

# PRODUCT MONOGRAPH

Pr **Silkis**<sup>®</sup>

(Calcitriol)

Ointment 3 µg/g

Topical Non-Steroidal Antipsoriatic Agent

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## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION .....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE .....	3
CONTRAINDICATIONS .....	3
WARNINGS AND PRECAUTIONS .....	4
ADVERSE REACTIONS.....	5
DRUG INTERACTIONS .....	7
DOSAGE AND ADMINISTRATION .....	7
OVERDOSAGE .....	8
ACTION AND CLINICAL PHARMACOLOGY.....	8
STORAGE AND STABILITY .....	9
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	9
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>10</b>
PHARMACEUTICAL INFORMATION.....	10
CLINICAL TRIALS.....	11
DETAILED PHARMACOLOGY .....	12
TOXICOLOGY .....	13
REFERENCES.....	17
<b>PART III: CONSUMER INFORMATION .....</b>	<b>18</b>

## SILKIS®

(calcitriol)

Ointment  
3 µg/g

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Ointment 3 µg/g	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

#### INDICATIONS AND CLINICAL USE

Silkis® (calcitriol) ointment 3 µg/g is indicated for topical treatment of mild to moderate plaque type psoriasis (psoriasis vulgaris) with up to 35% body surface area involvement in adults.

##### Limitations of Use:

- There is no experience of the concurrent use of Silkis (calcitriol) ointment and other medications for the treatment of psoriasis.
- Silkis ointment should not be applied to the eyes, lips, or facial skin.

##### Geriatrics (> 65 years of age):

Clinical studies of Silkis ointment did not include sufficient numbers of subjects 65 years and older to determine whether they respond differently from younger subjects. See Warnings and Precautions.

##### Pediatrics (< 18 years of age):

Silkis is not recommended for pediatric use. Safety and effectiveness in pediatric patients have not been established.

#### CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- NOT FOR OPHTHALMIC or INTERNAL USE.

- Patients with hypercalcemia and patients known to suffer from abnormal calcium metabolism.
- Patients on systemic treatment of calcium homeostasis.
- Patients with severe renal impairment or end-stage renal disease
- Patients with liver dysfunction.

## **WARNINGS AND PRECAUTIONS**

### **General**

Serum calcium levels should be monitored at regular intervals if risk factors for hypercalcemia are present. If the serum calcium level becomes elevated, calcitriol therapy should be discontinued and the serum calcium level monitored in these patients until it returns to normal.

Due to the potential effect of Vitamin D and its metabolites on calcium metabolism, substances that may increase the absorption of calcitriol must not be added to the ointment or used concomitantly with the ointment.

Silkis ointment must not be covered with an occlusive dressing.

Silkis is not recommended for severe, extensive psoriasis (*i.e.*, involvement of more than 35% of the body surface).

Silkis is not approved for use in other clinical forms of psoriasis.

No more than 30 g of Silkis ointment should be used per day.

### **Carcinogenesis and Mutagenesis**

Animal data suggest that the vehicle of Silkis ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumours (see Toxicology - Carcinogenicity). Patients who apply Silkis ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid using phototherapy in patients who use Silkis ointment.

### **Endocrine and Metabolism**

If abnormal serum calcium levels are observed, treatment with calcitriol should be discontinued.

### **Renal**

Silkis is not recommended in patients with mild to moderate renal impairment.

### **Skin**

Silkis should not be applied to the lips or facial skin. Hands should be washed after applying Silkis in order to avoid unintentional application to other areas. In case of severe irritation or a contact allergic reaction, patients should be advised to discontinue treatment with Silkis and

seek medical attention. (See Contraindications – Hypersensitivity)

### **Special Populations**

**Pregnant Women:** There are no adequate and well-controlled studies in pregnant women, although studies in experimental animals have not shown teratogenic effects. Silkis should be used during pregnancy only if the anticipated benefit clearly outweighs the potential risk (see Toxicology - Reproduction).

**Nursing Women:** It is not known whether calcitriol is excreted in human milk. Silkis has been found in the milk of lactating rats. Calcitriol should be used by nursing women only if the anticipated benefit clearly outweighs the potential risk (see Toxicology – Reproduction).

**Geriatrics (> 65 years of age):** Of the total number of subjects in clinical studies of Silkis, 14% were 65 and over. The incidence of drug-related adverse events, serious adverse events, and adverse events leading to discontinuation were higher in subjects 65 or older than in subjects 18 to < 65. In general, use in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Pediatrics (< 18 years of age):** There are insufficient data in patients under 18 years of age to determine the safety and efficacy in this population. Silkis is not recommended in pediatric patients.

### **Monitoring and Laboratory Tests**

Serum calcium levels should be monitored at regular intervals if risk factors for hypercalcemia are present. If serum calcium becomes elevated, treatment with calcitriol should be discontinued.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The clinical trial adverse reaction data for Silkis is largely based on two 8-week randomized, vehicle-controlled trials as well as one long term (1 year) safety study. These data provide information on twice daily exposure in 743 patients, including 239 exposed for 6 months and 116 exposed for at least one year. The most common adverse reactions experienced were laboratory test abnormality, skin discomfort, pruritus, and psoriasis.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Silkis was studied in two vehicle-controlled 8 week studies with 419 patients treated with Silkis twice daily. Drug-related adverse reactions that occurred in at least 1% of patients in the Silkis

group are shown in the following table:

**Table 1: Summary of Drug-related Adverse Events (at least 1%) of the Two Pooled Vehicle-Controlled Studies**

	Calcitriol ointment 3 µg/g (n=419)	Calcitriol vehicle ointment (n=420)
Total number of AEs	58	71
Total number of subjects with AEs	36 (8.6%)	45 (10.7%)
<b>SKIN AND APPENDAGES</b>		
Discomfort skin	11 (2.6%)	9 (2.1%)
Pruritus	6 (1.4%)	4 (1%)
<b>LAB TEST ABNORMAL</b>		
Lab test abnormality	14 (3.3%)	15 (3.6%)

In these two studies, among subjects having laboratory monitoring, hypercalcemia (albumin-adjusted calcium above the upper limit of normal) at any post-baseline point during the 8 week trials, was observed in 24% (18/74) of calcitriol-exposed subjects compared to 16% (13/79) of vehicle-exposed subjects. No subject had an albumin-adjusted calcium result over the alert level (10% above the upper limit of the normal range) at any time-point throughout the study. Hypercalcemia was not reported as an adverse event during either study.

A one-year multi-center, open-label, non-comparative study enrolled 324 patients with psoriasis. Silkis was applied twice daily for up to 52 weeks. The most common adverse events were laboratory test abnormality (8%), urine test abnormality (4%), psoriasis (4%), flu syndrome (4%), hypercalciuria (3%), pruritus (3%) and skin infection (3%). There were 10 cases (3%) of hypercalcemia (defined as an albumin-adjusted serum total calcium concentration above the upper limit of the reference range (2.15 to 2.55 mmol/L). With one exception (2.72 mmol/L), all other albumin-adjusted serum total calcium concentrations were less than 5% above the upper limit of normal. There were 3 subjects with reported kidney stones.

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

**Skin and Appendages:** psoriasis (0.2%)

**Post-Market Adverse Drug Reactions**

Because post-market adverse drug reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following post-market adverse reactions have been reported with the use of Silkis ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, skin oedema, contact dermatitis and skin discomfort. Two serious, unexpected related reports have been received which describe skin atrophy (1) and blisters over the body, burning sensation and extensive flare-up of weepy eczema (2).

## **DRUG INTERACTIONS**

### **Overview**

Silkis (calcitriol) ointment must be used with caution in patients receiving medications known to increase serum calcium levels, such as thiazide diuretics, or medications with pharmacological effects impacted by a change in calcium levels, such as digoxin. Caution must also be exercised in patients receiving calcium supplements or high doses of vitamin D. There is no experience of the concurrent use of Silkis (calcitriol) ointment and other medications for the treatment of psoriasis.

Information on interaction of systemic medications after the use of Silkis (calcitriol) ointment is limited.

Silkis has a slight irritant potential, and therefore it is possible that concomitant use of peeling agents, astringents, or irritant products may produce an additive irritant effect.

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- Silkis is for TOPICAL USE ONLY and not for oral, ophthalmic or intravaginal use.
- There is no clinical trial experience with the use of Silkis in children and there is limited experience with the use of Silkis in the elderly (see Warnings and Precautions).
- Silkis should be used in pregnant or nursing women only if the benefit versus risk is favourable (see Warnings and Precautions).
- Silkis is contraindicated in patients with severe renal impairment or end-stage renal disease.
- Silkis is contraindicated in patients with liver dysfunction.
- Silkis is not recommended in patients with mild to moderate renal impairment (see Warnings and Precautions).

### **Recommended Dose and Dosage Adjustment**

Silkis (calcitriol) ointment should be applied to the areas affected with psoriasis twice daily, morning and evening, after washing and gentle drying. No more than 30 g of Silkis ointment should be used daily. No more than 35% of the body can be treated.

No additional therapeutic benefit has been demonstrated with higher doses or more frequent application.

### **Missed Dose**

If a dose of Silkis is missed, it should be applied as soon as the patient remembers and further dosing resumed as usual.

### **Administration**

The affected area should be washed and dried gently. The ointment should be applied and rubbed in gently until the medication is no longer visible. The treated area should not be bandaged or occluded in any way.

Hands should be washed thoroughly with soap and water after each application.

After satisfactory improvement has occurred, the drug should be discontinued. If recurrence takes place after discontinuation, the treatment may be reinstated.

### **OVERDOSAGE**

The accidental ingestion of Silkis (calcitriol) ointment may produce symptoms that are consistent with vitamin D toxicity and hypercalcemia. The initial clinical signs (polyuria, polydipsia, dyspepsia) should be confirmed with a serum analysis of calcium levels prior to initiating treatment for hypercalcemia. The most common symptoms which may occur after accidental administration are anorexia, nausea, vomiting, constipation, hypotonia and depression. Lethargy and coma are occasionally observed.

Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects. If signs of hypercalcemia occur with the prescribed use of Silkis, treatment should be discontinued.

If the medication is applied excessively no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.

### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

Calcitriol (1 $\alpha$ -25-dihydroxyvitamin D<sub>3</sub>) is the naturally occurring and biologically active metabolite of vitamin D<sub>3</sub>, primarily produced in the skin by exposure to the ultraviolet rays of the sun. Vitamin D<sub>3</sub> must be metabolically activated in the liver and the kidney before it is fully active at target tissues as calcitriol.

Calcitriol primarily regulates systemic calcium and phosphate homeostasis by effects on the gastrointestinal tract, bone, and kidney. The mechanism of action of calcitriol in the treatment of psoriasis has not been established.

#### **Pharmacokinetics**

The systemic exposure of calcitriol ointment was assessed in 23 patients with chronic plaque psoriasis over 21 days with a total of 30 g/day application to 35% body surface area. At Day 21, the geometric mean plasma concentration values of C<sub>max</sub> increased by 36% over baseline and the geometric mean value of AUC<sub>(0-12hr)</sub> increased by 44%. There was no correlation between the observed elevated calcitriol levels and the pharmacodynamic parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus.



**Absorption:** Considerable inter-subject variability in calcitriol permeation through the skin is observed.

#### **STORAGE AND STABILITY**

Store at room temperature (15° - 30° C).

#### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Silkis (calcitriol) ointment 3 µg/g is available in collapsible aluminium tubes coated internally with an epoxy-phenolic resin and fitted with a white high density polyethylene or polypropylene screw cap. Tubes contain 5 g or 60 g of ointment.

Silkis is a white, translucent, ointment containing 3 µg/g (0.0003% w/w) of calcitriol. Other components of the ointment are vitamin E (dl-α tocopherol) added as an antioxidant, mineral oil, and white petrolatum.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

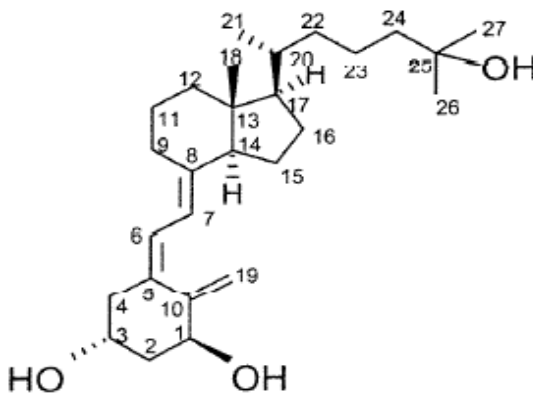
Proper name: Calcitriol

Chemical name: (5*Z*, 7*E*)-9, 10-secocholesta-5, 7, 10(19)-triene-1 $\alpha$ , 3 $\beta$ , 25-triol  
(1 $\alpha$ , 3 $\beta$ , 5*Z*, 7*E*)-9, 10-secocholesta-5, 7 10(19)-triene-1, 3, 25-triol

Molecular formula: C<sub>27</sub>H<sub>44</sub>O<sub>3</sub>

Molecular mass: 416.6

Structural formula:



Physicochemical properties: White to almost white crystalline powder. Air, heat, and light sensitive. Calcitriol is practically insoluble in water, freely soluble in alcohol, and soluble in fatty oils.

## CLINICAL TRIALS

The efficacy of Silkis (calcitriol) Ointment for the treatment of psoriasis has been demonstrated in two randomized, double-blind, placebo-controlled studies in adult patients with mild to moderate psoriasis. Patients were treated twice daily for 8 weeks with Silkis or vehicle ointment. The primary efficacy parameter in both studies was Success Rate at Endpoint for the ITT population, defined as the proportion of subjects with a Global Severity Score of 0 (clear) or 1 (minimal) on the global, static, dichotomized, 6-point scale.

### Study Demographics and Trial Design

**Table 2 - Summary of Patient Demographics for Pivotal Clinical Trials in Psoriasis Indication**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range), years	Gender M/F
RD.06.SRE.18053	Randomized, double blind placebo controlled	3 µg/g or vehicle sufficient to treat up to 35% BSA twice daily (up to 30 g/day) Topical 8 weeks	418 209 Silkis 209 Vehicle	47.1 (12-81)	278/140
RD.06.SRE.18054			421 210 Silkis 211 Vehicle	48.6 (13-87)	254/167

### Study Results

**Table 3 - Results of Pivotal Studies in Psoriasis - Treatment Success Rate, Based on Assessment of Global Severity of Psoriasis<sup>1</sup>**

Study #	Number (%) of Patients Treated with Silkis Who Achieved Treatment Success at Endpoint <sup>2</sup>	Number (%) of Patients Treated with Vehicle Who Achieved Treatment Success at Endpoint <sup>2</sup>	P value <sup>3</sup>
RD.06.SRE.18053	72 (34.4%)	47 (22.5%)	p=0.005
RD.06.SRE.18054	70 (33.3%)	26 (12.3%)	p<0.001

<sup>1</sup>Success was defined as "Clear" or "Minimal" (up to light red or pink coloration; surface dryness; difficult to ascertain, slight elevation above normal skin) on the global severity score of psoriasis (score of 0 or 1).

<sup>2</sup>Endpoint was defined as the last observation for a subject during the treatment period, including Baseline if no post-baseline data were available

<sup>3</sup>P values are based on the Cochran-Mantel-Haenszel test, controlling for centre

Efficacy (success rate) was seen as early as Week 2 with a statistically significant difference from vehicle of 7%. At the end of treatment (Week 8) success rate was 37.3% and 36.9% in the Silkis ointment groups and 25.3% and 13.3% in the vehicle groups in Study 18053 and Study 18054 (p=0.009 and p<0.001), respectively.

In one long-term (52 week) uncontrolled, open label study in 324 subjects, efficacy did not appear to change over time.

## **DETAILED PHARMACOLOGY**

### **Safety Pharmacology**

ECGs were recorded in a 13-week dermal dog and in a 9-month dermal mini-pig study. Ointments containing 3 µg/g calcitriol were applied in the dog study and up to 15 µg/g were applied to 10% body surface area (BSA) in the mini-pig study. There were no calcitriol-related effects on ECG morphology, heart rate or cardiac conduction.

### **Clinical Pharmacology**

#### *Pharmacodynamics and Pharmacokinetics*

Twenty three adult male and female subjects with psoriasis applied 15 g of calcitriol ointment twice daily to 35% of their body surface area (BSA) for 3 weeks. To ensure homogeneity in daily calcium intake, a 500 mg calcium tablet was taken daily for the duration of the study. Blood samples to determine calcitriol plasma levels and serum levels of calcium, phosphorus, albumin and creatinine were drawn on Days -8, -1, 0, and 21 (at times 0, 1, 2, 3, 4, 6, 9, 12, 16, and 24 hours) and on Day 14 (at times 0, 1, 2, 3, 4, 6, 9, and 12 hours).

The pharmacodynamic parameters (serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus) were used for the assessment of any effects of the topical application of calcitriol ointment on calcium homeostasis.

The calcitriol plasma profiles in all subjects were relatively flat, and no terminal log-linear segment corresponding to a marked concentration decrease appeared on the concentration-time curves. Therefore, the terminal half-life was not determined.

The intra-individual endogenous calcitriol plasma levels (determined on Days -1 and -8) were stable during the day. No marked concentration peak appeared. The variability of calcitriol plasma level was also low. Conversely, the inter-subject variability was high, as shown by the coefficients of variation of approximately 50% both for  $C_{max}$  and  $AUC_{(0-12h)}$ . The maximum endogenous calcitriol plasma levels ( $C_{max}$ ) varied from 20 to 121 pg/mL. Arithmetic Mean  $C_{max} \pm SD$  was  $56.1 \pm 26.3$  pg/mL on Day -8 and  $58.2 \pm 28.6$  pg/mL on Day -1.

Steady-state was achieved by Day 14 with no significant differences in pharmacokinetic parameters between Day 14 and Day 21. The mean values of  $C_{12h}$ ,  $C_{max}$ , and  $AUC_{(0-12h)}$  on Day 21 were 27%, 32% and 37% higher than the corresponding mean Baseline values (mean values for Days -1 and -8). No marked concentration peak appeared on Day 21, the mean value of  $C_{max}$  was approximately 40% higher than the mean value of  $C_{12h}$ .

There were no clinically meaningful changes in albumin-adjusted calcium values, although some mean values were statistically significant. The mean serum levels of albumin-adjusted calcium decreased from 2.37 mmol/L at Baseline to 2.32 mmol/L at Day 14 ( $p=0.0162$ ), and the mean serum levels of phosphorus decreased from 1.2 mmol/L at Baseline to 1.13 mmol/L at Day 14 ( $p=0.0372$ ). Although neither mean value returned to Baseline at Day 21 (calcium 2.33 mmol/L; phosphorus 1.17 mmol/L), neither was statistically significant at this point ( $p=0.0618$  and  $p=0.2713$ , respectively).

There were no statistically significant or clinically meaningful changes in the mean 24-hour urine

calcium value over the course of this study. The mean 24-hour urine phosphorus value increased from 25.53 mmol/dL at Baseline to 28.77 mmol/dL at Day 21 (p=0.0064). Individual values were within the normal range, except for two subjects who had elevated urine phosphorus on Day -1 and on Day 21.

#### *Local Tolerance*

Local tolerance, as the primary endpoint, was assessed in healthy subjects in five Phase 1 local tolerance studies of calcitriol ointment. In these studies, 50 µL of calcitriol ointment was applied under an occlusive patch, which would result in greater exposure levels than expected clinically with unoccluded use. These studies are summarized in Table 4 below. In these studies, there was no evidence suggesting that calcitriol ointment was irritating, sensitizing, phototoxic, or photosensitizing.

**Table 4 - Tolerance Assessments from Phase 1 Studies for Which Local Tolerance was the Primary Endpoint: Calcitriol Ointment 3 µg/g**

Study	Study objective	Subjects (N)	Treatment duration	Type of control	Tolerance scale
1	Cumulative irritancy potential	25	21 days	Tacalcitol 4 µg/g calcipotriol 50 µg/g white petrolatum <sup>a</sup>	<ul style="list-style-type: none"> <li>- Erythema response on 5-point scale</li> <li>- Cumulative Irritation Index calculated for each zone and subject</li> <li>- Local reactions recorded</li> <li>- Data regarding patch application collected</li> </ul>
2	Cutaneous contact sensitization and cumulative irritancy potential	225	21 days (induction) 2 weeks (rest period) 48 hours (challenge) single application <sup>a</sup>	Vehicle ointment white petrolatum <sup>b</sup>	
3	Photoallergic contact sensitization potential	25	21 days (induction) 24 hours (challenge) <sup>a,b</sup>	Vehicle ointment white petrolatum	
4	Phototoxicity potential	28	24 hours	Vehicle ointment white petrolatum no treatment	
5	Cumulative irritancy potential	25	21 days	Calcipotriol 50 µg/g ointment calcipotriol 50 µg/g cream	

a Sensitization reaction ratings: 0=negative, 1=equivocal, 2=positive

b Investigator opinion of photoallergic contact sensitization made at end of challenge phase

## **TOXICOLOGY**

### **Single-dose Toxicity**

In rats and mini-pigs, single dermal application of 15 µg/g ointment to 20% BSA, providing an acute dose of 42 and 51 µg/kg respectively, was not associated with any calcitriol-related signs of toxicity. In rabbits, treatment with 15 µg/g ointment to 20% BSA (19.1 µg/kg) caused severe toxicity including mortality. The observed differences in species sensitivity to calcitriol may be

related to (a) higher permeability of rabbit skin (rabbit>rat>mini-pig) and/or (b) inter-species differences in the regulation of calcitriol metabolism and calcium homeostasis.

### **Repeat-dose Toxicity**

The chronic toxicity profile of calcitriol was primarily evaluated in a series of dermal repeat-dose studies up to 26 weeks in rats at daily doses of 0, 0.3, 1, 3 and 9 µg/g calcitriol to 10% BSA (unoccluded), and 9 months in mini-pigs at daily doses of 0, 1, 3, 9 and 15 µg/g calcitriol to 10% BSA (semi-occluded). Total daily calcitriol intake corresponded to 0, 0.6, 2, 6, 18 µg/kg/day in rats and 0, 1.7, 5.1, 15.3 and 25.5 µg/kg/day in mini-pigs. Other repeat-dose dermal studies were conducted in dogs, mice and rabbits. Of the species evaluated, the dermal permeability and skin characteristics of mini-pigs most closely resembles that of humans. The primary effects observed were consistent with exaggerated pharmacological alterations including marked increases in serum calcium concentration, urinary calcium and phosphorus excretion, and mineralization in multiple tissues.

A 13-week oral repeat-dose toxicity study was conducted in rats at doses of 0, 0.01, 0.1 and 0.3 µg/kg/day. Calcitriol-related findings were consistent with the results of dermal studies and were attributed to the pharmacological effects of the compound.

### **Mutagenicity**

Calcitriol is an endogenous substance with no anticipated genotoxicity potential. Calcitriol was not mutagenic in an *in vitro* mouse lymphoma assay.

### **Carcinogenicity**

A 12-month photocarcinogenicity study was conducted in UVR-irradiated hairless mice. Animals were dermally administered calcitriol at doses corresponding to 0, 0.3, 0.6 and 1.0 µg/kg five days per week. Toxicity was observed in mid- and high-dose mice, necessitating premature discontinuation of calcitriol administration. UVR exposure continued as scheduled and vehicle was applied for the remainder of the study. Topical administration of the vehicle slightly enhanced photocarcinogenicity with a reduced latency period of 3-4 weeks for appearance of skin tumours of ≤1 mm diameter when compared with UVR-irradiated control mice. The effect was attributed to the presence of mineral oil in the formulation, which is represented at ~44% w/w in the drug product (see Warning and Precautions). Topical administration of calcitriol at dose levels ≤ 1 µg/kg/day did not enhance photocarcinogenicity above the effect observed with the vehicle.

A 104-week mouse carcinogenicity study was conducted wherein males and females were dermally administered calcitriol at doses of 0, 0.3, 0.6 and 1.0 ppm to 10 % BSA. Toxicity, including mortality and likely related to exaggerated pharmacological effects, was observed at 0.6 and 1.0 ppm and the frequency of application was reduced from daily to 3 times a week. There was no evidence to suggest that application of calcitriol was associated with an increased incidence of tumours in male or female mice.

A 104-week rat carcinogenicity study was conducted wherein males and females were orally administered calcitriol at doses of 0, 0.005, 0.03, and 0.1 µg/kg/day. An increased incidence of proliferative non-neoplastic and neoplastic lesions was observed in the adrenal medulla (hyperplasia, pheochromocytoma) of males and females at 0.03 and 0.1 µg/kg/day. In the thyroid,

focal C-cell hyperplasia and C-cell adenoma was observed at 0.1 µg/kg/day, particularly in females. These changes are likely due increased calcemia and are considered to be specific to the rat.

### **Reproduction**

There were no effects on fertility (males or females) or early embryonic development in the rat at oral doses of 0.1, 0.3, and 0.6 µg/kg/day.

#### *Embryo-fetal and Post-natal Development*

Calcitriol was orally administered to pregnant rats at doses of 0.1, 0.3, or 0.9 µg/kg/day. Results indicated that calcitriol, at up to toxic dose levels, was not associated with any effect on gonad function, mating behaviour and reproductive performance of the male and female rats. Fetal toxicity and teratogenicity were not observed at any dose levels, despite a significant maternal toxicity.

Calcitriol ointment was dermally administered to pregnant rabbits onto 0.4, 1.6 and 6.4% BSA (corresponding to 0.08, 0.32 and 1.26 µg/kg/day). Teratogenicity was not observed.

Developmental anomalies were attributed to high maternal toxicity and were not considered a direct calcitriol-mediated effect. Specifically, mid- and high-dose groups exhibited an increased incidence of retarded ossification of the pubic bones, and the high-dose displayed an increased incidence of skeletal variations. Overt maternal toxicity was observed in high-dose rabbits, which was associated with an increased incidence of post-implantation loss and a reduced number of live fetuses.

In a rat post-natal development study, no effects were observed on fertility, development, or reproductive performance of offspring at oral doses at 0.1, 0.3, or 0.6 µg/kg calcitriol per day.

#### *Pregnancy and Nursing*

The placental transfer of total radioactivity following a single oral administration of 0.9 µg/kg [<sup>3</sup>H]-calcitriol was evaluated in pregnant female rats. Peak radioactivity in fetal tissue occurred 22 hours later than in maternal plasma. A maximum of 0.8% of the administered dose was recovered in the whole fetus at 72 hours post-dose. The total exposure of the fetus was 3-fold lower than the total exposure of maternal plasma.

The secretion of total radioactivity in the milk of lactating rats was evaluated following administration of a single oral dose of 0.6 µg/kg [<sup>3</sup>H]-calcitriol. Drug-related radioactivity (calcitriol and/or calcitriol metabolites) was detected in milk. The mean concentration of radioactivity was the highest at 4 hours post-dose and was higher in plasma than in milk at all time points evaluated. Radioactivity was cleared in plasma and milk at the same rate.

### **Local Tolerance**

There was no evidence to suggest that calcitriol and calcitriol-containing ointment exhibits the potential to induce delayed contact hypersensitivity in guinea pigs.

Single or repeated dermal applications and single ocular exposure to 15 µg/g calcitriol ointment induced slight local irritation in rabbits and guinea pigs. Repeated dermal administration of 2.5

or 8.75 µg/g calcitriol ointments was not associated with signs of local irritation in rats or rabbits. Thus, although calcitriol ointment is well tolerated slight, individual, local irritation may occur.



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**PART III: CONSUMER INFORMATION**

Silkis®  
(calcitriol)  
Ointment 3 µg/g

**This leaflet is part III of a three-part "Product Monograph" published when Silkis® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Silkis®.**

**Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION****What the medication is used for:**

Silkis® is used for the topical treatment of mild to moderate psoriasis on your body.

**What it does:**

Silkis® contains the active ingredient calcitriol, a vitamin D- like agent.

Psoriasis results from skin cells growing and multiplying too quickly, causing plaques (scaly, red patches) to form on your skin. Calcitriol acts in a way that aims to return the growth of skin cells to normal.

**When it should not be used:**

Silkis® should not be used if you:

- Are allergic to calcitriol, or any medications that contain a vitamin D-like agent (vitamin D derivative), or any of the other ingredients in Silkis®.
- Have high blood calcium levels (hypercalcemia);
- Are being treated for conditions affecting normal calcium levels (abnormal calcium metabolism).
- Have severely reduced kidney function, or end-state kidney disease,.
- Have liver problems.

Silkis® should not be used in or near your eyes, lips or on your face. Silkis should not be used internally (e.g. orally or intravaginally).

**What the medicinal ingredient is:**

Calcitriol

**What the important nonmedicinal ingredients are:**

Vitamin E (dl-α tocopherol) added as an antioxidant, mineral oil, and white petrolatum.

**What dosage forms it comes in:**

Silkis® is available as an ointment at a concentration of 3 µg/g.

**WARNINGS AND PRECAUTIONS**

The ointment component of Silkis® may increase the risk of developing skin tumours caused by ultraviolet radiation (UVR). Silkis® ointment alone does not cause cancer. Avoid excessive exposure of areas being treated with Silkis® to either natural or artificial sunlight, including tanning booths and sun lamps.

BEFORE you use Silkis® talk to your doctor or pharmacist if:

- You have severe extensive psoriasis or other forms of psoriasis (the use of Silkis® is not recommended).
- You receive other treatments for psoriasis or other skin conditions.
- You have liver or kidney disease.
- You are pregnant or planning to become pregnant.
- You are breastfeeding or plan to breastfeed an infant.
- You are using sun tanning beds or sun lamps.

Silkis® is not recommended for use in patients under 18 years of age.

It is not recommended to use Silkis® with an occlusive dressing, such as a bandage, or to cover the treated area(s) tightly.

In case of severe irritation or an allergic reaction, stop using Silkis® and contact your healthcare provider.

**INTERACTIONS WITH THIS MEDICATION**

Before using Silkis®, tell your doctor or pharmacist about your other medications, including non-prescriptions, vitamin or mineral supplements. Drugs that may interact with Silkis® include:

- Medications that may increase blood calcium levels, such as thiazide (water pill) and calcium supplements.
- Medications that may change blood calcium levels, such as digoxin.
- High doses of vitamin D.

Silkis® has a slight irritant potential, and therefore it is possible that use of peeling agents, astringents, or other irritants at the same time may make the irritation worse.

**PROPER USE OF THIS MEDICATION****Usual dose:**

Apply Silkis® to the skin areas affected with psoriasis twice a day (morning and evening) after washing and gentle drying. Rub the ointment in carefully until you can no longer see it.

Do not apply Silkis® to more than 35% of your body area each time. Do not use Silkis® in your eyes, on your lips or face. Do not use more than 30 grams of Silkis®

ointment per day. After applying the ointment, wash your hands thoroughly with soap and water. Do not bandage or cover the treated area tightly.

You will not get better or faster results by applying Silkis® more often. If more than the recommended amount of medication is used, marked redness, peeling or discomfort may occur. Once your psoriasis improves your doctor may ask you to stop using Silkis®. If your psoriasis returns, treatment may be re-started.

**Overdose:**

Excessive use or accidental ingestion of Silkis® may result in signs of high blood calcium levels such as upset stomach, excessive thirst, and increased urination. If you have overdosed, contact your local poison control centre or contact your physician or pharmacist.

**Missed Dose:**

If you miss a dose, apply it as soon as you remember. Then go back to your usual dosing schedule at the next dose.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The most common side effects with Silkis® are skin discomfort, itching, psoriasis, flu syndrome and skin infection. Other side effects reported for Silkis® include: skin swelling and skin irritation (rash, redness or flaky skin). Silkis® may affect the results of certain laboratory tests or the level of calcium in your urine (hypercalciuria).

In case of severe irritation or an allergic reaction, stop using Silkis® and contact your healthcare provider.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHT TO DO ABOUT THEM</b>				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very rarely: hypercalcaemia (high blood calcium levels)	Nausea, vomiting, excessive thirst, excessive urination	X		X

*This is not a complete list of side effects. For any unexpected effects while taking Silkis®, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store at room temperature (15° - 30°C).

Do not use past the expiry date stamped on the tube.

Keep out of the reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance.

You can report any suspected adverse reactions associated with the use of health products in the Canada Vigilance Program by one of the following 3 ways:

1. Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
2. Call toll-free at 1-866-234-2345
3. Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 1908C  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.galderma.ca> or by contacting the sponsor, Galderma Canada Inc., at: 1-800-467-2081

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