Table of Contents

How to use this document [1]

The Evaluation Report (facsimile copy of the first page shown below) represents an official documents released by the branch of the Japanese regulatory authorities – the Pharmaceuticals and Medical Device Evaluations Center (PMDEC) [2] entrusted with the review and critical evaluation of all applications for medicinal products submitted in Japan. The language of the translated document reflects the very characteristic condensed style of the original, and outcome – acceptance of rejection of the inquiries made by the evaluator and the responses of the applicant.

調 査 報 告 書

平成 11 年 10 月 12 日
新医薬品第一調査会

調査品目	一般名	カルシポトリオール
	販売名	ドボネックス軟膏
輸入承認を申請した会社名		帝國製薬（株）

調査の概要

<調査品目の概要>

カルシポトリオールは、デンマークのレオ社が開発した、表皮細胞の角化異常を正常化させる作用が強く、全身性のカルシウム代謝に対する作用が弱いビタミン D3 誘導体で、化学名は (5Z,7E,22E,24S)-24-cyclopropyl-9,10-seco-5,7,10(19),22-ergostatetraene-1α,3β,24-triol である。本薬は、ビタミン D の活性体である 1α,25-ジヒドロキシビタミン D3（1α,25(OH)2D3）が、臨床的にも乾癬の治療に対して有効であるにも関わらず、血中カルシウム値を上昇させるなどの副作用を示すために製剤化に至っていないことから、カルシウム代謝に対する作用の少ないビタミン D 誘導体を求めて検討が行われた結果、見出されたものである。

今回、「尋常性乾癬」を効能・効果とする薬剤として、1g 中にカルシポトリオール 50 μg を含有する軟膏の輸入承認申請が帝國製薬（株）からなされた。

<規格及び試験方法>

物理的化学的性質並びに製法及び試験方法に関する調査会審議では、資料概要の規格に関する部分全般について、根拠となるデータ及びその説明が十分提示されていないので、必要なデータを示した上で十分な説明を加え、原薬の旋光性、熱異性化、吸光度、類縁物質、残留溶媒、定量法及び標準品、並びに製剤の類縁物質、定量法及び製剤設計などの項目に関して、多数の指示事項を出して回答を求めた。特に、製剤の含量均一性並びに類縁物質規格に関しては、下記の安定性試験の結果が、保存条件中有効期間を見出すことなく、という幅広い含量規格を設定する方向であったので、これを再検討させるとともに、分解生成物の安全性について論証することを求めた。これらに対する回答も含めて検討した結果、本原薬及び製剤の理性及び品質の解析は適正になされており、規格及び試験方法も品質の恒常性を保る上で製剤の類縁物質の規格を除き適切に設定されていると判断した。製剤の類縁物質の規格に関しては設定値が幅く、その妥当性当時における安全性が完全には明かにされていないことから市販後に反復投与時における安全性を確認することを承認条件とした。

<安定性>

安定性に関しては、原薬については、苛酷試験においてエルゴカルシフェロールなどのビタミン D 類と同様に、熱及び光に対して非常に不安定であることが分かったため、長期保存試験（30 箇月）を褐色ガラス製気密容器中に入れ、室温（-20℃及び 5℃）に保存して行ったが、いずれの測定項目においても変化は認められず安定であった。一方、製剤については、苛酷試験において光に対して非常に不安定であり、熱に対しても温度依存的に変化を起こすことが分かったため、長期保存試験（30 箇月）をアルミニウムチューブに入れて 25℃に保存して行ったところ、カルシポトリオールの含量が　　低下し、類縁物質の量が　　増加するという結果が得られている。また、アルミニウムチューブに入れて行った 35℃、75%RH における加速試験では 3 箇月後に　　の、40℃、75%RH における加速試験では 3 箇

1

Further details related to authorities and the evaluation process can be found in the web site of JKS, in the Key and Basic documents available in the JKS Document Store or by enquiring directly to JKS at regulatory@jouhoukoukai.com.

[1] Comments by the publisher.
[2] As of 2000.

Synopsis of the Key Approval Points

General name:	**Calcipotriol**
Trade name:	**Dovonex Ointment**
Name of the approval holder:	**Teikoku Seiyaku KK**
Approval Date:	**January 18, 2000**
Use/indication:	**Psoriasis vulgaris**

EVALUATION REPORT

October 12, 1999

New Drug Evaluation Division I [3]

Investigated Items	**Generic name**	**Calcipotriol**
	Trade name	**Dovonex Ointment**
Application submitted by		**Teikoku Seiyaku KK**

Outline of the Investigated Items

Calcipotriol is a vitamin D3 derivative originally developed by Leo Pharmaceutical Products Ltd. A/S in Denmark. It is highly effective in normalizing abnormal cornification of epidermis cell, on the other side, it less affects systemic calcium metabolism. Therefore, the drug is expected to be useful. Its chemical name is (+)-(5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol. Vitamin D activator, 1α, 25-dihydroxy-vitamin D3[1α,25(OH)2D3], was known as effective in treating psoriasis, however, it had such adverse reactions as rising the blood calcium rate. Calcipotriol, a vitamin derivative was found through a

[3] Of the Pharmaceuticals and Medical Device Evaluation Center (PMDEC), commonly known in Japanese as Shinsa-sentaa.

development to seek an active substance with less impact to the calcium metabolism.

An application for importing an ointment that contains 50 µg /1g Calcipotriol as its active ingredient for treatment of psoriasis vulgaris was filed by Teikoku Seiyaku KK.

Standards and Testing Methods

As for the physical and chemical properties, specifications, and testing methods the evaluator [4] concluded that the application lacked data and satisfactory explanation in majority of the specifications. As for the active substance, the evaluator required (the applicant) to provide appropriate data and explanation on such factors as, optic rotation, heat isomerization, absorbance, analogous substances, residual solvent, assays and standardization, and as for the drug, equivalency, assay and design. The evaluator especially requested the applicant to review the specifications of content and analogous substances of the drug, and at the same time, prove the safety of the analysis component, seeing that the stability test shown below was on the basis of a wide-ranging standard without reconsidering the storage condition and term of validity of the drug. As a result of investigation, including the revised data on the above factors, the evaluator approved that the analysis on the properties and quality of the active substance and the drug are appropriate. The specification and testing methods were also adequate, except for the specification for the analogous substances of the drug. It was considered that safety of repeated dosage is not clarified because of the wide-ranged value of the specification. Therefore, approval was made under condition that

[4] In this translation, the term "evaluator" shall be used instead of the full name "New Drug Evaluation Division I" as used in the Japanese original.

safety of repeated dosage be proved in post-marketing surveillance studies.

Stability

Like other vitamin D group (members) such as ergocalciferol, the active substance turned out to be extremely unstable against heat and light at severe test. Therefore, long-term storage test (30 months) in brown glass airtight container, at low temperature (-20° C and 5° C) was conducted and the result showed to be stable in all test items. As for the drug, it turned out to be extremely unstable against light and depended on heat as a result of severe test. Therefore, it was conducted a long-term storage test (39 months) in aluminum tube, at 25 ° C. As a result, quantity of Calcipotriol decreased (blank) [5] and analogous substances increased (blank) . In the acceleration test in aluminum tube, when at 35 ° C, 75 % RH, quantity of (blank) decreased 8 months later, and when at 40 ° C 75 % RH, quantity of (blank) decreased 6 months later under.

From these results, long-term quality of the active substance is guarantied when kept in airtight container in low temperature (-20 ° C and 5 ° C).

[5] Left blank (censored) in the Japanese original. Under the Japan's Public Access to Information Law (PAIL) pharmaceutical manufacturers may agree documents related to the submission and approval process to be disclosed with parts containing sensitive information (such as exact data values, or other deemed to be trade secrets) to be blanked. Further information on PAIL (original text in English) could be found at the JKS Document Store by clicking here.

For the drug, as is stated in 'Specifications and Testing Methods', the evaluator requested the applicant to seek a revision in the storage condition and term of validity, and to avoid widening the range of specification directly after the achievement of results. After various reconsideration, the applicant responded that, considering the convenience of distribution and benefit of usage duration, the drug will be kept in shielded airtight container under room temperature, and term of validity be shortened from '3 years' to '2 years', and quantity specification altered from (blank) to (blank) , and this was approved.

General Toxicity

Acute toxicity test was performed in rat and dog. Rat subcutaneous rate of LD_{50} is 2 mg/kg, rat percutaneous is over 15 mg/kg and dog percutaneous over 1.5 mg/kg. Repeated dose toxicity test was done by percutaneous administration in rat and dog for 4 and 26 weeks, subcutaneous administration on rat for 26 weeks. As a result, in both administrations in rat, cornea and renal tubules showed a sclerosis and the calcium amount in urine increased. After percutaneous administration, a change in the administrated skin area was found. For dog, a change in administered area and increase of calcium amount in urine was found. No adverse effect causing amount was determined to be 0.4 - 4 μg/kg.

Cornea and renal sclerosis did not recover in the recovery test of repeated dose toxicity test in rat after a percutaneous administration for 4 weeks. Therefore, the evaluator inquired the applicant on the safety of administration to human. The applicant replied that this change is caused by the high calcium blood symptom that required time to recover but it is unique to rats and considering the absorption of human, the possibility of this symptom to appear in human is extremely low. In overseas clinical trials, however, a rise in calcium concentration in blood serum by large dose administration is reported. Therefore, the applicant has articulated in the precaution that caution should be taken

regarding the blood serum calcium concentration deviation. The evaluator approved. In addition, evaluator inquired on the relevancy of the drug and the fact that, in general, high calcium blood concentration is known to cause hyperplasia of suprarenal medulla. The applicant reported that the rise in blood calcium concentration and the increase in suprarenal gland weight was found in one case in rat 26 weeks administration test, and therefore, there is estimated potentiality of the drug to induce hyperplasia, and this was consented.

Antigenicity test, skin sensitizing test and photosensitization test results were all negative. Mutation was tested by reverse mutation test by bacterium, chromosomal aberration test by cultured mammal cells, and mouse micronucleus test were conducted and results were all negative.

Local irritation was verified by cutaneous primary irritation test, cutaneous accumulative irritation test, ocular mucosa irritation test, and phototoxicity test. Primary irritation showed weak pungency, accumulative irritation revealed extremely mild to moderate pungency, edema in conjunctiva was found in ocular mucosa irritation test, but phototoxic was negative.

The evaluator considered that the drug has stronger local irritation compared to the analog drug, (blank) , therefore, requested the applicant to explain this. The applicant answered that

manifestation rate of each parameter of the two ointments do not differ in large and the possibility of reaction specific to the investigational drug is considered low and this was consented.

Difference was not found in the two drugs on toxicity of analogous substances, metabolite and resolution by acute toxicity test.

Reproductive and Development Toxicity

Reproductive and development toxicity tests were performed in rat and rabbit (organogenesis period administration test) by subcutaneous administration. In large dose administration group of each test, an increase in the embryo and fetal death, skeleton modification, and offspring growth inhibition were found, however, teratogenicity was not found. Non toxicity amount of F1 generation were, 25 μg/kg in rat pre-pregnancy and initial pregnancy administration, 12.5 μg/kg on rat and 0.5 μg/kg in rabbit in organogenesis period administration, 12.5 μg/kg on rat in perinatal period administration.

Pharmacology

Characteristic for psoriasis vulgaris is the cornification of epidermis cell and differentiation failure. Therefore, in order to substantiate the efficacy of the drug, cytostatic action and cell differentiation derivation action were studied.

As a result, the drug inhibited 50% of the growth of human histiocytic lymphoma cell line U937 with 14 nM, inhibited approximately 50% of 3H-thymidine absorption with 100 nM, inhibited approximately 50% of growth of orthokeratosis cells with 10 nM and inhibited around 50% of orthokeratosis cell with approximately 200 nM. This cytostatic action was approximately similar to that of activated vitamin D3 (1α,25(OH)2D3). On the other hand, human histiocytic lymphoma cell line U937, cell adhesion on dish was small in the contrast culture liquid. Cells that indicated esterase activity were rare among the non-adhesive cells. The investigational drug and 1α,25(OH)2D3, however, increased adhesive cells at over 1 nM depending on the quantity and increased the number of esterase positive cells in the non-adhesive cells.

Since vitamin D3 induces high calcium blood disorders, investigation was made on its effect calcium metabolism. Calcium increasing effect in urine and serum was less than 1/200 of that of the 1α,25(OH)2D3. Decrease in the bone weight and calcium

quantity of metaphysis were also less than 1/200 of 1α,25(OH)2D3. Affinity of histiocyte lymphoma cell line U937 to the 1α,25(OH)2D3 acceptor was approximately the same with the investigational drug and 1α,25(OH)2D3.

Regarding the metabolites, and mixed and degraded substances, similar action as the investigational drug was found but the effect was weaker than the investigational drug. An increased activity of the calcium in urine and blood was approximately the same or less with the investigational drug, and it was weak when compared with 1α,25(OH)2D3.

In term of the general pharmacological effect, it inhibited the agonist contraction of isolated ileum with 10 μM; 200 μg/kg subcutaneously affected the calcium metabolism, however, and 20μg/kg did not show any influence.

The evaluator inquired the applicant in regard to the inhibitory action of thymidine absorption in human histiocyte lymphoma cell line U937 since there exists a 7-fold difference between cytostatic IC_{50} rate and thymidine absorption inhibitory concentration. The evaluator consented to the applicant explanation on the difference between IC_{50} rate and ^{3}H-thymidine absorption inhibitory concentration that IC50 rate was obtained from counting the number of cells and it indicates the most precise cytostatic effect of the investigational drug. The ^{3}H-thymidine

absorption action, however, is influenced by growth stage of the cell and thymidine pool in the cell, and the concentration rate is obtained from ^{3}H thymidine addition for 4 hours between 92 hours to 96 hours after adding the investigational drug, and its positive control 1α,25(OH)2D3 has the same result. Other than this, errors in entry were pointed out. With the investigational drug and 1α,25(OH)2D3, the affinity to *in vitro* 1α,25(OH)2D3 acceptor is approximately the same, whereas there is a large difference in the calcium metabolism. The applicant explained that metabolism of the drug is fast and when administered the same amount, there is a large difference, more than 100-fold, in the AUC. This explanation was also accepted. In the *in vitro* test applied to indicate the efficacy of the drug, some cases showed high activity concentration. Therefore, the evaluator asked for explanation whether it reflects the condition at *in vivo* test and the reply was that hypodermic concentration of the administered area is considered to reach approximately 1 μM which is above the concentration rate of the *in vitro* test system of the case, and this was consented.

Absorption, Distribution, Metabolism and Excretion

ADME tests of the investigational drug were conducted in rat and dog. At single percutaneous administration of ^{3}H-labeled Dovonex ointment (5 μg/body) on back of normal skin of male rat, plasma radioactive concentration was C_{max} (146 pg eq./mL) and disappeared after 2.9 days. The $AUC_{0-\infty}$ at the time was 10.61 ng eq x hr/mL and absorption rate was 18%. On the other side, administration of ^{3}H-labeled Dovonex ointment to damaged skin of rat, absorption rate rose 4-fold. Repeated for 7 times percutaneous administration to the normal rat skin revealed stability after the 5th time (administration). Microautography assay led to the conclusion that the drug is absorbed through the corneum.

Radioactivity concentration of each tissue, when at single percutaneous administration of ^{3}H-labeled Dovonex ointment to normal rat skin, showed the highest rate after 24 to 96 hours. The tissue that revealed the highest concentration rate was the skin where the ointment was administered, followed by the liver, muscle directly beneath the administrated area, Harderian gland, large bowels, brown fat, adrenal glands, kidneys and eyeballs had the lowest. The drug showed high affinity to rat, dog and human plasma proteins.

After a single subcutaneous administration of ^{3}H-labeled Calcipotriol in male rat, the quantity of the unchanged (as formula) substance in plasma after 15 minutes was 50.5% of the total radioactivity of plasma. Also a 24-carbonyl position derivative of the drug, 22-23 double bond reduction derivative, a 23-24-alcohol derivative produced by oxidization cleavage and a carboxylic acid derivative, and 9 unknown metabolites were found as plasma metabolites. Repeated subcutaneous administration was conducted for 21 times, and here again, as the unchanged (as formula) substance in plasma and metabolite concentration was similar to those of the single administration. Partial drift in drug metabolism activation was accepted at the repeated percutaneous administration to male rat, however the drift was small and reversible. Therefore, the influence to liver drug metabolism enzyme was estimated to be limited.

Excretion rate of urine, feces, and perspiration after 168 hours of single percutaneous administration of ^{3}H-labeled Dovonex ointment to normal male rat skin were 2.0, 13.3, and 0.6%. The main excretion path was excretion in feces. As a result of subcutaneous administration in lactating rat, the drug is considered that it does not excrete in milk.

Unchanged (as a formula) substance in serum was not found in healthy human when administered (50 or 100 μg/g ointment) 2 g or 4 g, once or twice a day for 5 days. Unchanged (as a formula) and

metabolite in serum was hardly found except for only in a few cases, when the drug (50 μg/g ointment) was repeatedly administered to psoriasis vulgaris patients 4 or 8 g twice a day for 4 weeks. Human and laboratory animals have different surface configuration of the skin including the thickness of corneal layer of epidermis, therefore percutaneous absorption of human is considered to be of a lesser degree.

The group requested the applicant to add the gist of the plasma radioactivity concentration transition data gained from absorption test on damaged rat skin. The applicant followed the instruction and was accepted.

Clinical Trials

Phase I clinical trial was carried out on healthy male adults, 6 cases with 50, 100 μg/g ointment single administration and 2 cases of ointment base. Safety of 100 μg/g ointment up to 4 g/day was confirmed. Further, 3 cases of repeated administration were conducted on healthy male adults and total and topical influence was not found when administered 4 g of 100 μg/g ointment 2 times/day for 5 days. On the skin safety test on 30 healthy volunteers and 22 skin disease patients, a number of skin irritations were seen with 100 μg/g ointment treatment.

Early II trial was conducted on 48 psoriasis vulgaris patients. Ointment base, 25, 50 and 100 μg/g of investigational drug were administered up to 1 g each time, twice a day, same amount symmetrically on the left and right side of the patients' skin. Forty-four cases improved after application of the investigational drug as analyzed by the degree of skin damage, and the Overall improvement rate after 4 weeks were 55.3%, 86.8%, 92.1%, and 92.1% by ointment base, 25, 50, and 100 μg/g investigational drug, respectively. Adverse drug reactions such as skin irritation were found in only 3 cases of 100μg/g ointment treatment.

In the Late Phase II trial, 105 psoriasis vulgaris patients took part. Ointment base and 25, 50 μg/g ointment was administered up

to 2 g each time, twice a day, same amount symmetrically on the left and right side of the patients' skin for 6 weeks. Overall improvement rate analyzed in 102 patients were, 52.1%, 87.5%, 93.1% on ointment base, 25 and 50 μg/g ointment, and in comparison, 25, 50 μg/g ointment was superior to the ointment base, 50 μg/g was superior to 25 μg/g. Mild to moderate skin irritation was found in 5 cases (4.9%).

For clinical pharmacology trial, 10 psoriasis vulgaris patients were administered 4 g or 8 g of 50 μg/g ointment, twice a day for 4 weeks. Unusual changes were not found in the blood concentration of the derivative 25(OH)D3、24R,25(OH)2D3. Two cases showed decline in 1α,25(OH)2D3 concentration, although changes were not found in values of calcium, phosphorus, and serum intact-PTH in serum and urine.

Phase III trial was conducted to 157 psoriasis vulgaris patients, with Betamethasone valerate as control substance. Fifty μg/g investigational ointment was administered 2 g at a time, twice a day, for 6 weeks. In total, 144 cases were analyzed. Symptoms such as erythema, infiltration, hypertrophy and shedding improved by the investigational drugs. Overall improvement rate was 91% for the investigational drugs, significantly excelling the 68.1% of the control drug group. Adverse drug reactions were found in 5 cases of the investigational drugs and 1 in the control drug group.

In a long term administration test 111 psoriasis vulgaris patients went through the application of 50μg/g ointment containing the drug, 2 to 7g at a time, 1 to 2 times a day for 12 weeks or 6 months at the longest. Improvement rate after 12 weeks from the initial treatment was 84.6%, which had no difference in once a day administration or twice a day. Overall improvement rate after 8 weeks of the second treatment was 87.5%. Adverse drug reactions were found in 10 cases (9.1%), in what was skin irritation. Alterations in serum calcium/phosphorus concentrations were not found, however, clinical trial value disorder occurred in 8 cases. In 5 cases 1α,25(OH)2D3 concentration decreased and 1 case increased, and in 2 cases the serum phosphorus concentration decreased.

The investigational drug was not found in healthy adult blood, whereas it was spontaneously found in psoriasis vulgaris patient blood at the concentration rate of 6.8 to 17.0 pg/mL. Therefore, it is considerable that the drug is absorbed percutaneously. The evaluator requested the applicant on the relation with dose range and its safety. The applicant made clear that, the largest administration of the trial was 120 g in a week of which 17 cases were over 90 g. In 3 cases out of 5 cases which were administered 56 g a week, 4 cases out of 4 which were administered 112 g, unchanged substance of the drug were found in blood. High calcium blood effect was found in the overseas case when administered over 200 g a week. Based on such results, the evaluator group required the applicant to include in the precaution

that the highest administrative amount of the drug should be not more than 90 g a week, to discontinue administration when improvement in symptom is not achieved, to pay attention to serum calcium concentration alteration, and to immediately stop administration when symptoms of high calcium blood concentration are recognized.

Additionally, the applicant was inquired about the state on the objective ground applied to judge the efficacy of all trials. The applicant made a post-trial analysis that the attending physicians put significance in the diagnosis of skin of symptoms such as erythema, infiltration, hypertrophy, and shedding for the criteria of the trial. The evaluator accepted this under the condition that applicants shall settle the judgment criteria that are more objective from the next time. In addition, the evaluator requested a caution from the applicant on the fact that multiple administrations were made to one patient (symmetrical comparison of left and right or 4 dose comparison) in early and late phase II trials and Phase III trial comparison test, and that such protocol should not be designed hereafter.

Conclusion

As a result of such investigation, the evaluator reached the conclusion that it is approvable under the following conditions, and therefore will submit the case to the Special Committee. [6]

[6] Special Committee - Special Committee for Medicinal Products to the Central Pharmaceutical Affairs Council (CPAC) – the (then) highest approval authority within the Japanese pharmaceuticals affairs system, responsible for making the definitive recommendation for approval to the Minister of Health and Welfare.

Condition of Approval

The safety of repeated administration is not completely clarified regarding the derivatives of the investigational drug. Therefore, approval was made under the condition that the safety of the repeated dosage shall be proved through a post-marketing surveillance and immediate reports of the results shall be made to the authorities.