WO 2008/153582 A1 discloses a concentrate esmolol formulation, which comprises the active substance at a concentration of 50 mg/mL and a buffering agent, like sodium acetate and acetic acid. Such concentrate is usually diluted before infusion, so to minimize adverse reactions, like local skin irritation at the site of infusion.

"ESMOCARO LYO 2500 mg powder for concentrate for solution for infusion", 7 September 2010, pages 1-13 (URL: http://db.cbg_meb.nl/mri/spc/nih-0779-003.pdf) and "PACKAGE LEAFLET: INFORMATION FOR THE USER: ESMOCARO LYO", 9 November 2010, pages 1-8 (URL: http://db.cbg_meb.nl/mri/pil/nih-0779-003.pdf) describe an esmolol Lyo wherein the final formulation has a concentration of 10 mg/mL.

While it would be desirable to administer high concentrations of esmolol hydrochloride to shorten the treatment time, there is the risk of infusion site reactions including inflammation and induration, like edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation phlebitis, which side effects are commonly minimized by administering the diluted formulation.

Typically a 2500 mg/10 mL concentrate for solution for infusion is provided for further dilution to obtain a 100 mg/10 mL solution for injection.

WO 2009/079679 A2 describes a storage-stable Esmolol HCl solution comprising cyclodextrin as pharmaceutical solubilizer to ease the dilution of a concentrate.

ESMOCARD LYO (Orpha-Devel Handels und Vertriebs GmbH, Austria) comprises esmolol hydrochloride in the lyophilized form. It is provded as a 2500 mg powder for concentrate for solution for infusion. The reconstituted concentrate contains 50 mg/mL, is further diluted to a concentration of 10 mg/mL.

It is the object of the invention to provide a concentrated i.v. solution of esmolol hydrochloride that can be safely used for the treatment of tachycardic patients.

SUMMARY

The object is solved by the subject matter as claimed.

According to the present disclosure, there is provided a parenteral formulation of esmolol hydrochloride for use in the treatment of a patient suffering from tachycardia

comprising a lyophilized powder consisting of pure esmolol hydrochloride, wherein said powder is reconstituted to obtain a ready-to-use i.v. solution of esmolol hydrochloride at a concentration of 20-100 mg/mL, and said i.v. solution is directly administered to the patient.

In one aspect of the present disclosure, there is provided a use of a parenteral formulation of esmolol hydrochloride in the manufacture of a medicament for the treatment of a patient suffering from tachycardia comprising a ready-to-use i.v. solution of esmolol hydrochloride at a concentration of 20-100 mg/ml, which is reconstituted from a lyophilized powder consisting of at least 95% purity esmolol hydrochloride with a solvent, and wherein said solvent is an i.v. solvent devoid of alcohol or a buffer excipient, selected from the group consisting of water for injection (WFI), glucose solution, glucose and saline solution, and saline solution, and said i.v. solution is to be directly administered to the patient.

Specifically said powder is reconstituted in an i.v. solvent devoid of alcohol or a buffer excipient. For example, said powder is reconstituted in an aqueous i.v. solvent selected from the group consisting of water for injection (WFI), glucose solution, glucose and Ringer solution, glucose and saline solution, saline solution, Ringer Lactate solution or Ringer Lactate and saline solution.

According to a specific embodiment said powder is reconstituted to obtain an iso-osmotic i.v. solution.

Preferably, said i.v. solution has a pH of 4.5 to 5.0.

Specifically, said powder, comprising e.g. at least 100, at least 250, or at least 2500 mg esmolol hydrochloride, is easily reconstituted with at least 5 mL, or at least 10 mL, alternatively at least 50 mL, in some cases at least 100 mL, at least 250 mL or at least 500 mL, with the i.v. solvent. The reconstitution time at room temperature usually is short, which is a great advantage for the clinician. Depending on the concentration, the i.v. solvent and means for reconstitution, the reconstitution time typically is within 15 seconds up to 5 minutes. As an example, the lyophilized powder containing 2500 mg esmolol hydrochloride is reconstituted in 50 mL WFI within less than 1 min, typically less than 30 sec, in most cases immediately, i.e. within 15 seconds by slight agitation at room temperature.

It is preferred that said esmolol hydrochloride concentration is at least 50 mg/mL.

Said i.v. solution is specifically administered as infusion or continuous infusion.

In particular, said i.v. solution is administered as maintenance infusion, e.g. at a dose of at least 25 µg/kg/min, optionally following an initial infusion, e.g. at a dose of at least 300 µg/kg/min. A start with the maintenance infusion is also possible.

Said initial infusion may specifically be at a dose of at least 300 µg/kg/min, preferably more than 300 µg/kg/min, such as at least 400 or at least 500 µg/kg/min.

Said maintenance infusion may specifically be at a dose of at least 25 µg/kg/min, preferably at least 50 µg/kg/min, or at least 100 µg/kg/min, such as at least 200, at least 300, typically within the range of 100 to 300, in some cases up to 500 µg/kg/min.

For the short-term treatment, e.g. the initial infusion the infusion time typically is less than 60 min, in some cases longer, such as less than 120 min or less than 180 min.

The maintenance dose of said i.v. solution is typically administered during a longer period of time, such as an infusion time of at least 60 min, or at least 2h, 3h, 4h, 5h or 6h, in some cases at least 12 or at least 24 hours.

In specific cases the high dose short-term treatment is preferred in cases of blood pressure lowering during aortic dissection or for controlled hypotension to avoid blood loss in ear/ nose/ throat surgery.

The i.v. solution according to the present disclosure may be advantageously administered intraveneously to patients who could be given only small volumina. Specifically treatment of patients suffering also from cardiac decompensation and/or hyperhydratation and/or renal decompensation and/or hypernatremia and/or hyperchloramic acidosis and/or hyperhydratation is possible.

Said i.v. solution specifically is local tissue tolerant at the infusion site. In particular, it is administered to a patient in a way not causing venous irritation or skin necrosis. Therefore, the specific use of the formulation according to the present disclosure is for preventing local venous irritation or skin necrosis at the infusion site.

According to a specific embodiment, a patient is treated according to the present disclosure, who is

a. suffering from any of acute tachycardia selected from supraventricular tachycardia, ventricular tachycardia or hypertension and non-compensatory sinus tachycardia, atrial fibrillation, atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate is desirable, or

b. in need of blood pressure lowering during aortic dissection or for controlled hypotension to avoid blood loss in ear/ nose/ throat surgery or for diagnostic purposes.

According to the present disclosure, there is further provided a method of producing a ready-to-use i.v. solution of esmolol hydrochloride by reconstituting a lyophilized powder consisting of pure esmolol hydrochloride with a solvent, characterized in that said solvent is an i.v. solvent devoid of alcohol or a buffer excipient, in an amount necessary to obtain a ready-to-use i.v. solution at a concentration of 20-100 mg/mL.

According to the present disclosure, there is also provided a ready-to-use i.v. solution containing a parenteral formulation of 20-100 mg/mL pure esmolol

hydrochloride in an infusion device. Said i.v. solution is specifically ready-to-use without further dilution.

According to the present disclosure, there is also provided a ready-to-use i.v. solution comprising or consisting of a parenteral formulation of 20-100 mg/mL pure esmolol hydrochloride, WFI and/or saline solution, specifically a formulation devoid of any alcohol or further excipients, such as buffer excipients.

Specifically, the i.v. solution is consisting of pure esmolol hydrochloride, WFI and optionally saline.

According to the present disclosure, there is further provided a kit or set of parts for preparing a parenteral formulation according to the present disclosure, comprising the components

a) a lyophilized powder consisting of pure esmolol hydrochloride, and

b) WFI or saline solution.

Component a) specifically comprises 2500 mg of the powder contained in a 50 mL vial.

The kit optionally further comprises an infusion device suitable for i.v. administration.

DETAILED DESCRIPTION OF THE INVENTION

Specific terms as used throughout the specification have the following meaning.

The term "i.v. solution" as used herein shall mean an aqueous solution suitable for direct administration into the venous circulation of a subject, employing an infusion device, e.g. via a syringe or intravenous catheter or tube. The i.v. solution according to the invention may be freshly prepared by reconstituting the lyophilized powder, or else prepared well before its administration to the subject, specifically when it is storage stable as determined by suitable stability studies.

An iso-osmotic i.v. solution is understood as a solution containing the same concentration of particles and thus exerting equal osmotic pressure as blood. For example, a 0.9 % solution of NaCl (Normal Saline) is iso-osmotic with blood. Further examples are 5 % glucose, Ringer solution or Ringer lactate solution.

An i.v. solvent is herein understood as a water-miscible solvent for intravenous injection. By using a suitable aqueous medium or carrier as an i.v. solvent, the respective i.v. solution of the active ingredient esomolol hydrochloride is suitably prepared according to the present invention. Suitable i.v. solvents are e.g. water for

CLAIMS

1. Use of a parenteral formulation of esmolol hydrochloride in the manufacture of a medicament for the treatment of a patient suffering from tachycardia comprising a ready-to-use i.v. solution of esmolol hydrochloride at a concentration of 20-100 mg/ml, which is reconstituted from a lyophilized powder consisting of at least 95% purity esmolol hydrochloride with a solvent, and wherein said solvent is an i.v. solvent devoid of alcohol or a buffer excipient, selected from the group consisting of water for injection (WFI), glucose solution, glucose and saline solution, and saline solution, and said i.v. solution is to be directly administered to the patient.

2. The use according to claim 1, wherein said i.v. solution has a pH of 4.5 to 5.0.

3. The use according to claim 1 or 2, wherein said esmolol hydrochloride concentration is at least 50 mg/mL.

4. The use according to any of claims 1 to 3, wherein said i.v. solution is to be administered as continuous infusion.

5. The use according to any of claims 1 to 4, wherein said i.v. solution is to be administered as maintenance infusion at a dose of at least 25 µg/kg/min, optionally following an initial infusion at a dose of at least 300 µg/kg/min.

6. The use according to any of claims 1 to 5, wherein said i.v. solution is local tissue tolerant at the infusion site, preventing local venous irritation or skin necrosis at the infusion site.

7. The use according to any of claims 1 to 6, wherein said patient is

a. suffering from any of acute tachycardia selected from supraventricular tachycardia, ventricular tachycardia or hypertension and non-compensatory sinus

16. The use according to any of claims 1 to 7, wherein said patient is having renal decompensation and any of hypernatremia, hyperchloramic acidosis, cardiac decompensation or hyperhydration.

17. The use according to any of claims 1 to 7, wherein said patient is having renal decompensation, hypernatremia and any of hyperchloramic acidosis, cardiac decompensation or hyperhydration.

18. The use according to any of claims 1 to 7, wherein said patient is having hyperchloramic acidosis and any of cardiac decompensation, hyperhydration, renal decompensation or hypernatremia.