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(54) **Composition and method for parenteral administration of ibuprofen D, L-or L-Lysine salt**

Zusammensetzung und Verfahren zur parenteralen Anwendung von Ibuprofen-D,L-, oder L-Lysinat

Composition et procédé pour l'administration parentérale de D,L- ou L-lysinate d'ibuprofène

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(56) References cited:
EP-A- 0 085 544 **EP-A- 0 137 668**
US-A- 5 895 789

- **OVERMEIRE, B. ET AL.: "A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus" THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 343, no. 10, 7 September 2000 (2000-09-07), pages 674-681, XP008001115**
- **MOSCA, F. ET AL.: "Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus" THE JOURNAL OF PEDIATRICS, vol. 131, no. 4, October 1997 (1997-10), pages 549-554, XP008004217**
- **VARVARIGOU A ET AL: "EARLY IBUPROFEN ADMINISTRATION TO PREVENT PATENT DUCTUS ARTERIOSUS IN PREMATURE NEWBORN INFANTS" JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, CHICAGO,IL, US, vol. 275, no. 7, 21 February 1996 (1996-02-21), pages 539-544, XP008004417 ISSN: 0098-7484**

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Description

FIELD OF THE INVENTION

[0001] This invention relates to pharmaceutical compositions of the d,l- or l-lysine salt of R,S or S-ibuprofen having analgesic, anti-inflammatory and anti-pyretic activity. The invention further relates to a method of treating pain or inflammation or of reducing fever by parenterally administering the pharmaceutical compositions to a mammalian subject in need of such treatment, especially to a patient who is a neonate or who is suffering from kidney disease. The invention further relates to R,S or S-ibuprofen-d,l or l-lysine especially formulated for babies born at 28 to 32 weeks of gestational age to treat patent ductus arterious (PA) and to treat or prevent intraventricular hemorrhage (IVH). The invention also relates to a process for preparing the pharmaceutical compositions of the d,l- or l-lysine salt of R,S or S-ibuprofen.

BACKGROUND OF THE INVENTION

[0002] Lysine salts of ibuprofen having anti-inflammatory and analgesic activity are known in the art. See U.S. Patent 4,994,604 to Tung et al. The Tung et al patent is specifically directed to the formation and resolution of ibuprofen-(S)-lysine into the (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine salts. There is no mention or suggestion of preparing compositions containing either optical isomer suitable for parenteral administration.

[0003] . U.S. Patents 5,510,385 and 5,622,990 also disclose lysine salts of ibuprofen. Both patents disclose that the lysine salts of ibuprofen are in a solid form suitable for oral administration such as tablets, caplets, powders and granulates. Once again there is no suggestion of forming a lysine salt of ibuprofen in a solution suitable for parenteral administration.

[0004] U.S. Patent 4,279,926 is directed to pharmaceutical compositions containing among the salts of phenylalkanoic acids, the D,L and L lysine salts of ibuprofen. Compositions are prepared which are suitable for parenteral administration and include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. The only aqueous composition suitable for parenteral administration disclosed in this patent contains 3 ml of 95% aqueous ethanol and 500 mg of ibuprofen. Such a system with its ethanol content would be not at all suitable to administer to a patient who is a neonate or a patient who suffers from kidney disease.

[0005] U.S. Patent 5,895,789 is directed to an improvement in the invention disclosed in U.S. Patent 4,279,926. According to this patent the compositions suitable for parenteral administration, containing an alkylammonium salt of a 2-arylpropionic acid, including ibuprofen, include an aqueous solution having an osmolarity between 270 and 310 mOsm/kg and a pH in the range of 7.0 to 7.5. The solution is free of preservatives and of supporting substances and is prepared and kept in an inert gas atmosphere and away from light. According to the reference the use of an inert gas during the preparation of the compositions and their subsequent storage enables reaching a degree of stability sufficient to avoid the need for adding preservatives and co-solvents for example alcohols or glycols for preventing the progressive yellowing of the solution. It is noted that while this patent mentions ibuprofen among the 2-arylpropionic acids and mentions the d,l lysine and l lysine salts as specific alkylammonium salts of the 2-arylpropionic acids, there is no express mention and certainly no example of any lysine salt of ibuprofen.

[0006] Because U.S. Patent 5,895,789 requires that the pH of the aqueous solution containing the alkylammonium salts of the 2-arylpropionic acids to remain between 7.0 and 7.5 and to have an osmolarity of between 270 and 310 mOsm/kg, the compositions are buffered with a C_3 to C_5 di- or tricarboxylic acid or an alkali or alkaline earth metal salt thereof selected from the group consisting of tartronic, malic, tartaric and citric acids. The preferred buffer is a citric acid/sodium hydroxide and/or sodium citrate buffer. It is also required that the compositions according to this patent be packaged in dark glass containers opaque to light radiation.

[0007] One of the problems often associated with premature neonates (babies born at 28 to 32 weeks of gestational age) is patent ductus arterious (PDA). The drug presently used to treat this indication is indomethacin. A major side effect of indomethacin after administration to neonates is renal failure. Indomethacin is effective in the treatment of PDA because indomethacin inhibits the biosynthesis of prostaglandin.

OBJECTS OF THE INVENTION

[0008] It is an object of the invention to prepare stable pharmaceutical compositions of the d,l or l-lysine salt of R,S or S-ibuprofen having anti-inflammatory, analgesic and anti-pyretic activity and which are suitable for parenteral administration, need not be prepared and stored under an inert gas atmosphere and need not be packaged in dark glass containers opaque to light radiation.

[0009] It is a further object of the invention to obtain stable pharmaceutical compositions of the d,l- or l-lysine salt of R,S or S-ibuprofen having anti-inflammatory, analgesic, and anti-pyretic activity that are safe for administration to any patient in need of said treatment, including neonates and patients suffering from a kidney disorder.

[0010] It is a further object of the invention to provide stable pharmaceutical compositions that may be administered to neonates to treat patent ductus arterious (PDA) and intraventricular hemorrhage (IVH) to inhibit the biosynthesis of prostaglandin and that are free of the side effects caused by administration of indomethacin.

SUMMARY OF THE INVENTION

[0011] We have found that pharmaceutical compositions which satisfy all of these requirements consist of a therapeutically effective amount of the d,l- or l-lysine salt of R,S or S-ibuprofen as active ingredient dissolved in sterile water to form a solution in the absence of an inert atmosphere and containing no more than 1% by weight of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient and capable of storage in the absence of an inert atmosphere.

[0012] We have also found a method of treating pain or inflammation or of reducing fever in a mammalian subject by parenterally administering to said mammalian subject a therapeutically effective amount of the pharmaceutical composition described in the preceding paragraph. Such a mammalian subject may include human patients, including neonates who may have been born prematurely and patients suffering from a kidney disorder, including nephritis, nephrosis, cancer of the kidney and kidney failure.

[0013] A preferred feature of the present invention is the administration of the present composition to premature neonates (especially neonates born at 28 to 32 weeks of gestational age). The compositions of the present invention may be administered to these very small patients to block the biosynthesis of prostaglandin and at the same time the patients are free of the side effects associated with indomethacin, e.g. renal failure, the inhibitor of prostaglandin biosynthesis known in the art for treating this condition.

[0014] According to the present invention the d,l- or l-lysine salts of R,S or S ibuprofen are prepared without any addition of sodium chloride thus making the product safer for infants or other patients whose renal function, especially electrolyte elimination, is already compromised. The dosage form of this solution is 10 mg of R,S or S ibuprofen d,l or l lysinate (calculated on the basis of the ibuprofen not the salt) per ml of water. Preferably 1 to 2 ml of the solution are administered by injection to a patient as a daily dosage.

[0015] The new pharmaceutical compositions of the present invention may be prepared alternatively as follows:

(a) dissolving the d,l- or l-lysine salt of R,S or S ibuprofen in sterile water to form a solution in the absence of an inert atmosphere and containing no more than 1% by weight of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient and capable of storage in the absence of an inert atmosphere; or

(b) dissolving d,l- or l-lysine and R,S or S ibuprofen in sterile water to form in situ a solution of the l-lysine salt of R,S ibuprofen in the absence of an inert atmosphere and containing no more than 1% by weight of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient and capable of storage in the absence of an inert atmosphere.

[0016] The compositions according to the present invention are prepared either without the addition of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient or with the addition of only a minor amount (no more than 1% by weight) of the excipient, organic solvent, buffer, acid, base, salt other than the active ingredient to either control the solution osmolarity or the solution pH. For instance aqueous solutions prepared according to the present invention contain no more than 1% sodium chloride and preferably no more than 0.75% sodium chloride. Thus there is either no addition or substantially no addition of NaCl, HCL, citric acid or any of the other buffering agents or osmolarity adjusting compounds that have been included in the prior art pharmaceutical compositions. Such compositions which avoid sodium are especially suitable for administration to neonates and to kidney patients who cannot readily remove sodium from their systems.

[0017] The preferred concentration of the d,l or l ibuprofen lysine suitable for parenteral administration expressed in terms of percentage by weight with respect to the sterile water is between 1 to 20% by weight or strength. The preferred route of parenteral administration is through injection. Preferably the injection is intravenous, intramuscular or subcutaneous.

[0018] The preferred concentration of the ibuprofen lysinate is 1 to 20 mg, preferably 10 mg per ml of sterile aqueous solution calculated on the basis of the ibuprofen content and not on the basis of the lysinate salt irrespective as to whether the solution is substantially free or absolutely free of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient. When preparing the compositions that are substantially free, the percentage of salt (pharmaceutically acceptable) in the solution is either identical to that of an isotonic solution or less than that of an isotonic solution. Sodium chloride is the preferred pharmaceutically acceptable salt and is preferably added to the ibuprofen lysinate in a percentage ranging from 0.75 to 1.0. When preparing solutions that are absolutely free the product is especially safe for infants or other patients whose renal function, especially electrolyte elimination, is already compromised.

[0019] A preferred strength of the product in terms of the ibuprofen content of the sterile aqueous solution ranges between 1 and 20%, preferably 5.95 to 10%.

[0020] The following examples show preparation of the new compositions according to the present invention:

Example 1

[0021] 352g of R,S ibuprofen d,l-lysine are dissolved in sterile distilled water without any excipient to adjust osmolarity, organic solvent, buffer, acid, base, or salt other than d,l-lysine in the absence of an inert atmosphere. Under mixing the desired sterile solution is formed. A quantity of the sterile solution is placed in an ampoule and is ready for use.

Example 2

[0022] 234g of R,S ibuprofen and 166g of l-lysine are each dissolved in sterile distilled water without any excipient to adjust osmolarity, organic solvent, buffer, acid, base, or salt other than l-lysine in the absence of an inert atmosphere. Under vigorous mixing a solution of the desired R,S ibuprofen d,l-lysine sterile solution is formed. A quantity of the sterile solution is placed in an ampoule and is ready for use.

Example 3

[0023] The same procedures and reaction conditions as employed in Example 2 are employed here except that a small amount of sodium chloride is added so that the resulting aqueous solution contains 0.75% by weight sodium chloride. The resulting aqueous solution contains 10 mg of R,S ibuprofen d,l-lysine per ml of solution.

Examples Directed to Manufacturing and Packaging the Product

Example 4

Formulation substantially free of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient

[0024] 54.0 kg of water for injection (WFI) are added to a vessel whose weight has been determined. The temperature is determined and if required, the temperature is raised or lowered to a range between 15°C and 30°C. This temperature range is maintained throughout the formulation process. Mixing is begun at 600 to 800 RPM. 504.24 g of sodium chloride UMP/E are added. The weighed vessel which contained sodium chloride is rinsed with 3 increments of WFI. The rinses are added to the vessel and the contents of the vessel are mixed for another ten minutes.

[0025] By visual determination a check is made to learn whether all of the sodium chloride has been dissolved. Once the dissolution is completed, 650 g of ibuprofen lysinate are then added to the vessel. The weighed containers which once held ibuprofen lysinate are rinsed with 3 increments of WFI. All rinses are added to the vessel and mixed for another 10 minutes. Then a check is made to determine if all of the isoprufen lysinate has been dissolved. Once dissolved a 10 ml sample is withdrawn and its pH measured against a standardized pH meter. The pH is adjusted to 7.2 to 7.6 by adding 0.1N sodium hydroxide or 0.1N hydrochloric acid solution. The amount of WFI needed to achieve the final qs weight is determined. The WFI is added to qs until the final vessel and solution weight is reached. The solution is then mixed for 10 minutes. Once again 10 ml of the sample are withdrawn and the pH is measured. The pH is adjusted once again to a level of 7.2 to 7.6 with a target of 7.4. Then 20 ml of sample are taken from the vessel for quality control. In addition two 20 ml bioburden samples are submitted to environmental control. Mixing is then discontinued, the vessel is closed, and the contents are transferred to the filtering area. After filtering, the solution is transferred to an aseptic filling area. The concentration of the solution is 10 mg/ml based on the weight of the ibuprofen only, not the weight of the ibuprofen lysinate.

[0026] Through filters, the solution is transferred to the filling vessel. Sterile vials are filled from the filling vessel and each vial is provided with a sterilized, dry stopper. The vials are then closed with a sterile dried stopper. The vials are sterilized at 123°C at a cycle time of 22 minutes and have a D/Value of 1.14.

Example 5

Formulation absolutely free of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient

[0027] 54.0 kg of water for injection (WFI) are added to a vessel whose weight has been determined. The temperature is determined and if required, the temperature is raised or lowered to a range between 15°C and 30°C. This temperature range is maintained throughout the formulation process. Mixing is begun at 600 to 800 RPM. 650 g of ibuprofen lysinate

are then added to the vessel. The weighed containers which once held ibuprofen lysinate are rinsed with 3 increments of WFI. All rinses are added to the vessel and mixed for another 10 minutes. Then a check is made to determine if all of the ibuprofen lysinate has been dissolved. Once dissolved a 10 ml sample is withdrawn and its pH measured against a standardized pH meter. The pH is determined to be 6.9. The amount of WFI needed to achieve the final qs weight is determined. The WFI is added to qs until the final vessel and solution weight is reached. The solution is then mixed for 10 minutes. Then 20 ml of sample are taken from the vessel for quality control. In addition two 20 ml bioburden samples are submitted to environmental control. Mixing is then discontinued, the vessel is closed, and the contents are transferred to the filtering area. After filtering, the solution is transferred to an aseptic filling area. The concentration of the solution is 10 mg/ml based on the weight of the ibuprofen only, not the weight of the ibuprofen lysinate.

[0028] Through filters, the solution is transferred to the filling vessel. Sterile vials are filled from the filling vessel and each vial is provided with a sterilized, dry stopper. The vials are then closed with a sterile dried stopper.
The vials are sterilized at 123°C at a cycle time of 22 minutes and have a D/Value of 1.14.

[0029] The following data in the table have been obtained for the composition according to Example 4. The data show that the composition has excellent storage stability over a period of over two years. The solution over that time period remains colorless, the pH remains constant, the assay remains constant, the levels of impurities remain low, the compositions remain sterile and there is no sign of particulates.

Table 1

Summary Sheet

Product Ibuprofen Lysinate Injection **Container** Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial

LotNumber 927-41-45822 **Closure** West 4416/50 V-35, 13 mm, plug, minimum silicone

Dosage 2 ml/vial, 10 mg/mL **Raw Material** Ibuprofen L-Lysinate

Raw Material Manufacturer Central Research Institute for Chemistry

			Assay Dates	02/24/1998	05/14/1998	06/12/1998	07/20/1998	10/09/1998	12/30/1998	03/22/1999	10/14/1999	04/25/2000		
Temp (°C)	Parameter	Limits	Orient	Initial	1 Month	2 Month	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month	30 Month	36 Month
25/60 %RH	Appearance	Clear, colorless solution essentially free from visible contminants	UP	MR			MR	MR	MR	MR	MR	MR		
				JLR-02			DXW-03	PAS-07	JJL-02	JJL-03	DLB-19	FLS-11		
				p137			p40	p44	p39	p12	p139	p47		
25/60 %RH	Appearance	Clear, colorless solution essentially free from visible contminants	INV	N/A			MR	MR	MR	MR	MR	MR		
							DXW-03	PAS-07	JJL-02	JJL-03	DLB-19	FLS-11		
							p40	p44	p39	p12	p139	p47		
25/60 %RH	pH	6.5 to 8.5 on a pooled sample	UP	7.5			7.3	7.3	7.3	7.3	7.3	7.3		
				JLR-02			DXW-03	PAS-07	JJL-02	JJL-03	DLB-19	FLS-11		
				p137			p41	p45	p39	p12	p139	p47		
25/60 %RH	pH	6.5 to 8.5 on a pooled sample	INV	N/A			7.3	7.4	7.3	7.3	7.4	7.3		
							DXW-03	PAS-07	JJL-02	JJL-03	DLB-19	FLS-11		
							p41	p45	p39	p12	p139	p47		
25/60 %RH	Assay	90.0% to 110.0% of the labeled amount	UP	103.8%			105.2%	100.2%	104.8%	102.7%	103.5%	100.7%		
				JLR-02			DXW-03	PAS-07	JJL-02	JJL-03	DLB-19	FLS-11		
				p146			p40	p48	p165	p15	p142	p52		

N/A = Test not required for test interval
NMT = Not More Than
MR = Meets Requirements
Vials stored at RT prior to putting them on station
* = Initial testing performed on upright vials

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Table 2

Summary Sheet

Product	**Ibuprofen Lysinate Injection**	**Container**	**Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial**
LotNumber	**927-41-45822**	**Closure**	**West 4416/50 V-35, 13 mm, plug, minimum silicone**
Dosage	**2 ml/vial, 10 mg/mL**	**Raw Material**	**Ibuprofen L-Lysinate**
		Raw Material Manufacturer	**Central Research Institute for Chemistry**

Assay Dates			02/24/1998	05/14/1998	06/12/1998	07/20/1998	10/09/1998	12/30/1998	03/22/1999	10/14/1999	04/25/2000		
Temp (°C)	**Parameter**	**Limits**	**Orient**	**Initial**	**1 Month**	**2 Month**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**18 Month**	**24 Month**	**30 Month**	**36 Month**
25/60 %RH	Assay	90.0% to 110.0% of the labeled amount	INV	N/A			105.0%	100.2%	104.2%	102.5%	100.4%	100.6%		
							DXW-03 p40	PAS-07 p48	JJL-02 p165	JJL-03 p15	DLB-19 p142	FLS-11 p52		
25/60 %RH	Impurities	Individual Impurity: NMT 1.0%	UP	0.03%			0.06%	0.02%	0.02%	0.02%	0.05%	0.02%		
				JLR-02 p148			DXW-03 p120	PAS-07 p51	JJL-02 p80	JJL-03 p60	HLA-06 p167	FLS-11 p63		
25/60 %RH	Impurities	Individual Impurity: NMT 1.0%	INV	N/A			0.04%	0.02%	0.02%	0.02%	0.03%	0.02%		
							DXW-03 p121	PAS-07 p51	JJL-02 p80	JJL-03 p60	HLA-06 p168	FLS-11 p65		
25/60 %RH	Impurities	Total Impurity: NMT 2.0%	UP	0.05%			0.1%	0.08%	0.09%	0.1%	0.1%	0.2%		
				JLR-02 p148			DXW-03 p120	PAS-07 p51	JJL-02 p80	JJL-03 p60	HLA-06 p167	FLS-11 p63		
25/60 %RH	Impurities	Total Impurity: NMT 2.0%	INV	N/A			0.1%	0.08%	0.09%	0.1%	0.1%	0.1%		
							DXW-03 p121	PAS-07 p51	JJL-02 p80	JJL-03 p60	HLA-06 p168	FLS-11 p65		

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Vials stored at RT prior to putting them on station
* = Initial testing performed on upright vials

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Table 3

Summary Sheet

Product	**Ibuprofen Lysinate Injection**	**Container**	**Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial**
LotNumber	**927-41-45822**	**Closure**	**West 4416/50 V-35, 13 mm, plug, minimum silicone**
Dosage	**2 ml/vial, 10 mg/mL**	**Raw Material**	**Ibuprofen L-Lysinate**
		Raw Material Manufacturer	**Central Research Institute for Chemistry**

				Assay Dates	**02/24/1998**	**05/14/1998**	**06/12/1998**	**07/20/1998**	**10/09/1998**	**12/30/1998**	**03/22/1999**	**10/14/1999**	**04/25/2000**		
Temp (°C)	**Parameter**	**Limits**	**Orient**	**Initial**	**1 Month**	**2 Month**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**18 Month**	**24 Month**	**30 Month**	**36 Month**
25/60 %RH	Particulate Matter (HIAC)	NMT 6,000/10um	UP	38			N/A	N/A	N/A	34	N/A	46		
				H980122 PC						H990299P C		H 000457 PC		
25/60 %RH	Particulate Matter (HIAC)	NMT 6,000/10um	INV	N/A			N/A	N/A	N/A	146	N/A	78		
										H990299P C		H 000457 PC		
25/60 %RH	Particulate Matter (HIAC)	NMT 600/25um	UP	0			N/A	N/A	N/A	0.4	N/A	4		
				H980122 PC						H990299P C		H 000457 PC		
25/60 %RH	Particulate Matter (HIAC)	NMT 600/25um	INV	N/A			N/A	N/A	N/A	1.2	N/A	6		
										H990299P C		H 000457 PC		
25/60 %RH	Sterility	Sterile	INV	Sterile*			N/A	N/A	N/A	Sterile	N/A	Awaits		
				S980152L F						S990358LF		Results		

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Vials stored at RT prior to putting them on station
* = Initial testing performed on upright vials

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Table 4

Summary Sheet

Product	**Ibuprofen Lysinate Injection**	**Container**	**Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial**
LotNumber	**927-41-45822**	**Closure**	**West 4416/50 V-35, 13 mm, plug, minimum silicone**
Dosage	**2 ml/vial, 10 mg/mL**	**Raw Material**	**Ibuprofen L-Lysinate**
		Raw Material Manufacturer	**Central Research Institute for Chemistry**

				Assay Dates	**02/24/1998**	**05/14/1998**	**06/12/1998**	**07/20/1998**	**10/09/1998**	**12/30/1998**	**03/22/1999**	**10/14/1999**	**04/25/2000**		
Temp (°C)	**Parameter**	**Limits**	**Orient**	**Initial**	**1 Month**	**2 Month**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**18 Month**	**24 Month**	**30 Month**	**36 Month**
25/60 %RH	Bacterial Endotoxins	Contains NMT 0.5 USP EU/mg	INV	<0.1667*			N/A	N/A	N/A	N/A	N/A	<0.1667		
				PLAL980166								PLAL 000682		
				QCL								QCL		
40/75 %RH	Appearance	Clear, colorless solution essentially free from visible contaminants	UP	MR	MR	MR	MR	MR						
				JLR-02	CMS-01	PAS-05	DXW-03	PAS-07						
				p137	p134	p182	p40	p44						
40/75 %RH	Appearance	Clear, colorless solution essentially free from visible contaminants	INV	N/A	MR	MR	MR	MR						
					CMS-01	PAS-05	DXW-03	PAS-07						
					p134	p182	p40	p44						
40/75 %RH	pH	6.5 to 8.5 on a pooled sample	UP	7.5	7.3	7.3	7.2	7.1						
				JLR-2	CMS-01	PAS-05	DXW-03	PAS-07						
				p137	p135	p182	p41	p45						

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MR = Meets Requirements
Vials stored at RT prior to putting them on station
* = Initial testing performed on upright vials

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Table 5

Summary Sheet

Product	**Ibuprofen Lysinate Injection**	**Container**	**Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial**
LotNumber	**927-41-45822**	**Closure**	**West 4416/50 V-35, 13 mm, plug, minimum silicone**
Dosage	**2 ml/vial, 10 mg/mL**	**Raw Material**	**Ibuprofen L-Lysinate**
		Raw Material Manufacturer	**Central Research Institute for Chemistry**

			Assay Dates	02/24/1998	05/14/1998	06/12/1998	07/20/1998	10/09/1998	12/30/1998	03/22/1999	10/14/1999	04/25/2000		
Temp (°C)	**Parameter**	**Limits**	**Orient**	**Initial**	**1 Month**	**2 Month**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**18 Month**	**24 Month**	**30 Month**	**36 Month**
40/75 %RH	pH	6.5 to 8.5 on a pooled sample	INV	N/A	7.4	7.3	7.3	7.2						
					CMS-01 p135	PAS-05 p182	DXW-03 p41	PAS-07 p45						
40/75 %RH	Assay	90.0% to 110.0% of the labeled amount	UP	103.8%	99.4%	99.4%	104.8%	99.2%						
				JLR-02 p146	CMS-01 p138	PAS-05 p185	DXW-03 p46	PAS-07 p48						
40/75 %RH	Assay	90.0% to 110.0% of the labeled amount	INV	N/A	99.3%	99.2%	105.0%	99.3%						
					CMS-01 p138	PAS-05 p185	DXW-03 p46	PAS-07 p48						
40/75 %RH	Impurities	Individual Impurity: NMT 1.0%.	UP	0.03%	0.02%	0.03%	0.07%	0.1%						
				JLR-02 p148	CMS-01 p140	PAS-05 p188	DXW-03 p123	PAS-07 p57						
40/75 %RH	Impurities	Individual Impurity: NMT 1.0%	INV	N/A	0.02%	0.02%	0.06%	0.07%						
					CMS-01 p139	PAS-05 p188	DXW-03 p125	PAS-07 p58						

N/A = Test not required for test interval
NMT = Not More Than
MR = Meets Requirements
Vials stored at RT prior to putting them on station
* = Initial testing performed on upright vials

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Table 6

Summary Sheet

Product	**Ibuprofen Lysinate Injection**	**Container**	**Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial**
LotNumber	**927-41-45822**	**Closure**	**West 4416/50 V-35, 13 mm, plug, minimum silicone**
Dosage	**2 ml/vial, 10 mg/mL**	**Raw Material**	**Ibuprofen L-Lysinate**
		Raw Material Manufacturer	**Central Research Institute for Chemistry**

Temp (°C)	Parameter	Limits	Assay Dates	Orient	02/24/1998 Initial	05/14/1998 1 Month	06/12/1998 2 Month	07/20/1998 3 Month	10/09/1998 6 Month	12/30/1998 9 Month	03/22/1999 12 Month	10/14/1999 18 Month	04/25/2000 24 Month	30 Month	36 Month
40/75 %RH	Impurities	Total Impurity: NMT 2.0%		UP	0.05%	0.06%	0.1%	0.4%	0.4%						
					JLR-02	CMS-010.1%	PAS-05	DXW-03	PAS-07						
					p148	p140	p188	p123	p57						
40/75 %RH	Impurities	Total Impurity: NMT 2.0%		INV	N/A	0.05%	0.1%	0.3%	0.3%						
						CMS-01	PAS-05	DXW-03	PAS-07						
						p139	p188	p125	p58						
40/75 %RH	Particulate Matter (HIAC)	NMT 6,000/10um		UP	38	N/A	N/A	N/A	65						
					H980122 PC				H980832P C						
40/75 %RH	Particulate Matter (HIAC)	NMT 6,000/10um		INV	N/A	N/A	N/A	N/A	144						
									H980832P C						
40/75 %RH	Particulate Matter (HIAC)	NMT 600/25um		UP	0	N/A	N/A	N/A	3						
					H980122 PC				H980832P C						

N/A = Test not required for test interval
NMT = Not More Than
MR = Meets Requirements
Vials stored at RT prior to putting them on station
* = Initial testing performed on upright vials

Table 7

Summary Sheet

Product	**Ibuprofen Lysinate Injection**	**Container**	**Wheaton 2702 B33 BA, 2 cc, 13 mm, flint tubing type I vial**
LotNumber	**927-41-45822**	**Closure**	**West 4416/50 V-35, 13 mm, plug, minimum silicone**
Dosage	**2 ml/vial, 10 mg/mL**	**Raw Material**	**Ibuprofen L-Lysinate**
		Raw Material Manufacturer	**Central Research Institute for Chemistry**

			Assay Dates	**02/24/1998**	**05/14/1998**	**06/12/1998**	**07/20/1998**	**10/09/1998**	**12/30/1998**	**03/22/1999**	**10/14/1999**	**04/25/2000**
Temp (°C)	**Parameter**	**Limits**		**Orient Initial**	**1 Month**	**2 Month**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**18 Month**	**24 Month**	**30 Month**	**36 Month**
40/75 %RH	**Particulate Matter (HIAC)**	**NMT 600/25um**		**INV N/A**	**N/A.**	**N/A**	**N/A**	**2**						
								H980832P C						

N/A = Test not required for test interval
NMT = Not More Than
MR = Meets Requirements
Vials stored at RT prior to putting them on station
*** = Initial testing performed on upright vials**

Claims

1. A pharmaceutical composition suitable for parenteral administration having anti-inflammatory, anti-pyretic and analgesic properties, which consists of a therapeutically effective amount of the d,l or l-lysine salt of R,S or S-ibuprofen

as active ingredient dissolved in sterile water to form a solution in the absence of an inert atmosphere and containing no more than 1% by weight of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient and capable of storage in the absence of an inert atmosphere.

2. The composition according to claim 1, wherein the lysine salt of R,S- or S-ibuprofen is the l-lysine salt.

3. The composition as defined in claims 1 or 2 for use as a medicament.

4. The composition according to claim 3 for the use specified therein, wherein the medicament is for treating pain or inflammation or for reducing fever in a mammalian subject.

5. The composition according to claim 4 for the use specified therein, wherein the pharmaceutical composition is administered parenterally to said mammalian subject.

6. Use of the pharmaceutical composition as defined in claims 1 or 2 for the preparation of a medicament for treating pain or inflammation or for reducing fever in a mammalian subject by a method wherein the pharmaceutical composition is administered parenterally to said mammalian subject in a therapeutically effective amount.

7. The composition according to claims 4 or 5, or the use according to claim 6, wherein the mammalian subject is a human patient.

8. The composition or the use according to claim 7 wherein the human patient is a premature neonate.

9. The composition or the use according to claims 7 or 8 wherein the human patient suffers from kidney disease.

10. The composition according to any one of claims 3, 4, 5, 7, 8 or 9 or the use according to any one of claims 6 to 9 wherein the pharmaceutical composition is administered by injection.

11. The composition or the use according to claim 10 wherein the injection is intravenous, intramuscular or subcutaneous injection.

12. The composition according to claim 3 for the use specified therein, wherein the medicament is for treating patent ductus arterious or intraventricular hemorrhage in a prematurely born neonate by a method wherein the pharmaceutical composition is administered parenterally to said prematurely born neonate.

13. Use of the pharmaceutical composition as defined in claims 1 or 2 for the preparation of a medicament for treating patent ductus arteriosus or intraventricular hemorrhage in a prematurely born neonate by a method wherein the pharmaceutical composition is administered parenterally to said prematurely born neonate in a therapeutically effective amount.

14. A method of preparing a pharmaceutical composition as defined in claims 1or 2 which comprises the step of dissolving the d,l- or l-lysine salt of R,S or S-ibuprofen in sterile water to form a solution in the absence of an inert atmosphere and containing no more than 1% by weight of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient and capable of storage in the absence of an inert atmosphere.

15. A method of preparing a pharmaceutical composition as defined in claims 1 or 2 which comprises the step of dissolving d,l- or l-lysine and R,S or S-ibuprofen in sterile water to form in situ a solution of the d,l- or l-lysine salt of R,S or S-ibuprofen in the absence of an inert atmosphere and containing no more than 1% by weight of any excipient, organic solvent, buffer, acid, base, salt other than the active ingredient and capable of storage in the absence of an inert atmosphere.

Patentansprüche

1. Pharmazeutische Zusammensetzung mit entzündungshemmenden, antipyretischen und schmerzlindernden Eigenschaften zur parenteralen Anwendung, die aus einer therapeutisch wirksamen Menge des d,l- oder l-Lysinsalzes des R,S- oder S-Ibuprofens als aktivem Wirkstoff besteht, das in Abwesenheit einer inerten Atmosphäre in sterilem Wasser zu einer Lösung gelöst wird, die nicht mehr als 1 Gewichtsprozent eines Arzneimittelträgerstoffs,

organischen Lösungsmittels, einer Puffersubstanz, Säure oder Base oder eines von dem aktiven Wirkstoff verschiedenen Salzes enthält, und die in Abwesenheit einer inerten Atmosphäre gelagert werden kann.

2. Zusammensetzung nach Anspruch 1, in der das Lysinsalz des R,S- oder S-Ibuprofens das l-Lysinsalz ist.

3. Zusammensetzung nach Anspruch 1 oder 2 zur Verwendung als Arzneimittel.

4. Zusammensetzung nach Anspruch 3 für die darin spezifizierte Verwendung, wobei das Arzneimittel zur Behandlung von Schmerzen oder Entzündungen oder zur Senkung von Fiebertemperaturen in einem Säugetier bestimmt ist.

5. Zusammensetzung nach Anspruch 4 für die darin spezifizierte Verwendung, wobei die pharmazeutische Zusammensetzung dem Säugetier parenteral verabfolgt wird.

6. Verwendung der pharmazeutischen Zusammensetzung nach Anspruch 1 oder 2 für die Herstellung eines Arzneimittels zur Behandlung von Schmerzen oder Entzündungen oder zur Senkung von Fiebertemperaturen in einem Säugetier mittels eines Verfahrens, bei dem die pharmazeutische Zusammensetzung dem Säugetier in einer therapeutisch wirksamen Menge parenteral verabfolgt wird.

7. Zusammensetzung nach Anspruch 4 oder 5 oder Verwendung nach Anspruch 6, wobei das Säugetier ein menschlicher Patient ist.

8. Zusammensetzung oder Verwendung nach Anspruch 7, wobei der menschliche Patient ein Frühgeborenes ist.

9. Zusammensetzung oder Verwendung nach Anspruch 7 oder 8, wobei der menschliche Patient an einer Nierenerkrankung leidet.

10. Zusammensetzung nach einem der Ansprüche 3, 4, 5, 7, 8 oder 9 oder Verwendung nach einem der Ansprüche 6 bis 9, wobei die pharmazeutische Zusammensetzung durch Injektion verabfolgt wird.

11. Zusammensetzung oder Verwendung nach Anspruch 10, wobei die Injektion eine intravenöse, intramuskuläre oder subkutane Injektion ist.

12. Zusammensetzung nach Anspruch 3 für die darin spezifizierte Verwendung, wobei das Arzneimittel zur Behandlung von persistierendem Ductus arteriosus (PDA) oder intraventrikulärer Hämorrhagie in einem Frühgeborenen bestimmt ist, nach einem Verfahren, bei dem die pharmazeutische Zusammensetzung dem Frühgeborenen parenteral verabfolgt wird.

13. Verwendung der pharmazeutischen Zusammensetzung nach Anspruch 1 oder 2 für die Herstellung eines Arzneimittels zur Behandlung von persistierendem Ductus arteriosus (PDA) oder intraventrikulärer Hämorrhagie in einem Frühgeborenen mittels eines Verfahrens, bei dem die pharmazeutische Zusammensetzung dem Frühgeborenen in einer therapeutisch wirksamen Menge parenteral verabfolgt wird.

14. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wie in Anspruch 1 oder 2 definiert, welches die Stufe umfasst, in der das d,l- oder l-Lysinsalz des R,S- oder S-Ibuprofens als aktiver Wirkstoff in Abwesenheit einer inerten Atmosphäre in sterilem Wasser zu einer Lösung gelöst wird, die nicht mehr als 1 Gewichtsprozent eines Arzneimittelträgerstoffs, organischen Lösungsmittels, einer Puffersubstanz, Säure oder Base oder eines von dem aktiven Wirkstoff verschiedenen Salzes enthält, und die in Abwesenheit einer inerten Atmosphäre gelagert werden kann.

15. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wie in Anspruch 1 oder 2 definiert, welches die Stufe umfasst, in der das d,l- oder l-Lysinsalz des R,S- oder S-Ibuprofens in Abwesenheit einer inerten Atmosphäre in sterilem Wasser in situ zu einer Lösung des d,l- oder l-Lysinsalzes von R,S- oder S-Ibuprofen gelöst wird, die nicht mehr als 1 Gewichtsprozent eines Arzneimittelträgerstoffs, organischen Lösungsmittels, einer Puffersubstanz, Säure oder Base oder eines von dem aktiven Wirkstoff verschiedenen Salzes enthält, und die in Abwesenheit einer inerten Atmosphäre gelagert werden kann.

Revendications

1. Composition pharmaceutique apte à l'administration parentérale, ayant des propriétés anti-inflammatoires, antipyrétiques et analgésiques, qui consiste en une quantité thérapeutiquement efficace du sel de d,l- ou l-lysine de R,S- ou S-ibuprofène comme ingrédient actif, dissoute dans de l'eau stérile pour former une solution en l'absence d'atmosphère inerte et ne contenant pas plus de 1 % en poids d'un quelconque agent consistant en excipient, solvant organique, tampon, acide, base, sel autre que l'ingrédient actif, et apte au stockage en l'absence d'atmosphère inerte.

2. Composition suivant la revendication 1, dans laquelle le sel de lysine de R,S- ou S-ibuprofène est le sel de l-lysine.

3. Composition telle que définie dans la revendication 1 ou 2, destinée à être utilisée comme médicament.

4. Composition suivant la revendication 3, destinée à l'utilisation spécifiée dans le présent mémoire, dans laquelle le médicament est destiné au traitement de la douleur ou de l'inflammation ou pour réduire la fièvre chez un sujet mammifère.

5. Composition suivant la revendication 4, destinée à l'utilisation spécifiée dans le présent mémoire, ladite composition pharmaceutique étant administrée par voie parentérale audit sujet mammifère.

6. Utilisation de la composition pharmaceutique telle que définie dans la revendication 1 ou 2 pour la préparation d'un médicament destiné au traitement de la douleur ou de l'inflammation ou pour réduire la fièvre chez un sujet mammifère par une méthode dans laquelle la composition pharmaceutique est administrée par voie parentérale audit sujet mammifère en une quantité thérapeutiquement efficace.

7. Composition suivant la revendication 4 ou 5, ou utilisation suivant la revendication 6, dans laquelle le sujet mammifère est un patient humain.

8. Composition ou utilisation suivant la revendication 7, dans laquelle le patient humain est un nouveau-né prématuré.

9. Composition ou utilisation suivant la revendication 7 ou 8, dans laquelle le patient humain souffre d'une maladie rénale.

10. Composition suivant l'une quelconque des revendications 3, 4, 5, 7, 8 et 9 ou utilisation suivant l'une quelconque des revendications 6 à 9, dans laquelle la composition pharmaceutique est administrée par injection.

11. Composition ou utilisation suivant la revendication 10, dans laquelle l'injection est une injection intraveineuse, intramusculaire ou sous-cutanée.

12. Composition suivant la revendication 3, destinée à l'utilisation spécifiée dans le présent mémoire, dans laquelle le médicament est destiné au traitement d'une hémorragie par persistance du canal artériel ou d'une hémorragie intraventriculaire chez un nouveau-né prématuré, par une méthode dans laquelle la composition pharmaceutique est administrée par voie parentérale audit nouveau-né prématuré.

13. Utilisation de la composition pharmaceutique telle que définie dans la revendication 1 ou 2 pour la préparation d'un médicament destiné au traitement d'une hémorragie par persistance du canal artériel ou d'une hémorragie intraventriculaire chez un nouveau-né prématuré par une méthode dans laquelle la composition pharmaceutique est administrée par voie parentérale audit nouveau-né prématuré, en une quantité thérapeutiquement efficace.

14. Procédé pour la préparation d'une composition pharmaceutique telle que définie dans la revendication 1 ou 2, qui comprend l'étape de dissolution du sel de d,l- ou l-lysine de R,S- ou S-ibuprofène dans de l'eau stérile pour former une solution en l'absence d'atmosphère inerte et ne contenant pas plus de 1 % en poids d'un quelconque agent consistant en excipient, solvant organique, tampon, acide, base, sel autre que l'ingrédient actif, et apte au stockage en l'absence d'atmosphère inerte.

15. Procédé pour la préparation d'une composition pharmaceutique telle que définie dans la revendication 1 ou 2, qui comprend l'étape de dissolution de d,l- ou l-lysine et de R,S- ou S-ibuprofène dans de l'eau stérile pour former in situ une solution du sel de d,l- ou l-lysine de R,S ou S-ibuprofène en l'absence d'atmosphère inerte et ne contenant

pas plus de 1 % en poids d'un quelconque agent consistant en excipient, solvant organique, tampon, acide, base, sel autre que l'ingrédient actif, et apte au stockage en l'absence d'atmosphère inerte.