SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Elidel® Cream 1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 g of cream contains 10 mg of pimecrolimus.

Excipients with known effect
10 mg benzyl alcohol, 40 mg cetyl alcohol, 40 mg stearyl alcohol, and 50 mg propylene glycol in 1 g of cream.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Whitish homogeneous cream.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Elidel cream 1% is indicated for the short-term treatment of the signs and symptoms of atopic dermatitis (eczema) and intermittent long-term treatment to prevent progression to flares in patients 3 months of age and above. Treatment with **Elidel Cream** is indicated in patients in whom the use of conventional topical corticosteroids therapy is deemed inadvisable because of potential risks or in patients who are not adequately responsive to or intolerant of conventional topical corticosteroids therapy.

4.2 Posology and method of administration
- The patient or caregiver should apply a thin layer of **Elidel Cream 1%** to the affected skin twice daily. The patient or caregiver should stop using when signs and symptoms (e.g., itch, rash and redness) resolve and should be instructed on what actions to take if symptoms recur.
- If signs and symptoms persist and beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis of atopic dermatitis.
- Continuous long-term use of **Elidel Cream** should be avoided, and application should be limited to areas of involvement with atopic dermatitis.

The safety of **Elidel Cream** under occlusion, which may promote systemic exposure, has not been evaluated. **Elidel Cream** should not be used with occlusive dressings.

Method of administration
- A patient or caregiver should wash their hands before using **Elidel Cream**. When applying **Elidel Cream** after a bath or shower, the skin should be dry.
- A patient or caregiver should apply a thin layer of **Elidel Cream** only to the affected skin areas, twice a day, as directed by the physician.
- A patient or caregiver should use the smallest amount of **Elidel Cream** needed to control the signs and symptoms of eczema.
- Caregivers applying **Elidel Cream** to a patient, or a patient who is not treating the hands should wash their hands with soap and water after applying **Elidel Cream**. This should remove any cream left on the hands.
- A patient should not bathe, shower or swim right after applying **Elidel Cream**. This could wash off the cream.

- A patient can use moisturizers with **Elidel Cream**. They should be sure to check with the physician first about the products that are right for them. Because the skin of patients with eczema can be very dry, it is important they keep up good skin care practices. If a patient uses moisturizers, he or she should apply them after **Elidel Cream**.

Paediatric population
For infants (3-23 months), children (2-11 years) and adolescents (12-17 years) the dosing recommendation is the same as for adults.

Use in babies under 3 months of age has not been evaluated.

Elderly patients
Clinical studies with **Elidel** did not include a sufficient number of patients in this age range to assess efficacy and safety.

4.3 Contraindications
Hypersensitivity to pimecrolimus, other macrolactams or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use
Pimecrolimus cream should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that causes immunosuppression.

Long-term effect on the local skin immune response and on the incidence of skin malignancies is unknown. Pimecrolimus should not be applied to potentially malignant or pre-malignant skin lesions.

Pimecrolimus should not be applied to areas affected by acute cutaneous viral infections (herpes simplex, chicken pox).

Elidel has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with **Elidel**, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with pimecrolimus may be associated with an increased risk of skin herpes simplex virus infection, or eczema herpeticum (manifesting as rapid spread of vesicular and erosive lesions). In the presence of herpes simplex skin infection, pimecrolimus treatment at the site of infection should be discontinued until the viral infection has cleared.

Patients with severe atopic dermatitis may have an increased risk of skin bacterial infections (impetigo) during treatment with pimecrolimus.
Use of **Elidel** may cause mild and transient reactions at the site of application, such as a feeling of warmth and/or burning sensation (see section 4.8). If the application site reaction is severe, the risk-benefit of treatment should be re-evaluated.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the cream should be thoroughly wiped off and/or rinsed off with water.

Physicians should advise patients on appropriate sun protection measures, such as minimisation of the time in the sun, use of sunscreen product and covering the skin with appropriate clothing (see section 4.5).

Elidel contains the active substance pimecrolimus, a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies.

Cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported in patients using pimecrolimus cream (see section 4.8). However, patients with atopic dermatitis treated with **Elidel** have not been found to have significant systemic pimecrolimus levels.

In clinical studies, 14/1,544 (0.9%) cases of lymphadenopathy were reported while using **Elidel** 10mg/g cream (see section 4.8). These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear aetiology or were known to resolve. Patients who receive **Elidel** 10mg/g cream and who develop lymphadenopathy should have the aetiology of their lymphadenopathy investigated. In the absence of a clear aetiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, treatment with pimecrolimus should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc.) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

Populations with potentially higher risk of systemic exposure.
Elidel has not been studied in patients with Netherton's syndrome. Due to the potential for increased systemic absorption of pimecrolimus, **Elidel** is not recommended in patients with Netherton's syndrome.

As the safety of pimecrolimus has not been established in erythrodermic patients, the use of **Elidel** in this patient population cannot be recommended.

The use of **Elidel** under occlusion has not been studied in patients. Occlusive dressings are not recommended.

In patients with severely inflamed and/or damaged skin, the systemic concentrations may be higher.

Elidel contains cetyl alcohol and stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis). Further **Elidel** also contains 10 mg benzyl alcohol per 1 g cream, which may cause allergic reactions and mild local irritation. **Elidel** also contains 50 mg propylene glycol per 1 g cream which may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction
Potential interactions between pimecrolimus and other medicinal products have not been systematically evaluated. Pimecrolimus is exclusively metabolised by CYP 450 3A4. Based on its minimal extent of absorption, interactions of pimecrolimus with systemically administered medicinal products are unlikely to occur (see section 5.2).

The present data indicate that pimecrolimus can be used simultaneously with antibiotics, antihistamines and corticosteroids (oral/nasal/inhaled).

Due to the minimal absorption of **Elidel**, a potential systemic interaction with vaccination is unlikely to occur. In patients with extensive disease, it is recommended to administer vaccinations during treatment-free intervals.

Application of pimecrolimus to vaccination sites, as long as local reactions persist, was not studied and is therefore not recommended. In a 5-year study in infants 3 months to less than 12 months of age at enrolment with mild to moderate atopic dermatitis patients with AD who were treated with **Elidel cream** or TCS displayed normal immune response maturation and developed effective immunisation against vaccine antigens (see section 5.1).

There is no experience with concomitant use of immunosuppressive therapies given for atopic eczema such as UVB, UVA, PUVA, azathioprine and ciclosporin A.

Pimecrolimus has no photocarcinogenic potential in animals (see section 5.3.). However, since the relevance to man is unknown excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA, UVA or UVB should be avoided during treatment with pimecrolimus.

Rare cases of flushing, rash, burning, itching or swelling have been observed shortly after the intake of alcohol in patients using pimecrolimus cream (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of pimecrolimus in pregnant women. Animal studies using dermal application do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Studies in animals after oral application have shown reproductive toxicity (see section 5.3). Based on the minimal extent of pimecrolimus absorption after topical application of pimecrolimus (see section 5.2), the potential risk for humans is considered limited. However, pimecrolimus should not be used during pregnancy.

Lactation

Animal studies on milk excretion after topical application were not conducted and the use of **Elidel** in breastfeeding women has not been studied. It is not known whether pimecrolimus is excreted in the milk after topical application.

However, based on the minimal extent of pimecrolimus absorption after topical application of pimecrolimus, (see section 5.2), the potential risk for humans is considered limited. Caution should be exercised when pimecrolimus is administered to breastfeeding women.

Breastfeeding mothers may use **Elidel** but should not apply **Elidel** to the breast in order to avoid unintentional oral uptake by the new-born.

Fertility

There are no clinical data on the effects of pimecrolimus on male or female fertility (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines
Elidel has no known effect on the ability to drive and use machines.

4.8 Undesirable effects
The most common adverse events were application site reactions which were reported by approximately 19% of the patients treated with **Elidel** and 16% of patients in the control groups. These reactions generally occurred early in treatment, were mild/moderate and were of short duration.

The following undesirable effects have been observed with the frequencies indicated below during clinical trials using pimecrolimus cream 1% and from spontaneous reporting.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000, including isolated reports).

Skin and subcutaneous tissue disorders	
Common	Skin infections (folliculitis)
Uncommon	Furuncle, impetigo, herpes simplex, herpes zoster, herpes simplex dermatitis (eczema herpeticum), skin papilloma and condition aggravated
Rare	Allergic reactions (e.g. rash, urticaria, angiooedema), skin discoloration (e.g hypopigmentation, hyperpigmentation)
Metabolism and nutrition disorders	
Rare	Alcohol intolerance (in most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol)
Infections and infestations	
Uncommon	Molluscum contagiosum
General disorders and administration site conditions	
Very common	Application site burning
Common	Application site reactions (irritation, pruritus and erythema)
Uncommon	Application site disorders (rash, pain, paraesthesia, desquamation, dryness, oedema)
Immune system disorders	
Very rare	Anaphylactic reactions, including severe forms

Post marketing: Cases of malignancy, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using pimecrolimus cream (see section 4.4).

Cases of lymphadenopathy have been reported in post-marketing use and in clinical trials, however a causal relationship with the pimecrolimus treatment has not been established (see section 4.4).

Paediatric population
The clinical safety database of children aged 3 months and older treated with pimecrolimus 1% cream is extensive with long-term safety data available for up to 5 years. The safety profiles in infants, children and adolescent were comparable in nature and frequency of the adverse events observed. The most common observed adverse reactions were application site reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose
There has been no experience of overdose with **Elidel**.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other dermatological preparations. Agents for dermatitis, excluding corticosteroids. ATC code: D11AH02

Mechanism of action
Pimecrolimus is a lipophilic anti-inflammatory ascomycin macrolactam derivative and a cell selective inhibitor of the production and release of pro-inflammatory cytokines.

Pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase calcineurin. As a consequence, it blocks the synthesis of inflammatory cytokines in T cells.

Pharmacodynamic effects
Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. In the pig model of allergic contact dermatitis, topical pimecrolimus is as effective as potent corticosteroids. Unlike corticosteroids, pimecrolimus does not cause skin atrophy in pigs and does not affect Langerhans´ cells in murine skin.

Pimecrolimus neither impairs the primary immune response nor affects lymph nodes in murine allergic contact dermatitis. Topical pimecrolimus penetrates similarly into, but permeates much less through human skin than corticosteroids, indicating a very low potential of pimecrolimus for systemic absorption.

In conclusion, pimecrolimus has a skin-selective pharmacological profile different from corticosteroids.

Clinical efficacy and safety

The efficacy and safety profile of **Elidel** has been evaluated in more than 2,000 patients including infants (≥ 3 months), children, adolescents, and adults enrolled in phase II and III studies. Over 1,500 of these patients were treated with **Elidel** and over 500 were treated with control treatment i.e. either **Elidel** vehicle and/or topical corticosteroids.

Short-term (acute) treatment:
Children and adolescents: Two 6-week, vehicle-controlled trials were conducted including a total of 403 paediatric patients aged 2 to 17 years. Patients were treated twice daily with **Elidel**. The data of both studies were pooled.
Infants: A similar 6-week study was conducted in 186 patients aged 3-23 months.
In these three 6-week studies, the efficacy results at endpoint were as follows:

		Children and adolescents			**Infants**		
Endpoint	**Criteria**	**Elidel 1% (N=267)**	**Vehicle (N=136)**	**p-value**	**Elidel 1% (N=123)**	**Vehicle (N=63)**	**p-value**
IGA*:	**Clear or almost clear [1]**	**34.8%**	**18.4%**	**<0.001**	**54.5%**	**23.8%**	**<0.001**
IGA*:	**Improvement [2]**	**59.9%**	**33%**	**not done**	**68%**	**40%**	**Not done**
Pruritus:	**Absent or mild**	**56.6%**	**33.8%**	**<0.001**	**72.4%**	**33.3%**	**<0.001**
EASI° :	**Overall (mean % change)[3]**	**-43.6**	**-0.7**	**<0.001**	**-61.8**	**+7.35**	**<0.001**
EASI° :	**Head/Neck (mean % change) [3]**	**-61.1**	**+0.6**	**<0.001**	**-74.0**	**+31.48**	**<0.001**

*** Investigators Global Assessment**
° Eczema Area Severity Index (EASI): mean % change in clinical signs (erythema, infiltration, excoriation, lichenification) and body surface area involved
[1]: p-value based on CMH test stratified by centre
[2]Improvement=lower IGA than at baseline
[3]: p-value based on ANCOVA model of EASI at Day 43 endpoint, with centre and treatment as factors and baseline (Day 1) EASI a covariate;

A significant improvement in pruritus was observed within the first week of treatment in 44% of children and adolescents and in 70% of infants.

Adults: **Elidel** was less effective than 0.1% betamethasone-17-valerate in the short-term treatment (3 weeks) of adults with moderate to severe atopic dermatitis.

Long-term treatment
Two double-blind studies of long-term management of atopic dermatitis were undertaken in 713 children and adolescents (2-17 years) and 251 infants (3-23 months). **Elidel** was evaluated as foundation therapy.

Elidel was used at first signs of itching and redness to prevent progression to flares of atopic dermatitis. Only in case of a flare of severe disease not controlled by **Elidel**, treatment with medium potency topical corticosteroids was initiated. When corticosteroid therapy was initiated for the treatment of flares, pimecrolimus 1% cream therapy was discontinued. The control group received **Elidel** vehicle in order to maintain blinding.

Both studies showed a significant reduction in the incidence of flares ($p<0.001$) in favour of pimecrolimus 1% cream treatment; pimecrolimus 1% cream treatment showed better efficacy in all secondary assessments (Eczema Area Severity Index, Investigators Global Assessment, subject assessment); pruritus was controlled within a week with pimecrolimus 1% cream. More patients treated with pimecrolimus 1% cream completed 6 months [children (61% **Elidel** vs 34% control), infants (70% **Elidel** vs 33% control)] and 12 months with no flare [children (51% **Elidel** vs 28% control), infants (57% **Elidel** vs 28% control)].

Elidel had a sparing effect on the use of topical corticosteroids: more patients treated with pimecrolimus 1% cream did not use corticosteroids in 12 months [children (57% **Elidel** vs 32% control), infants (64% **Elidel** vs 35% control)]. The efficacy of pimecrolimus 1% cream was maintained over time.

A 6-month randomised, double-blind, parallel group, vehicle-controlled study of similar design was performed in 192 adults with moderate to severe atopic dermatitis. Topical corticosteroid medication was used on 14.2 ± 24.2% of the days of the 24-week treatment period in **Elidel** group and on 37.2 ± 34.6% of the days in the control group ($p<0.001$). A total of 50.0% of the patients treated with pimecrolimus 1% cream did not experience any flare compared with 24.0% of the patients randomised to the control group.

A one year double-blind study in adults with moderate to severe atopic dermatitis was conducted to compare **Elidel** to 0.1% triamcinolone acetonide cream (for trunk and extremities) plus 1% hydrocortisone acetate cream (for face, neck and intertriginous areas). Both pimecrolimus 1% cream and topical corticosteroids were used without restrictions. Half of the patients in the control group received topical corticosteroids for more than 95% of study days. Pimecrolimus 1% cream was less effective than 0.1% triamcinolone acetonide cream (for trunk and extremities) plus 1% hydrocortisone acetate cream (for face, neck and intertriginous areas) in the long-term treatment (52 weeks) of adults with moderate to severe atopic dermatitis.

Long-term safety
A 5-year, open-label, randomised, active-controlled study was conducted in 2,418 infants 3 months to less than 12 months of age at enrollment with mild to moderate atopic dermatitis (AD). The primary objective was to compare safety by assessing adverse events (AEs), and the effects of treatments on the developing immune system and growth velocity. Infants were randomised to **Elidel** (n = 1,205; with short-term TCSs for disease flares) or low/mid potency topical corticosteroids (TCS; n = 1,213).

Elidel was well tolerated in subjects with mild to moderate AD who were 3 to 12 months of age at the start of the study. The profile and frequency of adverse events was similar in the 2 treatment groups. No impairment of systemic immune assessments was seen, and subjects with AD who were treated with pimecrolimus 1% cream or TCS displayed normal immune response maturation and developed effective immunization against vaccine antigens. There was no apparent difference in growth velocity.

Special studies
Tolerability studies demonstrated that **Elidel** has not shown contact sensitising, phototoxic or photosensitising potential, nor did they show any cumulative irritation.

The atrophogenic potential of **Elidel** in humans was tested in comparison to medium and highly potent topical steroids (betamethasone-17-valerate 0.1% cream,

triamcinolone acetonide 0.1% cream) and vehicle in sixteen healthy volunteers treated for 4 weeks. Both topical corticosteroids induced a significant reduction in skin thickness measured by echography, as compared to pimecrolimus 1% cream and vehicle, which did not induce a reduction of skin thickness.

Paediatric population
Results of relevant studies in infants, children and adolescents are detailed above in section 5.1.

5.2 Pharmacokinetic properties
Data in humans
Absorption in adults
Systemic exposure to pimecrolimus was investigated in 12 adults with atopic dermatitis who were treated with **Elidel** twice daily for 3 weeks. The affected body surface area (BSA) ranged from 15-59%. 77.5% of pimecrolimus blood concentrations were below 0.5 ng/ml and 99.8% of the total samples were below 1 ng/ml. The highest pimecrolimus blood concentration was 1.4 ng/ml in one patient.

In 40 adult patients treated for up to 1 year with **Elidel**, having 14-62% of their BSA affected at baseline, 98% of pimecrolimus blood concentrations were below 0.5 ng/ml. A maximum blood concentration of 0.8 ng/ml was measured in only 2 patients in week 6 of treatment. There was no increase in blood concentration over time in any patient during the 12 months of treatment. In 8 adult atopic dermatitis patients, in which AUC levels could be quantified, the $AUC_{(0\text{-}12h)}$ values ranged from 2.5 to 11.4 ng h/ml.

Absorption in infants, children and adolescents
Systemic exposure to pimecrolimus was investigated in 58 paediatric patients aged 3 months to 14 years, of those 41 were below 2 years of age. The affected BSA ranged from 10-92%. These children were treated with **Elidel** twice daily for 3 weeks. Five (8.6 %) of the 58 patients were treated for up to 1 year on a “as needed” basis with 2 patients being aged ≥ 3 to ≤ 6 months and 3 patients being aged > 6 to ≤ 12 months.

Pimecrolimus blood concentrations were consistently low regardless of the extent of lesions treated or duration of therapy. They were in a range similar to that measured in adult patients.

Around 67% of pimecrolimus blood concentrations were below 0.5 ng/ml and 93% of all samples were below 2 ng/ml in infants (aged 3 to 23 months). The highest blood concentrations measured in 2 paediatric patients aged 8 months to 14 years were 2.0 ng/ml.

In the age group ≥ 3 to ≤ 6 months, 31% of the blood samples had pimecrolimus concentrations below 0.5 ng/ml and 90% below 2.0 ng/ml with the highest blood concentration of 4.14 ng/ml measured in one patient sample which was suspected to be contaminated during venipuncture.

In the age group > 6 to ≤ 12 months, 66% of the blood samples had pimecrolimus concentrations below 0.5 ng/ml and 90% below 2.0 ng/ml with the highest blood concentration of 2.6 ng/ml measured in one patient sample.

In infant aged > 12 to < 24 months, 80% of the blood samples had pimecrolimus concentrations below 0.5 ng/ml and 97% below 2.0 ng/ml. The maximum pimecrolimus concentration in this age group was 2.0 ng/ml in one sample.

In the 5 children treated for 1 year with 2 of them aged ≥ 3 to ≤ 6 months and 3 aged > 6 to ≤ 12 months, blood concentrations were consistently low, with a (maximum blood concentration was of 1.94 ng/ml in one sample of a1 patient aged ≥ 3 to ≤ 6 months). There was no increase in blood concentration over time in any patient during the 12 months of treatment.

In children and adolescents (2 to 14 years) 68% of pimecrolimus blood concentrations were below 0.5 ng/ml and 99% of all samples were below 2 ng/ml, the highest blood concentration measured in one patient was 2.0 ng/ml.

In 8 paediatric patients aged 2-14 years, $AUC_{(0\text{-}12h)}$ ranged from 5.4 to 18.8 ng h/ml. AUC ranges observed in patients with <40% BSA affected at baseline were comparable to those in patients with ≥ 40% BSA.

The maximum body surface area treated was 92% in clinical pharmacology studies and up to 100% in Phase III trials.

Distribution
Consistent with its skin selectivity, after topical application, pimecrolimus blood levels are very low. Therefore, pimecrolimus metabolism could not be determined after topical administration.

In vitro plasma protein binding studies have shown that 99.6% of pimecrolimus in plasma is bound to proteins. The major fraction of pimecrolimus in plasma is bound to different lipoproteins.

Biotransformation
After single oral administration of radiolabeled pimecrolimus in healthy subjects, unchanged pimecrolimus was the major active substance-related component in blood and there were numerous minor metabolites of moderate polarity that appeared to be products of O-demethylations and oxygenation.

No metabolism of pimecrolimus was observed in human skin *in vitro*.

Elimination
After oral administration, active substance-related radioactivity was excreted principally via the faeces (78.4%) and only a small fraction (2.5%) was recovered in urine. Total mean recovery of radioactivity was 80.9%. Parent compound was not detected in urine and less than 1% of radioactivity in faeces was accounted for by unchanged pimecrolimus.

5.3 Preclinical safety data
Conventional studies of repeated dose toxicity, reproductive toxicity and carcinogenicity using oral administration produced effects at exposures sufficiently in excess of those in man to be of negligible clinical significance. Pimecrolimus had no genotoxic, antigenic, phototoxic, photoallergenic or photocarcinogenic potential. Dermal application in embryo/foetal developmental studies in rats and rabbits and in carcinogenicity studies in mice and rats were negative.

The bioavailability of pimecrolimus in mini-pigs following a single dermal dose (applied for 22h under semi-occlusion) was 0.03%. The amount of active substance-related material in the skin at the application site (almost exclusively unchanged pimecrolimus) remained practically constant for 10 days.

Effects on reproductive organs and altered sex hormone functions were seen in male and female rats in repeated dose toxicity studies after oral administration of 10 or 40 mg/kg/day (= 20 to 60 times the maximum human exposure after dermal application). This is reflected by the findings from the fertility study. The No Observed Adverse Effect Level (NOAEL) for female fertility was 10 mg/kg/day (= 20 times the maximum human exposure after dermal application). In the oral embryotoxicity study in rabbits, a higher resorption rate associated with maternal toxicity was observed at 20 mg/kg/day (= 7 times the maximum human exposure after dermal application); the mean number of live foetuses was not affected.

Dose-dependent increases in the incidence of lymphomas were observed at all doses in a 39 week monkey oral toxicity study. Signs of recovery and/or at least partial reversibility of the effects were noted upon cessation of dosages in a few animals. Failure to derive a NOAEL precludes an assessment of the margin of safety between a non-carcinogenic concentration in the monkey and exposures in patients. The systemic exposure at the LOAEL of 15 mg/kg/day was 31 times the highest maximum exposure observed in a human (paediatric patient). The risk for humans cannot be completely ruled out as the potential for local immunosuppression with the long-term use of pimecrolimus cream is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water (purified)
Triglycerides
Oleyl alcohol
Propylene glycol
Cetyl alcohol
Stearyl alcohol
Mono-and di-glycerides
Benzyl alcohol
Sodium cetostearyl sulphate
Citric acid (anhydrous)
Sodium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening the container: 12 months.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Pack sizes: 15 g, 30 g or 100 g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER(S)

126-12-30517-01

Revised in November 2024 according to MOH guidelines