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(54) **LIQUID PHARMACEUTICAL COMPOSITION COMPRISING NITISINONE**

FLÜSSIGE PHARMAZEUTISCHE ZUSAMMENSETZUNG MIT NITISINON

COMPOSITION PHARMACEUTIQUE LIQUIDE COMPRENANT DE LA NITISINONE

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- **HALL ET AL.: 'Pharmacokinetics and pharmacodynamics of NTBC (2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cycl ohexanedione) and mesotrione, inhibitors of 4-hydroxyphenyl puryvate dioxygenase (HPPD) following a single dose to healthy male volunteers' BRITISH JOURNAL OF CLINICAL PHARMACOLOGY vol. 52, 2001, pages 169 - 171, XP055139845**

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Description

TECHNICAL FIELD

[0001] This invention concerns pharmaceutical formulations comprising 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (nitisinone) as an active agent. The formulations are useful in the treatment of disorders and diseases in which inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD) is desirable, e.g. in hereditary tyrosinaemia type I.

BACKGROUND ART

[0002] The compound 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, also known as nitisinone or NTBC, was first disclosed as a herbicide (US 5,006,158; US 4,695,673; US 5,668,089).

[0003] Nitisinone is used under the brand name Orfadin® for the treatment of hereditary tyrosinemia type I (HT-1), a rare paediatric disease. HT-1 is a genetic metabolic disorder that results from an inability to break down the amino acid tyrosine. Because of resulting liver failure and liver cancer, children with HT-1 rarely survive into their twenties without a liver transplant.

[0004] As disclosed in e.g. US 5,550,165, nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase (HPPD), an enzyme upstream of fumarylacetoacetate hydrolase (FAH) in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity.

[0005] Further, nitisinone has been described as being useful in the treatment of other disorders, such as Parkinson's disease (WO 2006/090117); depression (WO 2008/020150); restless leg syndrome (WO 2010/054273); and alkaptonuria (Sunwanarat, P. et al., Metabolism 54: 719-728, 2005). The use of nitisinone has also been disclosed in a method for enhancing phagolysosomal fusion following infection of a patient with a microorganism (U.S. patent application, publication No. 2010-0227936).

[0006] Oral administration of drugs is one of the preferred routes for treatment, because of its simplicity. While drugs are generally administered in the form of tablets or capsules, such administration may be less preferred, for example when the dosage has to be finely adapted to treated subject, or may be less convenient, for example in the case of paediatric or veterinary drugs. The liquid dosage form may then be an advantageous alternative.

[0007] Consequently, there is a need for stable liquid nitisinone compositions which are adapted for administration to paediatric patients and overcome the drawbacks with solid pharmaceutical compositions.

DISCLOSURE OF THE INVENTION

[0008] According to the invention it has been shown that a liquid pharmaceutical formulation, comprising a suspension of micronized nitisinone, and having a pH of about 3, has surprisingly advantageous properties such as increased stability. Consequently, the present invention relates to a liquid pharmaceutical formulation suitable for oral administration, comprising (a) a suspension of an effective amount of micronized 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (nitisinone); and (b) citric acid buffer having a pH in the range of 2.5 to 3.5, preferably pH 3.0.

[0009] The term "effective amount" of nitisinone should be understood as an amount effective to inhibit 4-hydroxyphenylpyruvate dioxygenase. Preferably, the amount of nitisinone is 1 to 10 mg/ml, more preferably 4 mg/ml.

[0010] Nitisinone may be obtained by conventional procedures of organic chemistry already known for the production of structurally analogous materials. Thus, for example, nitisinone may be conveniently obtained by reaction of 2-nitro-4-trifluoromethylbenzoyl chloride with cyclohexane-1,3-dione in the presence of acetone cyanhydrin and a suitable base such as triethylamine, as disclosed in US 5,550,165. The starting 2-nitro-4-trifluoromethylbenzoyl chloride may itself be obtained from the corresponding benzoic acid, for example by reaction with thionyl chloride or oxalyl chloride as is described in Reagents for Organic Synthesis, (J Wiley and Sons, 1967; Vol. 1, pp. 767-769) and is generally used without special purification. Similarly, 2-nitro-4-triflurormethylbenzoic acid may be obtained, for example, as described by Haupstein et al. in J. Amer. Chem. Soc., 1954, 76, 1051, or by one of the general methods described in The Chemistry of Carboxylic Acids and Esters (J Wiley and Sons, 1969; editor: S. Patai) and Survey of Organic Synthesis (J Wiley and Sons, 1970; C. A. Buehler and D. F. Pearson).

[0011] Preferably, the formulation according to the invention in addition comprises one or more pharmaceutically acceptable constituents selected from the group consisting of suspending agents, sweeteners, preservatives, surfactants, and flavoring agents.

[0012] A suitable suspending agent is e.g. hydroxypropyl methylcellulose (HPMC) in an amount of 1 to 20 mg/ml, preferably 5 mg/ml.

[0013] A suitable sweetener is glycerol, in an amount which results in an acceptable taste. The amount of glycerol is preferably 100 to 500 mg/ml, more preferably 500 mg/ml.

[0014] The formulation according to the invention preferably comprises at least one preservative chosen from methyl paraben, propyl paraben and sodium benzoate. Preferably, the preservatives are methyl paraben in an amount of 1 to 2 mg/ml, more preferably 1.4 mg/ml; propyl paraben in an amount of 0.1 to 0.2 mg/ml, more preferably 0.14 mg/ml; and sodium benzoate in an amount of 0.2 to 5 mg/ml, more preferably 1.0 mg/ml.

[0015] The formulation according to the invention preferably comprises a surfactant, such as polysorbate 80 (polyoxyethylene (80) sorbitan monooleate; common commercial brand names include Alkest TW 80™ and Tween 80™). The amount of polysorbate 80 should be sufficient to wet nitisinone particles to facilitate the dispersion of nitisinone during manufacturing, as well as to avoid any agglomeration of the nitisinone particles during storage of the final product. Preferably the formulation according to the invention comprises Polysorbate 80 in an amount of 0.1 to 20 mg/ml, more preferably from 0.10 to 0.15 mg/ml, such as about 0.135 mg/ml.

[0016] The formulation according to the invention preferably comprises an aroma agent, such as strawberry flavor. The amount of flavor should be sufficient to achieve an acceptable taste of the formulation and preferably in an amount of 0.2 to 1.1 mg/ml, more preferably 0.7 mg/ml.

[0017] In an especially preferred form, the formulation according to the invention comprises

(a) nitisinone (4 mg/ml);
(b) citric acid monohydrate (9 mg/ml);
(c) trisodium citrate dihydrate (2.1 mg/ml)
(d) hydroxypropyl methylcellulose (5 mg/ml);
(e) glycerol (500 mg/ml);
(f) methyl paraben (1.4 mg/ml);
(g) propyl paraben (0.14 mg/ml); and
(h) polysorbate 80 (0.14 mg/ml).

[0018] In another especially preferred form, the formulation according to the invention comprises

(a) nitisinone (4 mg/ml);
(b) citric acid monohydrate (9 mg/ml);
(c) trisodium citrate dihydrate (2.1 mg/ml)
(d) hydroxypropyl methylcellulose (5 mg/ml);
(e) glycerol (500 mg/ml);
(f) sodium benzoate (1.0 mg/ml); and
(g) polysorbate 80 (0.14 mg/ml).

[0019] A further preferred form of the formulation comprises a flavoring agent such as:

(h) strawberry flavor (0.7 mg/ml).

[0020] The formulation according to the invention is useful for the treatment of medical disorders and diseases wherein inhibition of 4-hydroxyphenyl-pyruvate dioxygenase (HPPD) is desirable. Examples of such conditions include hereditary tyrosinaemia type 1 (HT-1), Parkinson's disease, depression, restless leg syndrome and alkaptonuria.

[0021] The formulation according to the invention is particularly useful for paediatric use. Specifically, is it suitable for newborn infants up to children 8-10 years of age, representing a body weight span of approximately 3.5 to 40 kg. A daily dose of 1 mg/kg thus corresponds to a dose range from 2x1.75 mg to 2x20 mg. A strength of 4 mg/ml will achieve acceptable dosage volumes corresponding 0.44 to 5 ml administered twice daily. An oral syringe is suitable as administration dispenser for accurate dosing in this range.

EXAMPLES

EXAMPLE 1: Micronization of nitisinone

[0022] A lab-scale air-jet mill, 2 inches qualification model, Sturtevant Inc., was used to micronize nitisinone obtained from the company Bachem, Switzerland. The mill was operated with tangential flow (i.e. the air and drug are fed in the same direction in the milling chamber). The unmilled drug was fed into the mill using a Venturi feed system, Syncron®, Magnet Feeder model F-TO-C, where air was used to draw the feed material into the milling chamber. A product filter bag was affixed to the outlet of the mill, through which the exhausts and the milled drug collects. The milling conditions

were set as follows:

- Grind air: Dry nitrogen gas
- Grind pressure: 90 psi
- Feed pressure: 85 psi
- Room conditions: Ambient

[0023] 5 g of the API was passed through the lab-scale micronizer and the resulting material was collected (3.7 g). The material was analyzed for/by particle size diameter (PSD), assay and purity by high performance liquid chromatography (HPLC), x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and polarized light microscopy (PLM). The results for PSD from the micronization are shown in Table I.

Table I

	Particle size diameter (microns)				
	d_{10}	d_{20}	d_{50}	d_{80}	d_{90}
Start material	20.50	33.10	60.01	94.42	115.11
Micronized material	0.30	0.47	1.29	2.59	3.59

EXAMPLE 2: Preparation of an oral suspension of micronized nitisinone containing methyl and propyl parabens as preservatives

[0024] A formulation according to the invention, as shown in Table II, was prepared according to standard procedures.

Table II

Ingredient	Quantity (mg)	Function
Nitisinone (micronized)	4.0	Active substance
Hydroxypropyl methylcellulose (HPMC)	5.0	Suspending agent
Glycerol	500	Sweetener
Polysorbate 80	0.135	Surfactant
Methyl paraben	1.4	Preservatives
Propyl paraben	0.14	
Citric acid monohydrate	8.98	Buffer (pH 3.0)
Trisodium citrate dihydrate	2.13	
Water purified	q.s. to 1.00 ml	Solvent

EXAMPLE 3: Preparation of an oral suspension of micronized nitisinone containing sodium benzoate as preservative and strawberry aroma as flavoring agent

[0025] A formulation according to the invention, as shown in Table III, was prepared according to standard procedures.

Table III

Ingredient	Quantity (mg)	Function
Nitisinone (micronized)	4.0	Active substance
Hydroxypropyl methylcellulose (HPMC)	5.0	Suspending agent
Glycerol	500	Sweetener
Polysorbate 80	0.135	Surfactant
Sodium benzoate	1.0	Preservative

(continued)

Ingredient	Quantity (mg)	Function
Strawberry aroma	0.7	Flavor agent
Citric acid monohydrate	8.98	Buffer (pH 3.0)
Trisodium citrate dihydrate	2.13	
Water purified	q.s. to 1.00 ml	Solvent

EXAMPLE 4: Preparation of a nitisinone solution for comparison

[0026] A nitisinone solution as shown in Table IV was prepared according to standard procedures.

Table IV

Ingredient	Quantity (mg)	Function
Nitisinone	2.0	Active substance
Methyl paraben	1.8	Preservatives
Propyl paraben	0.2	
KH_2PO_4	1.4	Buffer (pH 6.8)
$Na_2HPO_{4\cdot2}H_2O$	2.9	
NaOH (0.5M aqueous)	Adjust to pH 6.8	
Water purified	q.s. to 1.00 ml	Solvent

EXAMPLE 5: Optimization of the amounts of preservatives by microbial challenge studies according to the Europena Pharmacopoeia (Ph Eur 5.1.3) and the United States Pharmacopoeia (USP <51>)

[0027] The results of different amounts of preservatives are shown in Tables V and VI, below.

Table V

Oral suspension of micronized nitisinone prepared according to Example 2 containing different amounts of methyl and propyl parabens as preservatives.

		Methyl paraben/Propyl paraben (mg/mL)					Limits		
Microbe	Days	0	1.0/0.1	1.4/0.14	1.7/0.17	2.0/0.2	Ph Eur 5.1.3	USP <51>	Units
S.aureus	Initial	5.3-5.5	5.3-5.5	5.3-5.5	5.3-5.5	5.3-5.5	-	-	log
	14	>3.5	>3.5	>3.5	>3.3	>3.5	≥3	≥1.0	log red
	28	NI	NI	NI	NI	NI	NI	NI	log red
P. aeruginosa	Initial	5.3-5.5	5.3-5.5	5.3-5.5	5.3-5.5	5.3-5.5	-	-	log
	14	>3.3	>3.5	>3.5	>3.4	>3.5	≥3	≥1.0	log red
	28	NI	NI	NI	NI	NI	NI	NI	log red

(continued)

Oral suspension of micronized nitisinone prepared according to Example 2 containing different amounts of methyl and propyl parabens as preservatives.									
		Methyl paraben/Propyl paraben (mg/mL)					Limits		
Microbe	Days	0	1.0/0.1	1.4/0.14	1.7/0.17	2.0/0.2	Ph Eur 5.1.3	USP <51>	Units
E. coli	Initial	5.2-5.6	5.2-5.6	5.2-5.6	5.2-5.6	5.2-5.6	-	-	log
	14	>3.7	>3.6	>3.6	>3.2	>3.6	≥3	≥1.0	log red
	28	NI	NI	NI	NI	NI	NI	NI	log red
C. albicans	Initial	5.3-5.6	5.3-5.6	5.3-5.6	5.3-5.6	5.3-5.6	-	-	log
	14	1.4	>3.7	>3.7	>3.3	>3.7	≥1	NI	log red
	28	2.2	NI	NI	NI	NI	NI	NI	log red
A. brasiliensis	Initial	5.5-5.6	5.5-5.6	5.5-5.6	5.5-5.6	5.5-5.6	-	-	log
	14	1.0	2.2	2.1	3.2	>3.6	≥1	NI	log red
	28	1.0	NI	3.3	3.3	NI	NI	NI	log red
NI = No increase									

Table VI

Oral suspension of micronized nitisinone prepared according to Example 3 containing different amounts of sodium benzoate as preservative.								
		Sodium benzoate (mg/mL)				Limits		
Microbe	Days	0.2	1.0	3.0	5.0	Ph Eur 5.1.3	USP <51>	Units
S.aureus	Initial	5.3	5.3	5.3	5.3	-	-	log
	14	5	5	5	5	≥3	≥1	log red
	28	NI	NI	NI	NI	NI	NI	log red
P. aeruginosa	Initial	5.2	5.2	5.2	5.2	-	-	log
	14	5	5	5	5	≥3	≥1	log red
	28	NI	NI	NI	NI	NI	NI	log red
E. coli	Initial	5.4	5.4	5.4	5.4	-	-	log
	14	5	5	5	5	≥3	≥1	log red
	28	NI	NI	NI	NI	NI	NI	log red
C. albicans	Initial	5.8	5.8	5.8	5.8	-	-	log
	14	1.4	4.5	5	5	≥1	NI	log red
	28	4.1	5	NI	NI	NI	NI	log red

(continued)

Oral suspension of micronized nitisinone prepared according to Example 3 containing different amounts of sodium benzoate as preservative.								
		Sodium benzoate (mg/mL)				Limits		
Microbe	Days	0.2	1.0	3.0	5.0	Ph Eur 5.1.3	USP <51>	Units
A. brasiliensis	Initial	5.6	5.6	5.6	5.6	-	-	log
	14	1	3.3	5	5	≥1	NI	log red
	28	1.3	5	NI	NI	NI	NI	log red
NI = No increase								

[0028] The results show that all the above formulations according to the invention comply with the prescribed requirements for preservative effectiveness according to the European Pharmacopoeia (Ph Eur) and the U.S. Pharmacopeia (USP), including the preservative-free formulation indicating a self -preservative nature of the basic formulation.

EXAMPLE 6: Stability test

[0029] Samples from the oral suspension of micronized nitisinone prepared according to Example 2, as well as the nitisinone solution prepared according to Example 4, were put on stability at +5°C, +25°C and +40°C, respectively, for 12 months. The concentrations of nitisinone and the degradation product 6-(trifluoromethyl)-3,4-dihydro-1H-xanthenene-1,9(2H)-dione (oxotetrahydroxanthenone) were followed by HPLC with UV-detection. The results, shown in Tables VII to X, below, are expressed as percent of the nominal concentration of nitisinone (% of label claim).

Table VII

Oral suspension of micronized nitisinone prepared according to Example 2.						
Nitisinone (% of label claim)						
Temperature	Months					
	0	1	2	3	6	12
5°C	99,9	104,2	101,7	105,0	102,9	104,8
25°C	99,9	105,6	98,6	104,0	101,8	103,7
40°C	99,9	105,6	102,0	102,7	101,0	100,1

Table VIII

Oral suspension of micronized nitisinone prepared according to Example 2 (nd= not detected).						
Oxotetrahydroxanthenone (% of label claim)						
	Months					
Temperature	0	1	2	3	6	12
5°C	nd	nd	nd	nd	nd	nd
25°C	nd	nd	nd	nd	0,02	0,02
40°C	nd	nd	0,07	0,15	0,28	0,54

Table IX

Nitisinone solution prepared according to Example 4.						
Nitisinone (% of label claim)						
Temperature	Months					
	0	1	2	3	6	12
5°C	96,6	99,8	95,3	100,4	99,7	99,3
25°C	96,6	100,9	96,0	100,2	98,0	95,9
40°C	96,6	98,3	96,3	93,6	86,5	74,4

Table X

Nitisinone solution prepared according to Example 4 (nd= not detected).						
Oxotetrahydroxanthenone (% of label claim)						
Temperature	Months					
	0	1	2	3	6	12
5°C	nd	nd	nd	nd	0,03	0,05
25°C	nd	0,01	nd	0,39	0,58	0,78
40°C	nd	0,07	1,86	2,05	1,63	1,38

[0030] The results show that the formulation according to the invention (Tables VII and VIII) is more stable than the solution for comparison (Tables IX and X) under all storage conditions. In the solution for comparison, the main degradation product, oxotetrahydroxanthenone, is further degraded to secondary degradation products. As a consequence it is not possible to achieve a mass balance between nitisinone and degradation products for the reference solution.

EXAMPLE 7: Stability of oxtetrahydroxanthenone

[0031] The stability study of the main degradation product in Example 6, oxotetrahydroxanthenone, is performed under similar conditions as described in Example 6. Samples of oxotetrahydroxanthenone (OTHX), 81 μg/ml in either citrate buffer pH 3.0 or phosphate buffer pH 6.8, were put on stability at +5°C, +25°C and +37°C, respectively, for 6 months. The concentrations of OTHX and the secondary degradation products 1,3-cyclohexanedione (CHD) and 4-(trifluoromethyl)salicylic acid (TSA) were analyzed by LC-MS. The results, shown in Table XI, below, are expressed as percent of the initial concentration of OTHX. The mass balance expressed as the total recovery of CHD+OTHX+TSA compared to the initial concentration of OTHX were calculated from MmOTHX/(Mm CHD + MmTSA) x (CHDconc + TSAconc) + OTHXconc expressed in μg/ml where MmOTHX, MmCHD and MmTSA are the molecular masses corresponding to 282, 202 and 206 g/mol, respectively. The results for the mass balance, expressed as percent of initial concentration of OTHX, are shown in Table XII.

Table XI

Stability of solutions of oxotetrahydroxanthenone prepared according to Example 7.							
		Citrate buffer pH 3.0			Phosphate buffer pH 6.8		
		Months			Months		
Component	Temp (°C)	1,8	3	6	1,8	3	6
OTHX	5	96,7	96,9	91,6	96,7	91,0	83,1
	25	96,7	102,7	92,3	74,8	63,2	44,8
	37	97,9	97,7	95,3	33,5	13,7	0,4

(continued)

Stability of solutions of oxotetrahydroxanthenone prepared according to Example 7.							
		Citrate buffer pH 3.0			Phosphate buffer pH 6.8		
		Months			Months		
CHD	5	0,0	0,0	0,0	0,0	0,7	0,0
	25	0,0	0,0	0,0	7,7	9,7	25,2
	37	0,0	0,0	0,0	22,2	21,5	32,8
TSA	5	0,0	0,0	0,0	1,4	1,9	0,0
	25	0,0	0,0	0,0	13,0	20,2	36,4
	37	0,2	0,0	0,0	38,6	49,1	66,4

Table XII

Mass balance.						
	Citrate buffer pH 3.0			Phosphate buffer pH 6.8		
	Months			Months		
Temp (°C)	1,8	3	6	1,8	3	6
5	96,7	96,9	91,6	97,9	93,3	83,1
25	96,7	102,7	92,3	93,2	89,8	99,4
37	98,1	97,7	95,3	87,4	76,3	88,5

[0032] The results show that the formulation according to the invention is surprisingly stable also with respect to the formation of secondary degradation products. The results, close to 100% for the mass balance, confirm that the LC-MS method is capable of detecting and determining the majority of the secondary degradation products.

Claims

1. A liquid pharmaceutical formulation suitable for oral administration, comprising

   (a) a suspension of an effective amount of micronized 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (nitisinone); and
   (b) citric acid buffer having a pH in the range of 2.5 to 3.5, preferably pH 3.0.

2. The formulation according to claim 1 wherein the amount of nitisinone is 1 to 10 mg/ml, preferably 4 mg/ml.

3. The formulation according to claim 1, in addition comprising one or more pharmaceutically acceptable constituents selected from the group consisting of suspending agents, sweeteners, preservatives, surfactants, and flavoring agents.

4. The formulation according to claim 3 wherein the suspending agent is hydroxypropyl methylcellulose.

5. The formulation according to claim 4 wherein the suspending agent is hydroxypropyl methylcellulose in an amount of 1 to 20 mg/ml, preferably 5 mg/ml.

6. The formulation according to claim 3 wherein the sweetener is glycerol.

7. The formulation according to claim 6 wherein the sweetener is glycerol in an amount of 100 to 500 mg/ml, preferably 500 mg/ml.

8. The formulation according to claim 3 wherein the preservative is methyl paraben and/or propyl paraben.

9. The formulation according to claim 8 wherein the preservatives are methyl paraben in an amount of 1 to 2 mg/ml, preferably 1.4 mg/ml, and propyl paraben in an amount of 0.1 to 0.2 mg/ml, preferably 0.14 mg/ml.

10. The formulation according to claim 3 wherein the preservative is sodium benzoate in an amount of 0.2 to 5 mg/ml, preferably 1 mg/ml.

11. The formulation according to claim 3 wherein the surfactant is polysorbate 80.

12. The formulation according to claim 11 wherein the surfactant is polysorbate 80 in an amount of 0.1 to 20 mg/ml, preferably from 0.10 to 0.15 mg/ml.

13. The formulation according to any one of claims 1-9, 11 or 12, comprising:

(a) nitisinone (4 mg/ml);
(b) citric acid monohydrate (9 mg/ml);
(c) trisodium citrate dihydrate (2.1 mg/ml)
(d) hydroxypropyl methylcellulose (5 mg/ml);
(e) glycerol (500 mg/ml);
(f) methyl paraben (1.4 mg/ml);
(g)propyl paraben (0.14 mg/ml); and
(h) polysorbate 80 (0.14 mg/ml).

14. The formulation according to any one of claims 1-7 or 10-12, comprising:

(a) nitisinone (4 mg/ml);
(b) citric acid monohydrate (9 mg/ml);
(c) trisodium citrate dihydrate (2.1 mg/ml)
(d) hydroxypropyl methylcellulose (5 mg/ml);
(e) glycerol (500 mg/ml);
(f) sodium benzoate (1.0 mg/ml); and
(g) polysorbate 80 (0.14 mg/ml).

15. The formulation according to claim 13 or 14, in addition comprising a flavoring agent.

16. The formulation according to any one of claims 1 to 15, for use in the treatment of a medical condition selected from tyrosinaemia, Parkinson's disease, depression, restless leg syndrome, and alkaptonuria.

17. The formulation according to claim 16, for use in the treatment of hereditary tyrosinaemia type 1 (HT-1).

18. The formulation according to claim 17, for use in the treatment of hereditary tyrosinaemia type 1 (HT-1) in a paediatric patient.

Patentansprüche

1. Für die orale Verabreichung geeignete flüssige pharmazeutische Formulierung, umfassend:

(a) eine Suspension einer wirksamen Menge an mikronisiertem 2-(2-Nitro-4-trifluormethylbenzoyl)-1,3-cyclohexandion (Nitisinon) und
(b) Citronensäurepuffer mit einem pH-Wert im Bereich von 2,5 bis 3,5, vorzugsweise einem pH-Wert von 3,0.

2. Formulierung nach Anspruch 1, wobei die Menge an Nitisinon 1 bis 10 mg/ml, vorzugsweise 4 mg/ml, beträgt.

3. Formulierung nach Anspruch 1, welche zusätzlich ein oder mehrere pharmazeutisch unbedenkliche Bestandteile ausgewählt aus der Gruppe bestehend aus Suspensionsmitteln, Süßstoffen, Konservierungsstoffen, Tensiden und Geschmacksstoffen umfasst.

4. Formulierung nach Anspruch 3, wobei es sich bei dem Suspensionsmittel um Hydroxypropylmethylcellulose handelt.

5. Formulierung nach Anspruch 4, wobei es sich bei dem Suspensionsmittel um Hydroxypropylmethylcellulose in einer Menge von 1 bis 20 mg/ml, vorzugsweise 5 mg/ml, handelt.

6. Formulierung nach Anspruch 3, wobei es sich bei dem Süßstoff um Glycerin handelt.

7. Formulierung nach Anspruch 6, wobei es sich bei dem Süßstoff um Glycerin in einer Menge von 100 bis 500 mg/ml, vorzugsweise 500 mg/ml, handelt.

8. Formulierung nach Anspruch 3, wobei es sich bei dem Konservierungsstoff um Methylparaben und/oder Propylparaben handelt.

9. Formulierung nach Anspruch 8, wobei es sich bei den Konservierungsstoffen um Methylparaben in einer Menge von 1 bis 2 mg/ml, vorzugsweise 1,4 mg/ml, und Propylparaben in einer Menge von 0,1 bis 0,2 mg/ml, vorzugsweise 0,14 mg/ml, handelt.

10. Formulierung nach Anspruch 3, wobei es sich bei dem Konservierungsstoff um Natriumbenzoat in einer Menge von 0,2 bis 5 mg/ml, vorzugsweise 1 mg/ml, handelt.

11. Formulierung nach Anspruch 3, wobei es sich bei dem Tensid um Polysorbat 80 handelt.

12. Formulierung nach Anspruch 11, wobei es sich bei dem Tensid um Polysorbat 80 in einer Menge von 0,1 bis 20 mg/ml, vorzugsweise von 0,10 bis 0,15 mg/ml, handelt.

13. Formulierung nach einem der Ansprüche 1-9, 11 oder 12, umfassend:

(a) Nitisinon (4 mg/ml),
(b) Citronensäure-monohydrat (9 mg/ml),
(c) Trinatriumcitrat-dihydrat (2,1 mg/ml),
(d) Hydroxypropylmethylcellulose (5 mg/ml),
(e) Glycerin (500 mg/ml),
(f) Methylparaben (1,4 mg/ml),
(g) Propylparaben (0,14 mg/ml) und
(h) Polysorbat 80 (0,14 mg/ml).

14. Formulierung nach einem der Ansprüche 1-7 oder 10-12, umfassend:

(a) Nitisinon (4 mg/ml),
(b) Citronensäure-monohydrat (9 mg/ml),
(c) Trinatriumcitrat-dihydrat (2,1 mg/ml),
(d) Hydroxypropylmethylcellulose (5 mg/ml),
(e) Glycerin (500 mg/ml),
(f) Natriumbenzoat (1,0 mg/ml) und
(g) Polysorbat 80 (0,14 mg/ml).

15. Formulierung nach Anspruch 13 oder 14, welche zusätzlich einen Geschmacksstoff umfasst.

16. Formulierung nach einem der Ansprüche 1 bis 15 zur Verwendung bei der Behandlung eines medizinischen Leidens ausgewählt aus Tyrosinämie, Parkinson-Krankheit, Depression, Restless-Legs-Syndrom und Alkaptonurie.

17. Formulierung nach Anspruch 16 zur Verwendung bei der Behandlung von erblicher Tyrosinämie vom Typ 1 (HT-1).

18. Formulierung nach Anspruch 17 zur Verwendung bei der Behandlung von erblicher Tyrosinämie vom Typ 1 (HT-1) bei einem pädiatrischen Patienten.

Revendications

1. Formulation pharmaceutique liquide adaptée pour administration orale, comprenant

   (a) une suspension d'une quantité efficace de 2-(2-nitro-4-trifluorométhylbenzoyl)-1,3-cyclohexanedione micronisée (nitisinone) ; et
   (b) un tampon acide citrique ayant un pH dans la plage de 2,5 à 3,5, de préférence pH 3,0.

2. Formulation selon la revendication 1 dans laquelle la quantité de nitisinone est de 1 à 10 mg/ml, de préférence 4 mg/ml.

3. Formulation selon la revendication 1, comprenant en outre un ou plusieurs constituants pharmaceutiquement acceptables choisis dans le groupe constitué d'agents de suspension, édulcorants, conservateurs, tensioactifs, et agents aromatisants.

4. Formulation selon la revendication 3 dans laquelle l'agent de suspension est l'hydroxypropylméthylcellulose.

5. Formulation selon la revendication 4 dans laquelle l'agent de suspension est l'hydroxypropylméthylcellulose dans une quantité de 1 à 20 mg/ml, de préférence 5 mg/ml.

6. Formulation selon la revendication 3 dans laquelle l'édulcorant est le glycérol.

7. Formulation selon la revendication 6 dans laquelle l'édulcorant est le glycérol dans une quantité de 100 à 500 mg/ml, de préférence 500 mg/ml.

8. Formulation selon la revendication 3 dans laquelle le conservateur est le méthyl-parabène et/ou le propyl-parabène.

9. Formulation selon la revendication 8 dans laquelle les conservateurs sont le méthyl-parabène dans une quantité de 1 à 2 mg/ml, de préférence 1,4 mg/ml, et le propyl-parabène dans une quantité de 0,1 à 0,2 mg/ml, de préférence 0,14 mg/ml.

10. Formulation selon la revendication 3 dans laquelle le conservateur est le benzoate de sodium dans une quantité de 0,2 à 5 mg/ml, de préférence 1 mg/ml.

11. Formulation selon la revendication 3 dans laquelle le tensioactif est le polysorbate 80.

12. Formulation selon la revendication 11 dans laquelle le tensioactif est le polysorbate 80 dans une quantité de 0,1 à 20 mg/ml, de préférence de 0,10 à 0,15 mg/ml.

13. Formulation selon l'une quelconque des revendications 1 à 9, 11 ou 12, comprenant :

    (a) nitisinone (4 mg/ml) ;
    (b) acide citrique monohydraté (9 mg/ml) ;
    (c) citrate trisodique dihydraté (2,1 mg/ml) ;
    (d) hydroxypropylméthylcellulose (5 mg/ml) ;
    (e) glycérol (500 mg/ml) ;
    (f) méthyl-parabène (1,4 mg/ml) ;
    (g) propyl-parabène (0,14 mg/ml) ; et
    (h) polysorbate 80 (0,14 mg/ml).

14. Formulation selon l'une quelconque des revendications 1 à 7 ou 10 à 12, comprenant :

    (a) nitisinone (4 mg/ml) ;
    (b) acide citrique monohydraté (9 mg/ml) ;
    (c) citrate trisodique dihydraté (2,1 mg/ml) ;
    (d) hydroxypropylméthylcellulose (5 mg/ml) ;
    (e) glycérol (500 mg/ml) ;
    (f) benzoate de sodium (1,0 mg/ml) ; et
    (g) polysorbate 80 (0,14 mg/ml).

15. Formulation selon la revendication 13 ou 14, comprenant en outre un agent aromatisant.

16. Formulation selon l'une quelconque des revendications 1 à 15, pour utilisation dans le traitement d'une affection médicale choisie parmi la tyrosinémie, la maladie de Parkinson, la dépression, le syndrome des jambes sans repos, et l'alcaptonurie.

17. Formulation selon la revendication 16, pour utilisation dans le traitement de la tyrosinémie héréditaire de type 1 (HT-1).

18. Formulation selon la revendication 17, pour utilisation dans le traitement de la tyrosinémie héréditaire de type 1 (HT-1) chez un patient pédiatrique.

REFERENCES CITED IN THE DESCRIPTION

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NITIZINONT TARTALMAZÓ, FOLYÉKONY GYÓGYÁSZATI KÉSZÍTMÉNY

Szabadalmi igénypontok

1. Folyékony gyógyászati készítmény, amely alkalmas szájon át történő beadásra, és amely tartalmazza a következőket:

(a) mikronizált 2-(2-nitro-4-trifluormetilbenzoil)-1,3-ciklohexándion (nitizinon) hatásos mennyiségének szuszpenziója, és

(b) citromsavpuffer, melynek pH-ja 2,5-3,5, előnyösen 3,0.

2. Az 1. igénypont szerinti készítmény, ahol a nitizinon mennyisége 1-10 mg/ml, előnyösen 4 mg/ml.

3. Az 1. igénypont szerinti készítmény, amely tartalmaz egy vagy több, a következőkből álló csoportból választott, gyógyászatilag elfogadható alkotórészt is: szuszpendálószerek, édesítőszerek, tartósítószerek, felületaktív szerek és ízesítők.

4. A 3. igénypont szerinti készítmény, ahol a szuszpendálószer hidroxipropil-metilcellulóz.

5. A 4. igénypont szerinti készítmény, ahol a szuszpendálószer 1-20 mg/ml, előnyösen 5 mg/ml hidroxipropil-metilcellulóz.

6. A 3. igénypont szerinti készítmény, ahol az édesítőszer glicerin.

7. A 6. igénypont szerinti készítmény, ahol az édesítőszer 100-500 mg/ml, előnyösen 500 mg/ml glicerin.

8. A 3. igénypont szerinti készítmény, ahol a tartósítószer metil-parabén és/vagy propil-parabén.

9. A 8. igénypont szerinti készítmény, ahol a tartósítószer 1-2 mg/ml, előnyösen 1,4 mg/ml metil-parabén és 0,1-0,2 mg/ml, előnyösen 0,14 mg/ml propil-parabén.

10. A 3. igénypont szerinti készítmény, ahol a tartósítószer 0,2-5 mg/ml, előnyösen 1 mg/ml nátrium-benzoát.

11. A 3. igénypont szerinti készítmény, ahol a felületaktív szer poliszorbát 80.

12. A 11. igénypont szerinti készítmény, ahol a felületaktív szer 0,1-20 mg/ml, előnyösen 0,10-0,15 mg/ml poliszorbát 80.

13. Az 1-9., 11. és 12. igénypontok bármelyike szerinti készítmény, amely tartalmaz

(a) nitizinont (4 mg/ml),

(b) citromsav-monohidrátot (9 mg/ml),

(c) trinátrium-citrát-dihidrátot (2,1 mg/ml).

(d) hidroxipropil-metilcellulózt (5 mg/ml),
(e) glicerint (500 mg/ml),
(f) metil-parabént (1,4 mg/ml),
(g) propil-parabént (0,14 mg/ml) és
(h) poliszorbát 80-at (0,14 mg/ml).

14. Az 1-7. és 10-12. igénypontok bármelyike szerinti készítmény, amely tartalmaz
(a) nitizinont (4 mg/ml),
(b) citromsav-monohidrátot (9 mg/ml),
(c) trinátrium-citrát-dihidrátot (2,1 mg/ml),
(d) hidroxipropil-metilcellulózt (5 mg/ml),
(e) glicerint (500 mg/ml),
(f) nátrium-benzoátot (1,0 mg/ml) és
(g) poliszorbát 80-at (0,14 mg/ml).

15. A 13. vagy 14. igénypont szerinti készítmény, amely tartalmaz ízesítőszert is.

16. Az 1-15. igénypontok bármelyike szerinti készítmény tirozinémia, Parkinson-betegség, depresszió, nyugtalanláb-szindróma és alkaptonuria közül választott betegség kezelésében történő alkalmazásra.

17. A 16. igénypont szerinti készítmény örökletes, 1-es típusú tirozinémia (HT-1) kezelésében történő alkalmazásra.

18. A 17. igénypont szerinti készítmény, gyermek páciensben örökletes, 1-es típusú tirozinéma (HT-1) kezelésében történő alkalmazásra.