ph.Eur.).

Package sizes:
Single pack:
1 infusion bottle with 100 ml
1 infusion bottle with 250 ml
1 infusion bottle with 500 ml

Multiple pack:
10 x 1 infusion bottle with 100 ml
6 x 1 infusion bottle with 250 ml
6 x 1 infusion bottle with 500 ml

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

| | |
|---|---|
| Proper name: | Octalbin 5% |
| Chemical name: | Human Albumin |
| Molecular formula and molecular mass: | not applicable |
| Structural formula: | not applicable |
| Physicochemical properties: | Human serum albumin (HSA) is a monomeric protein, made up only of amino acids without prosthetic or carbohydrate groups. Albumin has a high percentage of ionic amino acids, glutamic acid and lysine, which confer a relatively high solubility to the protein. |

### Product Characteristics

Octalbin 5% is a solution containing plasma proteins in a concentration of 50 g/l with a content of human albumin of at least 96%. Octapharma has manufactured human albumin since 1990 according to the cold ethanol fractionation method.

### Viral Inactivation

The plasma used for the manufacture of Octalbin is obtained from collection centres that are inspected by national health authorities and audited by Octapharma.

The product is manufactured by the cold ethanol fractionation process followed by ultra- and diafiltration. The manufacturing process includes final container pasteurisation and an additional bulk pasteurisation at 60 ± 0.5°C for 10 – 11 hours. The Octalbin 5% manufacturing process provides a significant viral reduction in in vitro studies. These reductions are achieved through a combination of process steps including cold ethanol fractionation and final container pasteurisation.

## CLINICAL TRIALS

Not applicable.

## DETAILED PHARMACOLOGY

Albumin is a protein of 584 amino acids. It is highly soluble and has a strong negative charge. Several variants in the amino acid sequence, alloalbumins, coexist with normal albumin. Albumin makes up half the normal intravascular protein mass and is responsible for 75%-80% of the plasma colloid osmotic pressure.

In a healthy person, 9-12 grams of albumin are synthesized in the liver per day. The rate of synthesis is controlled primarily by changes in the colloid osmotic pressure and the osmolality of the extravascular space. Insulin, thyroxin, and cortical also stimulate the production of albumin; however, growth hormone has no significant effect on albumin synthesis. Importantly, in severe protein malnutrition, the production of albumin may be decreased.

Albumin is a predominantly extravascular protein with a total extravascular mass of approximately 160 grams, despite a lower interstitial concentration compared with serum concentration. The serum concentration of albumin is about 4 grams/dL in normal individuals and the total intravascular mass is about 120 grams. Under normal circumstances, the albumin concentration in the interstitial space is half that in the intravascular space. The half-life of albumin is 17-19 days.

The catabolism of albumin takes place mainly in the vascular endothelium at a rate of 9-12 grams per day, or 4% of total body albumin. The rate of albumin degradation is related to its concentration. Calorie and protein deprivation also accelerate albumin catabolism. Serum levels of albumin may fall during periods of stress, trauma, or sepsis despite its long half-life. The drop may result from accelerated redistribution from the intravascular space, decreased synthesis, and increased catabolism. Injury and infection result in a decrease of serum albumin level of approximately 1-1.5 grams/dL within 3-7 days.

Under normal circumstances, albumin circulates from the intravascular space across the capillary wall into the interstitial compartment, and returns to the intravascular space through the lymphatic system. Albumin has a circulation half-life of approximately 16 hours. The movement of albumin across the capillary walls can be measured as the transcapillary escape rate (TER), which is defined as the percentage of intravascular albumin leaving the intravascular compartment per hour. In healthy volunteers, TER is around 4%-5%. The TER is determined by the capillary and interstitial free albumin concentrations, the capillary permeability to albumin, solvent and solute movements and, to a lesser degree, the electrical charge across the capillary wall.

Clearance of proteins from the interstitium is dependent upon the lymphatic flow, which in healthy individuals is around 120 mL/h, with a protein content of about 80% of plasma. The flow of lymph itself is dependent upon interstitial fluid pressure, intrinsic pumping by the lymphatic vessels and external compression of vessels by muscle contraction, arterial pulsation, and body movement.

The distribution of exogenous albumin between body compartments has been examined by the injection of radiolabeled albumin. Over the first 2 days, there is a rapid phase of disappearance from the plasma that correlates with the transcapillary exchange rate of 4.5% per hour. The distribution half-time is about 15 hours. Then there is a slower decay of about 3.7% per day with an elimination half time of about 19 days.

The major physiologic functions of albumin are:

- Binding and transport of molecules
- Colloid osmotic pressure effect
- Free radical scavenging
- Inhibition of platelet function and antithrombotic effects
- Capillary membrane permeability

## TOXICOLOGY

Albumin is a normal constituent of the human organism. In animals, single dose toxicity testing is of no relevance, since the high doses required would result in Albumin overload. Repeated dose toxicity testing, and embryo-fetal toxicity studies with albumin preparations are impracticable due to the induction of, and the interference with antibodies. Effects of the preparation on the immune system of new-born animals have not been studied.

Since the clinical experience does not provide any evidence of tumorigenic or mutagenic effects of Albumin, experimental studies, particularly in heterologous species, are not considered to be necessary.

## REFERENCES

1. CPMP (Committee for Proprietary Medicinal Products), Core SPC for Human Albumin, CPMP/PhVWP/BPWG/2231/99, (2000)

**PART III: CONSUMER INFORMATION**

**OCTALBIN 5%**
Albumin (Human) 5%

This leaflet is part III of a three-part "Product Monograph" published when Octalbin 5% was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Octalbin 5%. Contact your doctor or pharmacist if you have any questions about the drug.

## ABOUT THIS MEDICATION

What the medication is used for:
The product is given to patients to restore and maintain circulating blood volume where a deficiency in volume has been demonstrated.

What it does:
The main task of albumin is the maintenance of the colloidal osmotic (= oncotic) pressure. This type of pressure arises from the ability of albumin to bind to water. The presence of albumin in the plasma ensures that the liquid remains within the vessels and does not diffuse into the tissue.

Albumin is also a transport protein. It binds substances produced by the body, such as hormones or fatty acids as well as drugs such as penicillin, and transports them around the body.

Albumin also acts as a kind of protein reserve. If the body requires building blocks for the repair of large wounds or in inflammations, albumin can be broken down, and the breakdown products can be used as building blocks for other proteins.

When it should not be used:
Octalbin 5% should not be used if you are hypersensitive to albumin preparations or any of the other ingredients of the product

What the medicinal ingredient is:
Human albumin from human plasma source

What the important nonmedicinal ingredients are:
Sodium, Potassium, N-acetyl-DL-tryptophan, Caprylic acid, Aluminium, Water for injections

*For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.*

What dosage forms it comes in:
Solution for infusion

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**
This product is made from human plasma, which may contain infectious agents, such as viruses that cause hepatitis and other viral diseases. Your doctor should discuss the risks and benefits of this product with you before giving you this product.

BEFORE you use Octalbin 5% talk to your doctor or pharmacist:

- If you are allergic to the active substance or to any of the nonmedicinal ingredients.

## INTERACTIONS WITH THIS MEDICATION

No interactions of human albumin with other products are known so far. However, Octalbin 5% solution should not be mixed in the same injection with other drugs, whole blood or packed red cells.

## PROPER USE OF THIS MEDICATION

Usual dose:
As dosage and treatment duration depend on your clinical situation, your physician will decide on your treatment on an individual basis.

Overdose:
If the dosage and rate of infusion are too high, you may develop headache, high blood pressure and discomfort breathing. The infusion should be stopped immediately and your doctor will decide if any other treatment is necessary.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Not applicable because Octalbin is administered in a hospital setting by health care professionals.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| rare | hypotension | | | X |
| very rare | headache | X | | |
| | tachycardia<br>bradycardia | | | X |

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| | hypertension | | | X |
| | flushing | | | X |
| | dyspnoea | | | X |
| | nausea | X | | |
| | urticaria | | | X |
| | angioneurotic edema | | | X |
| | rash erythematous | | | X |
| | hyperhidrosis | X | | |
| | fever | | | X |
| | chills | | | X |

*This is not a complete list of side effects. For any unexpected effects while taking Octalbin, contact your doctor or pharmacist.*

## HOW TO STORE IT

Store and transport at +2 °C to +25 °C.
Store in the original container in order to protect from light.
Do not use after expiry date. Do not freeze.
Keep out of the reach of children!

## REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

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- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.octapharma.ca
or by contacting Octapharma Canada Inc.,
at: 1-888-438-0488

This leaflet was prepared by Octapharma Pharmazeutika Produktionsges.m.b.H

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