HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

16 December 2009

SOLARAZE 3 %, gel
25 g tube (CIP: 349 080-3)
50 g tube (CIP: 349 082-6)

Applicant: ALMIRALL SAS

Diclofenac

ATC code: D11AX18

List I

Marketing authorisation date: 17 December 1998

Reason for request: inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Diclofenac

1.2. Novel aspects

SOLARAZE is a 3% diclofenac gel formulated in hyaluronic acid.

1.3. Indication

"Local treatment of actinic keratoses."

1.4. Dosage

"Adults:
SOLARAZE is applied locally twice a day, smoothed in gently.
The quantity needed depends on the size of the lesion. Normally 0.5 g of gel (the size of a pea) is sufficient for a 5 cm x 5 cm lesion. The usual duration of therapy is from 60 to 90 days.
Maximum efficacy has been observed with treatment durations towards the upper end of this range. Complete healing or optimal therapeutic effect may only be evident 30 days following cessation of therapy. A maximum of 8 grams of gel daily should not be exceeded.
Long-term efficacy has not been established.

Elderly subject:
The usual adult dose should be used.

Children:
Dosage recommendations and indications have not been established for use in children."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

D : Dermatologicals
D11 : Other dermatological preparations
D11A : Other dermatological preparations
D11AX18 : Diclofenac

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines

SOLARAZE is the only medicine in its pharmaco-therapeutic category that is indicated for the local treatment of actinic keratosis.

2.2.2. Medicines that are not strictly comparable

None

2.3. Medicines with a similar therapeutic aim

These are other treatments available for the treatment of actinic keratosis:

Medicines:

- ALDARA (imiquimod): not reimbursable in this indication (Committee's opinion dated 26 November 2008: substantial AB)
- EFUDIX (5-fluorouracil)
- METVIXIA (methyl aminolevulinate in the context of a dynamic phototherapy protocol).

The indications for ALDARA and METVIXIA are more limited than those for EFUDIX and SOLARAZE:

- ALDARA is a second-line treatment for "clinically typical forms of non-hypertrophic, non-hyperkeratotic actinic keratosis of the face or scalp in immunocompetent adults when the size or number of lesions limits the efficacy and/or safety of cryotherapy and if other topical treatments are contraindicated or less appropriate";
- METVIXIA is indicated in the "treatment of fine or non-hyperkeratotic and non-pigmented forms of actinic keratosis of the face and scalp".

Non-drug treatments: cryotherapy (standard treatment when lesions are not too extended), radiotherapy, CO_2 laser and electrocoagulation curettage.

3 ANALYSIS OF AVAILABLE DATA

The pharmaceutical company's request is based mainly on:

- two placebo-controlled studies which have already been assessed by the Transparency Committee (opinion dated 19 December 2001);
- a new study versus active comparators: 5-fluorouracil (5-FU) and cryotherapy.

3.1. Efficacy

3.1.1. Reminder of placebo-controlled studies

Study CT-1101-3[1]

Randomised, double-blind study comparing the efficacy of a 3% diclofenac gel formulated in hyaluronic acid (SOLARAZE) with a placebo (hyaluronic acid gel) in the treatment of actinic keratosis after three months of treatment.

The patients included were adults who were found on clinical examination to have at least five actinic keratosis lesions in one to three blocks of 5x5 cm^2 located on the forehead, the face, the scalp and the backs of the hands. Patients must not have been treated for at least 60 days prior to randomisation.

Patients were treated with a 3% diclofenac gel or with a placebo at a dosage of 0.5 g twice a day for three months. They were monitored for a further month after three months of treatment.

Assessment criteria evaluated at the end of the monitoring period (D120):

[1] Wolf JE et al. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *International Journal of Dermatology 2001; 40: 709-713*

- percentage of patients in whom all the initial target lesions had disappeared from all the major areas of the body examined (TLNS[2] = 0);
- percentage of patients with no (initial or new) lesion for all the major zones examined (CLNS[3] = 0);
- overall assessment by the investigator and the patient in terms of the percentage of "complete improvement" (IGII[4] = 4 and PGII[4] = 4).

Results:

A total of 120 patients were included. 118 of these started treatment and 98 completed the study. Twenty-two patients withdrew from the study: 14 in the diclofenac group (eight because of adverse effects and six because of non-compliance with treatment) and eight in the placebo group (four because of adverse effects, two because of non-compliance with treatment and two because of withdrawal of consent).

The patients, mainly men, had an average age of 65. Approximately 85% of patients had fair skin (levels I and II on the Fitzpatrick classification scale[5]). Most of the actinic keratosis lesions were mild to moderate in severity according to the "Baseline Severity Index[6]" and were most often located on the forehead.

Average exposure to treatment was 74.2 days ± 21.1 days and 72.9 days ± 24.3 days in the placebo group.

The percentage of patients whose initial lesions disappeared after three months of treatment and the follow-up period was higher in the diclofenac group than in the placebo group (50% versus 20%, $p<0.001$).
A similar finding was observed in respect of the percentage of patients with no (initial or new) lesions and the global assessment by the patient or the investigator in respect of the percentage of patients experiencing "complete improvement" (see table 1).

[2] "Target Lesion Number Score"

[3] "Cumulative Lesion Number Score": "Target Lesion Number Score" + "New Lesion Number Score"

[4] "Investigator's Global Improvement Index" and "Patient's Global Improvement Index": score ranging from -2 (much worse) to +4 (complete improvement).

[5] The Fitzpatrick classification scale is a standardised method of classifying skin types according to their colour and their response to exposure to the sun (tanning/burning).
I: white skin, very sensitive; always burns, never tans.
II: white skin, very sensitive; always burns, tans with difficulty.
III: cream white skin, sensitive; sometimes mild burn, gradually tans.
IV: brown skin, moderately sensitive; rarely burns, tans with ease.
V: dark brown skin, does not burn, tans very easily (brown Mediterranean, mid-Eastern skin types).
VI: black skin, not at all sensitive; never burns.

[6] Baseline Severity Index: a scale used by the investigator to assess the severity of lesions (from 0: tactile and visual examination showed no lesion to 3: several thick, hypertrophic and/or florid lesions which are clearly visible and palpable, with clear boundaries). N.B.: the relationship between severity and grading on this scale is not explained.

Table 1: Primary efficacy endpoint results at the end of the monitoring period (D120) (ITT population)

Endpoints examined*	Diclofenac N =59	Placebo N =59	p
Patients whose initial target lesions had completely disappeared (TLNS = 0)	29 (50)	12 (20)	< 0.001
Patients with no (initial or new) lesion (CLNS = 0)	27 (47)	11 (19)	< 0.001
Patient assessment: PGII = 4	24 (41)	10 (17)	0.001
Investigator assessment: IGII = 4	27 (47)	11 (19)	<0.001

* : expressed as number of patients and percentage of patients: n (%)

N.B.: The meaningfulness of these results is limited since:
- several primary endpoints were assessed, but the criterion used to calculate the study cohort size was not indicated and the significance level was not corrected with risk α;
- no histological examination was carried out to confirm the clinical diagnosis or the disappearance of the lesions.

Study CT-1101-04[7]
Randomised, double-blind study comparing the efficacy of a 3% diclofenac gel formulated in hyaluronic acid (SOLARAZE) with a placebo (hyaluronic acid gel) in the treatment of actinic keratosis after one or two months of treatment.

The patients included were adults who had been clinically diagnosed with at least five actinic keratosis lesions in one to three blocks of 5x5 cm^2 located on the forehead, the face, the scalp and the backs of the hands. Patients must not have been treated for at least 60 days prior to randomisation.

The patients were divided into four groups: 3% diclofenac gel or placebo for one month and diclofenac gel or placebo for two months at a dose of 0.5 g twice a day. They were monitored for one month after the end of treatment.

The results for the groups treated for one month will not be described since this duration of treatment does not fit with the marketing authorisation.

Assessment criteria evaluated at the end of the monitoring period:

- percentage of patients in whom all the initial target lesions had disappeared from all the major areas of the body examined (TLNS = 0);
- percentage of patients with no (initial or new) lesion for all the major zones examined (CLNS = 0);
- assessment of the lesion thickness on a scale of 0 (lesion visible but not palpable) to 3 (hyperkeratotic lesion, > 1 mm in thickness);
- overall assessment by the investigator and the patient in terms of the percentage of "complete improvement" (IGII[8] = 4 and PGII[4] = 4).

[7] Rivers J.K. et al. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *British Journal of Dermatology 2002; 146: 94-10*
[8] « Investigator's Global Improvement Index » and « Patient's Global Improvement Index »: score ranging from -2 (much worse) to +4 (complete improvement).

Results:

A total of 195 patients were included, and 184 of them completed the study. Among the withdrawals from the study, eight were due to adverse effects, one for non-compliance with treatment, one because consent was withdrawn and in one case contact with the patient was lost.
The patients, mainly men, had an average age of 67. Most of the men had fair skin (levels I and II on the Fitzpatrick classification scale), but the proportion of patients with these skin types was lower in the group receiving diclofenac for one month (61%) than in the other groups (81 to 85%). The lesions were mainly mild to moderate in severity and located mainly on the forehead.

The percentage of patients whose initial lesions disappeared after two months of treatment and the follow-up period was higher in the diclofenac group than in the placebo group (33% versus 10%, p<0.0111).
Diclofenac was also observed to be superior to the placebo in respect of the percentage of patients with no (initial or new) lesions, the reduction in the thickness of the lesions and the global assessment by the patient or the investigator in terms of the percentage of patients experiencing "complete improvement" (see table 2).

Table 2: Primary efficacy endpoint results at the end of the monitoring period among patients treated for two months (ITT population)

Endpoints examined*	Two months treatment		p
	Diclofenac N =48	Placebo N =49	
Patients whose initial target lesions had completely disappeared (TLNS = 0)	16 (33)	5 (10)	0,0126
Patients with no (initial or new) lesion (CLNS = 0)	15 (31)	5 (8)	0,0214
Lesion thickness score = 0	12 (25)	3 (6)	0,0340
Patient assessment: PGII = 4	14 (29)	5 (10)	0,0269
Investigator assessment: IGII = 4	15 (31)	5 (10)	0,0213

* : results expressed as number of patients and percentage of patients: n (%)

N.B.: The meaningfulness of these results is limited since:
- there were multiple treatment groups and the number of patients in each group was low, below that of the preceding study which had the same objectives;
- the expected difference between the four lesion groups in order to calculate the cohort size is not justified;
- no histological examination was carried out to confirm the clinical diagnosis or the disappearance of the lesions at the end of the monitoring period;
- multiple endpoints were used and the significance level was not corrected with risk α.

3.1.2. Study versus 5-FU and cryotherapy[9]

This was a phase IV open-label, randomised, single-blind pilot study comparing 3% diclofenac gel to 5% 5-FU in a cream formulation (EFUDIX) and cryotherapy in immunocompetent patients with actinic keratosis lesions.

[9] Stockfleth E. A randomized study of topical 3% diclofenac in a 2.5% hyaluronate base (SOLARAZE ® 3% gel) *versus* topical 5% 5-fluoroucacil (Efudix® cream) *versus* liquid nitrogen cryotherapy in immunocompetent patients with actinic keratoses (Charité study code 01-2206). *Clinical Study Report. January 27, 2009*

The patients included were adults who had been suffering from slight to moderate actinic keratosis for at least three months. On clinical examination they had to be found to have at least five actinic keratosis lesions in one to three blocks of 5x5 cm^2 located on the forehead, the face, the scalp or the backs of the hands.

Patients were split into three treatment groups:
- 3% diclofenac gel applied twice a day for three months
- 5% 5-FU gel applied twice a day for one month
- cryotherapy (liquid nitrogen) in a single 10- to 20-second session which could be repeated after two weeks if the lesions persisted.

The efficacy of treatment was assessed one month after the end of treatment in each of the three groups. Twelve months after the end of treatment, patients with persistent lesions underwent histological examination of all suspicious lesions in order to exclude carcinoma.

Primary endpoints: assessment one month after the end of treatment to ascertain the percentage of patients with complete clinical disappearance of lesions and the percentage of patients with complete disappearance of lesions confirmed by histological examination. The histological assessments were conducted by two independent experts on biopsies at least 4 mm in size.

Results:
A total of 75 patients were included. Among these, four patients in the diclofenac group withdrew from the study prematurely (two because of adverse effects, one for protocol violation and contact with one patient was lost).
The patients included, mainly men, had an average age of 71. Most of them had fair skin (level I, II or III on the Fitzpatrick classification scale) and 68% of them had already undergone treatment.

A statistically significant difference between the three groups was observed one month after the end of treatment in respect of the complete clinical disappearance of lesions ($p<0.0001$) and the complete disappearance of lesions confirmed by histological examination ($p = 0.0022$) (see table 3).

Table 3: Clinical and histological results one month after the end of treatment (ITT population)

Endpoints examined*	Diclofenac N =25	5-FU N=25	Cryotherapy N =25	P
Complete clinical disappearance of lesions	12 (48)	15 (60)	2 (8)	< 0.0001
Complete histological disappearance of lesions	19 (76)	17 (68)	11 (44)	0.0022

* : results expressed as number of patients and percentage of patients: n (%)

N.B.:
- The number of patients included in the study was low and was not calculated on the basis of a statistical hypothesis.
- Two primary endpoints were selected and the significance level was not corrected.
- The statistical analysis of these results does not include a two-by-two comparison of the groups.
- results obtained from clinical assessment and from histological examination are not concordant. This calls the assessment criteria into question, particularly the histological assessment of lesions which was performed on only one lesion per patient.
- The results obtained from cryotherapy appear very weak when set against the results obtained in practice (difficulty in assessing the clinical appearance of lesions, liquid nitrogen applied for too short a time?).

Consequently, it is not possible to judge the efficacy of diclofenac compared to 5-FU and cryotherapy from this study.

3.2. Adverse effects

Study versus placebo:

The most frequent adverse events associated with diclofenac in the two studies versus placebo were: pruritus (55% and 36%), dry skin (36% and 27%), rash (33% and 34%), other adverse events at the application site (34% and 23%).
These adverse events were also observed with the placebo (hyaluronic acid gel): pruritus (49% and 59%), adverse effects at the application site (20% and 19%), dry skin (17% and 19%) and rash (15% and 29%).

The severity of these adverse events was regarded as mild in most cases. However, in study CT-1101-04, 7 patients in the diclofenac group reported 10 severe adverse events (pruritus, formication, alopecia, contact dermatitis, oedema and rash), six of which were regarded as attributable to treatment.

Study versus 5-FU and cryotherapy:

A total of 13 adverse events were reported by 12 patients. The breakdown and nature of these adverse events are as follows:

- diclofenac: one serious adverse event not related to treatment, two local adverse events (skin inflammation) and three non-serious adverse events (epididymitis, squamous cell carcinoma in the treated area, alopecia); it was considered that these events were definitely not or probably not treatment-related.
- 5-FU: four local adverse events were reported (pain at the area of treatment, inflammatory reactions at the site of treatment); all of these events were considered to be probably related to the treatment;
- cryotherapy: two patients reported Bowen's disease, not related to treatment.

Summary of product characteristics:

The following adverse events are also mentioned as being among those which occur most frequently: conjunctivitis, skin rash, skin hypertrophy, skin ulcers, and hyperaesthesia, hypertonia and local paraesthesia.
The summary of product characteristics notes that systemic absorption is low, but that local application of large quantities of gel can cause systemic effects including hypersensitivity.
Caution is therefore advised in the case of patients with a history of or active gastroduodenal ulcer, haemorrhage or cardiac, hepatic or renal insufficiency.

Pharmacovigilance:
Analysis of the PSUR data for the periods from 25/11/2001 to 24/11/2006 and from 15/05/2007 to 14/05/2008 did not lead to any change in the adverse effects profile of diclofenac gel.

3.3. Conclusion

The efficacy of 3% diclofenac in a hyaluronic acid gel (applied twice a day) has been assessed versus placebo (hyaluronic acid gel) in two randomised double-blind studies on patients with mild to moderate actinic keratosis lesions undergoing treatment for one, two or three months. Complete disappearance of lesions was observed in 33% of patients treated with diclofenac for two months (versus 10% of those treated with the placebo) and in 50% of patients treated with diclofenac for three months (versus 20% of those treated with the placebo) (statistically significant differences). Similar results were obtained for the other criteria examined (absence of new or initial lesion, global assessment by the patient and by the investigator). These effects appear to be modest. However, the validity of these findings

is not certain because of a lack of justification of the method used to calculate cohort size (or even any statistical hypothesis regarding the calculation), the absence of correction of the significance level to take into account the multiplicity of assessment criteria and the lack of a histological examination to confirm the diagnosis and to verify the disappearance of the lesions.

Diclofenac in gel applied twice a day for three months was compared to 5% 5-FU in cream and to cryotherapy in an open-label, randomised, single-blind pilot study performed on 75 patients with mild to moderate actinic keratosis. The results of this study cannot be interpreted because of important methodological bias.

The adverse events most commonly associated with diclofenac were observed in 30 to 50% of patients. They are local reactions: pruritus, skin dryness, inflammatory reactions. Local inflammatory reactions were also observed with 5-FU. Cryotherapy was well tolerated.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Actinic keratosis involves skin lesions developed on areas exposed to the sun, most frequently among elderly people. Patients often have multiple lesions which, if effective treatment is not administered, can progress to become skin cancers.

This medicine is intended for use as part of curative therapy.

Public health benefit:

Although these conditions are relatively common, the public health burden represented by actinic keratosis represents is small since they rarely develop into epidermoidal cancer.

Improving the management of actinic keratosis is not a public health need. Furthermore, there are alternative drug and non-drug treatments.

In view of clinical trial data, SOLARAZE is not expected to have any impact in terms of morbidity for patients with actinic keratosis treated with it. Moreover, there is no current record of its impact on quality of life.

Consequently, in the light of the available data and existing treatments, SOLARAZE is not expected to benefit public health in this indication.

The efficacy of the 3% diclofenac gel versus placebo in terms of complete disappearance of lesions on clinical examination appeared to be modest. However, important methodological bias means that the level of evidence of this demonstration of efficacy is low. Local reactions (pruritus, dryness, inflammation) were common, affecting 30 to 50% of patients. The efficacy/adverse effects ratio for this medicinal product is low.

There are alternative medicines and non-drug treatments which have been shown to be effective.

The positioning of this medicinal product in the therapeutic strategy cannot be assessed on the basis of the available data.

The actual benefit of SOLARAZE 3% gel is insufficient to justify its inclusion on the list of medicines reimbursed by National Health Insurance.

4.2. Therapeutic use

4.2.1. Treatment strategy

All cases of actinic keratosis should be treated as their course is unpredictable. A histological examination must be performed on lesions which do not respond to treatment. Cryotherapy (a simple, swift technique which does not require any particular equipment) is the standard treatment for patients with a small number of actinic keratosis lesions.

Practitioners treating patients who they think may have spinocellular carcinoma must perform a histological examination before administering nitrogen to destroy the lesions. Multiple keratoses are treated by topical administration of 5-FU or mechanical dermabrasion. The drawback of 5-FU is that it is an irritant substance, which undermines compliance as patients need to keep applying it for three to four weeks on average. Surgery is sometimes performed on large lesions, and can be followed by a graft if the area requiring treatment is extensive. Other treatment options include imiquimod, CO_2 laser vaporisation of lesions, curettage/electrocoagulation and dynamic phototherapy.

4.2.2. Role of the medicinal product

As 3% diclofenac gel is a topical product, it could be beneficial in the treatment of extensive forms in the same way as 5-FU.

However, its efficacy in this clinical situation cannot be assessed on the basis of the two placebo-controlled studies available since on the one hand they did not focus specifically on patients with extensive lesions and, on the other hand, they have significant methodological bias.

In addition, no study has established the benefit of 3% diclofenac gel in terms of efficacy or safety, in comparison with the other treatment options available (especially 5-FU), in particular situations or populations, or in association with cryotherapy.

This medicinal product offers no benefit in terms of duration of treatment, since treatment needs to be continued for two to three months, with efficacy assessed one month after treatment, as opposed to three to four weeks of treatment with 5-FU.

Consequently, in view of this information and the fact that alternative treatments exist and have been shown to be effective in the treatment of actinic keratosis, the positionning of this medicinal product in the therapeutic strategy cannot be assessed.

4.3. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Insurance or on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage of the marketing authorisation.