

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as amended**

**Elidel 1% cream
(pimecrolimus)**

DK/W/007/PdWS/001

**Marketing Authorisation Holder:
Novartis Healthcare A/S**

| | |
|--|------------------|
| Rapporteur: | Denmark |
| Start of the procedure (day 0): | 28 October 2009 |
| Date of this report: | 17 December 2009 |
| Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR)(day 70): | 06 January 2010 |
| Deadline for CMS's comments: | 21 January 2010 |
| Date for day 90 | 26 January 2010 |

ADMINISTRATIVE INFORMATION

| | |
|--|---|
| Invented name of the medicinal product: | Elidel |
| INN (or common name) of the active substance(s): | Pimecrolimus |
| MAH: | Novartis Healthcare A/S |
| Currently approved Indication(s) | <p>Treatment of patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. This may include:</p> <ul style="list-style-type: none"> • Intolerance to topical corticosteroids • Lack of effect of topical corticosteroids • Use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate |
| Pharmaco-therapeutic group (ATC Code): | D11AX15 |
| Pharmaceutical form(s) and strength(s): | Crème 1% |
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I. EXECUTIVE SUMMARY

Based on available clinical efficacy and safety data in children with atopic dermatitis submitted by the Applicant no SmPC and PL changes are proposed for Elidel cream 1%.

II. RECOMMENDATION

A significant number of children with corticosteroid-refractive atopic dermatitis have been exposed to Elidel cream 1% in clinical trials.

Elidel cream 1% has been shown to be an efficacious and safe treatment modality in children with corticosteroid-refractive atopic dermatitis or children with eczema in areas where corticosteroids are inappropriate due to risk of skin atrophy.

Elidel cream 1% is approved with the following posology.

Treatment of patients ages 2 years and over with mild to moderate atopic dermatitis, where treatment with topical corticosteroids is either inadvisable or not possible. This may include

- Intolerance to topical corticosteroids
- Lack of effect of topical corticosteroids
- Use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate.

It is recommended that the approved wording of the indication remain unchanged with identical posology in children and adults.

III. INTRODUCTION

The MAH has submitted one clinical paediatric study (study no.: ASM 981 CRU01) and a Regulatory Post-marketing Surveillance (PMS) Study for Elidel (pimecrolimus) study no.: CASM981CKR01

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Elidel cream 1% and that these are no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

Elidel cream 1% identical to the approved product.

IV.2 Non-Clinical aspects

Not relevant for the actual assessment.

IV.3 Clinical aspects

IV.3.1. Clinical studies

The MAH has submitted the following clinical studies:

- 1 Study No.: ASM981CRU01
- 2 Study No.: CASM981CKR01

1. Study No.: ASM981CRU01

1 Description

A 6 week open-label observational study to assess the efficacy and safety of Elidel (pimecrolimus) cream 1% in paediatric patients ≥ 3 months of age and adults with mild to moderate atopic dermatitis according to the approved Russian prescribing information.

2 Methods

1 Objectives

To assess the efficacy and safety of Elidel cream 1% in children and adults with mild to moderate atopic dermatitis according to the approved prescribing information (identical to that approved in EU).

2 Study design

A multicenter 6 week open label observational study.

3 Study population /Sample size

A total of 585 patients (502 paediatric (≥ 3 months and < 17 years)).

4 Treatments

Elidel cream 1% twice daily in areas with active eczema

5 Outcomes/endpoints

Primary efficacy endpoint: Facial Investigator Global Assessment (F-IGA).

Secondary efficacy endpoint: Investigator Global Assessment (IGA), number of days applying topical corticosteroids efficacy by means of a 4-point over scale and compliance after 6 weeks of therapy.

6 Statistical Methods

Routine statistical methods were applied to evaluate efficacy and safety data.

3 Results

Efficacy

As seen in the Table below Elidel treatment induced a rapid improvement in signs and symptoms of both facial atopic eczema (Table II-2) as well as atopic eczema in other locations (Table II-3).

Table 11-2 Distribution of IGA-sensitive (F-IGA) values by visit

| Visit \ Age | All patients | Adult ≥ 17 years | Children < 17 years | < 2 years | ≥ 2 and < 17 years |
|------------------|-------------------|------------------|---------------------|-------------------|--------------------|
| Number, N | 555 | 77 | 478 | 259 | 219 |
| Visit 1: | | | | | |
| clear | - | - | - | - | - |
| almost clear | - | - | - | - | - |
| mild | 274(46.9%) | 37(48.1%) | 237(49.6%) | 137(52.9%) | 87(39.7%) |
| moderate | 281(50.5%) | 40(51.9%) | 241(50.4%) | 122(47.1%) | 132(60.3%) |
| strong | - | - | - | - | - |
| very strong | - | - | - | - | - |
| | 2.51±0.5 (2 - 3) | 2.52±0.5 (2 - 3) | 2.5±0.5 (2 - 3) | 2.47±0.5 (2 - 3) | 2.54±0.5 (2 - 3) |
| Visit 2: | | | | | |
| clear | 52(9.4%) | 9(11.7%) | 43(9.0%) | 26(10.0%) | 17(7.8%) |
| almost clear | 242(43.6%) | 31(40.3%) | 211(44.1%) | 124(47.9%) | 87(39.7%) |
| mild | 216(38.9%) | 21(27.3%) | 195(40.8%) | 93(35.9%) | 102(46.6%) |
| moderate | 44(7.9%) | 16(20.8%) | 28(5.9%) | 16(6.2%) | 12(5.5%) |
| strong | 1(0.2%) | - | 1(0.2%) | - | 1(0.5%) |
| very strong | - | - | - | - | - |
| | 1.46±0.8 (0 - 4) | 1.57±0.95(0 - 3) | 1.44±0.75 (0 - 4) | 1.38±0.75 (0 - 3) | 1.51±0.74 (0 - 4) |
| Visit 3: | | | | | |
| clear | 375(67.6%) | 49(63.6%) | 326(68.2%) | 179(69.1%) | 147(67.1%) |
| almost clear | 143(25.8%) | 17(22.1%) | 126(26.4%) | 68(26.3%) | 58(26.5%) |
| mild | 25(4.5%) | 6(7.8%) | 19(4.0%) | 8(3.1%) | 11(5.0%) |
| moderate | 8(1.4%) | 5(6.5%) | 3(0.6%) | 1(0.4%) | 2(0.9%) |
| strong | - | - | - | - | - |
| very strong | - | - | - | - | - |
| Missing value | 4(0.7%) | - | 4(0.8%) | 3(1.2%) | 1(0.5%) |
| | 0.39±0.65 (0 - 3) | 0.57±0.9 (0 - 3) | 0.36±0.59 (0 - 3) | 0.34±0.56 (0 - 3) | 0.39±0.63 (0 - 3) |

Table 11-3 Distribution of IGA values by visit

| Visit \ Age | All patients | Adult ≥ 17 years | Children < 17 years | < 2 years | ≥ 2 and < 17 years |
|------------------|-------------------|-------------------|---------------------|-------------------|--------------------|
| Number, N | 555 | 77 | 478 | 259 | 219 |
| Visit 1: | | | | | |
| clear | - | - | - | - | - |
| almost clear | - | - | - | - | - |
| mild | 243(43.8%) | 36(46.8%) | 207(43.3%) | 120(46.3%) | 87(39.7%) |
| moderate | 310(55.9%) | 41(53.2%) | 269(56.3%) | 137(52.9%) | 132(60.3%) |
| strong | 2(0.4%) | - | 2(0.4) | 2(0.8%) | - |
| very strong | - | - | - | - | - |
| | 2.57±0.5 (2 - 4) | 2.53±0.5 (2 - 3) | 2.57±0.5 (2 - 4) | 2.54±0.51 (2 - 4) | 2.6±0.5 (2 - 3) |
| Visit 2: | | | | | |
| clear | 28(5.0%) | 6(7.8%) | 22(4.6%) | 16(6.2%) | 6(2.7%) |
| almost clear | 219(39.5%) | 30(39.0%) | 189(39.5%) | 114(44.0%) | 75(34.2%) |
| mild | 247(44.5%) | 21(27.3%) | 226(47.3%) | 105(40.58%) | 121(55.3%) |
| moderate | 60(10.8%) | 20(26.0%) | 40(8.4%) | 24(9.3%) | 16(7.3%) |
| strong | 1(0.2%) | - | 1(0.2%) | - | 1(0.5%) |
| very strong | - | - | - | - | - |
| | 1.62±0.75 (0 - 4) | 1.71±0.94(0 - 3) | 1.6±0.72 (0 - 4) | 1.53±0.75 (0 - 3) | 1.68±0.67 (0 - 4) |
| Visit 3: | | | | | |
| clear | 327(58.9%) | 46(59.7%) | 281(58.8%) | 159(61.4%) | 122(55.7%) |
| almost clear | 183(33.0%) | 18(23.4%) | 165(34.5%) | 84(32.4%) | 81(37.0%) |
| mild | 32(5.8%) | 7(9.1) | 25(5.2%) | 12(4.6%) | 13(5.9%) |
| moderate | 9(1.6%) | 6(7.8%) | 3(0.6%) | 1(0.4%) | 2(0.9%) |
| strong | - | - | - | - | - |
| very strong | - | - | - | - | - |
| missing value | 4(0.7%) | - | 4(0.8%) | 3(1.2%) | 1(0.5%) |
| | 0.5±0.68 (0 - 3) | 0.65±0.94 (0 - 3) | 0.47±0.63 (0 - 3) | 0.43±0.6 (0 - 3) | 0.52±0.65 (0 - 3) |

The severity of pruritus was evaluated as a subjective measure of clinical efficacy.

Table 11-4 demonstrates distributions of pruritus severity scores for all patients included in the efficacy analysis and, separately, for age subgroups.

An assessment of pruritus showed a similar improvement in children and adults treated with Elidel cream 1%. Treatment with Elidel cream 1% resulted in a significant reduction in the percentage of days in which the patients used topical corticosteroids (see Table II-7)

Table 11-7 Use of Corticosteroids during the study (by patients included in the efficacy analysis)

| Parameter \ Age | All patients | Adult ≥ 17 years | Children < 17 years | < 2 years | ≥ 2 and < 17 years |
|--|---------------------------|--------------------------|---------------------------|---------------------------|---------------------------|
| Number, N | 555 | 77 | 478 | 259 | 219 |
| Missing value | 4(0.7%) | 1(1.3%) | 3(0.6%) | 1(0.4%) | 2(0.9%) |
| Corticosteroid use: Yes / No | 72(13.0%) / 479(86.3%) | 12(15.6%) / 64(83.1%) | 60(12.6%) / 415(86.8%) | 32(12.4%) / 226(87.3%) | 28(12.8%) / 189(86.3%) |
| Duration of corticosteroid therapy, days | 6.04±3.43 (2 - 16) | 8.4±2.77 (5 - 14) | 5.6±3.4 (2 - 16) | 5.13±3.53 (2 - 16) | 6.2±3.2 (2 - 14) |

Safety

The observed adverse events were rare (n= 5) consisting of a local application burning, itching and erythema. No systemic or serious adverse events could be related to the treatment with Elidel cream 1%.

2. Study No.: CASM981CKR01

1 Description

Atopic dermatitis.

Regulatory Post-Marketing Surveillance (PMS) Study for Elidel (pimecrolimus).

2 Methods

Objectives

To assess the efficacy and safety of Elidel cream 1% in population of children and adults with mild-to-moderate atopic dermatitis as second-line therapy according to the approved indication.

Study design

An open-label, multicenter observational post-marketing Surveillance study of 12 weeks duration.

Study population/sample size

A total of 7067 patients were enrolled. Safety analysis was performed in 6823 patients receiving at least one application of Elidel cream 1%, and efficacy analysis was conducted in 6696 patients.

The demographics of the patients' population are shown below.

Table 2 Demographic characteristics

| | | Male n (%) | Female n (%) | Total n (%) |
|--------------------------|-------------------|----------------|-----------------|-------------------|
| Gender | Total | 3,342 (48.98) | 3,481 (51.02) | 6,823 (100.00) |
| Age | mean±std (years) | 17.86 ± 15.16 | 17.42 ± 14.99 | 17.64 ± 15.08 |
| | min~max | 0.00 ~ 83.00 | 0.00 ~ 90.00 | 0.00 ~ 90.00 |
| | < 2 years | 87 (2.60) | 79 (2.27) | 166 (2.43) |
| | 2~11 years | 1,421 (42.54) | 1,572 (45.19) | 2,993 (43.89) |
| | 12~17 years | 396 (11.86) | 417 (11.99) | 813 (11.92) |
| | 18~29 years | 836 (25.03) | 847 (24.35) | 1,683 (24.68) |
| | 30~39 years | 300 (8.98) | 242 (6.96) | 542 (7.95) |
| | 40~49 years | 129 (3.86) | 155 (4.46) | 284 (4.16) |
| | 50~59 years | 87 (2.60) | 83 (2.39) | 170 (2.49) |
| | ≥ 60 years | 84 (2.51) | 84 (2.41) | 168 (2.46) |
| | Total | 3,340 (48.98) | 3,479 (51.02) | 6,819 (100.00)* |
| Month age (< 2 years) | mean±std (months) | 11.66 ± 6.16 | 11.73 ± 7.12 | 11.69 ± 6.66 |
| | min~max | 0.00 ~ 23.00 | 0.00 ~ 24.00 | 0.00 ~ 24.00 |
| | < 7 months | 16 (18.39) | 25 (32.05) | 41 (24.85) |
| | 7~13 months | 38 (43.68) | 15 (19.23) | 53 (32.12) |
| | 13~18 months | 15 (17.24) | 17 (21.79) | 32 (19.39) |
| | 18~24 months | 18 (20.69) | 21 (26.92) | 39 (23.64) |
| | Total | 87 (52.73) | 78 (47.27) | 165 (100.00)** |
| Children | < 12 years | 1,412 (42.28) | 1,541 (44.29) | 2,953 (43.31) |
| | ≥ 12 years | 1,928 (57.72) | 1,938 (55.71) | 3,866 (56.69) |
| | Total | 3,340 (48.98) | 3,479 (51.02) | 6,819 (100.00)* |
| Elderly | < 65 years | 3,280 (98.20) | 3,426 (98.48) | 6,706 (98.34) |
| | ≥ 65 years | 60 (1.80) | 53 (1.52) | 113 (1.66) |
| | Total | 3,340 (48.98) | 3,479 (51.02) | 6,819 (100.00)* |
| Pregnancy | Yes | 0 (0.00) | 2 (0.06) | 2 (0.03) |
| | No | 3,342 (100.00) | 3,472 (99.94) | 6,814 (99.97) |
| | Total | 3,342 (49.03) | 3,474 (50.97) | 6,816 (100.00)*** |

Treatment

Elidel cream 1% twice daily in areas with active atopic dermatitis.

Outcomes/Endpoints

Efficacy was assessed using an Investigator's Global Assessment (IGA) of the whole body on a 5 point scale.

Results

A significant number of patients achieved either clearance or almost clearance of the eczema (see table below). The mean treatment duration was 60.35 ± 36.50 days.

Table 10 Efficacy analysis (II)

| | Male n (%) | Female n (%) | Total n (%) |
|---------------------|---------------|-----------------|----------------|
| Clear | 769 (23.37) | 819 (24.05) | 1,588 (23.72) |
| Almost clear | 1,733 (52.67) | 1,850 (54.32) | 3,583 (53.51) |
| Mild disease | 630 (19.15) | 585 (17.18) | 1,215 (18.15) |
| Moderate disease | 139 (4.22) | 131 (3.85) | 270 (4.03) |
| Severe disease | 18 (0.55) | 17 (0.50) | 35 (0.52) |
| Very severe disease | 1 (0.03) | 4 (0.12) | 5 (0.07) |
| Total | 3,290 (49.13) | 3,406 (50.87) | 6,696 (100.00) |

Safety

No unexpected adverse events were recorded. Elidel cream 1% was well tolerated in children with mild-to-moderate atopic dermatitis.

3 Discussion on clinical aspects

The submitted clinical trials have confirmed the efficacy and safety of Elidel cream 1% in children with mild-to-moderate atopic dermatitis.

No comments from CMS were received to the PPdAR.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**V.1 Overall conclusion**

Elidel cream 1% is approved for second-line treatment of children (> 2 years of age) with mild-to-moderate atopic dermatitis. The MAH has submitted 2 phase-IV post-marketing clinical studies that confirm the efficacy and safety of Elidel cream 1% in these children.

V.2 Recommendation

No further action required.

No comments from CMS were received to the PPdAR.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable.