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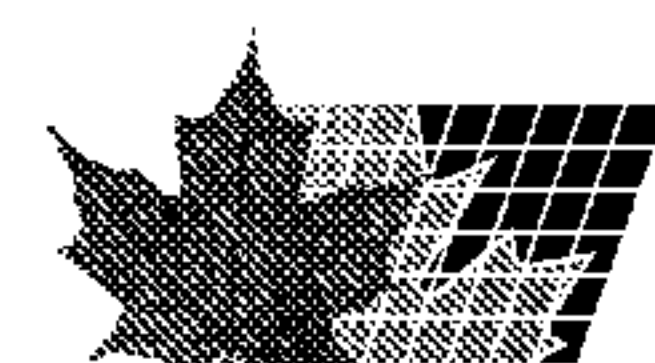
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(57) **Abrégé/Abstract:**

The preparation of an improved galenic delivery form of valnemulin, which is notable for its good tolerance and stability in storage, is described. The new delivery form in question is a non-aqueous or oily injection formulation, which is obtainable by means of in situ preparation and subsequent stabilisation of the free, relatively unstable base of the active ingredient. A further aspect of the present invention concerns the usage of such an injection formulation in a method of treating infectious diseases in productive livestock or domestic animals.



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(54) Title: VALNEMULIN FORMULATION

(57) **Abstract:** The preparation of an improved galenic delivery form of valnemulin, which is notable for its good tolerance and stability in storage, is described. The new delivery form in question is a non-aqueous or oily injection formulation, which is obtainable by means of *in situ* preparation and subsequent stabilisation of the free, relatively unstable base of the active ingredient. A further aspect of the present invention concerns the usage of such an injection formulation in a method of treating infectious diseases in productive livestock or domestic animals.

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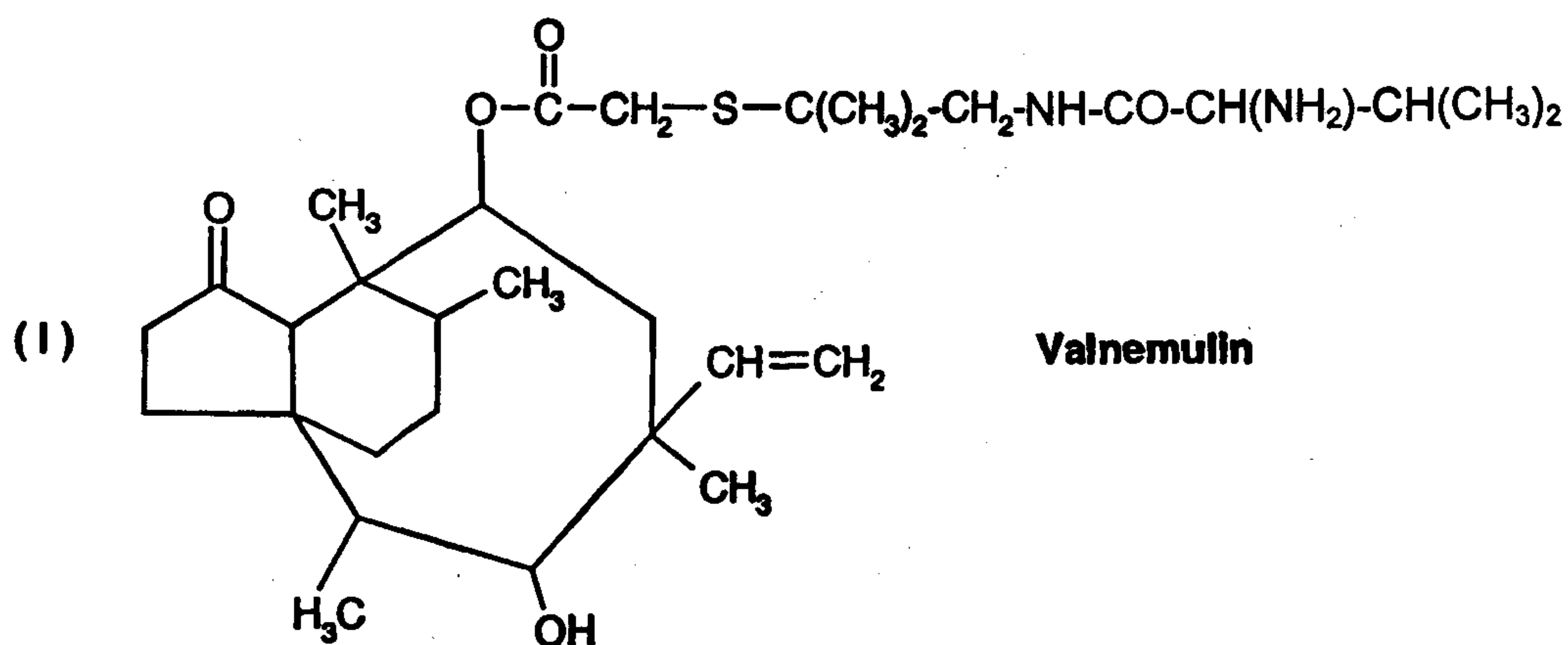
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VALNEMULIN FORMULATION

The present invention relates to the preparation of an improved galenic delivery form of valnemulin, which is notable for its good tolerance and stability in storage. The new delivery form in question is a non-aqueous or oily injection formulation, which is obtainable by means of *in-situ* preparation and subsequent stabilisation of the free, relatively unstable base of the active ingredient. A further aspect of the present invention concerns the oily injection formulation as such and its usage in a method of treating infectious diseases in productive livestock or domestic animals.

In connection with the present invention, valnemulin is understood to be the compound shown in the following formula I



Valnemulin is known from EP-0.153.277 and is described specifically therein in example 12. Valnemulin is also known by the commercial name Econor®.

As is generally known, this compound has antibacterial properties, e.g. following oral or parenteral administration, and is used for the prevention or cure of a series of bacterial infections in the field of animal health. The broad spectrum of activity includes *Streptococcus aronson*, *Staphylococcus aureus*, *Mycoplasma arthritidis*, *Mycoplasma bovis*, *Mycoplasma bovis mastitidis*, *Mycoplasma bovis rhinitis*, *Mycoplasma sp.*, *Mycoplasma canis*, *Mycoplasma felis*, *Mycoplasma fermentans*, *Mycoplasma gallinarum*, *Mycoplasma gallisepticum*, *A. granularum*, *Mycoplasma hominis*, *Mycoplasma hyorhinis*,

Actinobacillus laidlawii, *Mycoplasma meleagridis*, *Mycoplasma neurolyticum*, *Mycoplasma pneumonia* und *Mycoplasma hyopneumoniae*.

WO 98/01127 describes its excellent activity against an illness complex that can arise whenever animals are kept in a very restricted space (increased stocking density) e.g. for transport purposes, and are thus exposed to great stress. The most frequent pathogens that play a decisive role in this instance are *Mycoplasma hyopneumoniae*, *Serpulina* (formerly *Treponema*) *hyodysenteriae*, *Serpulina pilosicoli*, *Lawsonia intracellularis*, *Mycoplasma gallisepticum*, *Pasteurella multocida*, *Actinobacillus* (*Haemophilus*) *pleuropneumoniae* and *Haemophilus parasuis*, whereby diseases of the respiratory tract and other infections often occur together and lead to a complex clinical picture. All herd animals are affected, e.g. cattle, sheep and pigs, but also poultry.

In its free form (valnemulin base), valnemulin is relatively unstable and is therefore primarily used in the form of its salts, particularly as the hydrochloride. A current method of administering antibiotics in the field of animal health is the injection, since it is suitable for administering a controlled single dose and thus a quantity tailored to individual needs. This is often crucial to successful control of many infectious diseases in the field of animal medicines. In contrast, oral administration cannot be controlled nearly so well, and is more customary in human medicine.

However, it has been shown that aqueous injection solutions and even oily injection suspensions of the salts of valnemulin are poorly tolerated by most domestic animals and in particular by pigs. Damage ranging from mild skin irritation to poorly healing necroses, has been observed. This is also one of the reasons that valnemulin has mainly been used orally until now. In addition, aqueous solutions usually do not show the desired depot action. A further problem is that valnemulin cannot be produced in technical quantities in the free form, as the so-called valnemulin base, but occurs as the salt, and has therefore been used for therapy as the salt.

However, for commercial usage, it would be extremely desirable to have stable, storable, oily and, in addition, tolerable injection preparations.

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It has now surprisingly been found that chemically stable, non-aqueous injection preparations of valnemulin can be produced *in situ* and can be stabilised in non-aqueous or oily solvents.

5 According to one aspect of the present invention, there is provided a method of producing a non-aqueous injection formulation comprising: (a) as active ingredient the free valnemulin base; (b) optionally an antioxidant to protect against oxidising influences; and (c) optionally a
10 preservative to protect against microbial infestation; wherein the free valnemulin base is produced *in situ* from a salt form in a physiologically acceptable non-aqueous solvent or solvent mixture (i) and is stabilised by adding a further solvent (ii) and wherein the resulting free
15 valnemulin base is admixed with optional components (b) and (c), when optional components (b) and (c) are present.

 According to another aspect of the invention, there is provided an oily, stabilized injection formulation comprising free valnemulin base produced according to the
20 method defined herein and a pharmaceutically acceptable carrier or diluent. The formulation may be used to treat an infectious disease in productive livestock or domestic animals.

 Suitable non-aqueous or oily solvents (i) for the
25 *in situ* production of the valnemulin free base in connection with the present invention are isopropyl myristate, semi-synthetic and synthetic esters of glycerol, or ethylene or propylene glycol with short-chained to medium-chained mono- or dicarboxylic acids, for example mono-, di- and
30 triglycerides (e.g. neutral oils or miglyol).

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In order to stabilize the free base, other solvents (ii) are added to these solvents (i), e.g. esters of medium-chained to long-chained carboxylic acids (e.g. lactic, lauric, myristic, palmitic, stearic and oleic acid etc.) with monovalent alcohols (e.g. ethanol, n-propanol, 2-propanol, etc.), 1,2-O-isopropylidene glycerol, glycerol, ethanol, N,N-dimethylacetamide, benzyl benzoate or tetraethylene glycol, so that mixtures (iii) of solvents (i) with solvents (ii) are present in the end product. The addition of solvents (ii) serves to improve the galenic properties. Especially preferred as solvent (i) is isopropyl myristate with the addition of solvent (ii) benzyl benzoate or ethanol.

A preferred embodiment of the present invention is notable for the fact that solvents (i) and (ii) are present in the end product in a ratio of ca. 70:15.

As already mentioned, the free base of valnemulin has until now not been obtainable on a large scale. Therefore, in the following, a new and surprising way is shown of preparing this free base *in situ* and formulating it in a stable form.

To this end, 0.5 to 30% by weight, preferably 5 to 10% by weight of a salt of valnemulin is suspended in a non-aqueous solvent (i) in a concentration range of 50 to 99% by weight. Appropriate alkaline excipients are added to the suspension whilst stirring and heating gently at a temperature ranging from ca. 50 to 80°C, in order to release the valnemulin base *in situ*, whereby the free base immediately dissolves in the solvent (i).

Suitable alkaline excipients for the *in situ* release of the free valnemulin base are, for example, alkali and alkaline earth carbonates, hydrogen carbonates and hydroxides, or organic amines, such as triethylamine.

After completion of this process, the two phases which are immiscible together, the aqueous and the non-aqueous phase, are separated from one another at a temperature of ca. 50 to ca. 80°C. This phase separation may be assisted by centrifuging. The separated non-aqueous phase, which now contains the free base of (I), is washed many times with water at room temperature and undergoes fresh phase separation at a temperature of ca. 50 to 80°C. The non-aqueous phase is subsequently dried e.g. using a vacuum, in order to remove residual water and volatile substances such as organic amines, and is mixed with a solvent or solvent mixture from group (ii) to stabilise it. This addition of (ii) improves the galenic properties of the formulations.

To stabilise against oxidising influences, physiologically acceptable antioxidants may be added to the solution obtained, e.g. esters of ascorbic acid, butyl hydroxy toluene, butyl hydroxy anisole, propyl gallate, tocopherols or tocopherol derivatives, etc., and to stabilise against microbial infestation, physiologically acceptable preservatives may be added, e.g. benzyl alcohol, chlorocresol, chlorobutanol, esters of parahydroxybenzoic acid, phenoxy-ethanol, phenol and phenol derivatives, sorbic acid, etc.

The finished solutions are sterile-filtered or sterilised in the final container, e.g. in ampoules.

The present invention thus comprises essentially the following preferred aspects:

A method of producing a non-aqueous injection formulation which contains as active ingredient the free valnemulin base, optionally a stabiliser to protect against oxidising influences, and likewise optionally a stabiliser to protect against microbial infestation, and which is characterised in that the free valnemulin base is produced *in situ* from a salt form in a physiologically acceptable non-aqueous solvent or solvent mixture from the above-mentioned category (i) and is stabilised by adding a further solvent from the above-mentioned category (ii).

A preferred embodiment is characterised in that 0.5 to 30% by weight of a salt of valnemulin in a physiologically acceptable non-aqueous solvent or solvent mixture of the above-mentioned category (i) is released *in situ* whilst heating gently and adding an appropriate alkaline excipient.

Preferably one or more solvents are used as the non-aqueous solvent or solvent mixture from the above-mentioned category (i), these being selected from the series isopropyl myristate, semi-synthetic and synthetic esters of glycerol, or ethylene or propylene glycol with short-chained to medium-chained mono- or dicarboxylic acids, medium-chained to long-chained carboxylic acids with monovalent alcohols.

A further notable embodiment is characterised in that a salt of valnemulin is suspended in a solvent in a concentration range of 50 to 99% by weight, and the free base of valnemulin is produced *in situ* using an appropriate alkaline excipient, whilst heating gently and stirring.

In a preferred variant of the process, to physically stabilise the valnemulin base, an ester of medium-chained to long-chained carboxylic acids with monovalent alcohols, 1,2-O-isopropylidene glycerol, glycerol, ethanol, N,N-dimethylacetamide, benzyl benzoate or tetra-ethylene glycol is added as a stabilising solvent of the above-mentioned category (ii).

In the preferred embodiments, solvents (i) and (ii) are present in the end product in a ratio of ca. 70:15.

An especially preferred variant of the process is characterised in that a salt of valnemulin is suspended in a solvent or solvent mixture (i), an appropriate alkaline excipient is added to the suspension whilst stirring and heating gently in the range of ca. 50 to ca. 80°C in order to effect *in situ* release of the valnemulin base, the resulting free base being absorbed by this solvent (i); after completion of this process, the two phases which are immiscible together, the aqueous and the non-aqueous phase, are separated from one another at a temperature of ca. 50 to ca. 80°C; the separated non-aqueous phase, which now contains the free base of (I), is washed many times with water at room temperature and undergoes fresh phase separation at a temperature of ca. 50 to 80°C; the non-aqueous phase is subsequently dried and volatile components are removed, and it is mixed with a solvent or solvent mixture from group (ii) to stabilise it

A further object of the present invention is formed by an oily, stabilised injection formulation, containing as active ingredient the free valnemulin base, which is obtainable by one of the above-characterised releasing and stabilising processes. The present invention also includes the usage of the described oily injection formulation in a method of treating infectious diseases of productive livestock or domestic animals.

Formulation examples

Example 1: Injection formulations

Each 100 ml of the ready injection formulation contains 5 g of valnemulin base. The amounts of grams indicated before the parenthesis (formulation 1: 90.0 g, formulation 2: 85.0 g and formulation 3: 86.0 g) are a result of the different densities of the mixtures of isopropyl myristate, ethanol and benzyl benzoate. The reason for giving two figures lies in the preparation, since the ingredients are weighed in grams, but volumetric (ml) amounts are measured in.

Formulation 1	g
valnemulin	5.0
benzyl benzoate	15.1
isopropyl myristate	69.9
	90.0 (100.0 ml)

Formulation 2	g
valnemulin	5.0
ethanol	13.5
isopropyl myristate	66.5
	85.0 (100.0 ml)

Formulation 3	g
valnemulin	5.0
isopropyl myristate	81.0
	86.0 (100.0 ml)

Chemical stability data

Stability of an oily injection solution of valnemulin in %:

valnemulin content after	25°C/60% relative humidity			40°C/75% relative humidity		
	form. 1	form. 2	form. 3	form. 1	form. 2	form. 3
0 months	99.2	99.8	98.5	99.2	99.8	98.5
1 month	99.9	99.2	98.9	99.7	100.4	98.4
2 months	100.2	100.5	100.3	99.4	100.4	99.4
3 months	101.2	102.0	99.6	100.2	101.2	100.8
6 months	101.4	100.4	n.a.	98.9	99.2	n.a.

n.a. indicates not tested. Values greater than 100% result from deviations in the analysis method.

All three formulations proved to be chemically stable.

Stability of an oily suspension of valnemulin hydrochloride in %:

valnemulin content after	25°C/60% relative humidity	40°C/75% relative humidity
0 weeks	102.0	102.0
8 weeks	104.8	102.8

Values greater than 100% result from deviations in the analysis method.

Tolerance data

An investigation of tolerance was made by means of an intramuscular injection of the injection formulation to pigs and evaluating its effect on the adjacent tissue.

	diameter of necrosis in cm			
	formulation 1	placebo	formulation 2	placebo
neck area	1	0	4	n.a.
thigh	1	n.a.	3	5

The formulations are compared with the placebo. It is shown that the two formulations do not exhibit significantly poorer tolerance than the placebos.

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CLAIMS:

1. A method of producing a non-aqueous injection formulation comprising:

(a) as active ingredient the free valnemulin base;

5 (b) optionally an antioxidant to protect against oxidising influences; and

(c) optionally a preservative to protect against microbial infestation; wherein the free valnemulin base is produced *in situ* from a salt form in a physiologically acceptable non-aqueous solvent or solvent mixture (i) and is stabilised by adding a further solvent (ii) and wherein the resulting free valnemulin base is admixed with optional components (b) and (c), when optional components (b) and (c) are present.

15 2. A method according to claim 1, in which 0.5 to 30% by weight of a salt of valnemulin in a physiologically acceptable non-aqueous solvent or solvent mixture (i) is released *in situ* whilst heating at a temperature of about 50 to about 80°C and adding an appropriate alkaline excipient.

20 3. A method according to claim 1 or 2, in which one or more solvents are used as the non-aqueous solvent or solvent mixture (i), wherein the one or more solvents are selected from the group consisting of isopropyl myristate, esters of glycerol, ethylene glycol with short-chained to medium-chained mono- or dicarboxylic acids, and propylene glycol with short-chained to medium-chained mono- or dicarboxylic acids.

4. A method according to any one of claims 1 to 3, in which a salt of valnemulin is suspended in a solvent in a concentration range of 50 to 99% by weight, and the free

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base of valnemulin is produced *in situ* using an appropriate alkaline excipient, whilst heating at a temperature of about 50 to about 80°C and stirring.

5. A method according to any one of claims 1 to 4,
5 wherein in order to physically stabilise the valnemulin base, an ester of medium-chained to long-chained carboxylic acids with monovalent alcohols, 1,2-O-isopropylidene glycerol, glycerol, ethanol, N,N-dimethylacetamide, benzyl benzoate or tetraethylene glycol is added as a stabilising
10 solvent (ii).

6. A method according to any one of claims 1 to 5, wherein the solvents (i) and (ii) are present in a ratio of ca. 70:15.

7. A method according to claim 4, wherein a salt of
15 valnemulin is suspended in a solvent or solvent mixture (i), an appropriate alkaline excipient is added to the suspension whilst stirring and heating in a temperature range of about 50 to about 80°C in order to effect *in situ* release of the valnemulin base, the resulting free base is absorbed by this
20 solvent (i); after completion of this process, the two phases which are immiscible together, the aqueous and the non-aqueous phase, are separated from one another at a temperature of about 50 to about 80°C; the separated non-aqueous phase, which now contains the free base of (i), is
25 washed with water at room temperature and undergoes fresh phase separation at a temperature of about 50 to about 80°C; the non-aqueous phase is subsequently dried and volatile components are removed, and it is mixed with a solvent or solvent mixture from group (ii) to stabilise it.

30 8. An oily, stabilised injection formulation comprising free valnemulin base; wherein the free valnemulin base is obtained according to the method defined in any one

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of claims 1 to 7 and a pharmaceutically acceptable carrier or diluent.

9. Use of an injection formulation according to claim 8 for treating an infectious disease of productive
5 livestock or domestic animals.

10. Use of the *in situ*-formed valnemulin base formed by the method defined in any one of claims 1 to 7 in manufacture of a non-aqueous injection formulation for treatment of an infectious disease of productive livestock
10 or domestic animals.

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