STUDY 3

AN EXAMINATION OF NEW NON-BREAKTHROUGH (CATEGORY 3) PATENTED MEDICINES

Federal/Provincial/Territorial

Task Force on Pharmaceutical Prices

April, 1999

Approved by the Conference of F/P/T Deputy Ministers of Health
June 17 -18, 1999, Charlottetown, P.E.I.

EXECUTIVE SUMMARY

- For price review purposes the Patented Medicine Prices Review Board (PMPRB) classifies a new drug product that is a new medicine or new dosage form of an existing medicine that offer moderate, little or no therapeutic improvement over existing drugs as category 3 (Drugs commonly referred to as “me-too” drug products are included in category 3).

- According to the PMPRB, category 3 products account for about one-half of the new patented drug products in any year. In 1997, category 3 drugs accounted for about 47% ($1.75 billion) of the $3.7 billion in patented drugs sales at the manufacturers’ level.

- The Guidelines by which introductory prices of category 3 medicines are reviewed are an important public policy issue given the large portion of pharmaceutical spending that these drugs accounted for during the 1990's.

- This study compares the actual prices to the maximum allowable prices, that would presumed not to be excessive under the therapeutic class comparison (TCC) test of the PMPRB’s Guidelines, for three new category 3 drugs: losartan (Cozar), a medication used to treat hypertension; alendronate (Fosamax), which is a drug used to treat osteoporosis; and atorvastatin (Lipitor) a drug used to treat elevated cholesterol levels.

- The comparison revealed that prices of these new medicines were introduced between 16% and 88% of the most expensive drug in the medicine’s therapeutic class).

- From these three cases, it was observed that the cost of therapy with the new product was lower than the cost of therapy of the most expensive existing drug included in the TCC.

- A close examination of scientific (therapeutic) reviews of these three new category 3 drugs, as undertaken by the PMPRB and by the provincial drug benefit plans, reveals that these agencies conduct similar scientific assessments.

- However, once scientific assessments are completed (i.e., comparable medicines and dosage regimens are identified), the PMPRB determines if a drug product is excessively priced by comparing it to the range of prices of drugs in the therapeutic class. Provinces, on the other hand, use the information from the scientific assessments to determine the potential cost of listing a new medicine. New medicines that are found to be equivalent to existing medicines will normally be reimbursed if their inclusion in the formulary does not represent an incremental cost to the plan.

- The above highlights the difference in the objectives of the PMPRB and the provincial drug plans:

  – The PMPRB's mandate is to ensure that manufacturers' introductory prices of new patented pharmaceuticals are not excessive, as defined by factors set out in the Patent Act.

  – Provincial drug plans' objectives are to ensure that their beneficiaries have access to appropriate drug therapies while ensuring cost containment (e.g., public expenditures).

- As a result of these differences:

  – Provinces may not choose the highest priced comparator medicine to make listing decisions, but rather the price of the medicine that the drug is expected to replace in terms of utilization. This usually means that provincial plans compare a new drug to the least cost alternative (e.g., generic) version of comparators;

  – On the other hand, the PMPRB may include both brand name and generic versions to determine the range of prices of comparator medicines.

- These findings also highlight the importance of information sharing between the PMPRB and provincial drug plans to ensure therapeutic class comparison analyses are most effectively used in reviewing introductory prices of new patented medicines. PMPRB analyses comparing a new drug to other drugs in its therapeutic class are also a potentially valuable tool to provincial and other payers facing purchasing or reimbursement decisions. The PMPRB and the provinces are encouraged to seek new ways to share this information and make it available to all stakeholders in a timely manner.

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AN EXAMINATION OF NEW NON-BREAKTHROUGH

(CATEGORY 3) PATENTED MEDICINES

1.0 INTRODUCTION

In March, 1997, the Federal Provincial Territorial (F/P/T) Task Force on Pharmaceutical Prices prepared an overview paper which provided a description of the pharmaceutical sector in Canada, a summary of existing information on drug prices and spending, as well as mechanisms used by private and public payers for regulating and/or influencing pharmaceutical prices. From this research, it was concluded that more detailed analyses of such prices and expenditures were needed. It was noted, that further research should be undertaken not only at an aggregate level, but also according to key criteria including, for example, whether a product is available from one or several competing sources; and whether or not a medicine is patented.

The Task Force has since examined price and expenditure trends, price levels, and cost drivers as they relate to prescription drugs reimbursed under six provincial drug plans.[1] The first of these analyses measured how prices and spending have changed between 1990 and 1997. Subsequent studies have assessed prices of non-breakthrough patented drugs; single source non-patented drugs; and multiple source non-patented (generic) drugs; an inter-provincial price comparison study was also undertaken. Finally, the Task Force has developed and applied a "cost-driver" analysis that has accurately measured the role of changes in existing drug prices, changes in utilization, and the impact of newly introduced medicines to changes in total drug spending.

The purpose of this Paper has been to review the role and method of the Patented Medicine Prices Review Board (PMPRB) and the provincial drug benefit plans[2] in reviewing prices of new active substances that are classified by the PMPRB as category 3 drug products,[3] and to

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1 The Task Force has representatives from British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, Health Canada and the Patented Medicine Prices Review Board. It was established to examine one of six pharmaceutical issues identified at the April 1996 meeting of federal/provincial/ territorial Ministers of Health. The other issues included utilization, marketing, wastage, consumer education and research and development. The work is overseen by the Pharmaceutical Issues Committee (PIC) of the Advisory Committee on Health Services (ACHS), which reports to the Conference of Deputy Ministers of Health.

2 For this study, provincial drug benefit plans or “provinces” refers to the following jurisdictions: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Nova Scotia.

3 For a complete definition of the PMPRB’s three categories please see Appendix 1.

review the role and method of the provincial drug benefit plans[4] in making decisions on whether to reimburse these new drugs.

For price review purposes the PMPRB classifies a new drug product that is a new medicine or new dosage form of an existing medicine that offer moderate, little or no therapeutic improvement over existing drugs as category 3. (Drugs that are commonly referred to as "me-too"drug producs are included in category 3.)

An important objective of this analysis is to consider whether improvements can be made, and how each organization may benefit, from the input and information possessed by the other.

[4] For this study, provincial drug benefit plans or "provinces"refers to the following jurisdictions: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Nova Scotia.

2.0 METHODOLOGY

The report begins with an explanation of how the PMPRB and provincial drug benefit plans approach the regulation and reimbursement of new category 3 medicines. Next, each organization's roles and methods are discussed relative to recent market place experience for three new category 3 patented drugs: losartan (Cozaar), a medication used to treat hypertension; alendronate (Fosamax), which is a drug used to treat osteoporosis; and atorvastatin (Lipitor) a drug used to treat elevated cholesterol levels. These drugs are analyzed with respect to their introductory price and the correspondingprices of other drugs in the therapeutic class.[5]

The three drug products are then examined in greater detail to illustrate how provincial drug plans approach their decision on whether to add a new drug product to their formulary. In most cases provinces use pharmacoeconomic analysis to assess whether the new drug contains "value for money", and usually adds a new product (for which alternatives already exist) if its price is as low, or lower, than existing drug therapies.

[5] The introductory price of a new category 3 medicines can not exceed the range of prices of comparable medicines in the same therapeutic class.

3.0 BACKGROUND

Generally, both the PMPRB and the provincial drug plans evaluate the therapeutic merits of category 3 drug products that are introduced into the market. While these evaluations are similar, their objectives are different. The PMPRB's mandate is to ensure that manufacturers' introductory prices of new patented pharmaceuticals are not excessive, as defined by factors set out in the *Patent Act*. Provincial drug plans' objectives are to ensure that their beneficiaries have access to appropriate drug therapies while ensuring cost containment (e.g., public expenditures). The differences inherent in the PMPRB's mandate and the provincial drug plans' objectives must be clarified if one is to understand the importance of ensuring non-excessive introductory prices as well as fair and reasonable reimbursement prices. The following section sets out the different roles of the PMPRB and the provincial drug benefit plans for new category 3 patented medicines. The next section provides some information on the sales of these new patented medicines.

3.1 The Market for New Category 3 Patented Medicines

According to the PMPRB, category 3 drugs accounted for the largest sales and number of newer drugs over the period 1990 to 1997. In 1997, 361 category 3 drugs accounted for approximately 47% or $1.75 billion of $3.7 billion of total patented sales. These drugs typically account for about one half of the new patented drug products whose introductory prices are reviewed by the PMPRB in any one year.

3.2 The PMPRB's Role in Reviewing the Introductory Price of New Category 3 Patented Medicines

The PMPRB's mandate is to review the ex-factory gate prices[6] of patented drugs to ensure that they are not excessive.[7]

In determining whether a price is excessive, the PMPRB is required by legislation to take into account the following factors: consumer price index (CPI); prices of other medicines in the same therapeutic class in Canada; and the price of the medicine and of other medicines in other countries identified in the *Patented Medicine Regulations.*[8] These factors form the basis of price guidelines developed in consultation with its stakeholders, and administered by the PMPRB.

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6 Ex-factory prices are those prices sold to wholesalers, hospitals or pharmacies.

7 The PMPRB has no jurisdiction over drugs which have never been patented, or over those for which a patent has expired or is pending. The PMPRB also has no authority over the prices charged by wholesalers and retailers or over pharmacists' dispensing fees, nor can it govern how a drug is utilized or how it is paid for by provincial or private plans.

8 The seven countries are France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States.

These guidelines limit the introductory prices of new category 3 drugs so that the cost of therapy is no greater than that of similar drugs currently on the market that treat the same disease.

Introductory prices of category 3[9] will be presumed to be excessive if they exceed the maximum price based on a *Therapeutic Class Comparison Test* (TCC).In addition, the price may not exceed the range of prices for the same drug in the other countries. These drugs fall into two groups:

- new drug products that belong to an existing therapeutic class or the same 4th level Anatomical Therapeutic Chemical (ATC) class (e.g. Lipitor); and,

- new drug products that belong to a new therapeutic class (e.g., Cozaar).

3.3 The Provincial Role in the Reimbursement for Category 3 Patented Medicines

The provinces are primarily concerned with balancing access to new drug therapies while controlling the overall cost of the drug products they reimburse (whether they are existing or new drug products).

Under the *Canada Health Act*, medically necessary prescription drugs are provided without charge to in patients or out patients when administered in a hospital. Provision for prescription drugs for Canadians living in the community or residing in nursing homes or other long-term care facilities are not covered under the *Canada Health Act*. Consequently, each provincial and territorial government independently developed programs to provide drug coverage to some or all of its residents who are living in the community or in nursing homes.[10]

Provincial governments strive to deliver improvements to patients, enhance efficiency within their health systems while containing costs. Measures to influence the rate of growth of provincial spending on pharmaceuticals has been a focal point for these activities.

The overall approach is similar in each province—a manufacturer must make a submission for a drug to be considered as a benefit on each provincial drug formulary. The information in a drug submission is reviewed by experts, either internal or external. The expert review committee prepares a summary on the submission, including comments or recommendations regarding the drug's therapeutic effectiveness in comparison to other drugs and therapies and its cost-effectiveness. A recommendation is made to the Ministry of Health and a decision to list or not to list the drug is made, either at the senior bureaucrat level, by the Minister, or by

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[9] A drug will be considered a breakthrough/substantial improvement product whenever the drug offers substantial therapeutic advantage over existing medicines in any of the drug's approved indications in significant patient populations.

[10] Rosemary A. Bacovsky, *Drug Submission, Review and Approval Process for Provincial and Territorial Government Sponsored Prescription Drug Plans in Canada, 1997*.

Cabinet. Normally provincial drug benefit managers update their provincial drug benefit lists at regular intervals.[11]

4.0 CATEGORY 3 PATENTED MEDICINES PRICE REGULATION AND REIMBURSEMENT ANALYSIS

In its *Road Map for the Next Decade*, the PMPRB announced further consultations on its price review process for new patented drugs and the guidelines it uses to regulate prices of category 3 "me-too" drugs. This came as a result of public consultations by the PMPRB and concerns raised by provincial members of the Task Force on Pharmaceutical Prices (TFPP) and other stakeholders regarding the introductory prices of category 3 new drugs. The Guidelines require that the price set by the manufacturer for a category 3 drug product be reviewed by applying the Therapeutic Class Comparison test. The price of the new drug will be presumed to be excessive if the cost of treatment with the new drug is higher that the maximum cost of existing drugs which are similar and used to treat the same disease. In addition, the price in Canada may not exceed the highest foreign price.

From the drug plan administrator's perspective, subsequent entries into the same therapeutic class should be priced lower than existing therapies in order to ensure value for money. For example, the drug product Lipitor is the 5th entry in the class of statins yet its introductory pricecould have been as high as the most expensive drug product in the same therapeutic class provided it also met the other requirements of the guidelines.

4.1 Introductory Prices of Category 3 Drugs and their Maximum Therapeutic Class Price

The TFPP was interested in determining to what extent category 3 drugs are introduced at prices lower than the maximum price permitted under the PMPRB's guidelines. In addition, it was interested in knowing how the scientific and price reviews of provincial drug plans compared to one another and to the PMRPB's guidelines. A preliminary analysis comparing introductory prices of 15 new medicines to the range of prices of comparable medicines suggested that there are variations. From this analysis the TFPP concluded that it would be helpful for all governments to share detailed information on their reviews to allow more complete analysis in the future.

To that end, the TFPP asked the PMPRB and the participating provincial governments to provide information on how they reviewed the introductory prices of three new drugs: alendronate (Fosamax); losartin (Cozar); and atorvastatin (Lipitor).The PMPRB published its analysis of the three drugs as part of the Road Map for the Next Decade in September 1998. That report showed that the three durgs were priced within the Guidelines and less than the

[11] Ibid.

most expensive existing drug in the class. In fact, the prices of the new drugs raned from 16% to 88% of the most expensive comparator.[12]

4.2 In Terms of the PMPRB - Scientific Procedures and Price Review

The purpose of the TCC test as comparing the prices of drug products that are "clinically equivalent" and are sold in the same market at prices which are not excessive.

The objective of the criteria applied in the selection of comparable drug products for the TCC is to identify drug products that are most similar to the new patented drug product. Comparators are generally selected from among existing drug products that:

- are used to treat the disease(s) and/or patient group(s) targeted by the approved indication of the new patented drug product;

- are in the same therapeutic/pharmacological class (under the Guidelines comparators are generally restricted to drugs found at the same 4th level of the Anatomical Therapeutic Classification (ATC) system); and

- are of the same or comparable dosage forms as the drug products under review.

For new drugs with multiple indications, the drug*s primary indication (therapeutic use) must be identified. It may be that the primary indication for one DIN (strength)[13] differs from that of another DIN of the same medicine. As a result, comparators might differ for each DIN of a new medicine, if primary indications are different.

The patent status of comparator drugs, or the length of time they have been on the market, are not considerations in the selection process, (i.e., the TCC will include brand name and generic drug products that meet the selection criteria).

The objective of the TCC is to produce an "apples to apples" comparison between the drug product under review and the selected comparable drug products. The Guidelines call for consideration of the dosage regimen, and other clinically relevant variables, required to produce a "clinically equivalent effect". To define a comparable dosage regimen, data from comparative trials of the drug under review with the comparators will be used if available. However, data from comparative trials are often not available at the time of the PMPRB*s review. Therefore, scientific literature will be reviewed to determine the most clinically accepted dosage regimens for each strength under review. The dosage regimen identified "for comparisons purposes will not normally be higher than the maximum of the usual recommended dosage". Most often, particularly for drugs that are used for chronic therapy, a cost per day will be compared. Differences in the course of treatment among comparators will be considered if clinically relevant, (e.g., in acute situations). For a complete description of the

[12] See Appendix 2, PMPRB's *Road Map For the Next Decade* attachment Category 3 Drug Prices: Preliminary Outline of Issues.

[13] DIN - Drug Identification Number

selection of comparators and comparable dosage regimens for the TCC, see the PMPRB*s *Compendium, Scientific Review Procedures.*

The PMPRB contracts drug information centres to assist in this work and advice is sought from the PMPRB*s Human Drug Advisory Panel in more difficult cases.

4.3 In Terms of the Provinces — Process in Making Reimbursement Decisions Relating to Drugs with Comparable Existing Medicines Already Available

The following section presents an overview of the scientific procedures the provinces follow when conducting their therapeutic class comparison process in order to decide to reimburse and list a drug on their respective formularies.[14] Since each province has developed its own unique criteria when deciding to a list a product, this section is only an overview and is not a comprehensive analysis.

In order to review a new drug product and decide to list it on the formulary, the provinces have set up their own expert advisory committees[15] in order to assist and ensure a comprehensive therapeutic review of the product under question.

An initial step in the overall approach to deciding whether or not to list a particular drug on a provincial formulary is to determine the indication(s) of the particular drug product under review. In order to undertake this task, the provincial expert advisory committees take into account various factors which help define a drug's therapeutic use for comparison purposes. For instance, provinces will consider the indication(s) approved by the Health Protection Branch of Health Canada. They will also review the clinical data supporting the indication(s), review the current and relevant literature to ascertain support for non-approved indications and experience with other agents within the same therapeutic category. In addition, the manufacturer's promotional material, such as anticipated market share for the new product, is also considered when determining the product's indication(s).

Essentially, the provinces can make comparisons for several indications for which the drug is approved since it is possible to reimburse for one indication and not another. Therefore, the drug under review is compared against many different comparators and dosage regimens depending on the indication that is being examined.

However, once a primary indication has been determined, comparable drug products are then selected according to the advice of the provincial expert advisory groups. All of the comparable medicines, which might include drugs that are therapeutically equivalent such as generics, and those drugs that are not listed on the formulary, are examined in order to determine a drug's

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[14] This information is based on a questionnaire (Appendix 3) developed by the TFPP.

[15] British Columbia - Scientific Information and Education Committee of the Therapeutics Initiative; Alberta - The Expert Committee on Drug Quality and Therapeutics of Alberta Blue Cross; Saskatchewan - Drug Quality Assessment Committee; Manitoba - Drug Standards and Therapeutics Committee; Ontario - Drug Quality and Therapeutics Committee; Nova Scotia - Formulary Management Committee.

therapeutic effectiveness. Decisions about the appropriate comparators can be based upon a review of all the relevant literature, the ATC classification system and comparators used in the clinical trials. In addition, past experience with previously reviewed products is also taken under consideration. Furthermore, the provinces request information on how the product will be promoted and the products it will be positioned against.

Similarly, when deciding on a comparable dosage regimen for a particular drug, the provinces rely on product monographs, credible scientific literature and advice from experts who have clinical experience in the area that the medicine is approved for treatment. Furthermore, depending on the drug product, the comparison of the dosage regimen may be based upon daily cost, treatment cost or some other relevant period that is most applicable to the drug under review. The most appropriate strength of the drug will be chosen for a particular dosage regimen.

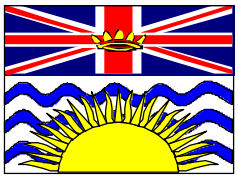
4.4 A Case Study — An Examination and Comparison of the Provincial and PMPRB Scientific Review of Three Non-Breakthrough Drug Products

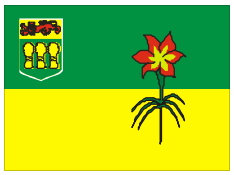
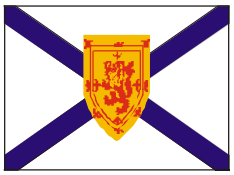
In the previous section, provincial and PMPRB scientific review procedures for category 3 medicines were described. However, in order to gain a more in-depth understanding of these methods, three category 3 drug products were examined in detail.

Based on the information provided to the TFPP concerning three drug products, some similarities and differences have emerged between the provinces and the PMPRB. For instance, the analysis reveals that for the large part, the provinces and the PMPRB identify the same comparators.[16] However, there were differences in the range of comparators employed.

[16] The analysis also revealed that when the same comparators were employed by both the PMPRB and the provinces, the same standard dosage regimens were also used.

Table 1

Comparators Used by the PMPRB and the Provinces for Three New Non-Breakthrough Medicines			
Drugs	**Fosamax**	**Lipitor**	**Cozaar**
Jurisdiction	**Comparators Employed**		
PMPRB 	Aredia Bonefos Calcimar Caltine Ces Tablets Congest; Didrocal (Etidronate) Estaderm. Estrace; and Hormone Replacement Therapy including: Ostac	Lescol Mevacor Pravachol Zocor	Accupril Ace Inhibitors including: Altace Capoten Inhibace Lotensin Monopril Prinivil/Zestril Vasotec
British Columbia 	Calcimar Didrocal (Etidronate) Hormone Replacement Therapy Placebo (published control trial)	Lescol Mevacor Pravachol Zocor	Accupril Adalat XL Altace Captoen Cardene Cardizem Inhibace Isoptin SR Lotensin Generic Captopril Generic Verapamil Monopril Norvasc Plendil Prinivil/Zestril Vasotec
Alberta 	N/A	Lescol Mevacor Pravachol Zocor	Accupril Adalat XL Altace Cardizem Coversyl Inhibace Isoptin SR Lotensin Monopril Plendil Prinivil/Zestril Vasotec

Drugs	Fosamax	Lipitor	Cozaar
Jurisdiction	**Comparators Employed**		
Saskatchewan 	Didrocal	Lescol Mevacor Pravachol Zocor	Accupril Adalat XL Altace Amlodipine Cardizem CD Coversyl Inhibace Lotensin Monopril Plendil Prinivil/Zestril
Manitoba 	Hormone Replacement Therapy Placebo (published control trial)	Lescol Mevacor Pravachol Zocor	Atenolol Captopril Enalapril HCTZ Plendil
Ontario 	Etidronate	Lescol Mevacor Pravachol Zocor	Accupril Adalat XL Capoten Cardizem CD Inhibace Isoptin SR Isoptin Lotensin Monopril Norvasc Plendil Prinivil/Zestril Renedil Vasotec
Nova Scotia 	Didrocal (Etidronate) Estrogen Replacement Therapy	Lescol Mevacor Pravachol Zocor	Accupril Acebutolol Altace Amlodipine Atenol Cardizem CD Coversyl Felodipine Inhibace Lotensin Metoprolol Monopril Privinil/Zestril

The review of the drug Fosamax illustrated that the therapeutic class comparison under the PMPRB was broader, (i.e. a comparison was done against a larger range of other medicines). Although the comparators for the provinces varied, they often included Etidronate and a Hormone Replacement Therapy. The PMPRB used these same comparators but also looked at other drugs. The exact opposite is true of the Zozaar review. The PMPRB compared Cozaar to a smaller range of products while the provinces looked at a larger group of medicines. However, the review of Lipitor illustrated that the provinces and the PMPRB used the exact same number of comparators.

The analysis illustrates that both the PMPRB and the provinces identified the same core comparators. Therefore, the analysis of the three products revealed that the provinces and the PMPRB undertake similar scientific analysis in order to determine if a product has a therapeutic advantage over existing products.

Once scientific assessments are completed (i.e., comparable medicines and dosage regimens are identified), the PMPRB determines if a drug porduct is excessively priced by comparing it to the range of prices of drugs in the therapeutic class. Provinces, on the other hand, use th einformaiton from the scientific assessments to determine the potential cost of listing a new medicine. New medicines that are found to be equivalent to existing medicines will normally be reimbursed if their inclusion in the formulary does not represent an incremental cost to the plan.

The above highlight the differences in the objectives of the PMPRB and the provincial drug plans:

- The PMPRB's mandate is to ensure that manufacturers'introductory prices of new patented pharmaceuticals are not excessive, as defined by factors set out in the *Patent Act*.

- Provincial drug plans'objectives are to ensure that their beneficiaries have access to appropriate drug therapies which ensuring cost containment (e.g., public expenditures).

As a result of these differences:

- Provinces may not choose the highest priced comparator medicine to make listing decisions, but rather the price of the medicine that the drug is expected to replace in terms of utilization. This usually means that provincial plans compare a new drug to the lease cost alternative (e.g., generic) version of comparators;

- On the other hand, the PMPRB may include both brand name and generic versions to determine th erange of prices of comparator medicines.

5.0 CONCLUSIONS

The findings of this analysis highlight the importance of information sharing between the PMPRB and all its stakeholders to ensure therapeutic class comparison analyses are most effectively used in regulating introductory prices of new medicines. PMPRB analyses comparing a new drug to other drugs in its therapeutic class are also a potentially valuable tool to provincial and other payers facing purchasing or reimbursement decisions. The PMPRB and the provinces are encouraged to seek new ways to make this information available to all stakeholders in a timely manner.

Furthermore, it would be useful for the PMPRB to consider whether other, or additional measures of maximum non-excessive price could be employed in conducting therapeutic class comparison analyses and whether pharmacoeconomic evaluations could be better employed to ensure that Canadians are receiving good "value" when these new drugs are introduced. The Task Force supports the PMPRB's ongoing consultations that have identified this matter as a priority issue for consideration.[17]

Finally, it may also be useful for provinces to compare their different ways of assessing whether a new drug will represent an incremental cost to the plan; if a preferred approach is identified it could be adopted by other plans.

[17] See the PMPRB's (1998) *Road Map for the Next Decade*

APPENDIX 1

THE PMPRB'S THREE CATEGORIES

A category 1 drug product is a new DIN of an existing dosage form of an existing medicine, or a new DIN of another dosage form of the medicine that is comparable to the existing dosage form.

A category 2 drug product is one that provides a breakthrough or substantial improvement. It is a new DIN pf a non-comparable dosage form of an existing medicine or the first DIN of a new chemical entity.

A category 3 drug product is a new DIN of a non-comparable dosage form of an existing medicine or the first DIN of a new chemical entity. These DINs provide moderate, little or no therapeutic advantage over comparable medicines. This group includes those new drug products that are not include in category 2 above.

APPENDIX 2

CATEGORY 3 DRUG PRICES: PRELIMINARY OUTLINE OF ISSUES

[ATTACHMENT TO THE *ROAD MAP TO THE NEXT DECADE*]

INTRODUCTION

During the Patented Medicine Prices Review Board's recent consultations, several stakeholders raised questions regarding the introductory prices of category 3 new drugs. There appears to be a consensus that the criteria used by the Board for reviewing the prices of these drugs require re-examination.

Some said that a review is necessary to ensure that Canadians are receiving good "value"; they argued that too many "me-too" drugs are being introduced into the Canadian health care system at prices which may not reflect their value. On the other hand, industry representatives stated that the guidelines for category 3 drugs are too restrictive.

This paper provides a preliminary outline of the important issues raised by stakeholders during the Board's consultations. The Board is establishing a working group in the fall of 1998 to make recommendations for consideration by the Board on changes to the price review process. This same working group will be asked to address issues concerning the price review methodology for category 3 drugs.

Many stakeholders encouraged the Board to publish more information on the application of its guidelines to new patented drugs. It was suggested that the price review process could be made more transparent for consumers by providing some examples. In response, this paper provides a brief overview of how Therapeutic Class Comparisons (TCC) are conducted and presents the TCC's used to review the price of three category 3 drugs as examples. These case studies are intended to allow readers to better understand the price review process and the issues raised during the consultations.

SUMMARY OF ISSUES RAISED

Few stakeholders stated that the current guidelines for category 3 patented medicines are appropriate in all cases.

Many stakeholders (e.g. provincial and territorial governments, consumer groups and patient advocacy groups) were concerned that the price of a new patented drug in category 3 may be as high as the most expensive drug in the therapeutic class. In particular, there were concerns that this standard is inappropriate for drugs that offer no therapeutic improvement over existing drugs. Many people refer to such drugs as "me-toos". There were also concerns that a high-priced drug holding a small share of the market, or a limited place in therapy, may be the most

expensive drug in a TCC and therefore set an upper price limit for non-breakthrough medicines that is too high or inappropriate.

The pharmaceutical industry, on the other hand, was concerned that the current guidelines limit the prices for newer medicines to the prices of older, and in some cases, less effective medicines. They argued that the guidelines do not recognize that some new drugs in category 3 may offer incremental improvements over existing ones. It was also argued that there is a need to develop a system that better recognizes the incremental progression of drug discovery. In addition, some expressed concerns that a more restrictive price review methodology would force manufacturers to delay the introduction of new drugs.

A number of stakeholders suggested the "value" of a new category 3 medicine should be considered in reviewing its introductory price, in other words, that its cost effectiveness be taken into consideration. The possibilities for greater use of pharmacoeconomic analysis for purposes of the guidelines will be the subject of a separate study and will form part of the PMPRB Research Agenda.

SOME SPECIFIC SUGGESTIONS FROM STAKEHOLDERS

Under the Board's existing Guidelines, the introductory price set by the patentee for a category 3 new drug product will be presumed to be excessive if it exceeds the prices of all of the comparable drug products based on a Therapeutic Class Comparison (TCC) test. In their submissions, stakeholders offered a number of possible alternatives. Among other things, they suggested that the guidelines be amended to limit the price of a new drug in category 3 so it cannot exceed:

- the median price, or as an alternative, the average price, of all the drugs in the TCC;
- the price of the most commonly prescribed drug within the TCC;
- the price of the "gold standard" among the comparator drugs. (A clear definition of the "gold standard" would have to be developed. For example is it the therapy that is recommended by evidence-based treatment guidelines; is it the "usual practice"; or is it the "drug of choice");
- an adjusted price based on the "added value" or potential therapeutic improvement of the new drug;
- an adjusted price based on the number of existing drugs in the therapeutic class and/or the relative use of brand name and generic drugs; or
- the lower of the highest price in the therapeutic class and the median or lowest international price for the same drug.

Some suggestions proposed distinguishing among category 3 drugs according to the degree of therapeutic improvement or the number of existing drugs that treat the same disease. In other words, different standards should be applied to different sub-groups of category 3.

OVERVIEW OF CURRENT APPROACH TO REVIEW CATEGORY 3 DRUGS

Under the Guidelines, a new patented medicine may be classified as category 3 if:

- it is a new active substance; a new, non-comparable dosage form of an existing medicine; or a new combination of existing medicines; and,

- no submission has been made by the patentee that the product be classified as a substantial improvement ; or,

- a submission made by the patentee fails to demonstrate that the product meets the criteria to be classified as a substantial improvement.

The Guidelines require that the price set by the manufacturer for a category 3 drug product be reviewed by applying the Therapeutic Class Comparison (TCC) test. The price of the new drug will be presumed to be excessive if the cost of treatment with the new drug is higher than the maximum cost of treatment of existing drugs which are similar and used to treat the same disease. (See the *PMPRB's Compendium of Guidelines, Policies and Procedures* for a more complete description of the guidelines and the policies on therapeutic class comparisons.)

THERAPEUTIC CLASS COMPARISONS

The Guidelines describe the TCC test as comparing the prices of drug products that are "clinically equivalent" and are sold in the same markets at prices that the Board considers not to be excessive.

The objective of the criteria applied in the selection of comparable drug products for the TCC is to identify drug products that are most similar to the new patented drug product. Comparators are generally selected from among existing drug products that:

- are used to treat the disease(s) and/or patient group(s) targeted by the approved indication of the new patented product;

- are in the same therapeutic/pharmacological class (under the Guidelines, comparators are generally restricted to drugs found at the same 4th level of the Anatomical Therapeutic Classification (ATC) system); and

- are of the same or comparable dosage forms of the drug product under review.

The patent status of comparator drugs, or the length of time they have been on the market, are not considerations in the selection process. In other words, the TCC will include brand name and generic products that meet the selection criteria; "old drugs" that are still being used are not excluded because of their age.

The objective of the TCC is to produce an "apples to apples" comparison between the drug product under review and the selected comparable drug products. The Guidelines call for consideration of the dosage regimen, and other clinically relevant variables required to

produce a “clinically equivalent effect”. The dosage regimens identified “for comparison purposes will not normally be higher than the maximum of the usual recommended dosage”. For a complete description of the selection of comparators and comparable dosage regimens for the TCC, see the *Compendium*, Scientific Review Procedures.

The Board contracts drug information centres to assist in this work. Advice is sought from the Board’s Human Drug Advisory Panel (HDAP) in more difficult cases or when the recommended TCC is contested by the patentee.

For purposes of the introductory price review, the Board uses the price information provided by the patentee pursuant to the *Patented Medicines Regulations* showing the average transaction price of the new medicine, net of discounts and rebates. Prices of the comparator products are also obtained from the information filed by patentees in the case of a patented drug, and from publicly available sources of price information for non-patented drugs. Under the Guidelines, the Board ordinarily uses the Ontario Drug Benefit Formulary because previous experience has shown that its prices most closely approximate the average transaction prices for patented drugs.

Most often, particularly for drugs that are used for chronic therapy, a cost per day will be calculated. Differences in the course of treatment among comparators will be considered if clinically relevant, e.g., in acute situations.

EXAMPLES OF THERAPEUTIC CLASS COMPARISONS

Recently, the Federal/Provincial/Territorial Task Force on Pharmaceutical Prices asked the Board to report specifically on how its guidelines had been applied in the review of the prices of three new drugs introduced between 1995-97: Cozaar, Fosamax, and Lipitor.

The TCC’s conducted for these drugs are included here for information purposes to illustrate the application of the guidelines to category 3 drugs. In all three cases, the introductory prices set by the patentee were found to be within the Guidelines; the cost of therapy with the new product was lower than the cost of therapy of the existing drugs included in the TCC.

The comparators and the pricing information used in the TCC examples presented reflect the situation at the time the drug product was first introduced in Canada.

Cozaar (losartan)

Cozaar (losartan) is sold by Merck Frosst Canada. It was introduced in Canada in September 1995. The introductory prices set by the patentee for each strength were reviewed by the Board and found to be within the Guidelines; the cost per day of Cozaar was found to be lower than the cost per day of treatment of available ACE-inhibitor drugs.

Losartan was the first drug of a new therapeutic class, known as “angiotensin II receptor antagonists”. It is indicated for the treatment of high blood pressure. It was introduced in 25 mg and 50 mg tablets; recently, a 100 mg strength was introduced. The example provided looks at the comparators used in the price review of Cozaar 50 mg.

The following information was taken into consideration in setting out the TCC:

- In accordance with the Guidelines, it was necessary to look at other ATC classes for relevant comparators since losartan was the first entry in a new 4th level ATC class. Other drugs used to treat high blood pressure include ACE-inhibitors; beta-blockers; calcium channel blockers and diuretics.

- The Guidelines state that the selection criteria will include indication and therapeutic use and may include other factors such as mode of action, spectrum of activity or chemical family. The TCC for losartan was restricted to a comparison with the ACE-inhibitor drugs. The information reviewed suggested that they were the most relevant comparators; both the ACE-inhibitors and angiotensin II receptor antagonists act on the renin-angiotensin system to lower blood pressure (same 3rd level ATC) and there are clinical trials comparing drugs from the two classes.

- All comparators are solid oral dosage forms.

Cozaar: Comparison to other drugs used in the treatment of high blood pressure

Drug (*Brand name*)	**Dosage regimen**	**Cost per day**[18]
Losartan (*Cozaar)*	50 mg daily	$1.10
Benazapril (*Lotensin*)	20 mg twice daily	$1.56
Captopril *(various brands)*[19]	75 mg, 3 times a day	$2.70 - 4.90
Cilazapril (*Inhibace*)	2.5 mg twice daily	$1.36
Enalapril (*Vasotec*)	10 mg twice daily	$1.92
Fosinopril *(Monopril*)	20 mg twice daily	$1.90
Lisinopril (*Prinivil, Zestril*)	20 mg twice daily	$1.94
Quinapril (*Accupril*)	20 mg twice daily	$1.64
Ramipril (*Altace*)	5 mg twice daily	$1.50

N.B: Drug cost based on publicly available prices in the Ontario and/or Québec formulary.

Fosamax (alendronate)

Fosamax (alendronate) is sold by Merck Frosst Canada and was introduced in Canada in 1996. The introductory prices set by the patentee for each strength were reviewed by the

[18] This medication is administered on a chronic basis, therefore the cost per day was used as the basis for cost comparison with the comparators.

[19] Including generics.

Board and found to be within the Guidelines; the price of Fosamax was found to be within the range of the prices of existing drugs with the same therapeutic use.

Alendronate belongs to a class of drugs known as “the bisphosphonates”. When it first came on the Canadian market, it was approved by Health Canada for use in the treatment of osteoporosis and Paget’s Disease. Later it was approved for the prevention of osteoporosis. It is available as a 5 mg, 10 mg and 40 mg tablet. The different strengths have different therapeutic uses. For example, the 10 mg strength is used to treat osteoporosis. The example provided looks at the TCC used in the price review of Fosamax 10 mg.

The following information was taken into consideration in setting out the TCC:

- Alendronate was the 4th entry in the “bisphosphonates” therapeutic class. In 1996, the use of bisphosphonates was a relatively new treatment approach for osteoporosis. Only one other bisphosphonate, etidronate, was being used. Didrocal (combination of etidronate and calcium) was the first oral bisphosphonate to be approved by Health Canada for the treatment of osteoporosis.

- Other drug therapies used for the treatment of osteoporosis include hormone replacement therapy (HRT; oral estrogens and estrogen transdermal patches) and calcitonin (injectable). In practice, HRT is considered therapy of first choice although it has not been approved for that indication by Health Canada[20]; calcitonin and the bisphosphonates are second line therapies.

- The Guidelines provide that comparable medicines used for purposes of a TCC “are clinically equivalent in addressing the approved indication that is anticipated to be the primary use of the new drug product under review”. The Guidelines state that while the comparators will normally be selected from the same 4th level ATC class, the selection criteria will include indication and therapeutic use and may include other factors such as mode of action, spectrum of activity or chemical family.

- The only published comparative clinical trial available for alendronate at the time of the review was against calcitonin; this trial suggested that alendronate is an improvement over calcitonin.

- In view of the foregoing, the HDAP recommended that the TCC for Fosamax be expanded beyond the 4th level ATC class (i.e. the bisphosphonates) to include HRT and calcitonin.

- Under the Guidelines, comparators will normally be of the same or comparable dosage form as the drug product under review. Estrogens are available in oral forms and transdermal patches. Both the oral and transdermal forms are clinically equivalent. As the transdermal patch is widely used by patients on hormone replacement therapy, it is difficult to argue that transdermal patches should be excluded from the TCC.

[20] We are unaware that any manufacturer of hormone replacement therapies has submitted the available scientific evidence to Health Canada to seek approval for treatment of osteoporosis.

- Calcitonin is considerably more expensive than the other drugs and is only available in an injectable form. Medical references consulted show that it is still used in the treatment of osteoporosis, albeit less commonly. Given that the only comparative clinical trial for alendronate compared it to calcitonin and that the most commonly prescribed therapy (i.e. HRT) is not approved by Health Canada for this indication, it was difficult to argue that calcitonin should be excluded from the TCC.

- It is recognized that, with all of the drugs in the therapeutic class comparison, oral supplementation of calcium and Vitamin D is recommended in clinical practice. Since this is common to all therapies, the costs were not factored into the TCC.

Fosamax: Comparison to other drugs for treatment of osteoporosis

Drug (*Brand name*)	Dosage regimen	Cost of 90 day treatment[21]
Alendronate (*Fosamax*)	10 mg daily	$157.95
Calcitonin (*Calcimar, Caltine*)	100 IU injection daily	$735.25 -969.03
Conjugated estrogens (*CES, Congest, Premarin*)[22]	0.625 mg daily	$38.22 -42.39
Estradiol (*Estrace*)	2 mg daily	$62.91
Estradiol patch (*Estraderm*)	100 mcg patch-2 per week	$97.94
Etidronate/calcium (*Didrocal kit*)	400 mg/day for 14 days, 1250 mg for 76 days	$57.67

NB: Drugs cost based on publicly available prices in the Ontario and/or Québec formulary.

Lipitor (atorvastatin)

Lipitor (atorvastatin) is sold by Warner-Lambert Canada. It was introduced in Canada in March 1997. The introductory prices set by the patentee for each strength were reviewed by the Board and found to be within the Guidelines; the price of Lipitor was within the range of the prices of the other "statins" already on the market.

Atorvastatin is the 5th entry in the therapeutic class referred to as the "HMG CoA reductase inhibitors" (also known as "the statins"). It is used to reduce cholesterol and triglyceride levels in the blood, a condition referred to as hyperlipidemia. It is supplied in tablets of 10 mg, 20 mg and 40 mg. The example provided looks at the comparators used in the price review of Lipitor 10 mg.

[21] The various dosage regimens as described in the approved product monographs were taken into account in determining comparable dosage regimens.

[22] As one of the comparators is available as a 90-day kit (Didrocal), a 90-day course of treatment was used as the basis for the cost calculation.

The following information was taken into consideration in setting out the TCC:

- The types of drugs that are used for this indication include the statins, fibrates, bile acid sequestrants and nicotinic acid;

- In accordance with the Board's Guidelines, the TCC for Lipitor was limited to the other drugs in the same 4th level ATC class i.e. the other statins; all comparators are solid oral dosage forms;

- The introductory prices of the other "statins" were reviewed previously by the Board and found to be within the Guidelines . Mevacor (lovastatin) was the first statin to be reviewed by the Board. It was classified in 1988 as a category 2 drug product. The prices of other drugs used to reduce cholesterol and triglycerides were taken into consideration when the first statins were reviewed.

- Lipitor (atorvastatin) may have a greater effect on triglyceride levels than the other statins. Nevertheless, all statins are considered to be clinically comparable for purposes of the TCC.

Lipitor: Comparison to other drugs used in the treatment of hyperlipidemia

Drug (*Brand name*)	**Dosage regimen**	**Cost per day**[23]
Atorvastatin (*Lipitor*)	10 mg daily	$1.60
Fluvastatin (*Lescol*)	20 mg daily	$0.75
Lovastatin (*Mevacor*)	20 mg daily	$1.73
Pravastatin (*Pravachol*)	10 mg daily	$1.51
Simvastatin (*Zocor*)	10 mg daily	$1.80

NB: Drug cost based on publicly available prices in the Ontario and/or Québec formulary.

[23] This medication is administered on a chronic basis, therefore the cost per day was used as the basis for cost comparison with the comparators.

APPENDIX 3

QUESTIONNAIRE: PROVINCIAL THERAPEUTIC DRUG REVIEW PROCESS - CATEGORY 3

INTRODUCTION

The process by which drugs are reviewed for benefit status is similar across the provinces. The material in drug submissions is reviewed by experts, either internal or external. The reviewer prepares a summary of the submission, including comments or recommendations regarding the drug's therapeutic effectiveness in comparison to other drugs and therapies and its cost-effectiveness (Rosemary A. Bacovsky - *Drug Submission, Review and Approval Process for Provincial and Territorial Government Sponsored prescription Drug Plans in Canada*, 1997).

This questionnaire is concerned with how the provinces determine a: "drug's therapeutic effectiveness in comparison to other drugs and therapies and its cost-effectiveness". Please answer the following questions and please list, if possible, all provincial policies that deal with a particular question or if there is not a policy in place, how is a decision reached, (i.e., by committee):

1. If a drug has several indications, how do you define a drug's therapeutic use for comparison purposes?

2. How do you choose comparator drug product(s) to determine whether a new medicine is cost-effective?

3. Do you use one, more than one, or all comparable medicines to make this determination? Do you only choose comparator drug product(s) that are listed on the formulary to do so?

4. Do you always choose the lowest priced drug product(s) when establishing a set of comparators (i.e., do you always pick the generic)?

5. How do you establish the dosage regimens in order to compare drug products? Do you always use the same approach to determine dosage regimens?

6. **FOR DISCUSSION**: *[Please provide a document explaining the comparators you used / would have used to assess the drug products Lipitor and Fosamax in deciding whether to list such drugs on your formulary]*