Decision: PMPRB-04-D2-DOVOBET

IN THE MATTER OF the *Patent Act* R.S.C. 1985, c. P-4, as amended

AND IN THE MATTER OF LEO Pharma Inc. (the "Respondent") and the medicine "Dovobet"

A. INTRODUCTION AND SUMMARY OF CONCLUSIONS

On November 29, 2004, the Chairperson of the Board issued a Notice of Hearing to inquire into the price of the medicine "Dovobet", which is distributed in Canada by LEO Pharma Inc. ("LEO Pharma"). LEO Pharma holds a patent pertaining to Dovobet and is thus subject to the price regulation provisions of the *Patent Act* (the "*Act*") as they may apply to Dovobet. A public hearing was held and evidence was presented by Board Staff and by LEO Pharma over the course of 10 days during 2005 and (subject to some updating of evidence after the end of the public hearing) the proceeding was concluded by two days of oral argument in December 2005.

Psoriasis and Dovobet

Psoriasis is an auto-immune condition that causes red scaly plaques and lesions on the skin. Psoriasis is a chronic disease, in the sense that there is no known cure for it; a person is afflicted with it for life. Psoriasis manifests itself typically in varying levels of severity, such that, for a given patient, the amount of skin affected and the thickness of the plaques will vary from time to time, and the treatment can vary in relation to the severity of the symptoms.

Dovobet is an ointment that is applied to mitigate the symptoms of psoriasis where there has been a mild to moderate occurrence of those symptoms. Before and after such a period, if necessary, other medicines can be used as maintenance therapy to control or mitigate the less significant manifestations of the disease.

Dovobet does not contain a single chemical compound as an active ingredient. Rather, it is an ointment that combines the active ingredients of two other ointments (or creams) that can be used to treat psoriasis. The two medicines in Dovobet are the non-steroidal antipsoriatic "calcipotriol" (a vitamin D analogue) and the corticosteroid "betamethasone dipropionate". Each has a potential role in treating psoriasis. Calcipotriol is the active ingredient in an ointment or cream marketed by LEO Pharma under the name "Dovonex". Betamethasone dipropionate is the active

ingredient in an ointment or cream marketed both generically and under the names “Diprosone” and “Diprolene” (hereafter for convenience referred to collectively as “Diprosone”).

Dovonex can be used alone to treat psoriasis, often as a maintenance therapy for symptoms that are generally under control, or in combination with a corticosteroid product such as Diprosone or mometasone furorate (Elocom), often to bring an increase in symptoms under control. When used in combination, one ointment will often be applied in the morning and the other ointment applied in the evening (a combination therapy sometimes referred to as an “a.m. / p.m. regimen”). Dovonex is also sometimes used by itself in an a.m. / p.m. regimen to bring an increase in symptoms under control, for example when a corticosteroid is not indicated for the patient.

The salient feature of Dovobet is that it allows the two medicines (calcipotriol and betamethasone dipropionate) to be applied in a single ointment in one daily application. These two active ingredients in Dovobet tend to favour different carriers (one acidic, the other basic) such that a blend of them deteriorates rapidly, and the accomplishment of LEO Pharma in developing Dovobet was in finding a carrier that could hold the two medicines compatibly in a single ointment.

The pricing of Dovobet

Dovobet is a “patented medicine” (a medicine to which a patent pertains within the meaning of the *Act*) and so it is subject to the jurisdiction of the Board. As a result, the Board is mandated by the *Act* to ensure that the price of Dovobet is not excessive. The Board determines whether or not the price of a patented medicine is excessive by exclusive reference to the factors that are stipulated in section 85 of the *Act*.

As is discussed in detail below, section 85 is framed in very general terms, and so the Board consulted with the pharmaceutical industry and other stakeholders and developed the “Excessive Price Guidelines” (the Guidelines) to assist Board Staff and the Board in the application of section 85 to specific medicines.

Given the insight and expertise that went into the development of the Guidelines, the Board has reference to them and gives them due consideration when assessing whether the price of a given medicine is or has been excessive. However, the Guidelines are not in any sense binding on the Board and in each proceeding before the Board, the Board will consider the Guidelines but be governed by section 85 of the *Act*.

Generally speaking, subsection 85(1) requires the Board to assess whether or not the price of a medicine in Canada is excessive by comparing its price to the prices of comparable medicines in Canada, and to the prices of the medicine and comparable

medicines in other countries. If no reasonable comparisons along those lines can be made, the Board may, pursuant to subsection 85(2), consider the costs of producing the medicine when determining whether its selling price in Canada is excessive.

In the case of Dovobet, it was agreed by Board Staff and LEO Pharma that the appropriate price of Dovobet can be determined using the factors in subsection 85(1) of the *Act*; that is, by reference to the prices of comparable medicines in Canada and/or the prices of Dovobet or comparable medicines in other countries. Among several topics of contention, the debate between the parties centered primarily on two issues:

(1) the medicines to which Dovobet should be compared; and

(2) the quantities of the comparable medicines to which a given quantity of Dovobet should be compared.

As for the medicines to which Dovobet should be compared, Board Staff argued that, since the two active ingredients of Dovobet are sold as separate medicines in Canada, the price of Dovobet should be compared to the (combined) prices of those two medicines. LEO Pharma argued that the price of Dovobet also should be compared to the prices of other different medicines that, like Dovobet, are used to bring mild to moderate phases of psoriasis under control. Given that some of the medicines to which LEO Pharma would compare Dovobet could be higher-priced than the medicines containing Dovobet's active ingredients, the choice of comparable medicines is a central factor in the establishment of the appropriate price of Dovobet.

On this point, and for the reasons detailed below, the Board agrees with Board Staff and concludes that the evidence in this proceeding and the logic of subsection 85(1) overwhelmingly support the comparison of the price of Dovobet to the prices of the medicines that constitute its two active ingredients.

As for the quantities of Dovobet's two active ingredients to which a given quantity of Dovobet should be compared, Board Staff argued for a "gram-to-gram" comparison. In other words, the price of two grams of Dovobet should be compared to the price of a gram each of the medicines containing its two active ingredients.

LEO Pharma argued that the price of a "course of therapy" with Dovobet should be compared to the price of a course of therapy with whichever medicines are used in the comparison. LEO Pharma argued that the courses of therapy with the comparable medicines are longer than with Dovobet, requiring larger quantities of the comparable medicines, such that the comparison should be between the smaller quantity of Dovobet and the larger quantities of the comparable medicines.

The Board agrees with Board Staff on this issue. As is explained in detail below, the evidence that was presented to the Board established that there was no "course of

therapy" for Dovobet that had sufficient consistency in theory or in practice to warrant a price comparison on that basis. The only reliable comparison is between equal quantities of Dovobet and the ointments or creams containing its two active ingredients.

Policy of excessive pricing

Board Staff also argued that LEO Pharma had not only charged excessive prices for Dovobet, but had done so pursuant to a "policy of excessive pricing"; which is to say, LEO Pharma knew or ought to have known that the price at which it was selling Dovobet was excessive, given the factors set out in section 85 of the *Act*. In particular, from the outset of sales in Canada, LEO Pharma sold Dovobet at prices that exceeded the maximum non-excessive price ("MNE") established by Board Staff in its interpretation of the Guidelines; that is, it was consistently and markedly higher than the MNEs produced by the highest international and therapeutic class comparison tests.

The consequence of a finding of a *policy* of excessive pricing is that the Board may order that LEO Pharma not only refund the excessive revenues it received, but also pay an additional amount (up to 100% again as much as the refund of excessive revenues) as, in effect, a sanction for pricing Dovobet at a level that LEO Pharma knew or ought to have known was in violation of the *Act*.

LEO Pharma argued that, if the price for Dovobet was excessive, LEO Pharma nonetheless acted in good faith, believing that the price of Dovobet was in compliance with the Guidelines and, in all events, in compliance with section 85 of the *Act*.

The Board was quite concerned with LEO Pharma's conduct in the pricing of Dovobet. The Board is conscious of the significant market forces at play and the potential for patentees to pretend an interpretation of the *Act* that would permit the pricing they prefer. The willingness of a patentee to debate matters with Board Staff does not displace the potential for a finding of a policy of excessive pricing. In this case, certain actions of LEO Pharma constituted transparently artificial attempts to skew the application of the Guidelines.

However, of the two central subjects of contention in the hearing, one (the therapeutic class for a combination medicine) is not explicitly addressed in the Guidelines and the other (the comparable dosage regimen) could have been decided in LEO Pharma's favour if there had been sufficient evidence in support of LEO Pharma's theory on that point.

Accordingly, on balance, the Board cannot conclude that LEO Pharma knew or ought to have known that it was selling Dovobet at an excessive price, and cannot accept the position of Board Staff on this point.

The distribution of free Dovobet

Approximately a year after Board Staff sent its official letter of investigation to LEO Pharma alleging that Dovobet was and had been excessively priced, LEO Pharma began distributing quantities of Dovobet to doctors at no cost. If the quantities of Dovobet thus delivered to doctors at no cost were factored into the calculation of the average per-unit selling (transaction) price of Dovobet, it would reduce the quantum of the excessive revenues received by LEO Pharma.

The Board normally will adjust the average transaction price for a medicine to account for "compassionate use" programs that involve the distribution of free medicines in dosage forms that are otherwise sold in Canada.

Board Staff argued that the free distribution of Dovobet should not be factored into the calculation of the average transaction price of Dovobet because the free distribution was not intended for genuine compassionate purposes, but rather to reduce LEO Pharma's exposure to an order of this Board that LEO Pharma refund excessive revenues.

LEO Pharma argued that its program was a genuine compassionate use program and that the quantities of Dovobet distributed at no cost should be factored into the average transaction price of Dovobet for the purposes of any excessive revenue calculations.

While the Board respects the efforts of patentees to implement true compassionate use programs, the Board has no hesitation in rejecting the inclusion of the quantities of Dovobet distributed at no cost from the calculation of excessive revenues in this case. Indeed, the artificial nature of the distribution of free Dovobet, in combination with all of the evidence on the pricing of Dovobet, brought LEO Pharma perilously close to a finding that it engaged in a policy of excessive pricing. Though, as noted, the Board has found the evidence on that issue to be somewhat wanting, it will not have reference to quantities of Dovobet distributed at no cost when calculating the average transaction price of Dovobet.

The "usual practices" of Board Staff

LEO Pharma correctly pointed out, early in the evidentiary stage of the hearing into these matters, that the hearing panel should put no weight on the evidence of Board Staff that LEO Pharma was being treated in the same manner as other patentees, pursuant to the Board Staff's "usual practice". The Board agrees with LEO Pharma that, while evidence that a patentee was treated consistently with other patentees might rebut an allegation of bias, such evidence had no place in a hearing before the Board such as this one, where no such allegation was made.

Also, the Board agrees with LEO Pharma that Board Staff must convince the Board, with evidence presented in a hearing, of the basis for a conclusion that the medicine

in question is or has been excessively priced. Unless it is somehow relevant to an ancillary issue in the proceeding, evidence concerning how Board Staff reached its own conclusions as to the proper non-excessive price for a medicine (such as by consultations with experts on the Board's Human Drug Advisory Panel), such evidence can be given no weight in a hearing before the Board.

Before it can find that a medicine is or was excessively priced, a panel of the Board conducting a hearing into the pricing of a medicine should receive evidence that establishes *de novo* that the conclusion that Board Staff reached in its application of the Guidelines, or some other conclusion that the price of the medicine under review is or was excessive, is consistent with section 85 of the *Act*. The history of how Board Staff reached that conclusion or the fact that the conclusion was consistent with Board Staff's usual practices will not be pertinent to the Board's inquiry. The panel of the Board must reach its own conclusions on the evidence presented to it.

In this case, Board Staff did present compelling evidence *de novo* in the hearing before the Board, with witnesses called to testify under oath, as to the appropriate basis for the calculation of the non-excessive price for Dovobet. The Board ignored the evidence presented to it regarding what Board Staff "usually" does to ascertain the non-excessive price of a medicine, or what Board Staff did in this case to come to its own conclusion that Dovobet is or has been excessively priced.

Conclusion

LEO Pharma has had divided success in this proceeding, avoiding the potentially onerous sanctions applicable to a policy of excessive pricing, but failing to establish a maximum non-excessive price for Dovobet above that advocated by Board Staff. Board Staff met its onus on the latter point, but not the former. The panel of the Board considers it appropriate to note that it reached its conclusions in this case after having LEO Pharma's case put to them at its highest. LEO Pharma had excellent legal representation throughout the proceeding: the evidence of Board Staff was thoroughly tested, points of evidence and procedure convincingly argued, and in general LEO Pharma's case could not have been more persuasively advocated.

Also, the members of the panel were assisted by the very thorough oral and written submissions of LEO Pharma and Board Staff. These submissions were exemplary in summarizing the extensive documentary and oral evidence and describing the various decisions the parties would have the Board reach on that evidence, presented in conjunction with tables and attachments that were helpfully pertinent to the submissions. The panel would like to express its appreciation for the considerable effort that evidently went into the preparation of those submissions.

B. THE MAXIMUM NON-EXCESSIVE PRICE OF DOVOBET

Section 85 of the *Act*

Section 85 of the *Act* sets out the factors that the Board is obliged to consider when reviewing the price of a medicine for the purposes of a potential order under section 83 of the *Act*:

> **85.** (1) In determining under section 83 whether a medicine is being or has been sold at an excessive price in any market in Canada, the Board shall take into consideration the following factors, to the extent that information on the factors is available to the Board:
>
> (*a*) the prices at which the medicine has been sold in the relevant market;
>
> (*b*) the prices at which other medicines in the same therapeutic class have been sold in the relevant market;
>
> (*c*) the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada;
>
> (*d*) changes in the Consumer Price Index; and
>
> (*e*) such other factors as may be specified in any regulations made for the purposes of this subsection. [No regulations have been passed pursuant to this paragraph]

To simplify the terminology in subsection 85(1), it can be said that it requires the Board to determine whether or not the price of a medicine in Canada is excessive (taking into account changes in the Consumer Price Index) by comparing the price of the medicine in Canada [85(1)(a)] to:

1) the price of comparable medicines in Canada [85(1)(b)];

2) the price of the medicine in other countries [85(1)(c)]; and

3) the price of comparable medicines in other countries [85(1)(c)].

The factors set out in subsection 85(1) are exhaustive of the factors that the Board may consider and the Board must give due consideration to each of them when reviewing the price of a medicine for the purposes of a potential order under section 83 of the *Act*.

However, having directed the Board to the factors it must consider, section 85 does not stipulate how those factors must be used or weighed to assess whether or not the price of a medicine is excessive. In other words, section 85 does not provide a formula into which the Board can feed pricing information to calculate the MNE for a medicine.

In particular, two features of subsection 85(1) require the Board to exercise discretion, to apply judgment and expertise, and if appropriate to give consideration to the stakeholder input and compromise that went into the development of the Guidelines, when determining whether or not the factors in section 85 indicate that the price of a medicine is excessive.

First, performing a comparison does not dictate a conclusion that must result from that comparison. Section 85 leaves it within the discretion of the Board to determine the relevance of each comparison and of all of the comparisons taken together. For example, section 85 does not stipulate that if the price of a medicine is higher in Canada than in other countries it must be found to be excessive, nor that if it is lower in Canada than in other countries it must be found not to be excessive. The comparison of the price of the medicine in Canada with its price in other countries must be made, and then the relevance of that comparison must be assessed. So too with each of the other comparisons and then all of the comparisons taken together.

A second and related point is that each of the comparisons listed in section 85 could lead the Board towards a different conclusion. There are a number of permutations. For example, a medicine might be sold in Canada at a lower price than in other countries but at a higher price than comparable medicines sold in Canada, or vice versa. Each of the three comparisons must be considered, and then the weight to be given to each of them, and how they should relate to each other, must be determined.

A similar point was discussed by the Supreme Court of Canada in *Canada (Director of Investigations and Research, Competition Act) v. Southam Inc.*[1] The Competition Tribunal had been required by the *Competition Act* to consider a list of factors in reaching its conclusion, and the consideration of this list was discussed by Iacobucci J. on behalf of the Court:

> The suggestion remains, however, that the Tribunal might have erred in law by failing to accord adequate weight to certain factors. The problem with this is that it is inimical to the very notion of a balancing test. A balancing test is a legal rule whose application should be subtle and flexible, but not mechanical... These sorts of things are not readily quantifiable. They should not be considered as matters of law but should be left initially at least to determination by the Tribunal. The most that can be said, as a matter of law, is that the Tribunal should consider each factor; but the according of weight to the factors should be left to the Tribunal.

[1] [1977] 1 S.C.R. 748

The need for balancing is evident in the application of section 85 of the *Act* because each of the factors taken on its own does not merely pull directionally but, depending on the relevance of the comparison itself, could lead to a different conclusion. It could be logically impossible for the Board to give each of the factors equal weight, or it could be logical after consideration of all factors to give one or more factors primary or decisive weight, as otherwise there could be irreconcilable conflicts in the conclusions to be drawn from each of the factors.

In other words, the Board must come to a single specific price that is the MNE for a medicine, and, needless to say, the three different factors stipulated by subsection 85(1) do not generate that single figure, for both of the reasons mentioned: the act of comparing does not entail any specific conclusion, and for a given medicine each of the three factors could suggest an MNE that is different in direction and/or degree.

Generally speaking, the three comparisons stipulated by subsection 85(1) can be ranked as to what is likely to be their diminishing degrees of potential relevance.

For medicines that do not represent a substantial improvement on other medicines available in Canada, the closest comparison typically will be to the price of comparable medicines in Canada [85(1)(b)]. This directly reflects the options in the market that consumers face in Canada. The next comparison will be to the price of the medicine in other countries [85(1)(c)]. This indicates how Canadian consumers are being treated by the patentee relative to consumers in the countries designated by the Regulations as appropriate for comparison. The most distant comparison is to the price of comparable medicines in other countries [85(1)(c)], the comparison being, while potentially instructive, at two removes (different medicines, different markets) from the price of the medicine in Canada.

Accordingly, subject to what is said below about the international prices, the Guidelines provide that the starting point for the consideration of the prices of medicines that do not represent a substantial improvement on other medicines available in Canada is a comparison with the price of comparable medicines sold in Canada. When Board Staff are reviewing the price of such a medicine and a relevant set of comparable medicines can be identified, they will perform this comparison, and presume the price of the medicine to be non-excessive if it is no higher than the price of its highest comparator. This is a reasonable approach for the Guidelines: if the most accurate comparison yields a sound analysis and answer, that answer can be presumed to be the most reliable. If the patentee disagrees, the matter can be brought before the Board for determination.

The second comparison – with the price of the medicine in other countries – has two roles in the Guidelines. If Board Staff cannot find a class of medicines sold in Canada with which they can perform the first comparison, the <u>median</u> international price will be the reference point for the MNE. Also, for all categories of medicines, the <u>highest</u> international price is the point beyond which the price of any medicine

sold in Canada will be presumed to be excessive. In other words, the price of any patented medicine sold in Canada will be presumed by Board Staff to be excessive if the price is higher in Canada than in any of the comparator countries. These presumptions in the Guidelines are merely that: Board Staff will apply them, but a patentee can challenge their applicability to a given medicine, and a panel of the Board will determine the matter on the evidence.

The third comparison – to the prices of other medicines in other countries – does not create any presumptions in the Guidelines, given that it is the most distant comparison and more accurate analyses typically can be performed with the first two comparisons. However, as noted, the Board will consider this comparison in a hearing in order to determine the weight that should be given to it in establishing the MNE of a medicine.

In conclusion on this point, when the Board is reviewing the price of a medicine for the purposes of a potential order under section 83, it will consider all of the factors listed in subsection 85(1). The Board will weigh the factors and decide what influence they should have on the MNE for the medicine. The Board will consider the relative accuracy of the three comparisons for the medicine under review and whether any of the comparisons is sufficiently compelling to establish the MNE despite the due consideration of the other comparisons. This is the same logic that instructs the approach taken by the Guidelines, though the Board does not make any presumptions or stop after consideration of fewer than all of the subsection 85(1) factors.

The Excessive Price Guidelines

Needless to say, given the wide variability of results that could flow from the many possible analyses that would be consistent with the broad frames of reference provided by section 85, the Board determined, from the outset of its existence, that a framework was needed to assess the conclusions that could be drawn from the comparisons, generally and specifically, and then the relative weight to be given those conclusions for each of the three comparisons. Indeed, it is evident from the generality of section 85 that Parliament contemplated that such a framework would be developed by the Board.

In addition to the logical need for such Guidelines, as discussed above, such a framework is necessary for at least two important reasons arising from fairness and practicality.

First, it is essential that the pharmaceutical industry and health care stakeholders be aware of the tests that will be applied by Board Staff to the pricing of patented medicines. It would be quite unworkable and likely unfair to attempt to make individual determinations as to the manner in which the generalities of section 85 would be applied to each of the medicines under the Board's jurisdiction.

Second, the Board considers it important, as a matter of fairness, that all patentees be treated consistently and that there be stability in the principles governing the pricing of patented medicines. The Guidelines are always open to revision and interpretation, and the result of a hearing might be to depart from or add to their articulated principles if they are determined to be inapplicable or inconsistent with the *Act*, but the Guidelines play an important role in ensuring fair and consistent treatment of patentees.

Accordingly, (and as it was obliged to do by section 96 of the *Act*) the Board consulted (and continues to consult) extensively with the pharmaceutical industry and health care stakeholders and experts when developing guidelines for the application of the factors stipulated by section 85. Needless to say, there were and have been differing views on how the factors in section 85 should manifest themselves in the Guidelines. After these consultations and after deliberation on the representations of the pharmaceutical industry and other stakeholders, the Board published the Guidelines, which are part of its *Compendium of Guidelines, Policies and Procedures* (the "Compendium"). The Compendium was part of the record of this proceeding and relied on, albeit with differing conclusions, by both LEO Pharma and Board Staff.

The Guidelines have been in place and relied on by Board Staff, the pharmaceutical industry and other health care stakeholders for almost 20 years. From time to time and in the course of ongoing consultations, the Board issues updates to inform the industry and other stakeholders of interpretive clarifications or policies that bear on the Guidelines.

Given these considerations, the Board in its review of a particular medicine and the representations of its patentee will be cognizant of the fact that the Guidelines were developed with principled compromises after the receipt and balancing of much broader representations than those of Board Staff and the patentee in question. The Board, while never bound by the Guidelines, will give them due consideration in light of their provenance and the role that they play in assisting the pharmaceutical industry, other stakeholders and the Board in the application of the provisions of the *Act*.

At the risk of belabouring the point, it should be repeated that, while the Guidelines reflect broad input and expertise, and provide clarity and stability to those affected by the pricing of patented medicines, they are only guidelines. If the Board were ever to conclude that a provision in the Guidelines was inconsistent with any part of the *Act*, either generally or as it pertained to the pricing of a particular medicine, that provision would be given no consideration by the Board and, if appropriate, the provision would be eliminated or revised to accord with the *Act*.

Furthermore, in a hearing before the Board concerning the pricing of a medicine, the onus is on Board Staff to establish that the price of the medicine is or was excessive.

The Board agrees with LEO Pharma that the applicable standard for this onus is the balance of probabilities. Board Staff may have reference in this regard to the Guidelines, but the reasonableness of the application of the Guidelines to the medicine in question must be established by evidence and argument and, where there is debate as to the appropriateness, interpretation or application of the Guidelines, the panel of the Board hearing the matter must be satisfied on the evidence as to the appropriate conclusion for the medicine under review. In all events, when the Board is called on to determine the maximum non-excessive price of a medicine in a proceeding pursuant to section 83 of the *Act*, it does so in accordance with the provisions of section 85 of the *Act*.

Board Staff and LEO Pharma substantially agreed with the observations set out above concerning the respective roles of section 85 of the *Act* and the Guidelines. Indeed, both parties relied extensively on the Guidelines in their evidence and argument. They disagreed on the interpretation and/or application of the Guidelines and whether or not interpretations of the Guidelines were consistent with section 85.

In resolving this disagreement, the panel of the Board was mindful of the fact that the wording of section 85 of the *Act* does not dictate a given result for the pricing of any medicine. In applying the factors listed in subsection 85(1) of the *Act,* in interpreting and applying the Guidelines, and when reasoning in the interstices of the Guidelines, the panel was called on to apply its expertise and exercise its judgment in arriving at appropriate conclusions that were within the parameters established by the *Act*.

The categorization of Dovobet

The Guidelines provide that the first step in determining the appropriate MNE for a medicine is its categorization within one of three categories that, generally speaking, classify the medicine by reference to its composition or performance relative to existing medicines. The Guidelines provide for potentially different assessments of the MNE for a new medicine depending on its categorization. The categories (with highly simplified labels in square brackets following the wording in the Guidelines) are:

Category 1: A new DIN (Drug Identification Number) of an existing or comparable dosage form of an existing medicine. [Forms or dosages of an existing medicine]

Category 2: A new DIN of a non-comparable dosage form of an existing medicine, or the first DIN of a new chemical entity that is a breakthrough or provides a substantial improvement over comparable existing DINs. [Breakthrough/substantial improvement medicines]

Category 3: A new DIN of a non-comparable dosage form of an existing medicine or the first DIN of a new chemical entity that provides moderate, little or no therapeutic

advantage over comparable existing DINs. [Non-breakthrough and no substantial improvement medicines]

The Guidelines provide that the "substantial improvement" that can justify categorization as a "breakthrough" medicine can be identified in factors such as the time required to achieve optimal therapeutic effect and length of treatment required with the medicine. Dovobet is agreed by Board Staff and LEO Pharma to be a "Category 3" medicine; that is to say, it may provide moderate, little or no improvement over comparable existing DINs, and in particular does not provide substantial improvement over comparable existing DINs. While it is not necessary to go into detail on the point here, the effect of categorization as a Category 2 "substantial improvement" medicine can be to enable the patentee to price its medicine at higher levels than are indicated for Category 3 medicines.

LEO Pharma noted in its argument that the result of Board Staff's application of the Guidelines to the pricing of Dovobet (comparing Dovobet to the two ointments or creams containing its active ingredients on a gram-to-gram basis) was that LEO Pharma was not able to price Dovobet at a level that reflected the advantage it achieves by combining the two ointments in a single ointment. This combination saves the patient the effort of applying two separate ointments in an a.m. / p.m. regimen.

However, the Board considers the Guidelines to be appropriate and consistent with the *Act* in requiring that a medicine demonstrate (as it is agreed Dovobet does not) a substantial improvement over comparable existing DINs to warrant the potentially more advantageous price treatment suggested by the Guidelines for Category 2 medicines. Patentees are constantly developing patentable inventions for variations on, or combinations of medicines, but if such patents, when leading to no substantial improvement in the resulting medicines, enabled a patentee to achieve Category 2 pricing, the Guidelines and the provisions of section 85 of the *Act* would be rendered largely ineffectual in that context.

Paragraph 85(1)(b): the prices in Canada of other medicines in the same therapeutic class

(i) Determining the therapeutic class

The first comparison required by subsection 85(1) is between the price of Dovobet in Canada and the price of other medicines in Canada in the same therapeutic class as Dovobet.

The term "therapeutic class" is not defined in the *Act*. The evidence was that its normal meaning, outside the context of section 85, is the class of medicines that typically work for a particular condition, or are considered similar by the disease they treat and/or the effect they have on the body. The Guidelines refer to the clinical

equivalency of medicines in addressing the disease in question, and make reference to the World Health Organization Anatomical Therapeutic Chemical Classification System (the "ATC") as a starting point for the identification of the medicines in a therapeutic class. However, the Guidelines allow for considerable flexibility in the inclusion or exclusion of medicines from the therapeutic class of a medicine under review.

In interpreting subsection 85(1), the Board aims to marry the words of the section in their grammatical and ordinary sense in their context with the scheme and object of the *Act* and the intention of Parliament.[2] The object of the provisions of the *Act* that pertain to the Board's mandate is to prevent the excessive pricing of patented medicines. For the purposes of subsection 85(1), then, the therapeutic class of a medicine includes those medicines that are similar to the medicine under review in ways that are relevant to the pricing of the medicine, such as the condition the medicines treat, the way the medicines are delivered to the body, their chemical compositions, and the way they work in the body. The identification of the therapeutic class of a medicine under review can be a complex task that requires scientific and practical judgment and the consideration of the scheme and object of the *Act*.

The process of establishing the therapeutic class of a medicine under review may be characterized as beginning with the identification of the relevant characteristics of the medicine, and then identifying the medicines most similar to it with regard to the factors mentioned above. The therapeutic class is expanded until adding the next-most-similar medicine would involve introducing an element of difference that compromises the homogeneity of the class to a degree that, as a matter of scientific and practical judgment, is inappropriate.

In other words, the class will often be established when the most similar medicines are identified. There might be one medicine very similar in relevant ways to the medicine under review, and no others of comparable similarity, such that the medicine under review and that one comparable medicine constitute the therapeutic class for price comparison purposes; or there might be several medicines, all similar to the medicine under review in relevant (and perhaps different) ways, together constituting the therapeutic class.

Needless to say, then, the therapeutic class for a particular medicine under review might be large or small, and it might be highly homogeneous or less so. There might be a material difference between a medicine under review and a medicine that nonetheless belongs in its therapeutic class because of other similarities that are significantly relevant for price comparison purposes.

[2] *Rizzo & Rizzo Shores Ltd. (Re)* [1998] 1 S.C.R. 27

The ATC classification system often provides a starting point, but not always, and in many cases the establishment of the therapeutic class for price comparison purposes will require a degree of judgment. The principles in operation, however, are sound: in the majority of cases, the establishment of the therapeutic class for a medicine is not contentious, and in most cases where there is room for debate, the matter is resolved on a principled basis by the scientists working with the patentee and Board Staff respectively. This is the first case since the establishment of the Board in which the matter has not been resolved and has thus come before the Board for a decision.

The Guidelines do not provide any specific directions for the determination of the therapeutic class for a "combination medicine" such as Dovobet, the active ingredients of which are available in Canada as separate medicines. The Guidelines do contemplate the much more common situation in which a therapeutic class must be determined by looking for medicines that differ somewhat on the relevant criteria but are nonetheless sufficiently similar on those criteria to justify the comparison to the medicine under review.

The logic of the manner in which the therapeutic class is established for price comparison purposes, however, leads quite directly to a focused approach to the identification of a therapeutic class for a combination medicine where its active ingredients are sold in Canada as separate medicines: in most cases, the therapeutic class for the price comparison purposes of subsection 85(1) will consist of the medicine under review and the separate medicines that contain its active ingredients.

In the case of combination drugs, especially where the other medicines that contain the identical active ingredients as the combination drug are used in a combined therapy, there is an extremely compelling therapeutic class for price comparison purposes. The separate medicines used in combination are slightly different than the medicine under review because they are (for example, as in this case) two medicines rather than one, but beyond that their comparability is uncommonly rare for a therapeutic class comparison.

Being in the ideal situation of having such a logical and compelling therapeutic class, and absent reliable evidence to the contrary, it simply makes no sense to degrade the homogeneity of the therapeutic class by the addition of medicines that are more dissimilar than those very medicines containing the identical active ingredients. For the price comparison purposes of subsection 85(1), there will often be an extremely compelling case for concluding that the therapeutic class for price comparison purposes of a combination medicine consists of its constituent elements.

The use of separate active-ingredient medicine comparators for combination medicines is always, of course, subject to the caveat that it will not be appropriate if

there is reliable evidence that the separate medicines used in a combination therapy have a materially different clinical effect than the combination medicine.

The potential irrational consequences of expanding the therapeutic class for Dovobet beyond the medicines that contain its active ingredients was demonstrated in the evidence and argument of LEO Pharma to the effect that, while LEO Pharma proposed a specific list of five medicines in a dozen or so permutations, the therapeutic class of Dovobet arguably includes quite dissimilar products such as anthralin or even tars, and systemic therapies such as cyclosporin or new biologicals such as Amevive, the latter of which have costs ranging from $4,800 to $17,000 per year. It is true that these medicines could be included in LEO Pharma's broad definition of therapeutic class (medicines that typically work for a particular condition), but their chemical composition, their mode of action and their spectrum of activity is so divergent from Dovobet that it makes no sense whatsoever to use them for price comparison purposes.

The fact that, like Dovobet, these medicines typically work for treating psoriasis, and yet are so inappropriate for price comparison purposes, demonstrates the danger of equating "therapeutic class" with "therapeutic options"; that is, with interpreting the words "therapeutic class" in subsection 85(1) without reference to the context of the *Act,* and outside of the price comparison context of subsection 85(1) in particular. Though cyclosporin and Amevive and Dovobet are used to treat psoriasis, they share no other characteristic that is relevant for price comparison purposes. The other medicines proposed by LEO Pharma for inclusion in the therapeutic class of Dovobet are not as divergent from Dovobet as anthralin, tars, cyclosporin and Amevive, but these examples highlight the need for the establishment of a therapeutic class on principles that are relevant for price comparison purposes as opposed to therapeutic options.

Though not particularly persuasive one way or the other, it was somewhat instructive to note that the choice to prescribe either Dovobet or Dovonex plus Diprosone is influenced by whether the prescription will be covered by the insurance plan held by the patient. Typically, if treatment with Dovobet is indicated and the patient is not sensitive to the price of the treatment, Dovobet is prescribed; if the patient is sensitive to the price of the treatment, Dovonex plus Diprosone are prescribed in an a.m. / p.m. regimen. If Dovobet is prescribed and the patient balks at the price when purchasing the medicine, the pharmacist will likely be instructed to substitute Dovonex plus Diprosone in an a.m. / p.m. regimen. LEO Pharma argued that this combination therapy only became popular after the introduction of Dovobet, but that point seems to strengthen the comparison rather than weakening it: doctors soon recognized the most appropriate comparison to Dovobet.

Two points should be made in concluding on this point. First, it should be noted that the Board is not establishing a different method of establishing the therapeutic class for a combination medicine than for other medicines under review. It is simply that,

when applying the logic and judgment that the definition of any therapeutic class for price comparison purposes requires, and absent sound evidence to the contrary, the active ingredients of a combination medicine, if sold as separate medicines in Canada, constitute the most appropriate – and indeed uncommonly compelling – therapeutic class for price comparison purposes.

Second, Board Staff must of course meet the burden of establishing each element of its case. The scientific evidence and common sense of the constituent-elements approach to establishing the therapeutic class for a combination medicine, when established by scientific evidence and common sense to be appropriate for a given medicine, is a reasonable manner in which Board Staff can meet the legal burden pertaining to that element of its case, and it is always open to a patentee to present evidence to the contrary.

(ii) The pharmacological presumption regarding combination medicines

The evidence called by Board Staff was that scientists use a similar approach when they are applying a scientific, evidence-based medical approach to a different but related issue: the potential clinical effectiveness of a combination medicine in comparison with the clinical effectiveness of the combined use of its active ingredients. Absent scientifically persuasive evidence to the contrary, the clinical effectiveness of the two treatments will be presumed to be the same. This is sometimes termed the “null hypothesis”.

The scientific basis and general acceptance of this approach was described by the three scientists called by Board Staff to testify to, among other topics, this issue. Dr. Levine and Dr. McCormack are both extremely well-credentialed scientists in this area and Dr. Ho is both that and an experienced clinician.

As for the evidence that would rebut the null hypothesis in this case, the scientists called by Board Staff took the position that the only reliable evidence would be a properly structured and administered head-to-head trial in which the clinical effectiveness of Dovobet was compared to that of a combination therapy involving its active ingredients.

LEO Pharma argued that the hypothesis missed the point, and that the inquiry should not be into whether or not Dovobet is superior to the separate use of its constituent ingredients. LEO Pharma also presented expert scientific evidence that that other types of evidence, such as reviews of trials other than head-to-head trials, and clinical observations, could suffice to rebut the hypothesis, and did in this case with respect to Dovobet and its constituent ingredients. On this issue, the Board was fully satisfied on two points.

First, for Dovobet and any other combination medicine, the only reliable evidence that would establish greater clinical effectiveness than a combination therapy

involving the active ingredients of the combination medicine would be a properly structured and administered (presumably double-blind, head-to-head, statistically sound) trial. The evidence on this point was scientifically compelling, logically intuitive and consistent with the expectations of members of the hearing panel.

Second, though it is not essential to the Board's findings in this matter, it should be noted that the requirement for a proper trial is such a fundamental point regarding reliable evidence of clinical effectiveness that the need for such a trial to establish, in a scientific manner, the superior clinical effectiveness of Dovobet would or should have been evident to LEO Pharma from the time that it first investigated the possibility of the combination medicine.

A proper trial would have carried risk for LEO Pharma, given the possibility – Board Staff's witnesses would say the probability or perhaps the near certainty – that the trial would establish that Dovobet was not more effective or insufficiently more effective to warrant a higher price than the two ointments whose active ingredients it carries. However, a proper trial would or should have been recognized by LEO Pharma as necessary for scientific and regulatory acceptance of material clinical superiority of Dovobet over therapies using Dovobet's active ingredients.

It is worth noting the LEO Pharma's own consultant Dr. Guenther, who was also a witness for LEO Pharma at the hearing into this matter, testified that she recommended such a trial to LEO Pharma. Indeed, the Board would not have expected her advice to have been otherwise, as the situation cried out for a head-to-head trial. While LEO Pharma cited the cost of a proper trial and the apparent acceptance of Dovobet in the market without one as reasons that the trial was not performed, this is not consistent with either the expenditures of LEO Pharma on other studies or the Board's expectations as to the affordability of such a study for a medicine with sales of the magnitude of Dovobet. Again, while the essential point is that a proper trial was not done, not <u>why</u> it was not done, the Board concludes that LEO Pharma would or should have recognized that such a trial would be required in any context where the position was to be taken that reliable evidence established that Dovobet was materially more effective than the combined use of its active ingredients.

The "null hypothesis" arises in pharmacology in a somewhat different context than the establishment of a therapeutic class for price comparison purposes, and the Board does not begin with that hypothesis in reaching the conclusion that the therapeutic class for Dovobet for the purposes of subsection 85(1) of the *Act* consists of the medicines containing the active ingredients of Dovobet sold in Canada. Rather, the Board comes to that conclusion by the purposive and contextual interpretation of subsection 85(1), and then the identification of the burden that, as a matter of scientific and practical judgment, must be met to establish a proper therapeutic class for price comparison purposes. However, the Board finds support for this conclusion in the fact that the same logic is used by

pharmacologists and other scientists when considering the related issue of the predicted clinical effectiveness of a combination medicine relative to the combined use of separate medicines containing its active ingredients. This approach is not just based on scientific knowledge and experience, but on principles and logic that are accessible to an informed person knowledgeable in this area and that make common sense.

In concluding on this point, the Board wishes to note its general preference for the highest standards of evidence-based scientific conclusions when called-on to make findings that require the consideration of scientific evidence. Clinical observations and comparisons of separate trials can be useful for science and medicine in some contexts, and could have a role in some therapeutic class considerations. However, the history of reliance on evidence that is less dependable than properly conducted trials, specific to the question in issue, is replete with examples of conclusions that were thought to be sound, and that formed the basis of widely accepted treatment regimens, only to be determined later to have been quite erroneous. It is the Board's view, which we believe to have broad recognition in the scientific and regulatory communities, that important decisions related to health and medicine should be based on the best evidence that reasonably can be obtained within the parameters that govern scientific research.

(iii) LEO Pharma's proposed therapeutic class

LEO Pharma argued that the Board should consider as a minimum the following medicines as appropriate comparators on the basis that they fall within the same therapeutic class as Dovobet, either as monotherapies (a single medicine) or combination therapies (a non-steroidal antipsoriatic and a corticosteroid): Tazorac, Dovonex, Diprosone, Diprolene, and Elocom.

While the Board does not accept LEO Pharma's submission as to the appropriate scope of the therapeutic class comparison for Dovobet, the Board has considered all of the above medicines to see if they would assist the Board in making the appropriate price comparisons.

The Board would give no weight to any of the monotherapies proposed by LEO Pharma. None of the monotherapies is sufficiently clinically comparable to Dovobet. Also, Dovobet combines a non-steroidal antipsoriatic and a corticosteroid, and that combination is such a salient feature of the medicine that medicines containing only one of those elements would be too dissimilar as to chemical composition and mode of action to be given any weight in the price comparison.

As for the non-steroidal antipsoriatic tazarotene (sold as Tazorac), the chemical composition is different (tazarotene is a retinoid) but, more significantly, there is insufficient clinical equivalence, given that Tazorac is not used for the treatment of psoriasis to a significant degree. Though there was some evidence from LEO

Pharma of the current use of Tazorac for the treatment of psoriasis, on balance the Board accepts the evidence that Tazorac was initially and for a short period used for the treatment of psoriasis, but it was fairly quickly determined to be an inappropriate and inferior treatment for psoriasis relative to alternatives (including Dovobet).

Dr. Ho's evidence, which was persuasive and consistent with the statistical evidence, was that the proposed use of Tazorac was a marketing and clinical failure from the outset Tazorac is now "obsolete" for the treatment of psoriasis, and is marketed and used primarily for acne and, more recently, photoaging. Dr. Guenther testified that she does not prescribe Tazorac for new psoriasis patients.

Though there was appreciable use of Tazorac at the time that Dovobet was introduced, the Board cannot ignore the lesson learned since then: that Tazorac, alone or in combination with a corticosteroid, was never clinically comparable to Dovobet and is now infrequently prescribed for psoriasis. A medicine that was introduced for treatment of psoriasis on what has proven to have been, in effect, a mistaken marketing decision, should not be given any weight in a price comparison.

As for corticosteroids other than betamethasone dipropionate (e.g. Diprosone), there was evidence that mometasone furorate (sold as Elocom) is a corticosteroid that is prescribed in combination with non-steroidal antipsoriatics such as Dovonex. While the evidence of Board Staff began by identifying relevant differences (including potency) between Elocom and Diprosone, that evidence grew vague on cross-examination and if, contrary to the Board's conclusions on this point, there were a reason to go beyond the very corticosteroid contained in Dovobet when defining Dovobet's therapeutic class, it would appear fair to add Elocom to Diprosone in that regard.

(iv) Is the issue of the therapeutic class for Dovobet closed?

If, contrary to scientific expectations, Dovobet is materially more effective than its active ingredients used in a combination therapy, it was open to LEO Pharma to obtain and present in this proceeding scientifically reliable evidence to this effect, but LEO Pharma did not do so.

The question arises as to whether, if a proper trial comparing Dovobet to a therapy involving its active ingredients is conducted in the future, LEO Pharma should be able to return to the Board for reconsideration of Dovobet's therapeutic class.

The Board considered the position that this hearing was the occasion for LEO Pharma to present such evidence and that, not having done so, the result should be that the matter is closed.

However, the panel does not wish to foreclose the possibility of a future effort by LEO Pharma to present evidence on this issue to Board Staff and, if necessary, a panel of the Board. If this matter does come before the Board again, it will be for a

future panel to determine whether, having failed to address the issue persuasively in this hearing, LEO Pharma should nonetheless be entitled to try to have a new therapeutic class and MNE for Dovobet established. The possibility that such a future proceeding will be permitted does not alter the requirement for LEO Pharma to comply immediately with the order made by the Board in this case.

(v) Medicine categorization and therapeutic class

It is worth noting that there are two separate issues discussed in this decision that are related but should not be confused. One is the requirement that a medicine be a breakthrough or demonstrate a substantial improvement over existing comparable medicines in order to be classified as a Category 2 medicine such that its patentee has the potential for a more advantageous MNE. The second is the establishment of the therapeutic class for a combination medicine, where there must be reliable evidence that the combination medicine provides a material advantage over the medicines that contain its active ingredients before the therapeutic class will be expanded beyond those medicines.

The categorization of Dovobet as a Category 3 medicine that does not provide a breakthrough or substantial improvement over comparable existing medicines was not in debate in this proceeding; the therapeutic class for Dovobet was.

Each of these two issues involves an inquiry into the effectiveness of the medicine under review relative to the effectiveness of comparable existing medicines, but the inquiries will not necessarily consider the same criteria or require the same degree of relative improvement over existing medicines.

Given that there was no sufficiently reliable evidence on the point in this case, the Board is not called to determine what degree of improvement, as demonstrated by a properly structured and administered head-to-head trial, a combination medicine would have to demonstrate to have its therapeutic class expanded beyond the medicines containing its active ingredients.

However, for the guidance of patentees and other stakeholders, it will be noted that the Board has referred in this decision to the requirement that the evidence demonstrate a material difference in clinical effectiveness such as would warrant comparison for pricing purposes to medicines other than those containing the active ingredients of the combination medicine. To be material, the difference in clinical effectiveness would have to be at least statistically significant and therapeutically relevant.

If that point were ever established for a combination medicine, the therapeutic class for the medicine under review could still include the medicines that contain its active ingredients – medicines often will have material differences on the relevant criteria and yet be the closest comparators – but the therapeutic class for the combination

medicine could then also include other medicines that are comparable on the relevant criteria.

(vi) The comparable dosage regimen

In order to conduct a therapeutic class comparison, the Board, having identified the medicines in the therapeutic class, must determine the appropriate dosage regimen of the medicines for price comparison purposes. In other words, given that medicines are invariably sold on a per-unit basis, the question becomes: how many units of the medicine under review and the other medicines in the therapeutic class should be compared? If one unit of the medicine under review has the same clinical effect as ten units of a medicine in its therapeutic class, by being effective in smaller amounts and/or by working more quickly, this fact could be relevant for price comparison purposes.

The Guidelines provide that, when comparing a medicine under review to those in its therapeutic class, the dosages to compare can vary depending on whether the condition is chronic or acute. For acute conditions, the Guidelines suggest that a "course of treatment" with the medicine under review should be compared to a course of treatment for the medicines in the therapeutic class. For chronic situations, comparison on a "per-day" basis is appropriate.

The primary rationale for this distinction is that medicines to treat chronic diseases typically do not have a "course of treatment". They are taken indefinitely or until the medicine becomes ineffective or otherwise inappropriate. On the other hand, medicines to treat an acute condition are more commonly prescribed for a defined number of doses or period of time.

It was LEO Pharma's position that this bifurcation did not account for Dovobet and certain other medicines, which treat an acute phase of a chronic condition.

While Board Staff strongly disputed LEO Pharma's position that there was any room for a third category, the Board agrees with LEO Pharma on this point. If there were a chronic condition that had a clearly defined acute phase that was treated by a therapeutic class of medicines with identifiably consistent courses of treatment, it could be appropriate to compare the prices of those medicines on a "course of treatment" basis. The rationale for this would be the same as the rationale in the Guidelines for such a comparison for medicines that treat acute conditions. If such a condition and medicines to treat it existed, it would constitute, depending on how one preferred to frame it, either a third category or a reason to put the medicines as in the first (acute) category.

The evidence presented to the Board, however, fell far short of satisfying those conditions. Indeed, the evidence of the studies and from the clinicians called by both parties establishes that, while LEO Pharma recommends four weeks as the

usual period for the use of Dovobet (because it is often effective in that period and because it contains a corticosteroid that should be used for limited periods) there is actually no consistent course of treatment with Dovobet at all.

This is in part because psoriasis does not have a clearly defined acute phase, but rather (to use the most appropriate expression of several that emerged during the hearing) it “undulates” through phases of more and less severe symptoms.

It is also in part because doctors find that some patients respond sufficiently with just a few days of using Dovobet and others require two or three months of the use of Dovobet, or more. Dr. Ho testified that in his practice he finds it necessary to prescribe Dovobet for more than four weeks in over 70% of his patients. Dr. Ho is involved in the community of dermatologists, and testified that most if not all dermatologists in British Columbia are using Dovobet for more than four weeks.

As Dr. Guenther, testifying for LEO Pharma noted, the patients themselves administer the ointments to suit their symptoms. Acknowledging that psoriasis was sometimes treated with Dovobet for longer or shorter periods than four weeks, her evidence was only that the general period of treatment was four weeks. As noted, Dr. Ho disagreed even as to this level of consistency in treatment with Dovobet. The same is true of the way in which alternatives to Dovobet are prescribed and used by patients. Psoriasis is a highly variable condition both as to its manifestation and its response to medication, and there simply is no consistent course of treatment with Dovobet or alternative therapies.

It should also be noted that, in addition to the clinicians testifying to widely divergent courses of treatment and uses of Dovobet, the Dovobet product monograph is instructive on this point. While the product monograph recommends a general period of treatment of four weeks, it adds that “some patients will require longer treatment than four weeks, which should be based on physician assessment”. Long-term therapy with Dovobet is also addressed in the product monograph, with specific recommendations as to how this should be done to minimize the potential adverse effects of the corticosteroid component of Dovobet. A leading trial of Dovobet concluded that it was safe and effective when used for eight weeks.

Neither is there reliable evidence for the proposition by LEO Pharma that a four week course of treatment with Dovobet can be compared to an eight week course of treatment with a combination therapy utilizing the medicines containing its active ingredients, Dovonex and Diprosone. Such a comparison would require a proper head-to-head trial which, as noted, has not been undertaken. Clinical observations and interpolation from other data are not sufficiently reliable to support LEO Pharma’s position.

Accordingly, the Board concludes that the appropriate dosage regimen for the comparison of Dovobet to Dovonex plus Diprosone is the grams-to-gram comparison.

Conclusion

The Guidelines provide that where a satisfactory domestic therapeutic class comparison can be performed, this (in conjunction with the over-riding highest international price comparison test) will be presumed to establish the MNE for a Category 3 medicine under review. The use of the domestic therapeutic class comparison is especially appropriate in the case of a combination medicine such as Dovobet, given the very compelling therapeutic class that can be developed for it, and thus the Board will ascribe substantial weight to this price comparison when conducting a inquiry pursuant to section 83. However, the Board is required by the *Act* to consider all of the factors in subsection 85(1), and has done so during the course of this proceeding.

Paragraph 85(1)(c) part one: the international prices of Dovobet

Pursuant to paragraph 85(1)(c), the Board considers the prices at which Dovobet is sold in countries other than Canada. Seven countries have been designated for this purpose in Regulations to the *Act*: the United Kingdom, the United States, Germany, France, Italy, Switzerland and Sweden.

As noted earlier in these reasons, paragraph 85(1)(c) provides only that the Board give consideration to these international prices, not what the consequence of that consideration should be. The Board could have settled on any number of different tests that would have to be met for a price to be considered non-excessive: not more than 0%, 10%, 20% or 50% higher, or lower, than the international average, or median, or highest or lowest prices.

As it is, after the extensive consultations and deliberations that resulted in the Guidelines, the Board developed two international price comparison tests: (1) the price of a medicine will be presumed to be excessive if its price in Canada is higher than the highest international price of the medicine; and (2) for an existing medicine where a domestic therapeutic class comparison is inappropriate or impossible to conduct, primary weight should be given to the median of the international prices.

Given that it is appropriate to have reference to a domestic therapeutic class comparison when establishing the MNE for Dovobet, the question is whether the MNE of Dovobet should also be constrained by the highest international price of Dovobet; that is to say, the question is whether the highest international price constraint stipulated by the Guidelines is an appropriate implementation of the requirement in the *Act* that the Board consider the international prices of a medicine

under review when determining whether the price of that medicine in Canada is excessive.

The Board has no hesitation in concluding that – indeed as a minimum – the requirement in the Guidelines that Canada not be the country in which a patented medicine is the most expensive in the world (or at least of all of the comparator countries established by the *Regulations*), is an appropriate conclusion to draw from the consideration, mandated by paragraph 85(1)(C), of the price at which a medicine is sold in countries other than Canada. Indeed, this is quite a liberal test, and thus generally an appropriate "ceiling" for the non-excessive price of a patented medicine in Canada in the context of all of the factors listed in subsection 85(1). In a proceeding pursuant to section 83 the Board could conclude otherwise, but there was no evidence in this proceeding that convinced the Board to do so.

Where, as in the case of Dovobet, the Board can conduct a therapeutic class comparison, the effect of the overall requirement in the Guidelines that the price of Dovobet not exceed the highest international price is that the MNE for any given year will be the lower of the CPI-adjusted benchmark price established by the therapeutic class comparison and the highest international price.

The Board concludes that this is the appropriate manner in which to combine its consideration of the requirements in paragraphs 85(1)(b) and (c) that the Board consider the price of Dovobet to the prices at which comparable medicines are sold in Canada and the price at which Dovobet is sold in countries other than Canada.

Paragraph 85(1)(c) part two: the prices in other countries of other medicines in the same therapeutic class

The Guidelines do not instruct Board Staff to consider this most distant of comparisons for a Category 3 medicine, and, for the reasons noted below, the Board considers the Guidelines to be appropriate in that regard. However, early in these proceedings the Board recognized that, because it was being asked to make an order pursuant to section 83, it required evidence on this comparison. Shortly after the start of the hearing, the panel called on Board Staff to file additional evidence detailing the international prices of other medicines that were argued by Board Staff and LEO Pharma to be in the same therapeutic class as Dovobet.

The Board thus considered the international prices of medicines said to be in the same therapeutic class as Dovobet. The Board agrees with the submission of Board Staff that, when consideration is given to this comparison, the broad range of international prices should be rationalized by reference to the median international prices of the medicines in the therapeutic class in order to moderate the potentially wide range of those prices, and the resulting impact of outlier prices that differ markedly from the sample. In this most tenuous of the subsection 85(1) comparisons, Canadian consumers would not be protected if the MNE of a medicine

were governed by a comparison to (1) the highest price of; (2) a medicine sold outside of Canada; that is (3) not the medicine under review.

The Board observes that, on this basis, Dovobet was priced higher in Canada than the international prices of medicines said to be in its therapeutic class, whether reference was had to the therapeutic class found to be appropriate by the Board or the broader therapeutic class advocated by LEO Pharma.

Again, while this comparison provides further evidence that, directionally speaking, the price of Dovobet in Canada is and has been excessive, the Board does not give significant weight to this observation and concludes that the lower of the prices established by the domestic therapeutic class comparison and the highest international price comparison is the most appropriate MNE for Dovobet.

Foreign exchange rates

In submissions concerning the international price comparisons, there was disagreement between LEO Pharma and Board Staff as to whether or not the price comparisons over time should take account of fluctuations in exchange rates. The Board concurs with Board Staff on this point. International price comparisons over time must take account of fluctuations in exchange rates in order to be appropriately accurate. The Board sees no reason why this is administratively or practically difficult for Board Staff or patentees to accommodate.

Conclusion

Accordingly, having considered each of the factors stipulated by subsection 85(1) and weighed them in relation to each other, the Board concludes that the domestic therapeutic class comparison provides such an apt and reliable price comparison, with the highest international price of Dovobet as an appropriate ceiling, that those factors should establish the MNE for Dovobet in each year since its introduction in Canada.

Free Dovobet

Approximately a year after Board Staff sent its official letter of investigation to LEO Pharma alleging that Dovobet was and had been excessively priced, LEO Pharma began distributing quantities of Dovobet to doctors at no cost and, albeit later than required, reporting such distributions to the Board. This distribution was of the largest (120 gm) tubes of Dovobet and was in addition to the distribution of free “sample” sized tubes.

The panel concludes that this was an artificial program, and certainly not a compassionate use program in the sense that the Board applies when considering the average transaction price of a medicine. The Board concludes that this distribution of free Dovobet was introduced primarily for the purpose of reducing

artificially the average transaction price of Dovobet as reported to the Board. At times LEO Pharma was reporting almost as much free Dovobet in 120 mg tubes as it was selling in that size. The free distribution of only the larger 120 mg tubes (patients could not receive free 60 mg tubes) would have been markedly effective in reducing the average transaction price of Dovobet if it had been accepted by the Board as a compassionate use program but was contrary to common sense and LEO Pharma's professed concern of limiting the corticosteroid use entailed by the use of Dovobet. The explanation that the larger tube meets the needs of the most afflicted patients made no sense at all: distribution of the 60 mg size would allow doctors to give patients one or two 60 mg tubes as required by each patient's requirements. This ability to match the quantity of Dovobet prescribed with the conditions of individual patients, presumably, is the very reason that Dovobet is marketed in the 60 mg size.

The evidence also established that LEO Pharma chose to distribute free Dovobet in some measure to minimize the annoyance to doctors who found that patients who were not on a drug plan would arrive at the pharmacy to fill their prescription, be told of its price, and balk at the purchase. The pharmacists would then occupy the doctors' time by calling to confirm that, for example, Dovonex and Diprosone could be substituted. It is understandable that LEO Pharma did not want doctors to be dissuaded from prescribing Dovobet by the prospect of time-wasting "call-backs" from pharmacists. This is not a "compassionate use" objective.

In addition to using the larger size of Dovobet, the initial free distribution was made without any reference to the amount of free Dovobet that each doctor might need. LEO Pharma simply sent all doctors who expressed an interest in acquiring free Dovobet the same number of 120 mg tubes of Dovobet.

Perhaps the most important point is that LEO Pharma did not ask doctors to make any assessment of the financial need of their patients, which assessment is the hallmark of a compassionate use program. Such an assessment, which is, in any event, undertaken routinely for medicines such as Dovobet that are not covered by some insurance plans, need not be obtrusive, but in order for distribution to be deemed to be on compassionate grounds, the physician must form a view that the patient would benefit from the use of a medicine, but that its purchase by the patient likely would be sufficiently financially burdensome to dissuade the patient from the purchase.

For these reasons, the Board considers the free distribution of Dovobet to have been an attempt to reduce artificially the average transaction price of Dovobet in an effort to avoid the application of the Guidelines. Arguably, it was indicative of a policy of excessive pricing. However, while the panel has decided not to make such a finding, we have no hesitation in concluding that the distribution of free Dovobet should not be taken into account in determining the average transaction price of Dovobet.

In the event that LEO Pharma institutes a genuine compassionate use program, Board Staff will be entitled to include the quantities thus distributed in the calculation of the average transaction price of Dovobet. The Board would expect that, as a minimum, such a program will require doctors to assess the means of a patient before distributing free trade-size tubes of Dovobet, and that it would make the 60 mg tubes of Dovobet available. While the Board does not which to discourage patentees from initiating programs that benefit patients such as compassionate use programs, in the case of all distributions for which compassionate use treatment is sought by patentees, the Board will be watchful to ensure that the distribution is exclusively at the request of the particular physicians to whom it is distributed and that the program is used neither for marketing purposes nor an as attempt to reduce artificially the average transaction price of a medicine.

C. POLICY OF EXCESSIVE PRICING

Board Staff argued that Dovobet was priced above the level indicated by either the domestic therapeutic class or the highest or median international price comparisons stipulated in the Guidelines, and that LEO Pharma must therefore have realized that it was selling Dovobet at an excessive price.

For the reasons cited by Board Staff, the Board was very concerned with LEO Pharma's actions in this regard. LEO Pharma's arguments for a higher MNE (than that suggested by Board Staff) were strained and unconvincing. It could have been that LEO Pharma used the implausible arguments, rejected in this decision regarding the therapeutic class and dosage regimen of Dovobet, as a pretext for maintaining a price for Dovobet in Canada that would be high enough not be a drag on the price of Dovobet internationally, and in particular for the anticipated introduction of Dovobet in the United States. The artificial distribution of free Dovobet and the very peculiar one-time attempt at a sale in the United States despite the absence of regulatory approval for sale there, constituted some evidence of the intentions of LEO Pharma to manipulate the Guidelines.

The Board is quite prepared to draw reasonable implications and conclusions from the behaviour of patentees, and in this case it came very close to concluding that LEO Pharma engaged in a policy of excessive pricing. However, this panel is not comfortable in finding of a policy of excessive pricing on the evidence before it.

Accordingly, while LEO Pharma will be required to return the excessive revenues that it has collected on the sale of Dovobet in Canada, it will not be subjected to any additional consequences of having sold Dovobet in Canada at an excessive price.

D. CONCLUSION

Board Staff and LEO Pharma are requested to draft, for the Board's consideration, an order that will implement the findings in this decision with the most current sales and pricing information available, establishing the MNE for each period as the lower of the prices indicated by the Therapeutic Class Comparison and the Highest International Price test. The order should require the establishment of an MNE and the payment to the Crown of the excessive revenues determined in accordance with this decision. The panel will retain jurisdiction over this matter and if the panel can be of assistance in applying the findings in this decision to the requisite order, the parties may make submissions in that regard.

Board Members: Robert G. Elgie
Réal Sureau
Thomas (Tim) Armstrong

Board Counsel: Gordon Cameron

Sylvie Dupont
Secretary of the Board

April 19, 2006