Product Information

Lyfaquin®
लाइफाक्विन

℞Centhaquine Citrate Injection 1.0 mg

Lyophilized injection for intravenous infusion

1. Generic Name
Centhaquine citrate

2. Qualitative and quantitative composition
Each 10 mL vial contains:
Centhaquine citrate……...1.0 mg
Excipients……..q.s.

3. Dosage form and strength
Sterile Intravenous Injection (Lyophilized)
Centhaquine citrate 1.0 mg to be reconstituted in 10 mL of Sodium Chloride Injection I.P. (0.9% w/v).

4. Clinical particulars
4.1 Therapeutic indication
Hypovolemic Shock: **LYFAQUIN®** is indicated as a resuscitative agent for the treatment of patients with hypovolemic shock as an adjuvant to standard of care.

4.2 Posology and method of administration
Posology
LYFAQUIN® should be administered at a dose of 0.01 mg/kg body weight as an intravenous infusion over 1 hour in 100 mL normal saline.

Method of Preparation:
Dissolve the content of the vial in 10 mL of Sodium Chloride Injection I.P. (0.9% w/v). Gently swirl the content of the vial. Do not shake vigorously to avoid foaming. When reconstituted as directed, each vial contains a sterile solution equivalent to 0.1 mg of centhaquine citrate per mL (1.0 mg/10 mL). The reconstituted centhaquine solution (depending on body weight) should be added to normal saline to make up final volume of 100 mL. For example, for a 50 kg patient, 5 mL of reconstituted centhaquine solution should be added to 95 mL normal saline to make 100 mL of final volume.

Table 1: Preparation of reconstituted solution

Body weight of patient (kg)	LYFAQUIN® dose per vial (mg)	Reconstituted with 10 mL Sodium Chloride Injection I.P. (0.9% w/v) (mL)	Reconstituted volume taken from vial as per body weight (mL)	Volume of normal saline added to make up final volume of 100 mL (mL)
40	1	10	4	96
50	1	10	5	95
60	1	10	6	94
70	1	10	7	93
80	1	10	8	92
90	1	10	9	91

100	1	10	10	90

Method of Administration:

LYFAQUIN® should be administered at a dose of 0.01 mg/kg body weight as an intravenous infusion over 1 hour in 100 mL normal saline. The next dose of **LYFAQUIN®** should be administered if systolic blood pressure falls below or remains below 90 mmHg, but not before 4 hours of previous dose and total number of doses per day should not exceed 3. **LYFAQUIN®** administration, if needed, may continue for two days subject to a maximum of 6 doses within the first 48 hrs of treatment. The administration of **LYFAQUIN®** in more than 6 doses has not been studied during its clinical development, therefore use of more than 6 doses of **LYFAQUIN®** is not recommended.

Table 2: Highlights of LYFAQUIN® dose and administration

Dose	0.01 mg/kg body weight
Reconstitution solution	Sodium Chloride Injection I.P. (0.9% w/v)
Intravenous infusion rate	100 mL in 1 hour
Dosing interval	Minimum 4 hours. The time gap (end time of previous dose and start time of next dose) between two consecutive doses at least should be minimum 4 hours. For example, if end time of **LYFAQUIN®** intravenous infusion in a patient is 14:00 hours and patient required another dose of **LYFAQUIN®**, then next dose of **LYFAQUIN®** should not be administered before 18:00 hours.
Total doses in a day	3 doses **LYFAQUIN®** should not be administered more than 3 doses in a day (24 hours).
Maximum doses	6 doses **LYFAQUIN®** should not be administered more than 6 doses in 2 days (48 hours).

4.3 Contraindications

Hypersensitivity to centhaquine or to any of the excipients listed in section 2.

4.4 Special warnings and precautions for use

Hepatic failure, renal failure and decompensated heart failure: **LYFAQUIN®** should be administered with precautions in hepatic failure, renal failure and decompensated heart failure patient as safety and efficacy of **LYFAQUIN®** in hepatic failure, renal failure and decompensated heart failure has not been established.

4.5 Drugs interactions

None: No drug-drug interaction or drug-food interaction was observed during clinical development phase.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy: Animal reproduction studies have not shown any congenital anomaly in foetus and found to be safe during pregnancy. The safety and efficacy of **LYFAQUIN®** in pregnancy have not been established.

Lactating women: It is not known whether **LYFAQUIN®** is present in human milk. No data are available on the effects of **LYFAQUIN®** on breastfed child or the effects on milk production. The safety and efficacy of **LYFAQUIN®** in lactating women have not been established.

Paediatric patients: The safety and efficacy of **LYFAQUIN®** in paediatric patients have not been established.
Geriatric patients: In clinical studies a total of 15 subjects were aged 65 years and older. There was no drug related adverse event reported in any subject indicating that **LYFAQUIN®** can be safely administered in geriatric population.

4.7 Effects on ability to drive and use machines

None: No effect on ability to drive and use machines was observed during clinical development phase.

4.8 Undesirable effects

Clinical trial experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Phase I study

The adverse reactions reported are hypotension, high lactic acid in one subject dosed with a highest dose (0.15 mg/kg), and drowsiness, dry mouth and fall in respiratory rate in one subject dosed with 0.1 mg/kg dose. These events were mild in severity and resolved without any intervention and sequelae.

Phase II study

No Adverse/Serious Adverse Event related to **LYFAQUIN®** were observed during the conduct of phase II study.

Phase III study

The safety of **LYFAQUIN®** was evaluated in phase III study [see *Warnings and Precautions*].

Table 3: Adverse drug events observed in patients treated with LYFAQUIN® and normal saline.

Adverse events	LYFAQUIN® (N=71)	Normal saline (N=34)
Blood creatinine increased	2 (2.8%)	-
Vomiting	1 (1.4%)	-

The adverse events were not related to **LYFAQUIN®**. Patients in phase II and III study were in critically ill condition and received several medications including blood products and vasopressors in addition to **LYFAQUIN®** or normal saline as part of resuscitation protocol.

4.9 Overdose

At significantly higher (10 times or more) dose, the symptoms of hypotension, drowsiness, dry mouth and fall in respiratory rate can occur. Also, increased blood lactate levels may be observed, therefore necessitating close monitoring and supportive care. Treatment of overdose should be symptomatic. Effects are expected to be brief as the half-life of **LYFAQUIN®** is short i.e. 0.71-1.62 hours and no accumulation has been reported.

5. Pharmacological properties

5.1 Mechanism of Action

Centhaquine increases blood pressure and cardiac output by augmenting venous blood return to the heart (alpha-2_B adrenergic stimulation) and enhances tissue blood perfusion by arterial dilatation (sympatholytic due to central alpha-2_A adrenergic stimulation). Enhancing tissue blood perfusion is a significant advantage in reducing the volume of resuscitation and preventing extravasation of

fluid and adverse effect of lung oedema. Centhaquine does not act on beta-adrenergic receptors, and therefore the risk of arrhythmias is mitigated.

5.2 Pharmacodynamic properties

A multi-centric, randomized, double-blind, parallel, saline controlled phase III clinical study was conducted in 105 patients of hypovolemic shock (CTRI/2019/01/017196; NCT04045327). Considering efficacy and safety of centhaquine in phase II clinical studies, patients were randomized in 2:1 ratio into centhaquine and control groups, respectively after meeting the eligibility criteria. Primary objectives of the study were to determine number of patients with change in systolic and diastolic blood pressure, mean through 48 hours; change in blood lactate, mean through 48 hours; change in base-deficit, mean through 48 hours. Some of the key secondary endpoints included the following: proportion of patients with all-cause mortality at 48 hours and 28 days; change in multiple organ dysfunction syndrome score (MODS), mean through day 28; change in acute respiratory distress syndrome (ARDS), mean through day 28. A total of 197 patients were assessed, out of which 105 patients were enrolled in the study and 92 patients did not meet the eligibility criteria and were excluded. Out of 105 patients 71 were randomized in centhaquine cohort and 34 in saline cohort. In centhaquine cohort 1 patient withdrew consent and 2 patients were excluded by the investigator. A total of 34 patients in control and 68 patients in centhaquine group completed the study. Patient demographics were comparable and age, body weight, height and body mass index were similar in both groups.

Table 4: Summary of Demographics

Patient Demographics (Mean ± SEM)					
Group	Gender	Age (Years)	Body Weight (Kg)	Height (Cm)	BMI (Kg/m^2)
Standard Treatment + Saline (N=34)	(22M/12F)	36.50±2.81	56.74±1.62	162.35±1.60	21.56±0.59
Standard Treatment + Centhaquine (N=68)	(41M/27F)	42.93±2.31	58.90±1.37	161.31±1.46	22.72±0.51

Standard of care was provided to all patients. In both centhaquine and control groups haemoglobin levels, haematocrit, hospital stay, time in intensive care unit, time on ventilator were similar. Proportion of MODS patients with ≥60% of hospital stay in ICU were 35.48% in centhaquine compared to 53.33% in control. The amount of vasopressors, fluids and blood products infused were similar in centhaquine and control groups. Urine output in 48 hours of resuscitation was similar in both centhaquine and control groups.

Table 5: Efficacy Data on Primary Endpoints

End Points	Results (% patients)	Significance
Systolic Blood Pressure ≥110 mmHg at 24 hours	Control: 59.38% Centhaquine: 81.82%	P=0.0084
Diastolic Blood Pressure ≥70 mmHg at 24 hours	Control: 50.00% Centhaquine: 78.46%	P=0.0022
Blood Lactate of ≤1.5	Control: 46.88% Centhaquine: 69.35%	P=0.0168
Base-Deficit of <-2.0	Control: 46.88% Centhaquine: 68.25%	P=0.0217

Mortality	Control: 11.76% Centhaquine: 2.94%	P=0.0371

Acute Respiratory Distress Syndrome (ARDS) was compared between day 1 (before resuscitation) and day 3 of resuscitation. In control patients receiving standard treatment the difference between means was 0.04839 ± 0.05696 (P=0.4023). On the other hand, in centhaquine treated group the ARDS difference between means was 0.1065 ± 0.04464 (P=0.0202). These results indicate that centhaquine treatment significantly improved ARDS following resuscitation, whereas in control group there was insignificant improvement. Multiple Organ Dysfunction Score (MODS) was compared between day 3 and day 7 of resuscitation. There was no improvement in MODS in the control group and the difference between means was 0.00 ± 0.2697 (P>0.999), whereas in centhaquine group the difference between means was 0.9091 ± 0.1964 (P=0.0001). Centhaquine treatment significantly decreased MODS whereas in control the improvement was not significant. In 105 patient phase III study, a significant reduction in 28-day mortality was observed in centhaquine group compared to control group with standard of care (P=0.0371).

Table 6: Efficacy Data on Key Secondary Endpoint: Incidence of all-cause mortality at 28 days

Chi-square, df	3.188, 1
Odds ratio	4.400
P value	0.0371
Percentage Control (mortality)	11.76%
Percentage Centhaquine (mortality)	2.94%

In conclusion, an improvement in all the primary endpoints of blood pressure, lactate levels and base-deficit were statistically significant in patients receiving centhaquine compared to standard of care. Centhaquine significantly improved acute respiratory distress syndrome (ARDS) and multiple organ dysfunction score (MODS). A total of 155 patients with hypovolemic shock have been studied (combined phase II and III). Centhaquine reduced the mortality from 9.68% in patients receiving standard treatment to 2.15% in patients that received centhaquine (odds ratio 4.875; 95% CI 1.162-24.18; P=0.0190).

5.3 Pharmacokinetic properties

Pharmacokinetics in Rats: Pharmacokinetics of centhaquine was studied in rats at an intravenous bolus dose of 0.45 mg/kg. A non-compartmental analysis using the Bayesian posteriors showed the median (IQR) *Ke* of 8.8 (5.2–12.8) h^{-1}. Additionally, the volume of distribution (*V*) was estimated to be relatively large (median: 6.4 L; IQR: 2.8–10.4 L). In the model, drug left the central compartment (median: 11.9 h^{-1}; IQR 4.6–15.0) quicker than it re-entered (median: 3.7 h^{-1}; IQR 2.3–9.1). The median (IQR) predicted terminal half-life was short [0.6 (0.35–1.0) h], rapid time to maximum concentration, and the median (IQR) population predicted volume of distribution at steady state was high [17.6 (13.0–31.0) L]. The AUC, $AUC_{(0\text{-}inf)}$, C_{max}, T_{max}, Cl, V_{dss} and T_{half} were 3.0 ng/mL*h, 3.0 ng/mL*h, 14.8 ng/mL, 0.017 h, 35.2 L/h, 17.6 L and 0.55 h, respectively.

Pharmacokinetics in Humans: Single dose administration: Centhaquine showed the C_{max} of 0.59 ng/mL to 30.64 ng/mL; T_{max} of 0.08 h to 0.17 h; $T_{1/2}$ of 0.71 h to 1.62 h when administered intravenously with dose range of 0.005 mg/kg to 0.1 mg/kg. Multiple doses administration: Centhaquine when administered intravenously in multiple dose of 0.033 mg/kg, every 8 hourly for 02 days showed the C_{max} of 8.891 ng/mL and 7.973 ng/mL, reached within 5 mins of administration

of first and last dose. For 0.067 mg/kg dose, the C_{max} of 10.472 ng/mL and 13.019 ng/mL was reached within 5 mins of administration of first and last dose.
Pharmacokinetics at therapeutic dose: At the therapeutic dose of 0.01 mg/kg in hypovolemic shock, centhaquine showed the C_{max} of 2.5605 ng/mL reached in about 5 min, mean plasma clearance was 0.0043 mL/hr/kg and mean volume of distribution was 0.0084 mL/kg. Centhaquine was eliminated with a mean half-life of about 1.6234 h. The mean AUC $_{(0\text{-}8)}$, AUC all and AUC $_{(0\text{-}inf)}$ were 2.099, 2.5905 and 2.8735, respectively.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Single intravenous injection of centhaquine citrate in mice, rats and rabbits showed LD_{50} >100 mg/kg, 79.43 mg/kg and 9.55 mg/kg, respectively. The NOAEL of centhaquine citrate in mice, rats, rabbits and dogs was found to be at the dose of 1.0 mg/kg (100 times higher than the therapeutic dose). Centhaquine did not produce any effect on male fertility of rats when administered by intravenous route at and up to 1.0 mg/kg body weight. Centhaquine did not produce any teratogenic effects in developmental toxicity studies in animals. Centhaquine did not cause any genetic toxicity and is not a mutagen. Centhaquine citrate causes no skin sensitization and is non-mutagenic and was well tolerated by pregnant rats. Toxicological studies indicate its high safety margin.

7. Description

LYFAQUIN® injection is a sterile preparation of centhaquine citrate intended for intravenous use. The product is available as 10 mL amber tubular glass vial. It is soluble in Sodium Chloride Injection I.P. (0.9% w/v). It is a resuscitative agent indicated for the treatment of patients with hypovolemic shock as a frontline adjuvant to standard of care. Each vial of **LYFAQUIN®** contains 1.0 mg of centhaquine citrate. The active ingredient centhaquine citrate is white crystalline powder with empirical formula $C_{28}H_{33}N_3O_7$ and molecular weight of 523.58. The chemical name of centhaquine citrate is, 2-[2-[4-(3-Methylphenyl)-1-piperazinyl]ethyl] quinoline citrate. The structural formula of centhaquine citrate (Figure 1).

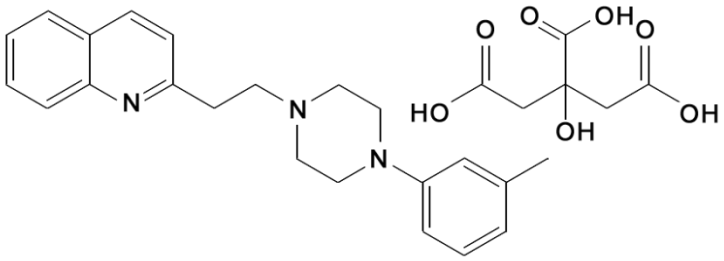

Figure 1: Structure of **LYFAQUIN®** (Centhaquine citrate)

8. Pharmaceutical particulars

8.1 Incompatibilities

Not known

8.2 Shelf-life

Stable for 2 year if stored at 2-8 °C.

8.3 Packaging information

Sterile 10 mL, USP Type I tubular amber glass vial, labelled and packed in unit carton.

8.4 Storage and handing instructions
LYFAQUIN® injection should be stored at 2-8 °C, protected from light and moisture. Do not freeze.

9. **Patient Counselling Information**
Importance of next dose: The next dose of **LYFAQUIN®** shall be administered if systolic blood pressure remains ≤ 90 mmHg or as per discretion of treating physician or doctor. The number of **LYFAQUIN®** doses shall be decided by physician or doctor based on patient's clinical condition.

10. **Details of manufacturer**
Pharmazz India Private Limited, At N.H. No.: 8, Near Grid, Kabilpore 396424, Navsari, Gujarat.

11. **Details of permission or licence number with date**
FDA permission no.: G/28A/5835-A; Date: 24 June 2020

12. **Date of revision**
02 July 2020

Manufactured by:

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