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Post-market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drugs approved in shorter periods of time are more likely to have post-market safety problems.
- Drugs approved with limited efficacy and safety data by the Food and Drug Administration and the European Medicines Agency are no more likely to have post-market safety problems than drugs approved through a standard review process.

WHAT THIS STUDY ADDS

- In Canada drugs approved with limited safety and efficacy data are more likely to receive a serious safety warning compared with drugs approved through a standard review process.
- The increased risk of receiving a safety warning may be because these drugs spend less time in the review process and because less safety data are available when they are reviewed.

AIMS

Health Canada has developed a pathway to approve drugs that have limited efficacy and safety data, the Notice of Compliance with conditions (NOC/c) policy. Increased safety reporting is required for these drugs but there has not been any systematic review of their post-market safety. This study compares safety warnings for NOC/c drugs with drugs with a priority and a standard review.

METHODS

A list of drugs approved between January 1 1998 and March 31 2013 was developed and serious safety warnings for these drugs were identified. Drugs were put into one of three groups based on the way that they were approved. Kaplan–Meier curves were generated to examine the likelihood of NOC/c drugs receiving a serious safety warning compared with drugs with a priority and a standard review. The time spent in the review process for each of the groups was also measured.

RESULTS

Compared with drugs with a priority review, NOC/c drugs were not more likely to receive a serious safety warning ($P = 0.5940$) but were more likely than drugs with a standard review ($P = 0.0113$). NOC/c drugs spent less time in the review process compared with drugs with a standard review.

CONCLUSIONS

Possible reasons for the increase likelihood of a serious safety warning are the limited knowledge of the safety of NOC/c drugs when they are approved and the length of time that they spend in the review process. Health Canada should consider spending longer reviewing these drugs and monitor their post-market safety more closely.

Introduction

The usual pathway to get a new active substance (NAS – a molecule never marketed before in Canada in any form) approved for marketing in Canada is for the pharmaceutical company involved to file a New Drug Submission (NDS) including preclinical and clinical scientific information about the product's safety, efficacy and quality and information about its claimed therapeutic value, conditions for use and side effects [1]. The key clinical evidence establishing the safety and efficacy of the new drug comes from the pivotal trials that Health Canada defines 'as trials of high scientific quality, which provide the basic evidence to determine the efficacy, properties and conditions of use of the drug' [2]. Health Canada then has up to 300 days to review the NDS and make a decision about whether or not to approve the drug or in the parlance of the agency issue a Notice of Compliance (NOC).

In an effort to ensure that promising therapies for serious illnesses can reach Canadians in a timely manner Health Canada has developed two other pathways for approving NAS. The first of these is the priority review of drug submissions intended 'for a serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness that the drug provides ... effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada or ... a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada' [3]. The company seeking approval still has to submit a complete NDS but the review period is reduced to 180 days.

The second mechanism is the Notice of Compliance with conditions (NOC/c). The goal of this policy is to 'provide patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs' where surrogate markers suggest that these new products offer 'effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada or significantly improved efficacy or significantly diminished risk over existing therapies' [4]. (In the case of cancer a surrogate outcome might be a shrinkage in tumour size or a longer time until the cancer recurs.) Besides data based only on trials with surrogate markers, other instances where a NOC/c might be used are for NAS with phase II trials that require confirmation with phase III trials or NAS with a single small to moderately sized phase III trial that requires confirmation of either the efficacy or safety of the agent under question [5]. In return for NOC/c status, companies sign a Letter of Undertaking to complete confirmatory clinical studies, that is studies that definitively establish efficacy, and submit the results of these to Health Canada. Should these post-market trials not provide sufficient evidence of clinical benefit the NOC/c could be revoked and the product removed from the market [6]. If companies apply for NOC/c status when they file the NDS and Health Canada agrees to the NOC/c application then drugs are reviewed in 200 days. If companies do not initially apply for NOC/c status then drugs are reviewed in either 180 or 300 days and Health Canada may grant NOC/c status at the end of the review.

Previous work has found that a NAS that receives a priority review (180 days) has a 34.2% (95% CI 24.3, 44.2) chance of acquiring a serious safety warning and/or being withdrawn compared with a 19.8% (95% CI 14.8, 24.8) chance if it is reviewed in 300 days ($P < 0.0005$) [7]. This difference was not attributable to the mechanism of action of the drug or due to the indication for the drug, leading to the conclusion that the reason was the shorter review period.

Health Canada acknowledges that safety information about drugs approved under the NOC/c policy may be limited as more safety reporting for these products is generally required in the form of patient registries, or Periodic Safety Update Reports [8]. To date there has not been any review of the post-market safety of this group of drugs. The purpose of this study is to examine the chance that a drug approved under this policy will receive a serious safety warning or be withdrawn from the market and to compare NOC/c drugs with those that received a priority review and those that received a standard review. The *a priori* null hypothesis is that despite the limited amount of safety information available for NOC/c drugs their chance of receiving a serious safety warning or being withdrawn from the market will be the same compared with the other two groups of drugs.

Methods

A list of NAS approved from the start of the policy on January 1 1998 until March 31 2013 was compiled from the annual reports of the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD) (henceforth collectively referred to as the TPD), available by directly contacting the directorates at <publications@hc-sc.gc.ca>. For each product the following information was abstracted: generic name, brand name, indication, date of application for a NOC or NOC/c, date of NOC and basis for approval – standard or priority review or NOC/c. Health Canada can issue a NOC/c for either a NAS or for a new indication for an existing product. For the purpose of this study only NAS were analyzed because there will be more known about the safety of drugs that are already on the market and then receive a NOC/c for a new indication. If a NAS received a NOC/c for more than one indication only the first indication was used.

Safety warnings and drug withdrawals for the period January 1 1998 to December 31 2013 were identified through advisories for health professionals on the MedEffect Canada web site <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>. For each safety advisory or notice of withdrawal of a product, the date and reason were recorded. All serious safety advisories (those using bolded black print or boxed warnings) were included except for those dealing with the withdrawal of a specific batch or lot number due to manufacturing problems or those issued because of misuse of a drug (e.g. an unapproved use) or medication errors (e.g. a warning about remembering to remove a transdermal patch before applying a second one).

Since there may be a trade off between a significant increase in therapeutic value and safety, the therapeutic value of NOC/c drugs was assessed using the ratings from the Patented Medicine Prices Review Board (PMPRB) and the French drug bulletin Prescrire International. Both of these organizations evaluate drugs once they have been approved for marketing. The PMPRB is a federal agency that is responsible for calculating the maximum introductory price for all new patented medications introduced into the Canadian market. As part of the process of determining the price, its Human Drug Advisory Panel (HDAP) determines the therapeutic value of each product it reviews [9]. For the purpose of this study, products that were deemed breakthrough and substantial improvement were termed 'significant therapeutic advance' and products in other groups were termed 'no therapeutic advance'. In some cases the PMPRB annual reports indicated that the therapeutic value of the product was still being determined and in those cases the PMPRB was contacted directly to determine the final classification.

If the PMPRB had not considered a product then its therapeutic value was determined from Prescrire evaluations (available at: http://english.prescrire.org/en/). Prescrire rates products using the following categories: bravo (major therapeutic innovation in an area where previously no treatment was available), a real advance (important therapeutic innovation but has limitations), offers an advantage (some value but does not fundamentally change the present therapeutic practice), possibly helpful (minimal additional value and should not change prescribing habits except in rare circumstances), nothing new (may be new molecule but is superfluous because does not add to clinical possibilities offered by previously available products), not acceptable (without evident benefit but with potential or real disadvantages) and judgment reserved (decision postponed until better data and more thorough evaluation). The first three Prescrire categories were defined as a significant therapeutic advance and the other Prescrire categories (except judgment reserved) were defined as no therapeutic advance. Previous work has shown a moderate level of agreement between the therapeutic evaluations from the PMPRB and Prescrire [10].

Kaplan–Meier survival curves were separately calculated for the period from receipt of NOC or NOC/c until a first safety warning for the following comparisons: a) drugs approved with a NOC/c *vs*. approval through a priority review and b) drugs approved with a NOC/c *vs*. approval through a standard review and the curves were compared using a log rank (Mantel–Cox) test. A Kaplan–Meier analysis accounts for the fact that some NAS had received a safety warning and some had not by the end of the study period (March 31 2013). The times between the application for a NOC or NOC/c and receipt of one and the time between receipt of a NOC or NOC/c and a safety warning and/or withdrawal from the market were calculated in days. If a drug received more than one serious safety warning only the time to the first warning was used. Medians are reported for both time periods as these values are not normally distributed (Shapiro–Wilk test) and were compared using the Mann–Whitney test. Values of $P < 0.05$ were considered significant. There were no power calculations as the entire population of NAS was evaluated rather than just a sample. Calculations were done using Excel 2011 for Macintosh (Microsoft) and Prism 6.0 (GraphPad Software).

Results

There were a total of 378 NAS approved in the period under study. Twenty-seven received a NOC/c, 86 had a priority review and 265 a standard review (see Appendix 1 for a complete list of the drugs and their review status). Eleven of the 27 (40.7%, 95% CI 28.9, 52.8) with a NOC/c received a safety warning only (9) or were withdrawn because of safety concerns (2). The corresponding numbers for drugs with a priority and standard review were 24 (23 with safety warnings only and one withdrawn) (27.9%, 95% CI 18.9, 36.9) and 50 (38 with safety warnings only and 12 withdrawn) (18.9%, 95% CI 12.9, 24.9), respectively (Table 1).

Figure 1 shows the Kaplan–Meier curves for the time from approval to the first serious safety warning and/or removal from the market for drugs with an approval through a NOC/c *vs*. those approved after a priority review. The curves indicate the proportion that did not have a safety warning. There is no statistically significant difference in the curves for the two groups of products ($P = 0.5940$, log rank (Mantel–Cox) test). Figure 2 presents the same information for drugs approved through a NOC/c *vs*. those approved after a standard review. In this case there is a statistically significant difference between the two curves ($P = 0.0113$, log rank (Mantel–Cox) test).

The date on which an application for a NOC or NOC/c was filed was only available for drugs approved from January 1 2005 onwards. The median time from application for a NOC or NOC/c to approval was 332 days (interquartile range 274–480) for drugs with a NOC/c, 228

Table 1

Drugs approved through Notice of Compliance with conditions *vs*. those approved through a priority and standard review

	NOC/c*	Approval based on Priority review	Standard review
Total number NAS†	27	86	265
Number (%) with serious safety warning and/or withdrawn from market for safety reason	11 (40.7)	24 (27.9)	50 (18.9)
Number withdrawn from market with prior safety warning	0	1	6
Number withdrawn from market without prior safety warning	2	0	6
Median time (interquartile range) from application for NOC§ or NOC/c to approval (days)	332 (274, 480)	235 (212, 487)¶	398 (349, 618)**
Median time (interquartile range) from NOC or NOC/c to first serious safety warning or withdrawal from market (days)	1614 (858, 1704)	944 (536, 1429)††	1159 (637, 1583)‡‡

*NOC/c = Notice of compliance with conditions. †NAS = New active substance. §NOC = Notice of compliance. ¶Compared with NOC/c, Mann–Whitney, $P = 0.0757$. **Compared with NOC/c, Mann–Whitney, $P = 0.0124$. ††Compared with NOC/c, Mann–Whitney, $P = 0.1265$. ‡‡Compared with NOC/c, Mann–Whitney, $P = 0.2486$.

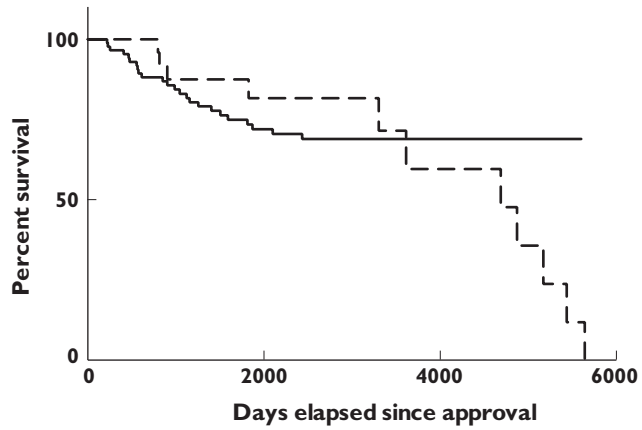

Figure 1

Kaplan–Meier curve showing time to first serious safety warning or removal from market for new active substances: approval through NOC/c *vs*. priority review. – –, NOC/c; ——, priority review. No significant difference between curves, $P = 0.5940$, log rank (Mantel–Cox) test

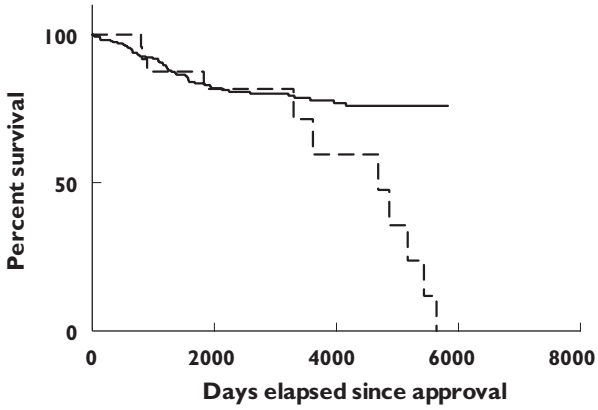

Figure 2

Kaplan–Meier curve showing time to first serious safety warning or removal from market for new active substances: approval through NOC/c *vs*. standard review. – –, NOC/c; ——, standard review. Curves significantly different, $P = 0.0113$, log rank (Mantel–Cox) test

days (interquartile range 213–484) for those with a priority review and 398 days (interquartile range 349–618) for those with a standard review. There was no significant difference in review times between drugs with a NOC/c and those with a priority review (Mann–Whitney, $P = 0.0757$) but there was for the comparison of drugs with a NOC/c and those with a standard review (Mann–Whitney, $P = 0.0124$) (Table 1).

The time from receipt of a NOC or NOC/c to when Health Canada issued a first safety warning for the product or the product was removed from the market was 1614 days (interquartile range 858–1704) for drugs with a NOC/c, 944 days (interquartile range 536–1429) for those with a priority review and 1159 (637–1583) for those with a standard review. There was no significant difference in time to a safety warning between drugs with a NOC/c and those with a priority review (Mann–Whitney, $P = 0.1265$) or those with a standard review (Mann–Whitney, $P = 0.2486$).

Ten of the 27 NOC/c drugs were for cancer, six for HIV/AIDS, three for various haematological disorders and one each for acute graft *vs*. host disease, Alzheimer disease, amyotrophic lateral sclerosis, congestive heart failure, cystic fibrosis, Fabry disease, Friedreich's ataxia and influenza. The PMPRB evaluated the therapeutic value of 24 out of 27 of the drugs with a NOC/c and rated 19 as no therapeutic advance. One of the remaining three was rated as no therapeutic advance by Prescrire and neither organization assessed the other two (see Appendix 2 for a list of the indications and therapeutic evaluations of the drugs).

Discussion

Compared with drugs approved after a standard review, drugs approved through a NOC/c were significantly more

likely to receive a serious safety warning and/or be removed from the market, whereas post-market safety as measured by receipt of a safety warning and/or removal from the market was the same for NOC/c drugs and those with a priority review. Therefore, the null hypothesis is rejected when it comes to the former comparison but not the latter. The greater likelihood of safety problems for NOC/c drugs may be due to two factors – the limited amount of safety data when they are approved and their shorter review time. An examination of drugs approved through a similar pathway, the accelerated approval process, used by the United States Food and Drug Administration (FDA), has found that the median number of patients in the intervention group is only half the number in the intervention group for drugs that had a standard review [11]. This statistically significant smaller number of patients could account for the relative paucity of safety information. The findings from this study also raise the question of whether Health Canada is adequately monitoring the safety of NOC/c drugs once they are marketed.

Given that 20 out of 25 NOC/c drugs were not rated as significant therapeutic advances, the increased safety risk with these drugs does not appear to be balanced by greater therapeutic value. The finding that there is no difference in the time taken to identify a safety issue for NOC/c drugs and those with a standard review can be seen as troubling as safety problems in drugs with a greater risk are not being identified earlier in their post-market phase.

The FDA accelerated approval process allows a drug for serious conditions that fills an unmet medical need to be approved based on a surrogate end point. As with the NOC/c policy, companies are required to conduct post-market studies to verify the clinical benefit [12]. The safety of oncology drugs approved under the accelerated approval process has been evaluated in two studies. Berlin looked at how often label revisions were made for oncology products approved between the start of 1992 and the end of 2006 under both accelerated approval and the standard approval process. The rate of revisions for accelerated products was approximately two times that of traditional products [13]. Richey and colleagues reviewed drugs approved through accelerated approval and the regular approval pathway between 1995 and 2008 and found no difference in safety between the two groups [14]. The difference between these two studies may be because Berlin looked at all labelling changes including those about efficacy [13]. The difference between this study and the two American ones may be because they focused only on oncology products whereas drugs for cancer were only 37% (10/27) of the NOC/c drugs. It is also possible that the FDA does a better job of identifying safety issues in drugs that enter the accelerated approval pathway.

The European Medicines Agency (EMA) has also adopted two pathways to get drugs through the approval system more rapidly, conditional approval (CA) and approval under exceptional circumstances (EC). The former is similar to the NOC/c policy whereby drugs are approved based on less comprehensive data than that required for standard applications but show a demonstrated positive benefit–risk balance and there is an expectation of more data in the near future via post-market studies [15]. Approval under exceptional circumstances is granted where the 'indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information' [16]. Two studies have compared drugs approved under a combination of the CA and EC procedures with those approved under the standard procedure and neither found an increased risk of safety problems with the CA and EC drugs [17, 18]. The difference between this study and the European ones may be that the EC drugs are used so rarely that safety problems are harder to detect. Also the EMA might do a better job of detecting safety issues in the premarket phase.

This study has a number of limitations. The definition of a serious safety warning was based on the way that Health Canada displayed the information (bolded black print and/or boxed text) but the criteria that Health Canada used to develop its safety warnings and the emphasis that it placed on any particular safety issue are extremely vague. One Health Canada document states 'Regulatory actions . . . are taken according to the regulatory framework in place. This implies an evaluation of the signal and the appropriate benefit–risk review of the information available' [19]. The date on which a NAS receives a NOC is not necessarily the date on which the company actually decides to market the drug and therefore the length of time the drug is available before it receives a safety warning may be shorter than what is reported here. The time NAS spent in the approval process could only be calculated for drugs approved after January 1 2005. It wa not possible to determine whether there were differences in the number of people who were potentially harmed by the safety problems that triggered the safety warnings for the various drugs. Similarly, all safety warnings were treated as equivalent regardless of the possible number of people affected or potentially affected or the nature of the safety issue. It is also important to note that the regulatory decision to issue a safety warning should not be equated with the actual degree of harm caused by the drug. Finally, there is the question of whether the assessment of therapeutic advance from the HDAP and Prescrire is more likely to be accurate compared with the assessment that Health Canada makes. However, Health Canada makes its decision based solely on the premarket clinical trials whereas HDAP's (and

Prescrire's) decision is made after approval when more information about the product is available.

Drugs that can treat serious and previously untreatable diseases should be provided as soon as possible to patients but not at the expense of potentially harming them. Health Canada should reconsider the amount of safety data that it requires for drugs approved through the NOC/c process and closely monitor these drugs once they are marketed.

Competing Interests

I have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. In the previous 3 years I have been the chair of the board of Health Action International – Europe.

Appendix 1

All new active substances approved between January 1 1998 and March 31 2013 and review status

Generic name	Brand name	Review status (NOC/c, priority, standard)
Abacavir	Ziagen	NOC/c
Abatacept	Orencia	Priority
Abiraterone	Zytiga	Priority
Acamprosate	Campral	Standard
Adalimumab	Humira	Standard
Adefovir	Hepsera	Priority
Afluzosin	Xatral	Standard
Agalsidase alfa	Replagal	NOC/c
Agalsidase beta	Fabrazyme	Priority
Alatrofloxacin	Trovan (IV)	Standard
Alefacept	Amevive	Standard
Alemtuzumab	Mabcampath	Standard
Alglucosidase alfa	Myozyme	Priority
Aliskiren	Rasilez	Standard
Alitretinoin	Toctino	Standard
Alitretinoin	Panretin	Standard
Almotriptan	Axert	Standard
Ambrisentan	Volibris	Standard
Aminolevulinic acid	Levulan	Standard
Amlexanox	Apthera	Standard
Amprenavir	Agenerase	NOC/c
Anakinra	Kineret	Priority
Ancestim	Stemgen	Standard
Anidulafungin	Eraxis	Standard
Anti-thymocyte globulin	Thymoglobulin	Standard
Apixaban	Eliquis	Standard
Aprepitant	Emend	Standard
Argatroban	Argatroban	Priority
Aripiprazole	Abilify	Standard
Atazanavir	Reyataz	Priority
Atomoxetine	Strattera	Standard
Axitinib	Inlyta	Standard
Azacitidine	Vidaza	Priority
Azilsartan	Edarbi	Standard
Aztreonam for inhalation solution	Cayston	NOC/c
Basiliximab	Simulect	Priority
Becaplermin gel	Regranex	Standard
Belimumab	Benlysta	Standard
Bendamustine	Treanda	Standard
Besifloxacin	Besivance	Standard
Bevacizumab	Avastin	Priority
Bicistate	OncoScint	Standard
Bimatoprost	Lumigan	Standard
Bivalirudin	Angiomax	Standard
Boceprevir	Victrelis	Priority
Boceprevir, perinterferon alfa-2b, ribavirin	Victrelis Triple	Priority
Bortezomib	Velcade	NOC/c
Bosentan	Tracleer	Priority

Appendix 1

Continued

Generic name	Brand name	Review status (NOC/c, priority, standard)
Botulinum toxin type B	Myobloc	Standard
Brinzolamide	Azopt ophthalmic suspension	Standard
Bupropion	Wellbutrin SR	Standard
Cabazitaxel	Jevtana	Standard
Cabergoline	Dostinex	Standard
Canakinumab	Ilaris	Priority
Candesartan	Atacand	Standard
Capecitabine	Xeloda	Priority
Capsular polysaccharide	Synflorix	Standard
Caspofungin	Cancidas	Priority
Catridecacog	Tretten	Priority
Cefdinir	Omnicef	Standard
Ceftobiprole	Zeftera	Standard
Celecoxib	Celebrex	Priority
Cerivastatin	Baycol	Standard
Certolizumab pegol	Cimzia	Standard
Cetrorelix	Cetrotide	Standard
Cetuximab	Erbitux	Priority
Choriogonadotropin alfa	Ovidrel	Standard
Ciclesonide	Alvesco	Standard
Cidofovir	Vistide	Standard
Cinacalcet	Sensipar	Priority
Citalopram	Celexa	Standard
Clevidipine	Cleviprex	Standard
Clofarabine	Clolar	Standard
Clopidogrel	Plavix	Standard
Colesevelam	Lodalis	Standard
Collagenase clostridium histolyticum	Xiaflex	Standard
Crizotinib	Xalkori	NOC/c
Dabigatran	Pradax	Standard
Daclizumab	Zenaprax	Priority
Dadolinium (III)	Gadolite	Standard
Dalfopristin	Synercid	Standard
Daptomycin	Cubicin	Standard
Darbepoetin alpha	Aranesp	Standard
Darifenacin	Enablex	Standard
Darunavir	Prezista	Standard
Dasatinib	Sprycel	NOC/c
Deferasirox	Exjade	NOC/c
Degarelix	Firmagon	Standard
Delavirdine	Rescriptor	NOC/c
Denosumab	Prolia	Standard
Desloratadine	Aerius	Standard
Desvenlafaxine	Pristiq	Standard
Dexlansoprazole	Dexilant	Standard
Dexmedetomidine	Precedex	Standard
Dextromethylphenidate	Attenade	Standard
Dienogest	Visanne	Standard
Docosanol	Abreva	Standard
Doripenem	Doribax	Standard
Doxercalciferol	Hectorol	Standard
Doxycycline	Efracea	Standard
Dronedarone	Multaq	Priority
Drospirenone	Yasmin 21/28	Standard
Drotrecogin alfa	Xigris	Standard
Dulasteride	Avodart	Standard
Duloxetine	Cymbalta	Standard
Eculizumab	Soliris	Priority
Efalizumab	Raptiva	Standard
Efavirenz	Sustiva	Priority
Eflornithine	Vaniqa	Standard
Eletriptan	Relpax	Standard
Eltrombopag	Revolade	Standard
Elvitgravir, emtricitabine, tenofovir, cobicistat	Stribild	Standard
Emedastine	Emadine ophthalmic solution	Standard
Emtricitabine	Emtriva	Standard
Enfuvirtide	Fuzeon	Priority

Appendix 1

Continued

Generic name	Brand name	Review status (NOC/c, priority, standard)
Entacapone	Comtan	Standard
Entecavir	Baraclude	Priority
Eplerenone	Inspra	Standard
Eprosartan	Teveten	Standard
Eptifibade	Integrilin	Standard
Eribulin	Halaven	Standard
Erlotinib	Tarceva	Priority
Ertapenem	Invanz	Standard
Escitalopram	Cipralex	Standard
Esomeprazole	Nexium	Standard
Etanercept	Enbrel	Priority
Ethinyl estradiol/etonogestrel	Nuvaring	Standard
Etravirine	Intelence	Priority
Everolimus	Afinitor	Standard
Exemestane	Aromasin	Standard
Exenatide	Byetta	Standard
Ezetimibe	Ezetrol	Standard
Ezogabine	Potiga	Standard
F-Fluorodeoxyglucose	Cantrace	Priority
Fampridine	Fampyra	Standard
Febuxostat	Uloric	Standard
Ferumoxytol	Feraheme	Standard
Fesoterodine	Toviaz	Standard
Fidaxomicin	Dificid	Standard
Fingolimod	Gilenya	Standard
Fluticasone	Avamys	Standard
Fomepizole	Antizol	Priority
Fondaparinux	Arixtra	Priority
Fosamprenavir	Telzir	Standard
Fosaprepitant	Emend IV	Standard
Fosfomycin	Monurol	Standard
Frovatriptan	Frova	Standard
Fulvestrant	Faslodex	Standard
Gadobenate	Multihance	Standard
Gadobutrol	Gadovist	Standard
Gadofosveset	Vasovist	Standard
Gadoversetamide	Optimark	Standard
Gadoxetate	Primovist	Standard
Galantamine	Reminyl	Standard
Ganirelix	Orgalutran	Standard
Gatifloxacin	Tequin	Standard
Gefitinib	Iressa	NOC/c
Gemifloxacin	Factive	Standard
Glimepiride	Amaryl	Standard
Glucagon, rDNA origin	Glucagon	Standard
Golimumab	Simponi	Standard
Grepafloxacin	Raxar	Standard
Hetastarch	Hextend	Standard
Histrelin	Vantas	Standard
Human C1 esterase inhibitor	Berinert	Standard
Ibritumomab	Zevalin	Priority
Ibutilide	Corvert injection	Standard
Icodextrin	Extraneal	Standard
Idebenone	Catena	NOC/c
Idursulfase	Elaprase	Priority
Imatinib	Gleevec	NOC/c
Indacaterol	Onbrez breezhaler	Standard
Infliximab	Remicade	Standard
Infliximab	Remicade	Priority
Influenza vaccine	Flumist	Standard
Insulin detemir	Levemir	Standard
Insulin glulisine	Apidra	Standard
Interferon beta-1A	Rebif	Standard
Ioxilan	Oxilan	Standard
Ipilimumab	Yervoy	Standard
Irbesartan	Avapro	Standard
Iron	Venofer	Priority

Appendix 1

Continued

Generic name	Brand name	Review status (NOC/c, priority, standard)
Ivacaftor	Kalydeco	Priority
Japanese encephalitis vaccine	Ixiaro	Standard
Lacosamide	Vimpat	Standard
Lanreotide	Somatuline autogel	Standard
Lanthanum	Fosrenol	Standard
Lapatinib	Tykerb	Standard
Laronidase	Aldurazyme	Priority
Leflunomide	Arava	Standard
Lenalidomide	Revlimid	NOC/c
Levetiracetam	Keppra	Standard
Levobupivacaine	Chirocaine	Standard
Lexidronam	Quadramet	Standard
Linagliptin	Trajenta	Standard
Linezolid	Zyvoxam	Standard
Lipoprotein-ospA antigen recombinant	Lymerix	Priority
Liraglutide	Victoza - 1.2 mg pen-injector	Standard
Lisdexamfetamine	Vyvanse	Standard
Lopinavir/ritonavir	Kaletra	Priority
Loteprednol	Alrex	Standard
Lumiracoxib	Prexige	Standard
Lurasidone	Latuda	Standard
Lutropin Alfa	Luveris	Standard
Mangafodipir	Teslascan	Standard
Maraviroc	Celsentri	Priority
Melanoma theraccine	Melacine	Priority
Meloxicam	Mobic	Standard
Memantine	Ebixa	NOC/c
Meningococcal group C polysaccharide, tetanus toxoid	Neisvac-C	Priority
Meningococcal oligosaccharides conjugated	Menveo	Standard
Mequinol/tretinoin	Solage	Standard
Methacoline	Methacoline	Standard
Methoxy polyethylene glycol-epoetin beta	Mircera	Standard
Methyl aminolevulinate	Metvix	Standard
Methylnaltrexone	Relistor	Priority
Micafungin	Mycamine	Standard
Miglitol	Glyset	Standard
Miglustat	Zavesca	Priority
Mirtazapine	Remeron	Standard
Modafinil	Alertec	Standard
Montelukast	Singulair	Standard
Moroctocog alpha	Refacto	Priority
Moxifloxacin	Avelox	Standard
Naratriptan	Amerge	Standard
Natalizumab	Tysabri	Priority
Nateglinide	Starlix	Standard
Nebivolol	Bystolic	Standard
Nelarabine	Atriance	NOC/c
Nelfinavir	Viracept	Standard
Nepafenac	Nevanac	Standard
Nesiritide	Natrecor	NOC/c
Nevirapine	Viramune	NOC/c
Nilotinib	Tasigna	NOC/c
Nitric oxide	Inomax	Priority
Norelgestromin/ethinyl estradiol	Evra	Standard
Ofatumumab	Arzerra	Standard
Olmesartan	Olmetec	Standard
Omalizumab	Xolair	Standard
Orlistat	Xenical	Standard
Oseltamivir	Tamiflu	Priority
Oxaliplatin	Eloxatin	Priority
Oxcarbazepine	Trileptal	Standard
Palifermin	Kepivance	Priority
Paliperidone	Invega	Standard
Paliperidone	Invega sustenna	Standard
Palivizumab	Synagis	Standard
Palonosetron	Aloxi	Standard
Panitumumab	Vectibix	NOC/c

Appendix 1

Continued

Generic name	Brand name	Review status (NOC/c, priority, standard)
Pantoprazole	Pantaloc M	Standard
Paricalcitol	Zemplar	Standard
Pazopanib	Votrient	Standard
Pegaptanib	Macugen	Priority
Pegfilgrastim	Neulasta	Standard
Peginterferon alfa-2a	Pegasys	Standard
Peginterferon alfa-2a ribavirin	Pegasys RBV	Priority
Peginterferon alfa-2b	Peg-intron	Standard
Peginterferon alfa-2b ribavirin	Pegetron	Standard
Pegvisomant	Somavert	Priority
Pemetrexed	Alimta	Priority
Penciclovir	Denavir	Standard
Perindopril	Coversyl	Standard
Pimecrolimus	Elidel	Standard
Pioglitazone	Actos	Priority
Plerixafor	Mozobil	Standard
Pneumococcal conjugate	Prevnar	Priority
Posaconazole	Spriafil (Posanol)	Priority
Pramipexole	Mirapex	Standard
Prasugrel	Effient	Standard
Pregabalin	Lyrica	Standard
Prucalopride	Resotran	Standard
Rabeprazole	Pariet	Standard
Raloxifene	Evista	Standard
Raltegravir	Isentress	NOC/c
Ranibizumab	Lucentis	Priority
Rasagiline	Azilect	Standard
Rasburicase	Fasturtec	Priority
Recombinant cholera toxin B subunit	Dukoral	Priority
Recombinant factor VIIa	Niastase	NOC/c
Recombinant human papillomavirus	Cervarix	Standard
Recombinant human papillomavirus	Gardasil	Priority
Recombinant-methionyl interferon consensus 1	Infergen	Priority
Remestemcel-L	Prochymal	NOC/c
Repaglinide	Gluconorm	Standard
Retapamulin	Altargo	Standard
Rilpivirine	Edurant	Standard
Riluzole	Rilutek	NOC/c
Risedronate	Actonel	Standard
Rituximab	Rituxan	Priority
Rivaroxaban	Xarelto	Standard
Rivastigmine	Exelon patch 10	Standard
Rivastigmine	Exelon	Standard
Rizatriptan	Maxalt	Standard
Rofecoxib	Vioxx	Priority
Roflumilast	Daxas	Standard
Romiplostim	Nplate	Priority
Rosiglitazone	Avandia	Priority
Rosuvastatin	Crestor	Standard
Rotavirus vaccine	Rotarix	Standard
Rotaviruses	Rotateq	Standard
Rubidium chloride rb 82	Ruby-fill	Priority
Rufinamide	Banzel	Standard
Ruxolitinib	Jakavia	Priority
Sapropterin	Kuvan	Priority
Saxagliptin	Onglyza	Standard
Senapine	Saphris	Standard
Sevelamer	Renvela	Standard
Sevelamer	Renagel	Standard
Sibutramine	Meridia	Standard
Sildenafil	Viagra	Standard
Silodosin	Rapaflo	Standard
Sirolimus	Rapamune	Standard
Sitaglipin	Januvia	Standard
Sitaxsentan	Thelin	Standard
Sodium oxybate	Xyrem	Standard
Solifenacin	Vesicare	Standard

Appendix 1

Continued

Generic name	Brand name	Review status (NOC/c, priority, standard)
Sorafenib	Nexavar	NOC/c
Stiripentol	Diacomit	Standard
Sulesomab	Leukoscan	Standard
Sulfur hexafluoride	Sonovue	Standard
Sunitnib	Sutent	NOC/c
Tadalafil	Cialis	Standard
Tamsulosin	Flomax	Standard
Tapentadol	Nucynta CR	Standard
Tegafur/uracil and leucovorin calcium	Orzel	Standard
Tegaserod	Zelnorm	Standard
Telaprevir	Incivek	Priority
Telavancin	Vibativ	Standard
Telbivudine	Sebivo	Priority
Telithromycin	Ketek	Standard
Telmisartan	Micardis	Standard
Temozolomide	Temodal	Standard
Temsirolimus	Torisel	Priority
Tenecteplase	Tnkase	Standard
Tenofovir	Viread	NOC/c
Teriparatide	Forteo	Priority
Thrombin alfa	Recothrom	Standard
Thyrotrophin	Thyrogen	Standard
Ticagrelor	Brilinta	Priority
Tigecycline	Tygacil	Standard
Tiotropium	Spiriva	Standard
Tipranavir	Aptivus	Priority
Tirofiban	Aggrastat	Standard
Tizanidine	Zanaflex	Standard
Tocilizumab	Actemra	Standard
Tolterodine	Detrol	Standard
Tolvaptan	Samsca	Standard
Toremifene	Fareston	Standard
Tositumomab	Bexxar	Priority
Trabectedin	Yondelis	Standard
Tramadol	Tramacet	Standard
Trastuzumab	Herceptin	Priority
Travoprost	Travatan	Standard
Treprostinil	Remodulin	Priority
Triptorelin	Trelstar	Standard
Trospium	Trosec	Standard
Trovafloxacin	Trovan (tablets)	Standard
Unoprostone isopropyl	Rescula	Standard
Ustekinumab	Stelara	Standard
Valdecoxib	Bextra	Standard
Valganciclovir	Valcyte	Standard
Valrubicin	Valstar	Priority
Vandetanib	Caprelsa	Standard
Vardenafil	Levitra	Standard
Varenicline	Champix	Standard
Varicella vaccine	Varivax	Standard
Varicella zoster vaccine	Varilrix	Priority
Velaglucerase alfa	VPRIV	Standard
Vemurafenib	Zelboraf	Priority
Verteporfin	Visudyne	Priority
Voriconazole	Vfend	Standard
Vorinostat	Zolinza	Standard
Yttrium-90	Yttrium-90	Priority
Zaleplon	Starnoc	Standard
Zanamivir	Relenza	NOC/c
Zoledronic acid	Zometa	Priority
Zolmitriptan	Zomig	Standard
Zucapsaicin	Civanex (Zuacta)	Standard

Appendix 2

Drugs approved under Notice of Compliance with Conditions

Generic name	Brand name	Indication	Therapeutic evaluation	
			Patented medicine prices review board	Prescrire international
Abacavir	Ziagen	HIV/AIDS	Not innovative	
Agalsidase alfa	Replagal	Fabry disease	Not innovative	
Amprenavir	Agenerase	HIV/AIDS	Innovative	
Aztreonam for inhalation solution	Cayston	cystic fibrosis	Not innovative	
Bortezomib	Velcade	multiple myeloma	Not innovative	
Crizotinib	Xalkori	lung cancer		Not innovative
Dasatinib	Sprycel	chronic myeloid leukemia	Not evaluated	
Deferasirox	Exjade	thalassemia	Innovative	
Delavirdine	Rescriptor	HIV/AIDS	Not innovative	
Gefitinib	Iressa	lung cancer	Innovative	
Idebenone	Catena	Friedreich's ataxia	Not innovative	
Imatinib	Gleevec	gastrointestinal tumour	Not innovative	
Lenalidomide	Revlimid	anaemia due to myelodysplastic syndrome	Not innovative	
Memantine	Ebixa	Alzheimer disease	Not innovative	
Nelarabine	Atriance	leukemia	Not innovative	
Nesiritide	Natrecor	congestive heart failure	Not innovative	
Nevirapine	Viramune	HIV/AIDS	Not innovative	
Nilotinib	Tasigna	chronic myeloid leukemia	Not innovative	
Panitumumab	Vectibix	colorectal cancer	Not innovative	
Raltegravir	Isentress	HIV/AIDS	Innovative	
Recombinant factor VIIa	Niastase	clotting disorders	Not innovative	
Remestemcel-L	Prochymal	acute graft vs. host disease	Not evaluated	
Riluzole	Rilutek	amyotrophic lateral sclerosis	Not innovative	
Sorafenib	Nexavar	renal cancer	Not innovative	
Sunitnib	Sutent	renal cancer	Not innovative	
Tenofovir	Viread	HIV/AIDS	Not innovative	
Zanamivir	Relenza	influenza	Innovative	

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