The invention relates to a medicament for the local treatment of inflammations of the eye that comprises diclofenac sodium as the active ingredient, has a more stable formulation and is tolerated very well by the eye.

Hitherto, predominantly corticosteroids have been used for the treatment of relatively severe acute or chronically recurrent inflammatory symptoms in the eye. The immunosuppressant action of these substances, however, conceals the risk of a deterioration in the clinical picture as a result of a bacterial or viral infection. Recently, therefore, strenuous efforts have been made to develop non-steroidal anti-inflammatory agents and to introduce them into ophthalmological therapy.

Diclofenac sodium, having the chemical name sodium 2-(2,6-dichloroanilino)-phenyl acetate, is a known non-steroidal anti-inflammatory agent; cf. DE-C 1 543 639 and DE-C 1 793 592. Its forms of

administration include all forms of tablets, capsules and dragées and also suppositories and ampoules.

The active ingredient has hitherto been used mainly in otorhinolaryngology, gynaecology, urology, paediatrics and rheumatology. In addition, however, the substance has also been used systemically in ophthalmology. A disadvantage of this type of use is that only a relatively low level of action is achieved at the site of action via the systemic route, and it cannot be assumed that an increase in the dose will result in a corresponding increase in the local level of action.

The topical administration of diclofenac sodium to the eye should bring advantages here in two respects: firstly, it will not be necessary to burden the entire organism with the active ingredient in order to obtain a local effect and, secondly, a locally higher level of action will be obtained with an eye drop solution.

A diclofenac sodium-containing solution for administration to the eye is known from JP-A-58/174310. The eye drops described in that publication comprise diclofenac sodium in a concentration of from 0.01 to 1%. They have a pH of preferably 7 to 8. Phosphates, boric acid, borax and organic acids are used as buffers. Sodium chloride and mannitol are named as isotonising additives. Polyoxyethylene sorbitan monooleate, polyoxyethyleneoxystearic acid triglyceride, polyoxyethylene glycol and α-and 8-cyclodextrin are mentioned as solution aids. Polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose and hydroxypropylcellulose are specified as thickeners. In addition, benzalkonium chloride, cetylpyridinium chloride, chlorobutanol and thiomersal are named as preservatives. Finally, pharmacologically tolerable calcium or magnesium salts are added, customarily in an

amount of from 0.3 to 2 mol per mol of active ingredient, in order to reduce eye irritation.

The addition of calcium or magnesium salts of physiologically tolerable acids in order to reduce eye irritation caused by anti-inflammatory eye drops that contain as active ingredient a non-steroidal anti-inflammatory agent having a carboxy group in the molecule is also described in JP-A-58/174309.

The eye drop formulations described in JP-A-58/174310 and JP-A-58/174309 have considerable disadvantages, however, which make them unsuitable for use as finished medicaments.

A considerable disadvantage of the known formulations is that they are unstable in the compositions described.

Also, in the case of eye drops, there is a statutory requirement in most European and other countries that the preparations should be preserved, that is to say protected against attack by micro-organisms and the subsequent multiplication thereof. Although JP-A-58/174310 gives information on the possible use of preservatives, the preservatives specified are unsuitable for the mentioned purpose in the formulations described for the following reasons: benzalkonium chloride and cetylpyridinium chloride are incompatible with diclofenac sodium without the addition of a suitable solution aid; their addition results in a precipitation in the preparation. Benzalkonium chloride is also incompatible with polyoxysorbates as proposed as solution aids in JP-A-58/174310. Chlorobutanol is stable only at a pH of less then 6 and is therefore not suitable for use in preparations that have a pH of from 7 to 8. Thiomersal, which is also named as a preservative in JP-A-58/174310, is incompatible with the sodium

chloride which is contained in the described formulations in order to produce isotonia. Furthermore, thiomersal is itself unstable in aqueous solution. The formulation examples given in JP-A-58/174310 do not mention a preservative.

A further disadvantage of the known formulations is that calcium or magnesium salts have to be added in order to prevent eye irritation by the active ingredient or by β-cyclodextrin which is the preferred solution aid. The addition of calcium and magnesium salts to the formulations has proved to be undesirable since the alkaline earth ions may form complexes with the active ingredient thereby impairing the latter's availability and stability.

For the reasons given, it is not possible according to the prior art to obtain diclofenac sodium-containing eye drops that are stable and preserved in conformity with statutory requirements and that do not irritate the eye.

The problem underlying the invention is therefore to formulate diclofenac sodium in the form of eye drops that have sufficient stability for a finished medicament, are preserved in conformity with requirements and are well tolerated by the eye.

This problem is solved by the surprising finding that, by using specific stabilisers, on the one hand sufficient stabilisation of the active ingredient can be achieved and at the same time, on the other hand, it becomes possible to use a preservative since the problems of stability and compatibility associated with its use are solved. Finally, it has also been found that, in the invention described here, it is not necessary to use calcium or magnesium salts to eliminate eye irritation.

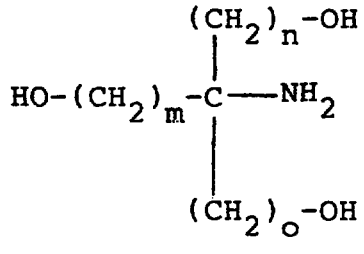
The invention therefore relates to a sufficiently

stable, preserved, well tolerated and effective medicament for the treatment of inflammations of the eye that comprises an aqueous solution of diclofenac sodium, a buffer, an isotonising agent, a solution aid and a preservative. The medicament is characterised in that it comprises an aminopolyol as the stabiliser for the active ingredient and the preservative.

By the addition according to the invention of a specific stabiliser to the aqueous diclofenac sodium preparation intended for use as eye drops, the difficulties associated with the known diclofenac sodium-containing eye drops are eliminated.

2-amino-2-hydroxymethyl-1,3-propanediol (trometamol) and its homologues having up to 10 carbon atoms, especially from 5 to 7 carbon atoms, have proved especially suitable for the desired purpose.

Trometamol and its homologues having up to 10, preferably from 5 to 7, carbon atoms can also be illustrated by the general formula I:



(I)

in which m, n, and o (independently of one another) each represents an integer of at least 1 and the sum of m, n and o is in the range of from 3 to 9, preferably from 3 to 6.

Especially preferred is 2-amino-2-hydroxymethyl-1,3-propanediol (trometamol) that corresponds to a

compound of the formula I in which m = n = o = 1.

By adding these stabilisers, the decomposition of the diclofenac sodium, which would otherwise occur during storage, is prevented in an effective manner. In addition, the use of a preservative is made possible, this preservative being necessary per se to prevent the preparation from being attacked by micro-organisms and being required by law. In particular, thiomersal, which has especially advantageous preservative properties but is unstable per se in aqueous solution, can be used in the formulation of the invention since it is co-stabilised indirectly by the stabiliser used. The stabiliser prevents the thiomersal from being adsorbed at the container wall thereby decisively improving its storability. Finally, it has been found that no eye irritation occurs with the formulation of the invention, so that it is not necessary to add calcium or magnesium salts, which are undesirable because of the active ingredient.

The individual constituents of the ophthalmic medicament of the invention are described below.

The active ingredient, diclofenac sodium, is used in a concentration of from 0.01 to 0.15%, preferably from 0.05 to 0.11%. An active ingredient concentration of approximately 0.1% is especially preferred.

The pH of the formulation is preferably from 6.8 to 7.5. There may be used as buffer substances, for example, boric acid, borates, phosphates and organic acids. The use of boric acid is preferred, the stabiliser added, for example trometamol, acting as the basic component of the buffer mixture.

The boric acid used as buffer substance is used preferably in such an amount that at the same time isotonia of the formulation is obtained. Optionally, it is also possible to use glucose, citrates,

phosphates, borates or other known substances as isotonising agents.

In order to avoid problems of compatibility with the thiomersal, sodium chloride is not used to isotonise the preparation when thiomersal is used as the preservative. On the other hand, however, sodium chloride can be used when benzalkonium chloride or cetylpyridinium chloride is used as the preservative.

As solution aids for the diclofenac sodium there are used in the preparations of the invention, for example, fatty acid glycerol polyglycol esters, fatty acid polyglycol esters, polyethylene glycols, glycerol ethers or mixtures of those compounds. Specific examples of especially preferred solution aids are reaction products of castor oil and ethylene oxide, for example the commercial product Cremophor EL®. Reaction products of castor oil and ethylene oxide have proved to be especially good solution aids having excellent eye tolerability. The concentration used depends principally on the concentration of the active ingredient. At least sufficient should be added to dissolve the active ingredient. For example, the concentration of the solution aid is from 1 to 100 times, especially from 5 to 60 times, the concentration of the active ingredient.

A preservative must be present in the preparations of the invention in order to prevent an attack by micro-organisms during the period of administration. Owing to its excellent preservative properties, the sodium salt of 2-(ethylmercurithio)-benzoic acid (thiomersal) is especially preferred for the purpose. It is used in a concentration of from 0.002 to 0.02%, preferably from 0.002 to 0.005% and especially approximately 0.004%. Apart from thiomersal, it is also possible to use other known

preservatives, such as benzalkonium chloride or cetylpyridinium chloride, in a concentration of from 0.005 to 0.02%. Combinations of the mentioned substances with the disodium salt of edetic acid are also suitable.

The stabiliser is added to the preparation of the invention in an amount of from 0.05 to 5%, preferably from 0.1 to 1.0%. In that amount, the stabiliser, as mentioned, brings about both stabilisation of the active ingredient against chemical decomposition and stabilisation of the preservative, thiomersal, against decomposition in aqueous solution. Furthermore, the stabiliser additionally ensures that the preservatives benzalkonium chloride and cetylpyridinium chloride which can also be used according to the invention are compatible with the active ingredient. When using these preservatives it may be necessary slightly to increase the amount of solution aid.

The preparation of the invention is formulated with water for injection purposes. An osmolality of approximately 0.9 (301 mosmol/kg) is established.

Owing to its excellent chemical stability, the preparation of the invention can be stored for a relatively long period even at room temperature and meets the requirements demanded of such a preparation in respect of its storability during therapeutic use.

The medicament of the invention is manufactured in a manner known per se by mixing all the components of the medicament homogeneously, and filling them, under sterile conditions.

The following formulation examples illustrate the invention:

Example 1

Constituent	Amount
diclofenac sodium	0.1%
2-(ethylmercurithio)-benzoic acid, sodium salt	0.004%
boric acid	1.9%
trometamol	0.6%
Cremophor EL®	5.0%
water for injection purposes	ad 100%

Example 2

Constituent	Amount
diclofenac sodium	0.1%
benzalkonium chloride	0.01%
boric acid	1.9%
trometamol	0.6%
Cremophor EL®	5.0%
water for injection purposes	ad 100%

Example 3

Constituent	Amount
diclofenac sodium	0.1%
cetylpyridinium chloride	0.01%
boric acid	1.9%
trometamol	0.6%
Cremophor EL®	5.0%
water for injection purposes	ad 100%

The formulations of Examples 1, 2 and 3 will keep for from 3 to 5 years at room temperature.

The tolerability of the eye drops was investigated in an eye irritant effect and toxicity study. The eye drop solution investigated corresponds to formulation example 1. The test solution is applied to the conjuctival sac five times a day over a period of four weeks. Two groups of six rabbits each are used for the study.

The following test scheme is used:

group	male	female	right eye	left eye
1	3 (389-391) *)	3 (395-397) *)	untreated	physio-logical saline
2	3 (392-394) *)	3 (398-400) *)	eye drops without active ingredient	eye drops with 0.1% diclofenac Na

*) Number assigned to the animal

The animals are examined for eye irritation twice a day, before the first and after the final daily administration.

The following is a summary of the results of the investigation:

After the four-week treatment with 50 ul of the 0.1% diclofenac sodium eye drop solution, none of the rabbits exhibits either symptoms of local irritation or systemic symptoms.

Schirmer's test [cf., for example, D. Vaughan and T. Asbury, Ophthalmologie, Springer, Berlin et al. 1983] is carried out as a specific investigative method for determining increased lacrimation resulting from local irritation:

Schirmer's test

(Measurement time: 2 minutes, measurements in millimetres)

Group 1

animal number/ sex	before the test		after 2 weeks		after 4 weeks	
	left	right	left	right	left	right
389/m	7	6	9	6	6	5
390/m	3	5	8	5	5	6
391/m	4	9	4	5	4	7
395/f	5	4	4	7	5	6
396/f	7	11	8	6	6	8
397/f	5	8	4	7	4	5
average	5.2	7.2	6.2	6.0	5.0	6.2

Group 2

animal number/ sex	before the test		after 2 weeks		after 4 weeks	
	left	right	left	right	left	right
392/m	8	7	3	6	2	8
393/m	8	10	6	5	10	9
394/m	5	4	5	7	4	9
398/f	7	10	5	12	5	6
399/f	4	8	7	6	5	2
400/f	5	5	3	6	4	7
average	6.2	7.3	4.8	7.0	5.0	6.8

m = male
f = female

Observations and measurements obtained with Schirmer's test show that there are no differences between treated eyes and control eyes that can be linked with the eye drops tested.

The differences that do occur can be regarded as individual cases having no biological or toxicological significance.

To summarise, it can therefore be stated that the administration of the diclofenac sodium-containing eye drop solution referred to in this patent specification as formulation example 1 to the eye of the rabbit over a period of four weeks is safe. This investigation at the same time demonstrates the local tolerability of

the adjuncts.

A supplementary 7-day eye irritant effect study was carried out on rabbits for the additive trometamol. Two groups of six animals each are again used:

test group	1		2	
dosage	1)		2)	
sex	m	f	m	f
number of test animals	3	3	3	3
observations and findings deviating from the norm	none	none	none	none

[1] Group 1 left eye: NaCl solution 0.9%
right eye: 0.5% trometamol

[2] Group 2 left eye: buffer
right eye: 2% trometamol

The eyes are examined twice daily, before the first and after the final administration. To summarise the result, trometamol is well tolerated by the eye of the rabbit.

The good tolerability proved in the animal experiment could be demonstrated also within the framework of clinical tolerability tests on humans. 221 people are

treated with eye drops corresponding to formulation example 1. Apart from an occasional brief and slight stinging immediately after administration, no specific side effects are observed.

Overall, therefore, the results lead to the conclusion that the present formulation is a solution for ophthalmological use that is tolerated well locally.

* C L M S *

Patent Claims for the Contracting States: BE, CH, FR, GB, IT, LI, LU, NL, SE

1. A medicament for the treatment of inflammations of the eye, comprising an aqueous solution of diclofenac sodium, a buffer, an isotonising agent, a solution aid and a preservative, characterised in that it comprises 2-amino-2-hydroxymethyl-1,3-propanediol or a homologue thereof having up to 10 carbon atoms as stabiliser for the active ingredient and the preservative.

2. A medicament according to claim 1, characterised in that it comprises 2-amino-2-hydroxymethyl-1,3-propanediol (trometamol) as stabiliser.

3. A medicament according to claims 1 and 2, characterised in that it comprises the stabiliser in an amount of from 0.05 to 5 %.

4. A medicament according to claims 1 to 3, characterised in that it comprises a 0.01 to 0.15 % aqueous solution of diclofenac sodium.

5. A medicament according to claims 1 to 4, characterised in that it comprises the sodium salt of 2-(ethylmercurithio)-benzoic acid (thiomersal) as preservative.

6. A medicament according to claims 1 to 4, characterised in that it comprises benzalkonium chloride as preservative.

7. A medicament according to claims 1 to 4, characterised in that it comprises cetylpyridinium chloride as preservative.

8. A medicament according to claim 1, characterised in

* C L M S *

that it comprises a 0.05 to 0.11 % aqueous solution of diclofenac sodium, boric acid in an amount of 1.9 % as buffer and isotonising agent, a reaction product of castor oil and ethylene oxide in an amount of 5.0 % as solution aid, the sodium salt of 2-(ethylmercurithio)-benzoic acid (thiomersal) in an amount of from 0.002 to 0.005 % as preservative and 2-amino-2-hydroxymethyl-1,3-propanediol (trometamol) in an amount of from 0.1 to 1.0 % as stabiliser.

9. A process for the manufacture of a medicament according to claims 1 to 8, characterised in that all of the components of the medicament are mixed homogeneously, and filled, under sterile conditions.

Patent Claims for the Contracting States: ES, GR

1. A process for the manufacture of a medicament for the treatment of inflammations of the eye, which medicament comprises an aqueous solution of diclofenac sodium, a buffer, an isotonising agent, a solution aid, a preservative, and 2-amino-2-hydroxymethyl-1,3-propanediol or a homologue thereof having up to 10 carbon atoms as stabiliser for the active ingredient and the preservative, characterised in that all of the components of the medicament are mixed homogeneously, and filled, under sterile conditions.

2. A process according to claim 1, characterised in that the medicament comprises 2-amino-2-hydroxymethyl-1,3-propanediol (trometamol) as stabiliser.

3. A process according to claims 1 and 2, characterised in that the medicament comprises the stabiliser in an amount of from 0.05 to 5 %.

4. A process according to claims 1 to 3, characterised in that the medicament comprises a 0.01 to 0.15 % aqueous solution of diclofenac sodium.

5. A process according to claims 1 to 4, characterised in that the medicament comprises the sodium salt of 2-(ethylmercurithio)-benzoic acid (thiomersal) as preservative.

6. A process according to claims 1 to 4, characterised in that the medicament comprises benzalkonium chloride as preservative.

7. A process according to claims 1 to 4, characterised in that the medicament comprises cetylpyridinium chloride

as preservative.

8. A process according to claim 1, characterised in that the medicament comprises a 0.05 to 0.11 % aqueous solution of diclofenac sodium, boric acid in an amount of 1.9 % as buffer and isotonising agent, a reaction product of castor oil and ethylene oxide in an amount of 5.0 % as solution aid, the sodium salt of 2-(ethylmercurithio)-benzoic acid (thiomersal) in an amount of from 0.002 to 0.005 % as preservative and 2-amino-2-hydroxymethyl-1,3-propanediol (trometamol) in an amount of from 0.1 to 1.0 % as stabiliser.