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Compositions For The Treatment Of Actinic Keratosis

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Abstract

Ibuprofen for use in the prevention and treatment of actinic keratosis.

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Compositions for the Treatment of Actinic Keratosis

The present invention relates to compositions for the treatment of actinic keratosis.

Actinic keratosis is a chronic damage to the keratinized epidermis caused by many years of intensive exposure to sunlight or ultraviolet radiation. Actinic keratosis is a facultative precancerosis and can transform into a squamous cell carcinoma.

Actinic keratosis occurs mainly among people in the second half of life, wherein skin areas that were exposed to sunlight without protection are particularly often affected, for example, the face, the back of the hands, the forehead, the nose or ear. In addition to humans, animals such as dogs and cats may also be affected in sparsely haired areas.

Typical treatment forms include surgical removal or treatment with, for example, imiquimod, 5-fluorouracil, hyaluronic acid with diclofenac, or photodynamic therapy with 5-aminolevulinic acid.

Especially in the region of the face, or when the disease affects larger areas, surgical methods may be undesirable from a cosmetic point of view. Therefore, topical treatment with gels and creams is preferred especially in the face. Currently, treatment with a combination of diclofenac/hyaluronic acid is best tolerated.

It is the object of the present invention to provide further possible treatments for actinic keratosis.

This object is achieved by the use of ibuprofen in the prevention and treatment of actinic keratosis.

Ibuprofen is an active substance that has been used for many years in the treatment of arthrosis, sports injuries, and rheumatoid diseases. In addition to systemic application, corresponding topical forms of application are also known.

Plasma levels on the order of 10 µg/ml or more are necessary for a general systemic effect to be achieved. In topical application, plasma levels of only about

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2 µg/ml are reached. Therefore, topical application does not cause systemic effects, and the side effects are also extremely low.

Therefore, according to the invention, ibuprofen is preferably employed in a topical formulation.

Particularly suitable formulations include ointments, creams and gels. A cream is an emulsion of an aqueous phase in a lipophilic phase; a gel is a disperse system of solid and liquid phases.

Concentrations of ibuprofen in a topical formulation of from 1 to 20% by weight have proven particularly suitable, concentrations of 5 to 10% by weight being particularly preferred. Preferably, the concentration is more than 5% or at least 6% or 7% by weight. The concentration is preferably around 10% by weight or below 10% by weight, for example, up to 9% by weight or up to 8% by weight. The range of from 5 to 10% by weight or from 6 to 8% by weight is preferred, in particular, for gel formulations.

In one embodiment, the formulation additionally contains penetration enhancers, which facilitate penetration through the skin. Such penetration enhancers are known to the skilled person in principle, including from the production of ibuprofen-containing topical formulations for the treatment of sports injuries, for example.

Particularly suitable formulations contain dimethyl isosorbide, poloxamers, laurocapram, pyrrolidones, dimethylsulfoxide, oleic acid, ethylene glycols and derivatives and mixtures thereof as penetration enhancers.

In one embodiment of the invention, ibuprofen is the only active ingredient in the formulation. Of course, ibuprofen requires auxiliary agents for the preparation of an administrable medicament, depending on the dosage form. However, no other active ingredients are contained in this embodiment.

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In particular, in one embodiment, no hyaluronic acid is contained, which could ne an auxiliary agent or an active ingredient.

In another embodiment, diclofenac is contained in addition to ibuprofen. Preferred amounts of diclofenac are also within a range of from 1 to 20% by weight, concentrations of from 3 to 10% by weight being preferred. Preferably, the total concentration of ibuprofen and diclofenac should be within a range of from 1 to 20%, preferably 5 to 10%, by weight.

A preferred gel formulation (microemulsion gel) contains:

- 5 to 10 g of ibuprofen;
- 10 to 25 g of isopropanol;
- 5 to 10 g of dimethyl isosorbide;
- 6 to 18 g of poloxamer;
- 1 to 4 g of medium-chain triglycerides;
- perfumes;
- water ad 100 g.

Another preferred gel contains:

- 5 to 10 g of ibuprofen;
- 30 to 60 g of ethanol 96%;
- 5 to 20 g of dimethyl isosorbide;
- 1 to 4 g of hydroxypropylcellulose;
- 0.75 to 4 g of potassium hydroxide;
- water ad 100 g.

The invention is further illustrated by means of the following Examples.

Examples

In a preliminary study, the treatment of actinic keratosis using ibuprofen is compared with a treatment using diclofenac. The study was performed according

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to the relevant criteria and was approved by the ethics commission of the dermatological society of Slovakia.

The study included 24 patients who showed five or more lesions in the area of the head, the face, the arms, or the hands.

12 of the patients were treated with 5% ibuprofen gel, and the others were treated with 3% diclofenac gel. The application frequency was twice a day. The success of the treatment was evaluated after 30, 60 and 90 days.

When included in the study, the severity of the lesions was evaluated according to the so-called BSI (baseline severity index) score from 0 to 3. Patients having a BSI score of 1 and 2 were exclusively included in the study.

BSI score (baseline severity index score 1 - 3)

0 = no actinic keratosis (AK) visible
1 = clearly visible lesion
2 = many small, moderately thick lesions or a few large scaly lesions visible
3 = many thick hypertrophic lesions that are clearly visible and palpable with clear bounds.

The main target parameters within the scope of effectiveness were the total number of lesions in the treatment area and the IGII (investigator global improvement index) score from –2 to +4. From round 1, the evaluations were always done in comparison with the preliminary round.

Table 1: Average number of lesions at the start of the study

	Ibuprofen	Diclofenac
Forehead	4.6	7.1
Face	5.7	7
Scalp	6.3	15.8
Hands	18.5	18.1

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Table 2: Average number of lesions after 90 days of treatment

	Ibuprofen	Diclofenac
Forehead	4	5.3
Face	4.8	5.5
Scalp	6	11.5
Hands	16.9	17.1

After 90 days of treatment, the average number of lesions was reduced from 35.1 to 31.7 in the ibuprofen group and from 48 to 39.4 in the diclofenac group. The severity of the lesions remained virtually unchanged during the 90 days of treatment. A small reduction of the BSI score occurred only on the forehead. None of the patients developed new lesions during their treatment.

IGII (investigator global improvement index)

–2	significant worsening
–1	slight worsening
0	unchanged
1	slight improvement
2	improvement
3	significant improvement
4	complete healing

The IGII was measured between each two rounds. It may take a value of –2 (significant worsening) to +4 (healing) and changed as follows during the 90 days of treatment:

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Table 3: Investigator global improvement index at the start of the study (V0) and after 90 days of treatment (V3)

	Ibuprofen		Diclofenac	
	V0	V3	V0	V3
Forehead	0	1.33	0	1.55
Face	0	1.38	0	1.7
Scalp	0	1	0	1.75
Hand	0	1	0	1

Result

In both groups, a reduction in the number of lesions could be seen, which, although it was only slight, in combination with the positive change of the IGII score underlines an about comparable effectiveness of the two treatments (ibuprofen and diclofenac). The differences in the reduction of the lesions when comparing ibuprofen and diclofenac are essentially due to the number of lesions at the start of the study. No undesirable side effects were found during the study. The therapy was well tolerated.

In another study, six patients were treated with 10% ibuprofen gel, and another six patients were treated with 3% diclofenac gel. The design of the study was the same as that of the first study.

The total number of lesions in the ibuprofen group changed from 18 at the beginning of the treatment to 3.7 at the end of the 90 days of treatment time. In the diclofenac group, there were 36.8 lesions at the start, which changed to an average of 19.2 lesions towards the end of the treatment.

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Table 4: Average number of lesions at the start of the study

	Ibuprofen	Diclofenac
Forehead	3.3	7.5
Face	5.2	12.3
Scalp	No evaluation since only 1 patient showed lesions	
Hands	9.5	17

Table 5: Average number of lesions after 90 days of treatment

	Ibuprofen	Diclofenac
Forehead	0.3	4.2
Face	0.7	6.2
Scalp	No evaluation since only 1 patient showed lesions	
Hands	2.7	8.8

The average IGII at the end of the treatment time was 3.7 (i.e., the lesions were almost completely healed) in the ibuprofen group and 2.29 in the diclofenac group, which corresponds to a moderately successful healing.

Table 6: Investigator global improvement index at the start of the study (V0) and after 90 days of treatment (V3)

	Ibuprofen		Diclofenac	
	V0	V3	V0	V3
Forehead	0	3.8	0	2.3
Face	0	3.7	0	2.17
Scalp	No evaluation since only 1 patient showed lesions			
Hand	0	3.6	0	2.4

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Result

Even if the small number of patients in the 2nd study is considered, the successful treatment in the 10% ibuprofen group shows nevertheless that the formulation has a pronounced effectiveness in the field of treating slight and moderate keratosis lesions. The therapeutic results of the diclofenac treatment are also good, although a complete healing was not yet to be seen because of the high initial number of lesions. It remains to be noted that three patients from the ibuprofen group were completely freed from the optically visible lesions at the end of the 90 days of treatment. The tolerability in both treatment groups was very good.

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CLAIMS:

1. Ibuprofen for use in the prevention and treatment of actinic keratosis.

2. Ibuprofen for use according to claim 1, wherein the ibuprofen is in a topical formulation.

3. Ibuprofen for use according to claim 2, wherein the ibuprofen is in the form of an ointment, a cream, or a gel.

4. Ibuprofen for use according to either of claims 2 or 3, wherein the concentration of ibuprofen is from 1 to 20% by weight.

5. Ibuprofen for use according to claim 4, wherein said concentration is from 5 to 10% by weight.

6. Ibuprofen for use according to claim 5, wherein said concentration is from 6 to 8% by weight.

7. Ibuprofen for use according to any of claims 2 to 6, wherein penetration enhancers selected from the group consisting of dimethyl isosorbide, poloxamers, laurocapram, pyrrolidones, dimethylsulfoxide, oleic acid, ethylene glycols and derivatives and mixtures thereof are contained therein.

8. Ibuprofen for use according to any of claims 1 to 7, whereinb ibuprofen is the only active ingredient.

9. Ibuprofen for use according to any of claims 1 to 7, wherein diclofenac is additionally contained therein.

10. Ibuprofen for use according to any of claims 2 to 9, wherein said formulation does not include any hyaluronic acid.

11. A pharmaceutical preparation comprising from 6 to 8% by weight of ibuprofen and from 2 to 15% by weight of penetration enhancers.

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12. The pharmaceutical preparation according to claim 11, wherein said penetration enhancer is dimethyl isosorbide.

13. The pharmaceutical preparation according to claim 11 or 12 in the form of a gel.