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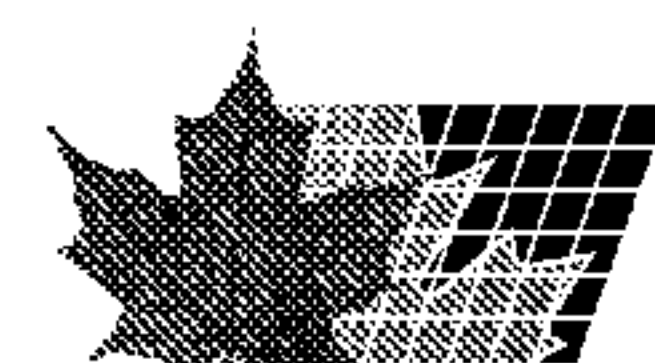
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(54) Titre : SOLUTIONS STABLES DE MELOXICAM A FORTE CONCENTRATION POUR INJECTION SANS AIGUILLE

(54) Title: HIGHLY CONCENTRATED STABLE MELOXICAM SOLUTIONS FOR NEEDLELESS INJECTION

(57) Abrégé/Abstract:

Aqueous cyclodextrin-free solution of meloxicam suitable for administration by needleless injection, containing a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more suitable excipients, the content of dissolved meloxicam salt being from 35 to 100 mg/ml. The formulation according to the invention has a shelf-life of up to 24 months or more.



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Abstract

Aqueous cyclodextrin-free solution of meloxicam suitable for administration by
needleless injection, containing a pharmacologically acceptable meloxicam salt of an
5 organic or inorganic base and one or more suitable excipients, the content of
dissolved meloxicam salt being from 35 to 100 mg/ml. The formulation according to
the invention has a shelf-life of up to 24 months or more.

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Highly concentrated stable meloxicam solutions for needleless injection

The present invention relates to highly concentrated stable meloxicam solutions for
5 intracutaneous or subcutaneous needleless injection for treating respiratory diseases
and inflammation in mammals.

Background of the invention

10 Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-
carboxamide-1,1-dioxide) is an active substance which belongs to the group of
NSAIDs (non-steroidal-anti-inflammatory drugs). Meloxicam and the sodium and
meglumine salt thereof (N-methyl-D-glucamine salt) are described in EP-A-0 002
482. EP-A-0 002 482 shows, *inter alia*, the example of a 0.2% injectable solution of
15 meloxicam consisting of the meglumine salt of the active substance, sodium chloride
and water.

EP-A-0 945 134 discloses the pH-dependent solubility characteristics of meloxicam
and its salts, i.e. the sodium salt, the ammonium salt and the meglumine salt, in
20 aqueous solution. According to this, meloxicam is an active substance which does
not dissolve readily in water. The meloxicam salts, particularly the meglumine salt,
exhibit improved solubility as the pH increases between 4 and 10, as shown in Table
1 of EP-0 945 134. However, up till now it has only been possible to produce stable,
clear, aqueous solutions with a low concentration of meloxicam. In addition to the *in*
25 *situ* formation of a meloxicam salt, e.g. meglumine salt, and the addition of
solubilisers, these solutions were required to have a pH in the range of maximum
possible solubility as well as being reasonably well tolerated and contain a high
proportion of organic solvent. Attempts to produce formulations with the same or a
similar recipe led to cloudiness of the solution, e.g. if the meloxicam concentrations
30 were higher, e.g. 2%.

WO9959634 A1 describes an eye drop solution containing 0.5% meloxicam but makes no reference to possible meloxicam concentrations over 1%. A commercially available 0.5% meloxicam solution is used in small animals such as dogs, heifers and calves to treat respiratory diseases and inflammation, for example.

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An active substance for needleless injection makes it possible for the animal keeper himself to administer a sterile solution to the animal. The requirements imposed on an active substance solution for needleless injection include *inter alia* small injectable volumes, the possibility of weight-related dosage and maximum possible flexibility in
10 the number of actuation processes per treatment unit. Accordingly, injection volumes of 50 µl per actuation, for example, are technically feasible. For this purpose, as described in DE10010123 A1, a sterile solution may be transferred under aseptic conditions into a sterile cartridge which is then inserted in the metering system.

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It has not hitherto been possible to treat large farm animals with a meloxicam solution that could be injected without a needle. The low concentration of active substance in the injectable solution did not allow an acceptable, well tolerated injection volume. The administration of meloxicam solutions by needlefree injection
20 requires that the solution be free from particles, as solutions of this kind are subject to the same requirements as solutions for parenteral administration. In addition to intracutaneous and subcutaneous administration transcutaneous administration should also be taken into consideration, involving administering the substance directly into the blood vessels. This latter route is directly comparable with
25 intravenous administration by injection through a syringe. The method of administration by needle-free injection has a relevant effect on bioavailability, which will be greater than with intracutaneous or subcutaneous administration, as transcutaneous absorption also takes place with needle-free injection. Organic solvents, solubilisers and water-soluble substances can only be used in certain
30 concentrations for reasons of drug tolerance. The problem of the present invention is to produce particle-free highly concentrated meloxicam solutions which are stable over long periods, which are suitable for needleless injection.

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Description of the invention

According to one aspect of the invention, there is provided aqueous cyclodextrin-free solution of meloxicam suitable for administration by needleless injection, containing a pharmacologically acceptable meloxicam salt of an organic or inorganic base,

- 5 wherein it contains a solubiliser, as well as one or more excipients selected from among the group comprising citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid and EDTA or the salts thereof, and the content of dissolved meloxicam salt is from 35 to 100 mg/ml.

- 10 Surprisingly, it has been found that highly concentrated meloxicam solutions with a content of active substance ranging from 35 to 100 mg/ml which contain, in addition to a meloxicam salt and certain excipients, another excipient selected from among citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid and EDTA or the salts thereof, may be produced so as to be particle-free and stable over long periods. The stability was achieved with an unexpectedly small amount of organic solubilisers.
- 15 The formulation was found to be stable even when subjected to the process of final sterilisation.

- This results in the solution to the problem according to the invention, as a formulation of a meloxicam solution which contains, in addition to a meloxicam salt, small concentrations of solubiliser, a preservative, a buffer substance for achieving the
- 20 optimum pH range and another excipient.

- The invention relates to aqueous cyclodextrin-free solutions of meloxicam for needle-free intracutaneous or subcutaneous administration which contain a pharmacologically acceptable meloxicam salt of an organic or inorganic base in a highly concentrated solution with 35 to 100 mg/ml of meloxicam together with suitable
- 25 excipients.

The formulation according to the invention overcomes the problem arising from the prior art of providing a solution of the active substance meloxicam which is suitable for needleless injection, by permitting a high concentration of active substance in a

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particle-free solution which is stable over the long term, having the composition described hereinafter.

The formulation according to the invention may contain, as the meloxicam salt, the meglumine, sodium, potassium or ammonium salt, preferably the meloxicam

5 meglumine salt.

The formulation may contain one or more excipients selected from among solubilisers.

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The solubilisers used may be, for example polyethyleneglycols, polyoxyethylene-polyoxypropylene copolymers (e.g. poloxamer 188), glycofurol, arginine, lysine, castor oil, propyleneglycol, solketal, polysorbate, glycerol, sorbitol, mannitol, xylitol, polyvinylpyrrolidone, lecithin, cholesterol, 12-hydroxystearic acid-PEG660-ester, 5 propyleneglycol monostearate, polyoxy-40-hydrogenated castor oil, polyoxyl-10-oleyl-ether, polyoxyl-20-cetostearylether and polyoxyl-40-stearate or a mixture of sorbitol, mannitol and xylitol, preferably polyethyleneglycols, polyoxyethylene-polyoxypropylene copolymers, glycofurol, polyvinylpyrrolidone, lecithin, cholesterol, 12-hydroxystearic acid-PEG660-esters, propyleneglycol monostearate, polyoxy-40-10 hydrogenated castor oil, polyoxyl-10-oleyl-ether, polyoxyl-20-cetostearylether and polyoxyl-40-stearate. Particularly preferred are polyethyleneglycols, glycofurol and polyoxyethylene-polyoxypropylene-copolymers, but especially polyethyleneglycols (e.g. Macrogol 300) and polyoxyethylene-polyoxypropylene copolymers (e.g. Poloxamer 188). The preservatives used may be, for example, ethanol, benzoic acid 15 and the sodium or potassium salts thereof, sorbic acid and the sodium or potassium salts thereof, chlorobutanol, benzyl alcohol, phenylethanol, methyl, ethyl, propyl or butyl-p-hydroxybenzoates, phenol, m-cresol, p-chloro-m-cresol or benzalkonium chloride. Particularly preferred are ethanol, benzoic acid and the sodium or potassium salts thereof, sorbic acid and the sodium or potassium salts thereof, 20 chlorobutanol, benzylalcohol, phenylethanol and methyl, ethyl, propyl or butyl p-hydroxybenzoates, but preferably ethanol, benzoic acid and the sodium or potassium salts thereof, sorbic acid and the sodium or potassium salts thereof, but especially ethanol.

25 The buffer system used to achieve a pH of between 8 and 10 may be, for example, glycine, a mixture of glycine and HCl, a mixture of glycine and sodium hydroxide solution, and the sodium and potassium salts thereof, a mixture of potassium hydrogen phthalate and hydrochloric acid, a mixture of potassium hydrogen phthalate and sodium hydroxide solution or a mixture of glutamic acid and glutamate. 30 Glycine, a mixture of glycine and HCl and a mixture of glycine/sodium hydroxide solution, especially glycine, are particularly preferred.

The aqueous solution of the invention may contain excipients selected from buffers and/or preservatives.

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Other suitable excipients are citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid and EDTA or the alkali metal salts thereof, preferably tartaric acid and EDTA or the alkali metal salts thereof, particularly disodium EDTA.

One embodiment of the invention contains, in addition to the meglumine
5 or sodium salt of the meloxicam, polyethyleneglycols, glycofurool and/or
polyoxyethylene-polyoxypropylene copolymers, but particularly polyethyleneglycols
(e.g. Macrogol 300) and/or polyoxyethylene-polyoxypropylene copolymers (e.g.
Poloxamer 188) as solubiliser, ethanol, benzoic acid and the sodium or potassium
salts thereof or sorbic acid and the sodium or potassium salts thereof, but particularly
10 ethanol, as preservative, and glycine, a mixture of glycine/HCl or a mixture of
glycine/sodium hydroxide solution, but preferably glycine, as buffer and disodium
EDTA as an additional excipient.

More particularly, the aqueous solution of the invention may contain
meloxicam, meglumine, a polyethyleneglycol, a polyoxyethylene-polyoxypropylene
15 copolymer, ethanol, glycine, disodium EDTA and optionally sodium hydroxide or
hydrochloric acid.

In an embodiment, the aqueous solution of the invention essentially
consists of meloxicam, meglumine, a polyethyleneglycol, a polyoxyethylene-
polyoxypropylene copolymer, ethanol, glycine, disodium EDTA, water suitable for
20 injection and optionally sodium hydroxide or hydrochloric acid.

The formulation according to the invention may contain meloxicam in a
concentration of 35-100 mg/ml, preferably 40-80 mg/ml, preferably 45-70 mg/ml,
particularly preferably 50-60 mg/ml, especially 55 mg/ml.

The meglumine concentration may be between 30 and 50 mg/ml,
25 preferably 35-45 mg/ml, preferably 38-42 mg/ml, especially about 40 mg/ml. The
possible sodium, potassium and ammonium concentrations are calculated
accordingly.

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The concentration of the solubilisers may be in the range from 20-200 mg/ml, preferably 30-150 mg/ml, preferably 40-130 mg/ml, more preferably 50-120 mg/ml, especially 70-100 mg/ml.

- 5 The concentration of the preservative ethanol may be in the range from 100-200 mg/ml, preferably 120-180 mg/ml, more preferably about 150 mg/ml.

The concentration of the preservatives benzoic acid and the sodium or potassium salts thereof, sorbic acid and the sodium or potassium salts thereof, chlorobutanol,
10 benzyl alcohol, phenylethanol, phenol, m-cresol and p-chloro-m-cresol may be in the

range from 0.5-50 mg/ml, preferably 1-10 mg/ml, more preferably 3-5 mg/ml.

The concentration of the preservatives benzalkonium chloride, phenylmercury nitrate and methyl-, ethyl-, propyl- or butyl-p-hydroxybenzoates may be in the range from
5 0.01-4 mg/ml, preferably 0.02-3 mg/ml, more preferably 0.1-0.5 mg/ml.

The concentration of the buffer substances may be between 4 and 138 mg/ml, preferably between 5 and 20 mg/ml, more preferably between 8 and 10 mg/ml.

10 The concentration of the other excipients mentioned above, i.e. EDTA, citric acid, lecithin, gluconic acid, tartaric acid and phosphoric acid or the salts thereof may be in the range from 0.2-3 mg/ml, preferably 0.3-2.5 mg/ml, preferably 0.5-2 mg/ml, most preferably 0.6-1.5 mg/ml, and in particular 0.7-1.0 mg/ml.

15 Meglumine and meloxicam may be used in a molar ratio of between 9:8 and 12:8, preferably in a molar ratio of 11:8, but especially in a molar ratio of 10:8.

In the formulation according to the invention, meloxicam and the other excipient, particularly disodium EDTA, may be present in a weight ratio of between 100:1 and
20 35:1, preferably between 80:1 and 40:1, preferably between 70:1 and 45:1, more preferably between 60:1 and 50:1, most preferably between 58:1 and 52:1, in particular about 55:1.

The formulation according to the invention may have a shelf-life after opening of 28
25 days or more.

The shelf-life of the solution in the sealed original packaging may be 1 month or more, in particular between 1 month and 24 months, but at least between 1 month and 18 months, preferably between 1 month and 12 months, more preferably
30 between 1 month and 9 months, most preferably between 1 month and 6 months, particularly between 1 month and 3 months.

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The formulation according to the invention should have a pH of between 8 and 10, preferably between 8.5 and 9, more preferably a pH between 8.7 and 8.9, particularly 8.8.

5 The formulation according to the invention is suitable for treating pain, inflammation, fever, acute mastitis, diarrhoea, lameness, oncological indications, problems with the locomotor apparatus, and respiratory complaints in animals, preferably acute mastitis, diarrhoea, lameness, problems with the locomotor apparatus and respiratory complaints, especially acute mastitis, diarrhoea, lameness, problems with
10 the locomotor apparatus and respiratory complaints, most preferably respiratory complaints and oncological indications. The treatment may be given in conjunction with antibiotic therapy.

The formulation according to the invention is suitable for treating animals, preferably
15 mammals, more particularly domestic pets, working animals or farm animals.

The formulation according to the invention is suitable for treating animals, preferably animals up to 500 kg, particularly domestic pets from 1 kg upwards, more preferably from 2 to 70 kg, most preferably 5 to 60 kg, or large animals up to 750 kg, preferably
20 50 kg to 500 kg, most preferably 100 to 400 kg.

The dosage of the formulation according to the invention should correspond to 0.1 to 1.0 mg of active substance per kg of bodyweight, preferably 0.4 to 0.8 mg/kg of bodyweight, more preferably 0.5 to 0.7 mg/kg of bodyweight, particularly preferably
25 0.6 mg/kg of bodyweight.

The formulation according to the invention may be prepared using the methods of preparing aqueous liquid formulations known from the literature. For example, the appropriate excipients may be added to a meloxicam salt solution.

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Formulations of the invention may be contained in a sterile cartridge, which can be used in a needleless injection system. Various commercial materials for aqueous liquid formulations which will allow sealing under inert gas and/or final sterilisation by autoclaving in the finished container may

be used as a packaging material for the formulation according to the invention. Such materials include for example ampoules or glass vials, particularly glass vials, e.g. 50 ml or 100 ml glass vials of glass Type I (according to Pharm. Eur/USP) in conjunction with rubber stoppers made of ethylenepropylenenorbornene terpolymer (EPDM) and
5 aluminium caps. Vials made of plastics, particularly COC (Cyclic Olefin Copolymer), and other types of rubber stoppers are also suitable.

The meloxicam solutions according to the invention will now be illustrated by the following Example. Anyone skilled in the art will be aware that the Example serves
10 only as an illustration and is not to be regarded as restrictive.

Example

4% meloxicam solution

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Ingredients:

	g/100 ml
Meloxicam	4.0
Meglumine	2.8
20 Macrogol 300* ¹	15.0
Poloxamer 188* ²	5.0
Ethanol	15.6
Glycine	0.5
EDTA-Na	0.1
25 1M HCl	q.s. ad pH 8.8
1M NaOH	q.s. ad pH 8.8
Water for injections	ad 100 ml

*¹ obtainable from Brenntag, Plochingen, Germany

30 *² obtainable from C.H. Erbsloeh, Krefeld, Germany

For example, dogs may be treated by needle-free injection with a 4% meloxicam solution according to the invention in a metered volume of 50 µl per spray jet in a

precise dosage related to body weight. A dog weighing 10 kg can be treated with a dose of 0.2 mg of meloxicam per kg of body weight with precisely one spray jet. Therapeutic accuracy is ensured in this case in steps of 10 kg.

5 Method of preparation:

4 g of meloxicam are dissolved in 50 ml of an aqueous meglumine solution (1.4 g/50 ml) at 90°C. The other excipients are added one after another to the solution according to the recipe given above. The pH is then adjusted to 8.8 using 1M hydrochloric acid and 1M sodium hydroxide solution. Water is added to the solution
10 until a volume of 100 ml is obtained.

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CLAIMS:

1. Aqueous cyclodextrin-free solution of meloxicam suitable for administration by needleless injection, containing a pharmacologically acceptable meloxicam salt of an organic or inorganic base, wherein it contains a solubiliser, as
5 well as one or more excipients selected from among the group comprising citric acid, lecithin, gluconic acid, tartaric acid, phosphoric acid and EDTA or the salts thereof, and the content of dissolved meloxicam salt is from 35 to 100 mg/ml.
2. Aqueous solution according to claim 1, wherein the meloxicam salt is the sodium or meglumine salt.
- 10 3. Aqueous solution according to claim 2, which contains meglumine and meloxicam in a molar ratio of between 9:8 and 12:8.
4. Aqueous solution according to claim 3, which contains meglumine and meloxicam in a molar ratio of 10:8.
5. Aqueous solution according to any one of claims 1 to 4, which contains
15 one or more excipients selected from among buffers and/or preservatives.
6. Aqueous solution according to any one of claims 1 to 5, which contains disodium EDTA.
7. Aqueous solution according to any one of claims 1 to 6, which has a pH of between 8.0 and 10.
- 20 8. Aqueous solution according to any one of claims 1 to 7, containing meloxicam, meglumine, a polyethyleneglycol, a polyoxyethylene-polyoxypropylene copolymer, ethanol, glycine and disodium EDTA, and optionally sodium hydroxide or hydrochloric acid.
9. Aqueous solution according to any one of claims 1 to 7, essentially
25 consisting of meloxicam, meglumine, a polyethyleneglycol, a polyoxyethylene-

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polyoxypropylene copolymer, ethanol, glycine, water suitable for injection and disodium EDTA, and optionally sodium hydroxide or hydrochloric acid.

10. Use of a solution of meloxicam according to any one of claims 1 to 9 for preparing a pharmaceutical composition for treating pain, inflammation, fever and
5 respiratory complaints in mammals.
11. Use of a solution according to claim 10, which corresponds to a dosage range of from 0.1 to 1.0 mg of active substance/kg of bodyweight.
12. Use of a solution according to any one of claims 10 or 11 for preparing a pharmaceutical composition for needleless injection.
- 10 13. Sterile cartridge containing a solution according to any one of claims 1 to 9, for use in a needleless injection system.