

[...] Any final intravenous infusion solution containing colistimethate sodium should be freshly prepared and used for no longer than 24 hours."

5 Promixin is a drug containing CMS approved for inhalation. The label instructs that
"solutions should be used immediately after reconstitution (see section 4.2). Any unused solution remaining in the nebulizer must be discarded following treatment."

10 A FDA alert published in 2007 following the death of a CF patient linked to the inhalation of an aged CMS solution states that *"Premixing colistimethate into an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution, increasing the potential for lung toxicity. [...] In aqueous solution, colistimethate undergoes spontaneous hydrolysis to form colistin."*

15 It has now been discovered that an aqueous solution comprising high concentration of a sulfomethylated polymyxin exhibits physicochemical properties suitable for long-term stability, even at room temperature. Thus it may be utilized in a pulmonary administration device, which may be utilized in the aforementioned therapeutic applications in humans.

Summary

20 In one aspect, there is provided a pulmonary administration device, comprising a spray nozzle unit and a cartridge containing an aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin. In another aspect, there is provided an aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin for use in therapeutic or prophylactic treatment of bacterial infection in the pulmonary system,
 25 wherein the composition/solution is for pulmonary administration. In another aspect, there is provided use of an aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin in the manufacture of a medicament for therapeutic or prophylactic treatment of bacterial infection in the pulmonary system in a patient in need thereof, wherein the use comprises that an inhaler comprising a spray nozzle unit and a cartridge containing said medicament is to be actuated for pulmonary administration of the medicament to the patient in the form of droplets having a mass median aerodynamic diameter of from 4 to 8 μm . In another aspect, there is provided use of an aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin in the manufacture of a medicament for therapeutic or prophylactic treatment of bacterial infection in the
 30 pulmonary system in a patient in need thereof, wherein the use comprises that an inhaler comprising a spray nozzle unit and a cartridge containing said medicament is to be actuated for pulmonary administration of the medicament to the patient in the form of droplets having a mass median aerodynamic diameter of from 5.5 to 7.5 μm . In a further aspect, there is provided use of an aqueous solution comprising from 90 to 100 mg A/mL of colistimethate sodium in the manufacture of a medicament for therapeutic or prophylactic treatment of bacterial infection in the pulmonary system of a patient in need thereof, wherein the use comprises that an inhaler comprising a spray nozzle unit having an orifice diameter of 1.7-2.0 μm and a cartridge containing the medicament is to be actuated for pulmonary administration of the medicament to the patient in the form of droplets
 35 having a mass median aerodynamic diameter of from 4 to 8 μm with an airflow of 15-20 L/min. Examples disclosed herein include a pulmonary administration device, comprising a spray nozzle unit and a cartridge containing an aqueous solution comprising from 70 to 400 mg A/mL of a sulfomethylated polymyxin, and its use in therapeutic or prophylactic treatment of bacterial infections in the pulmonary system by pulmonary administration.

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Detailed description

Brief Description of the Figures

Fig. 1. Interval plot of mass median aerodynamic diameter (μm) of the Example 4
 55 composition.

CLAIMS

1. A pulmonary administration device, comprising
a spray nozzle unit and
a cartridge containing an aqueous solution comprising from 80 to 400 mg A/mL of a
5 sulfomethylated polymyxin.
2. The device according to claim 1, wherein the sulfomethylated polymyxin is
colistimethate sodium.
- 10 3. The device according to claim 1 or 2, wherein the concentration of the
sulfomethylated polymyxin ranges from 80 to 200 mg A/mL.
4. The device according to claim 2, wherein the concentration of the colistimethate
sodium ranges from 80 to 120 mg A/mL.
- 15 5. The device according to claim 2, wherein the concentration of the colistimethate
sodium ranges from 85 to 113 mg A/mL.
6. The device according to claim 2-5, wherein the aqueous solution has a pH from 6
20 to 8.
7. The device according to claim 2-5, wherein the cartridge has a nominal volume
of 0.5-1.5 mL.

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8. An aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin for use in therapeutic or prophylactic treatment of bacterial infection in the pulmonary system, wherein the composition/solution is for pulmonary administration.

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9. The solution for use according to claim 8, wherein the sulfomethylated polymyxin is colistimethate sodium.

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10. The solution for use according to claim 8 or 9, wherein the concentration of the sulfomethylated polymyxin ranges from 90 to 150 mg A/mL.

11. The solution for use according to claim 9, wherein the concentration of the colistimethate sodium ranges from 90 to 110 mg A/mL.

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12. The solution for use according to claim 9, wherein the concentration of the colistimethate sodium ranges from 90 to 100 mg A/mL.

13. The solution for use according to claim 9, wherein the aqueous solution has a pH from 6 to 8.

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14. The solution for use according to claim 9-13, wherein the solution is provided in a cartridge having a nominal volume of 0.5-1.5 mL.

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15. Use of an aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin in the manufacture of a medicament for therapeutic or prophylactic treatment of bacterial infection in the pulmonary system in a patient in need thereof, wherein the use comprises that an inhaler comprising a spray nozzle unit and a cartridge containing said medicament is to be actuated for pulmonary administration of the medicament to the patient in the form of droplets having a mass median aerodynamic diameter of from 4 to 8 μm .
16. Use of an aqueous solution comprising from 80 to 400 mg A/mL of a sulfomethylated polymyxin in the manufacture of a medicament for therapeutic or prophylactic treatment of bacterial infection in the pulmonary system in a patient in need thereof, wherein the use comprises that an inhaler comprising a spray nozzle unit and a cartridge containing said medicament is to be actuated for pulmonary administration of the medicament to the patient in the form of droplets having a mass median aerodynamic diameter of from 5.5 to 7.5 μm .
17. The use according to claim 15 or 16, wherein the sulfomethylated polymyxin is colistimethate sodium.
18. The use according to claim 15 or 16, wherein the spray nozzle unit has orifices with a diameter of from 1.5 to 2.2 μm .
19. The use according to claim 15 or 16, wherein the patient is infected with a gram negative bacteria.
20. The use according to claim 17, wherein the aqueous solution comprises from 80 to 120 mg A/mL of colistimethate sodium.
21. The use according to claim 20, wherein the aqueous solution comprises from 85 to 113 mg A/mL of colistimethate sodium.
22. The use according to claim 19, wherein the gram negative bacteria is

Enterobacter aerogenes, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, or a combination thereof.

5 23. The use according to claim 20, wherein the bacterial infection in the pulmonary system of the patient is chronic lung disorder.

24. The use according to claim 22, wherein the chronic lung disorder is selected from among, asthma, cystic fibrosis (CF), non-CF bronchiectasis, a chronic obstructive pulmonary disease, or a combination thereof.

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25. The use according to claim 15, wherein the device is to be stored at a temperature of 2-8°C when it's not in use.

15 26. Use of an aqueous solution comprising from 90 to 100 mg A/mL of colistimethate sodium in the manufacture of a medicament for therapeutic or prophylactic treatment of bacterial infection in the pulmonary system of a patient in need thereof, wherein the use comprises that an inhaler comprising a spray nozzle unit having an orifice diameter of 1.7-2.0 μm and a cartridge containing the medicament is to be actuated for pulmonary administration of the medicament to the
20 patient in the form of droplets having a mass median aerodynamic diameter of from 4 to 8 μm with an airflow of 15-20 L/min.