CASE AUTH/2035/8/07

CONSULTANT DERMATOLOGIST v LEO PHARMA

Dovobet 'Dear Doctor' letter

A consultant dermatologist alleged that a letter from Leo Pharma recommended that most psoriasis patients on Dovonex Ointment (calcipotriol; discontinued) would be appropriately switched to Dovobet Ointment (calcipotriol/betamethasone). This was not the case. These were two distinct treatments, one a potent to very potent topical corticosteroid and the other a non-corticosteroid vitamin D analogue. The complainant alleged that to recommend a direct switch was inappropriate and put patient safety at risk.

By way of background, the complainant made general comments about the relative efficacy and safety of corticosteroid or corticosteroid/vitamin D analogues in psoriasis. In particular the complainant noted that it was important that both prescribers and patients knew that Dovobet contained a potent corticosteroid and were thus alert to possible side effects associated with such therapy. The complainant was suspicious that the 'diminished clinical usefulness' of Dovonex Ointment coincided with the UK patent expiry.

The complainant stated that the main issues were:

- **The letter suggested switching from Dovonex to Dovobet Ointment which, especially if carried out by those without particular experience in managing psoriasis could endanger patient safety.**
- **The UK withdrawal of Dovonex Ointment (but not cream, which was not produced generically), without much notice and without waiting for a generics manufacturer to take over production of an equivalent preparation (and assisting patients in being transferred over to this from Dovonex Ointment), while Leo was promoting Dovobet Ointment might make commercial sense. However, these actions were disappointing; perhaps naively the complainant should have liked to believe the letter's introductory paragraph claiming that the sole purpose of the Leo foundation was to research, develop and market efficacious treatments for the benefit of patients. This approach to promotion brought discredit upon, and reduced confidence in, the pharmaceutical industry.**

The Panel noted the complainant's explanation that he had commented on a number of general points by way of background. He did not however make specific allegations about these points. The Panel considered that it had specific allegations about whether the letter implied that patients should be switched from Dovonex Ointment to Dovobet and associated safety issues and the withdrawal of Dovonex.

The letter stated 'because the clinical usefulness of Dovonex Ointment (calcipotriol 50 micrograms/g) has diminished it is no longer supplied by Leo Pharma in the UK. As a result and in response to enquiries we are continuing to receive we would advise that for the majority of your patients, Dovobet (calcipotriol 50 micrograms/g, betamethasone 0.5 milligrams/g) can replace Dovonex Ointment (calcipotriol 50 micrograms/g)'. There followed discussion of Dovobet's efficacy.

There were important differences between the products. Dovobet was indicated for the topical treatment of stable plaque psoriasis whereas Dovonex Ointment was indicated more broadly for the topical treatment of plaque psoriasis. Dovobet had a recommended treatment period of four weeks after which repeated treatment could be initiated under medical supervision; there was no recommended treatment period for Dovonex. Dovobet was not recommended for use in children and adolescents below the age of 18 years whereas Dovonex Ointment could be used with care, and with some restrictions as to maximum weekly dose, in children aged 6 and above. There was limited experience of the use of Dovonex in children under 6 years and a maximum safe dose in that group had not been established. The Dovonex Ointment summary of product characteristics stated that in respect of children clinical experience had shown Dovonex to be safe and effective over eight weeks at a mean dose of 15g per week but with wide variability in dose amongst patients. In addition Dovobet contained a strong, potent topical corticosteroid and had a more extensive list of contraindications and special warnings and precautions for use than Dovonex.

The letter had a broad circulation including hospital and retail pharmacists, practice nurses, prescribing nurses as well as GPs and consultant dermatologists. The Panel considered that by stating that Dovobet could replace Dovonex Ointment for *the majority* of patients (emphasis added) without making the important differences between the products clear, the letter implied that most patients could be simply switched and that was not necessarily so. There were substantial differences between the products and any switch would have to be conducted with care and on a case by case basis. Dovobet was not recommended for use in patients below the age of 18 years. The reference later in the letter to Dovonex Cream as an option for patients ineligible for treatment with Dovobet did not negate the impression from the preceding paragraphs. The letter was misleading and could not be substantiated in that regard. Breaches of the Code were ruled.

The Panel noted the complainant's allegation that

switching from Dovonex to Dovobet, if carried out by those without particular experience in managing psoriasis could endanger patient safety and that it was important that prescribers were fully aware that they were using a potent steroid and to be alert to its side effects. The letter referred to 'Dovobet's established and reassuring safety profile'. The Panel noted its ruling above about the impression given by the letter and considered that within the context of a letter which advocated a switch from a non-steroidal treatment to a medicine containing a potent steroid it was important that the material fairly represented Dovobet's risk benefit profile. This was especially important given the wide circulation of the letter in question. The Panel considered that the failure to alert readers to the differing side effect profile of Dovobet versus Dovonex was misleading as alleged; the reference to the prescribing information would not suffice in this regard. A breach of the Code was ruled.

The Panel considered that the failure to make it clear that there were important differences between the products, noting in particular the differences in their side effect profiles, meant that the company had failed to maintain high standards. A breach of the Code was ruled. On balance the Panel did not consider that in this regard the material brought discredit upon or reduced confidence in the pharmaceutical industry.

The Panel noted the complainant's concern about the withdrawal of Dovonex Ointment from UK supply. The Panel noted that whilst discontinuation of products might give rise to concern and disappointment it was nonetheless a legitimate business activity. The Panel considered that the principle of product discontinuation was *prima facie* outside the scope of the Code. However any reference to product discontinuation within a promotional letter must comply with the Code. The Panel did not consider that the reference to Dovobet's discontinuation within the context of the letter failed to maintain high standards or brought discredit upon or reduced confidence in the pharmaceutical industry as alleged.

A consultant dermatologist complained about a letter (ref 1008/10488) dated 26 June from Leo Pharma which promoted Dovobet (calcipotriol/betamethasone) and also referred to the discontinuation of Dovonex Ointment (calcipotriol).

COMPLAINT

The complainant noted that the letter advised recipients that since Leo stopped supplying Dovonex Ointment in the UK (in April 2007), '…for the majority of your patients, Dovobet (calcipotriol 50 micrograms/g, betamethasone 0.5 milligrams/g) can replace Dovonex Ointment (calcipotriol 50 micrograms/g)'. The complainant alleged that this read as a direct recommendation that most psoriasis patients on Dovonex Ointment would be appropriately switched to Dovobet Ointment. This was not the case. These were two distinct treatments, one a potent to very potent topical corticosteroid and the other a non-corticosteroid vitamin D analogue. The complainant alleged that to recommend a direct switch was inappropriate and put patient safety at risk.

The complainant agreed that Dovobet was, as stated in the letter, more effective than its corticosteroid component betamethasone dipropionate (Diprosone) alone (Douglas *et al* 2002 and Kaufmann *et al* 2002). The complainant had not seen any studies to determine whether this slight to modest (but unlikely to be chance, that was statistically significant) greater efficacy was due to a synergy of the two compounds in Dovobet. Or was Dovobet, because of the vehicle required to allow mixing of the two main components, a more potent topical corticosteroid than betamethasone dipropionate ointment alone? The complainant considered that betamethasone dipropionate was probably, at least in clinical efficacy, a more potent steroid than the more commonly used betamethasone valerate, although both were in the same broad 'potent' class. Potent topical steroids, when used cautiously, had a place in psoriasis treatment. The letter stated that Dovobet had proved more cost effective than use of the two main constituents concomitantly. The complainant would like to know if any of these studies involved a direct comparison of clinical efficacy and cost effectiveness of once-daily Dovobet Ointment versus alternate days once-daily Diprosone and Dovonex.

However, regardless of the efficacy of Dovobet, it was a potent topical corticosteroid. As well as all the usual topical corticosteroid side effects there had to be particular concern about psoriasis rebound and exacerbation (including the risk of potentially fatal generalised pustular psoriasis, as listed in the prescribing information). Although follow-up under the carefully controlled conditions of a study had been fairly reassuring as regards early (within 1 year) adverse effects (Kragballe *et al* 2006) it was important that prescribers and more importantly, patients, were fully aware that they were using a potent steroid and to be alert to its side effects. Although it was fairly reassuring that a one-year study comparing three regimens (4 weeks of Dovobet then Dovonex Ointment, 1 year of alternating 4 week periods of Donovex Ointment alone and of Dovobet Ointment, 1 year of Dovobet Ointment) did not reveal more side effects generally (including the sometimes troublesome but rarely serious irritant side effects of Dovonex Ointment), 10 of 212 patients on the continuous Dovobet Ointment compared with 6 of 213 and 6 of 209 in the other groups had, 'adjudicated corticosteroid reactions'. Also, the report did not state what happened after one year of Dovobet Ointment – how many study participants had to be admitted or receive outpatient hospital therapy because of rebound psoriasis flares after completion of the study? (Thind and White 2006). This lack of reports of serious side effects probably reflected the expectation that Dovobet, a potent corticosteroid, would cause potent topical corticosteroid side effects, including rebound worsening of psoriasis, so that few thought to report side effects even when severe enough to require

referral to hospital (the complainant had seen several such cases, but never reported them).

The complainant stated that when he received the letter at issue he was already concerned about the marketing of Dovobet. First, Dovonex Ointment was withdrawn in April 2007 suspiciously coinciding with the expiry of the UK patent. In response to patient and GP queries the complainant noted that a generics company now manufactured calcipotriol ointment. On receipt of the letter at issue the complainant noted the statement about Dovonex Ointment no longer being supplied by Leo in the UK because of diminished clinical usefulness and so tried to find out if its usefulness had diminished equally in other countries. It was still listed as a product on Leo's South American website but the North American psoriasis patient association website commented that it was becoming difficult to obtain – the complainant hoped he was being over-suspicious when he wondered if the expiry of US patent protection coming on 12/08/2007 was related.

The main issues were:

- The letter suggested switching from Dovonex to Dovobet Ointment which, especially if carried out by those without particular experience in managing psoriasis (the complainant did not know if Leo's letter was only sent to consultant dermatologists or also to GPs) could, if done without extreme care and case by case selection of appropriate patients, be dangerous to patient safety.
- The UK withdrawal of Dovonex Ointment (but not cream, which was not produced generically), without much notice and without waiting for a generics manufacturer to take over production of an equivalent preparation (and assisting patients in being transferred over to this from Dovonex Ointment), while Leo was promoting Dovobet Ointment might make commercial sense. However, these actions were disappointing; perhaps naively the complainant should have liked to believe the introductory paragraph to the letter claiming that the sole purpose of the Leo foundation was to research, develop and market efficacious treatments for the benefit of patients. This approach to promotion brought discredit upon, and reduced confidence in, the pharmaceutical industry.

When writing to Leo the Authority asked it to bear in mind the requirements of Clauses 2, 7.2, 7.4, 7.9 and 9.1 of the code.

RESPONSE

Leo submitted that the letter was sent to all consultant dermatologists, GPs, dermatology nurses, district nurses, prescribing nurses, practice nurses, hospital pharmacists and retail pharmacists. This letter was sent subsequent to Leo's discontinuation of Dovonex Ointment in the UK market in April 2007 and in response to continuing enquiries from health professionals regarding suitable alternative treatments.

The letter was primarily intended to be informative, as a general response to the enquiries received by Leo. The company had accepted, however, that it also promoted Dovobet and Dovonex Cream and in that regard the requirements of the Code were followed.

Leo disagreed with the complainant's view that it was inappropriate for it to recommend a direct switch from Dovonex Ointment to Dovobet Ointment as they were two distinct treatments and such recommendation put patient safety at risk. The complainant had over-emphasised the degree of interchangeability between the products which the letter conveyed. The complainant admitted that when he received the letter he was already concerned about the marketing of Dovobet and Leo feared this might have coloured his response and led him to misinterpret the letter's meaning.

Leo agreed that Dovobet was not a straightforward replacement for Dovonex because Dovobet had an additional active ingredient which changed the safety profile and posology. However, a treatment regimen based upon Dovobet could satisfactorily replace a treatment regimen based on Dovonex in most patients.

It was this message that Leo's letter was intended to convey in a concise fashion. Not that the products were directly interchangeable as one element within an unchanged regimen but that treatment with one could replace treatment with the other. Both products had the same indication and for the most part were prescribed for similar types of patients, at the same stage of disease and in similar treatment regimens. The letter qualified the statement thus: 'for the majority of your patients, Dovobet … can replace Dovonex Ointment…'.

Leo had not recommended an automatic or direct switch and had not recommended that Dovobet should be used in all patients previously treated with Dovonex but only in those for whom it was suitable and with appropriate adjustment of the supporting elements of the treatment regimen. Leo used the phrase 'Dovobet can replace' as opposed to 'Dovobet is replacing', ie the replacement was optional not mandatory.

Leo stated that in its letter it justified why it believed Dovobet a suitable alternative and described how Dovobet should be used correctly with appropriate advice on maximum dosage and medical supervision of repeated courses. This advice was specific to Dovobet and did not imply that there should be a direct switch between products. On the contrary, giving such specific information on appropriate use implied that there were differences between the products that should be considered when prescribing. The letter included the advice that for patients ineligible for treatment with Dovobet, Dovonex Cream might be a suitable alternative. This explicitly acknowledged that there were differences between the products and that not all Dovonex-treated patients were suitable for Dovobet. The eligibility of the patient for Dovobet treatment needed to be considered. The prescribing information also made the differing side effect profiles and dosage and administration advice between the products apparent.

To summarise, Leo accepted and agreed with the complainant's concern that Dovonex should not be switched to Dovobet without care and case by case selection, however it did not intend, nor did it accept, that its letter suggested such a switch without regard for the differences in the way the products should be used and without taking the care that the complainant recommended.

Leo did not accept that its letter suggested a course of action that could be dangerous to patient safety but rather that it suggested a possible alternative treatment and described how to prescribe and use it appropriately.

Both Dovobet and Dononex Ointments were prescription only medicines, prescribable by GPs and appropriately qualified nurse prescribers as well as consultant dermatologists; approximately 97% of prescriptions for both products were written by GPs. It was entirely appropriate to distribute the letter to both GPs and dermatologists. Giving this advice to GPs did not prejudice patient safety but assisted in the correct and appropriate prescribing of products by a group of health professionals who were already the biggest prescribers of these products.

Leo knew of no studies which directly compared the clinical efficacy and cost effectiveness of once daily Dovobet Ointment versus alternative days once-daily Diprosone and Dovonex. The comparative cost-effectiveness claim that Leo made was based upon an indirect comparison used in Leo's submission to the Scottish Medicines Consortium (SMC) and subsequently presented as an abstract at a European dermatology meeting in 2006. A further fuller manuscript had since been published (Bottomley *et al* 2007).

Leo agreed with the complainant that it was important that prescribers were fully aware when prescribing Dovobet that they were using a potent steroid and to be alert to its side effects. This was why its letter and all its promotional material fully complied with the Code and provided the non-proprietary names of the active ingredients adjacent to the brand name and included prescribing information with appropriate precautions, warnings and side effects listed.

The complainant's statement that Dovonex Ointment was withdrawn in April 2007 to coincide with the UK patent expiry was incorrect; Dovonex Ointment was not withdrawn but rather its supply was discontinued, and the patent expired on 14 July 2006.

Leo currently had no specific information about the status of Dovobet or Dovonex Ointment in South America or in the US but would be happy to make enquiries should it be deemed relevant to this complaint.

Leo accepted that the complainant was disappointed by Leo's decision to discontinue supply of Dovonex Ointment and it apologised to him and his patients for any inconvenience this might have caused. However, it gave the required statutory notice period for discontinuing a product and issued a letter to clinicians on 23 February about the discontinuation, two months in advance of actually discontinuing supply to pharmacies.

Leo submitted that its discontinuation of supply of Dovonex Ointment was not a promotional activity but a commercial decision based on prescribing trends, the perceived decline in clinical usefulness compared with other available products, and the need to rationalise its product portfolio in the UK.

Leo had implemented the discontinuation process with consideration for patients and prescribers and had issued its best advice on alternative treatments in response to questions. Although data supported Dovobet as being the most efficacious topical treatment for plaque psoriasis (Douglas *et al*, Guenther *et al* 2002, Kragballe *et al*, van de Kerkhof *et al* 2005), the most pharmacologically similar product to Dovonex Ointment was Dovonex Cream, hence these were the two products recommended as alternatives.

Leo did not believe that its decision to discontinue Dovonex Ointment fell within the scope of the Code and, as such, it did not believe there was a case to answer in this regard. Leo submitted that all its activities in relation to the discontinuation of Dovonex Ointment, including the letter, had been conducted with due regard to, and in conformity with, the requirements of the Code.

PANEL RULING

The Panel noted the complainant's explanation that he had commented on a number of general points by way of background. He did not however make specific allegations about these points. The Panel considered that it had specific allegations about whether the letter implied that patients should be switched from Dovonex Ointment to Dovobet and associated safety issues and the withdrawal of Dovonex.

The Panel noted that the letter stated 'because the clinical usefulness of Dovonex Ointment (calcipotriol 50 micrograms/g) has diminished it is no longer supplied by Leo Pharma in the UK. As a result and in response to enquiries we are continuing to receive we would advise that for the majority of your patients, Dovobet (calcipotriol 50 micrograms/g, betamethasone 0.5 milligrams/g) can replace Dovonex Ointment (calcipotriol 50 micrograms/g)'. There followed discussion of Dovobet's efficacy.

The Panel noted that there were important differences between the products. Dovobet was indicated for the topical treatment of stable plaque psoriasis whereas Dovonex Ointment was indicated more broadly for the topical treatment of plaque psoriasis. Dovobet had a recommended treatment period of four weeks after which repeated treatment could be initiated under medical supervision; there was no recommended treatment period for Dovonex. Dovobet was not recommended for use in children and adolescents below the age of 18 years whereas Dovonex Ointment could be used with care, and with some restrictions as

to maximum weekly dose, in children aged 6 and above. There was limited experience of the use of Dovonex in children under 6 years and a maximum safe dose in that group had not been established. The Dovonex Ointment summary of product characteristics stated that in respect of children clinical experience had shown Dovonex to be safe and effective over eight weeks at a mean dose of 15g per week but with wide variability in dose amongst patients. In addition Dovobet contained a strong, potent topical corticosteroid and had a more extensive list of contraindications and special warnings and precautions for use than Dovonex.

The Panel noted that the letter had a broad circulation including hospital and retail pharmacists, practice nurses, prescribing nurses as well as GPs and consultant dermatologists. The Panel considered that by stating that Dovobet could replace Dovonex Ointment for *the majority* of patients (emphasis added) without making the important differences between the products clear, the letter implied that most patients could be simply switched and that was not necessarily so. There were substantial differences between the products and any switch would have to be conducted with care and on a case by case basis. Dovobet was not recommended for use in patients below the age of 18 years. The reference later in the letter to Dovonex Cream as an option for patients ineligible for treatment with Dovobet did not negate the impression from the preceding paragraphs. The letter was misleading and could not be substantiated in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted the complainant's allegation that switching from Dovonex to Dovobet, if carried out by those without particular experience in managing psoriasis could, if done without extreme care and case by case selection be dangerous to patient safety and that it was important that prescribers were fully aware that they were using a potent steroid and to be alert to its side effects. The letter referred to 'Dovobet's established and reassuring safety profile'. The Panel noted its ruling above about the impression given by the letter and considered that within the context of a letter which advocated a switch from a non-steroidal treatment to a medicine containing a potent steroid it was important that the material fairly represented Dovobet's risk benefit profile. This was especially important given the wide circulation of the letter in question. The Panel considered that the failure to alert readers to the differing side effect profile of Dovobet versus Dovonex was misleading as alleged; the reference to the prescribing information would not suffice in this regard. A breach of Clause 7.2 was ruled.

The Panel considered that the failure to make it clear that there were important differences between the products, noting in particular the differences in their side effect profiles, meant that the company had failed to maintain high standards. A breach of Clause 9.1 was ruled. On balance the Panel did not consider that in this regard the material brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

The Panel noted the complainant's concern about the withdrawal of Dovonex Ointment from UK supply. The Panel noted that whilst discontinuation of products might give rise to concern and disappointment it was nonetheless a legitimate business activity. The Panel considered that the principle of product discontinuation was *prima facie* outside the scope of the Code. However any reference to product discontinuation within a promotional letter must comply with the Code. The Panel did not consider that the reference to Dovobet's discontinuation within the context of the letter failed to maintain high standards or brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clauses 2 and 9.1 was ruled.

Complaint received	**16 August 2007**
Case completed	**12 October 2007**