Calcipotriol/betamethasone dipropionate: Daivobet®/Dovobet®

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Psoriasis is a common skin condition that causes significant morbidity. Treatments can be complex and time consuming. Calcipotriol plus betamethasone dipropionate ointment (Daivobet® or Dovobet®) is a stable, convenient, once-daily topical treatment for psoriasis. Compared with its individual ingredients or tacalcitol, it has a faster speed of onset and greater efficacy. Consistent Psoriasis Area Severity Index reductions of approximately 40% after 1 week and 70% after 4 weeks were seen in multicenter studies involving more than 6000 patients. After 4 weeks of once-daily therapy, approximately 50% of patients are clear or almost clear. This product is associated with a similar safety profile to betamethasone dipropionate ointment, 50% fewer cutaneous adverse events than calcipotriol ointment and 75% fewer than tacalcitol ointment.

Keywords: betamethasone dipropionate, calcipotriene, calcipotriol, Daivobet®, Dovobet®, fixed combination, psoriasis

Psoriasis affects 0.3 to 2.6% of the population and has a significant impact on the patient's quality of life [1–4]. A 1998 US survey of 17,488 National Psoriasis Foundation patient members showed that psoriasis had a significant impact on psychosocial activities (e.g., interacting in the workplace and with family/spouse, making and keeping friends, getting a job, and exclusion from public facilities) and activities of daily living (e.g., sleeping, sexual activities, using hands, walking, sitting or standing for long periods, and performing their job) [5]. A total of 10% of respondents in the 18- to 34-year old age group contemplated suicide.

Traditionally, treatment has occurred in a stepwise approach with topical agents acting as first-line therapy for mild-to-moderate disease [6].

Overview of the market

Combination therapy is commonly used in the treatment of psoriasis [7,8]. By combining medications with a different mechanism of action and safety profile, efficacy can be enhanced and/or safety improved. Unless drug stability is known, compounding should be avoided since it may result in drug degradation due to incompatibility. Application of different medications at different times of the day increases treatment complexity. Treatment complexity and the time requirement for frequent application of medication can hinder compliance. There is a need for a stable once-daily combination treatment.

Introduction to the compound

Calcipotriol is a standard acute and chronic treatment for plaque psoriasis. It is a vitamin D analog, which, after binding to the vitamin D receptor, acts as a heterodimer with the retinoid X receptor (RXR) [9]. Keratinocytes and lymphocytes have vitamin D receptors. In psoriasis, vitamin D analogues normalize differentiation and proliferation, induce apoptosis in inflammatory cells, induce a T-helper (Th)1 to 2 switch and are antiangiogenic [10–12]. Studies have shown that twice-daily monotherapy is more efficacious than vehicle [13], tar [14], short-contact anthralin [15] and fluocinonide ointment [16], and at least as efficacious as betamethasone 17-valerate 0.1% ointment [17,18]. Calcipotriol has an excellent long-term safety profile [19–23]. Calcipotriol is commonly used in combination with other treatments, particularly topical steroids [8]. Such a combination results in increased efficacy, faster onset of clinical response and decreased irritation. However, due to drug incompatibility, each medication must be applied at a different time of the day (e.g., morning or afternoon) [24]. Calcipotriol and topical steroids are stable at different pHs [25]. Corticosteroids are stable in acidic conditions, while calcipotriol is stable in alkaline and rapidly inactivated in acidic conditions.

Betamethasone dipropionate is a Class III topical steroid that has been used once or twice daily to treat psoriasis for several years [26]. Once-daily use in the evening for 6 weeks in a morning/afternoon regimen with calcipotriol, is more efficacious with fewer adverse events than twice-daily calcipotriol [27]. Irritation may be minimized when calcipotriol is used in an morning/afternoon regimen with a medium-strength steroid(e.g., clobetasone 17-butyrate-cream) [28]. In order to enhance efficacy, a potent (e.g., betamethasone) or superpotent

(e.g., halobetasol) steroid is required [28,29]. In contrast to the vitamin D analogues, corticosteroids bind to cytoplasmic glucocorticoid receptors and rapidly translocate to the nucleus where they inhibit or stimulate genes regulating inflammation [30]. This results in inhibition of cytokine production (e.g., interleukin-1 and -8, as well as tumor necrosis factor-α and interferon-γ) and reduced levels of nitric oxide, prostaglandins and leukotrienes [31,32].

Chemistry

Calcipotriol/betamethasone dipropionate (Daivobet® or Dovobet®) is a stable (for 2 years at room temperature), fixed-combination ointment containing the vitamin D3 analog, calcipotriol hydrate 50 µg/g, combined with the Class III steroid, betamethasone dipropionate 0.5 mg/g. The vehicle contains polyoxypropylene-15-stearyl ether [33].

Pharmacodynamics

In a vasoconstrictor assay using both an objective chromametric measurement of skin blanching and visual evaluation, calcipotriol/betamethasone dipropionate and diprosone had equivalent biological activity [34]. A sonographic study of skin thickness showed almost identical skin atrophy after treatment with calcipotriol/betamethasone dipropionate or betamethasone dipropionate, with skin thickness returning to normal shortly after a 4-week treatment course [35].

Pharmacokinetics

Pharmacokinetic studies have shown that the new vehicle and presence of the other active component do not affect the absorption of either of the two active components [33,36]. Systemic absorption of calcipotriol from Daivonex® and calcipotriol/betamethasone dipropionate was minimal as was the absorption of betamethasone dipropionate from calcipotriol/betamethasone dipropionate.

Clinical efficacy

Phase II study

In a study involving 25 patients, greater reduction in inflammation and restoration of normal differentiation were noted with calcipotriol plus betamethasone dipropionate than with the individual components or vehicle alone [25]. The percentage of vimentin-positive cells (inflammatory cells) were 1.6% in patients treated with the combination product, compared with 5.0% with calcipotriol, 4.1% with betamethasone dipropionate and 5.3% with vehicle.

Phase III studies

Six large international, multicenter, randomized, blinded studies involving more than 6000 patients have shown Psoriasis Area Severity Index (PASI) reductions of approximately 40 and 70% after 1 and 4 weeks, respectively, of calcipotriol plus betamethasone dipropionate therapy [37–42]. Baseline disease severity did not affect the percentage reduction in PASI, although fewer people with a baseline PASI of more than 17 were clear or almost clear at the end of treatment [43]. Approximately 50% were clear or almost clear after 4 weeks of once-daily therapy [40,41]. In all of these studies, patient demographics were similar:

- Mean age: approximately 48 years
- Mean duration of psoriasis: approximately 19 years
- Mean baseline PASI: approximately 10
- Gender: approximately 60% males

Since the head was not treated or assessed, the maximum possible PASI score was 64.8 rather than the standard 72. The PASI in the study was calculated as follows:

> 0.2(redness + thickness + scaling scores for arms) × area for arms + 0.3(redness + thickness + scaling scores for trunk) × area for trunk + 0.4(redness + thickness + scaling scores for legs) × area for legs

Area, thickness and scaling were rated on a 0- to 4-point scale and area on a 0- to 6-point scale.

A total of 1043 patients were randomized in a 3:3:3:1 ratio to 4 weeks of twice-daily calcipotriol plus betamethasone dipropionate, betamethasone dipropionate in the new vehicle, calcipotriol in the new vehicle, or vehicle alone [37]. Mean percentage decreases in PASI at 1 week were 48.1, 41.4, 28.4 and 21.5, respectively ($p < 0.001$ for the combination product versus each of the others). After 4 weeks of therapy, the mean percentage decreases in PASI were 73.2, 63.1, 48.8 and 28.8%, respectively ($p < 0.001$).

In a second study, 1106 patients were randomized in a 1:1:1 ratio to 4 weeks of twice-daily combination, betamethasone dipropionate or calcipotriol ointment [38]. After 1 week, the mean percentage reductions in PASI were 47.4, 39.8 and 31.0%, respectively ($p < 0.001$). After 4 weeks, the

mean PASI reductions were 74.4, 61.3 and 55.3%, respectively ($p < 0.001$) and the percentage of patients with at least 75% improvement was 68.0, 46.6 and 38.9%, respectively ($p < 0.001$). After the 4-week double-blind period, there was a 4-week open-label period in which patients were treated with calcipotriol ointment. At the end of the open-label period, the PASI in the combination group rose from 2.5 to 3.6; the PASI in the betamethasone dipropionate group from 3.9 to 4.1, and in the calcipotriol group it decreased from 4.4 to 3.7.

In a third study, 1603 patients were randomized in a 3:3:3:1 ratio to once-daily treatment with the combination product, betamethasone dipropionate in the new vehicle, calcipotriol in the new vehicle, or vehicle alone [39]. After 1 week of treatment, mean PASI reductions were 39.2, 33.3, 23.4 and 18.1%, respectively ($p < 0.001$). After 4 weeks, the mean PASI reductions were 71.3, 57.2, 46.1 and 22.7%, respectively ($p < 0.001$), and percentages with at least 75% improvement: 64.9, 45.7, 29.0 and 9.7%, respectively ($p < 0.001$).

The fourth study assessed the efficacy and tolerance of once- versus twice-daily therapy [40]. In this 4-week study, 828 patients were randomized to once-daily combination product plus once-daily vehicle, twice-daily combination product, twice-daily calcipotriol or twice-daily vehicle. The mean percentage reductions in PASI after 1 week were 45.5, 47.6, 33.6 and 20.0%, respectively ($p < 0.001$ for once- or twice-daily combination product versus calcipotriol or vehicle). The mean percentage reductions in PASI at the end of treatment were 68.6, 73.8, 58.8 and 26.6%, respectively ($p = 0.052$ for once- versus twice-daily combination; $p < 0.001$ for once- or twice-daily combination versus calcipotriol or vehicle). The rates for at least 75% improvement were 63.3, 73.5, 50.7 and 9.2%. A statistically significant improvement in quality of life was noted with the combination product once or twice daily and calcipotriol twice daily versus placebo [44].

The fifth study was investigator blinded and involved 972 patients [41]. These patients were treated with the combination product once daily for 8 weeks, or the combination product once daily for 4 weeks followed by 4 weeks of calcipotriol once-daily weekdays and combination therapy once-daily weekends, or twice-daily calcipotriol ointment for 8 weeks. The mean percentage reductions in PASI at 8 weeks were 73.3, 68.2 and 64.1%, respectively ($p < 0.001$). In the group treated for 8 weeks with the combination product, maximal improvement was noted after 5 weeks of therapy and maintained for the following 3 weeks. After the 8 weeks of treatment, those in the first group (i.e., those who had received 8 weeks of once-daily combination therapy) were switched to 4 weeks of once-daily calcipotriol therapy; those on intermittent combination/calcipotriol were maintained on the same therapy, and those on twice-daily calcipotriol were maintained on this regimen. At 12 weeks, there was no significant difference in PASI reduction between the three groups. Calcipotriol (Daivonex) maintenance was sufficient for two out of three patients treated with 8 weeks of therapy (PASI improvement in 24% or PASI increase of 0 to 1 in 40%).

In the sixth study, 501 patients were treated with either once-daily combination product or tacalcitol [42]. After 4 weeks, the mean percentage reduction in PASI was 65% with the combination product and 33.3% with tacalcitol, and the percentage of patients experiencing at least 75% improvement was 57.6 and 17.0%, respectively.

Postmarketing surveillance

No cases of atrophy have been spontaneously reported to postmarketing surveillance.

Safety & tolerability

No significant changes in serum calcium were noted in any of the clinical trials.

In the trial reported by Papp and colleagues involving 1043 patients treated twice daily for up to 4 weeks, 9.9% on the combination product, 8.6% on betamethasone dipropionate, 17.2% on calcipotriol and 15.7% on vehicle reported lesional/perilesional adverse events [37]. Two patients on betamethasone dipropionate and one on the combination product had reversible skin atrophy. Douglas and colleagues reported lesional/perilesional adverse-event rates of 8.1% for the combination product, 4.7% for betamethasone dipropionate and 12.0% for calcipotriol with 4 weeks of twice-daily treatment [38].

In a 4-week once-daily study involving 1603 patients, lesional/perilesional adverse events were noted in 6.0% on combination therapy, 4.9% on betamethasone dipropionate, 11.4% on calcipotriol and 13.6% on vehicle ($p = 0.45$, 0.003 and 0.002, respectively for the combination product versus betamethasone dipropionate, calcipotriol and vehicle) [39].

In another 4-week study, 9.9% on once-daily combination therapy, 10.6% on twice-daily combination therapy, 19.8% on twice-daily calcipotriol and 12.5% on vehicle had lesional/perilesional adverse events, with pruritus being the most common event [38]. Atrophy was noted in one patient on the combination product, one on calcipotriol and one on vehicle. Lesional/perilesional adverse events were noted in 2.9% treated with 4 weeks of once-daily combination therapy and 11.8% on once-daily tacalcitol ointment [42].

A total of 8 weeks of once-daily therapy was associated with a 10.9% rate of lesional/perilesional adverse events compared with 11.5% on 4 weeks of once-daily combination treatment followed by 4 weeks of weekday treatment with calcipotriol and weekend treatment with the combination product, and 22.3% with twice-daily calcipotriol for 8 weeks [41]. There was a single case of mild reversible skin atrophy after 5 weeks of the combination product.

A 52-week study assessed the safety of 52 weeks of combination therapy, 52 weeks of alternating 4-week periods of combination therapy and calcipotriol, and 4 weeks of combination therapy followed by 48 weeks of calcipotriol ointment. There were no statistical differences between the three groups with regards to the number of patients with adverse events associated with long-term topical corticosteroid use [45].

Regulatory affairs

In the EU, calcipotriol/betamethasone dipropionate is sold in Denmark, Ireland, UK, The Netherlands, Belgium, Portugal, Finland, Sweden, France, Spain, Greece, Italy, Germany, Malta, Austria, Poland, Latvia, Slovenia, Estonia and Lithuania. Calcipotriol/betamethasone dipropionate is also sold in Iceland, Switzerland, Norway, Canada and Australia. Furthermore, Dovobet is widely available in the Middle East, Asia and Central and South America. A registration file is with the US Food and Drug Administration (FDA) in the USA.

Highlights

- Calcipotriol/betamethasone dipropionate is a fixed-combination product containing the vitamin D derivative, calcipotriol hydrate 50 µg/g, plus the Class III steroid, betamethasone dipropionate 0.5 mg/g.
- Stable for 2 years at room temperature.
- Once-daily application.
- Approximately 40% reduction in Psoriasis Area Severity Index (PASI) after 1 week of therapy.
- Approximately 70% reduction in PASI after 4 weeks of therapy.
- Approximately 50% clear or almost clear after 4 weeks of therapy.
- Faster onset of action and greater efficacy than betamethasone dipropionate, calcipotriol or tacalcitol.
- Similar safety profile to betamethasone dipropionate.
- It is associated with half the cutaneous adverse events of calcipotriol and quarter as many as tacalcitol.

Conclusion

Calcipotriol plus betamethasone dipropionate ointment is a stable, convenient, once-daily topical treatment for psoriasis. It has greater efficacy and a faster speed of onset than its individual ingredients or tacalcitol. Consistent PASI reductions of approximately 40% after 1 week and 70% after 4 weeks were seen in randomized, multicenter, blinded studies involving more than 6000 patients. Approximately 50% of patients are clear or almost clear after 4 weeks of treatment. Calcipotriol plus betamethasone dipropionate ointment is associated with a similar safety profile to betamethasone dipropionate ointment, 50% fewer cutaneous adverse events than calcipotriol ointment, and 75% fewer than tacalcitol ointment.

Expert opinion

Calcipotriol/betamethasone dipropionate ointment is a highly efficacious, convenient once-daily topical therapy. Several of the author's patients have shown improvement and clearing not previously experienced with prior therapies. This product should be considered as initial induction therapy for patients who have psoriasis amenable to treatment with topical agents and wish rapid improvement. The product should also be considered for patients who are currently being treated with alternative medications with an inadequate response. Many patients in the clinical studies had had inadequate responses to previous therapies. Calcipotriol/betamethasone dipropionate should also be considered for resistant plaques in patients receiving phototherapy, traditional systemic therapy and/or biologic agents. It should also be considered as adjunctive initial therapy when one is waiting for the systemic agent to take effect.

Treatment should be once daily for 4 to 8 weeks, followed by maintenance therapy with either calcipotriol monotherapy or a combination of calcipotriol and the combination ointment. Maintenance with calcipotriol alone is sufficient for two out of three patients; however, intermittent calcipotriol administered on week days and the combination product on weekends might be prefera-

ble. Additional research is required to determine optimal maintenance regimens. Would a Monday, Wednesday and Friday combination product treatment or a Tuesday and Thursday treatment with calcipotriol on the remaining days be preferable so as to space treatment more evenly?

Studies in combination with systemic therapies including biologic agents should also be considered. Since calcipotriol/betamethasone dipropionate has a rapid onset of action, yet does not induce remissions, its use with alefacept, which has a slow onset of action (often 8 weeks), but induces remissions, should be studied.

Outlook

Calcipotriol/betamethasone dipropionate ointment will probably remain an excellent inductive agent and may additionally be considered in long-term maintenance treatment (52-week study). Initial combination use with biologic agents, traditional systemic agents and phototherapy may become standard.

Information resources

- Canadian LEO Pharma Inc. www.leopharma.ca/w-site/leo-caeng/docs-caeng.nsf (Accessed April 2005).

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