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NPDUIS

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About the PMPRB

The Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial body established by Parliament in 1987.

The PMPRB has a dual role: to ensure that prices at which patentees sell their patented medicines in Canada are not excessive; and to report on pharmaceutical trends of all medicines and R&D spending by patentees.

The PMPRB reports annually to Parliament, through the Minister of Health, on its activities, on pharmaceutical trends relating to all medicines, and on R&D spending by patentees.

The NPDUIS Initiative

The National Prescription Drug Utilization Information System (NPDUIS) is a research initiative established by federal, provincial, and territorial Ministers of Health in September 2001. It is a partnership between the PMPRB and the Canadian Institute for Health Information (CIHI).

Its purpose is to provide policy makers and public drug plan managers with critical analyses of price, utilization and cost trends, so that Canada's health care system has more comprehensive and accurate information on how prescription drugs are being used and on sources of cost pressures.

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Disclaimer

NPDUIS is a research initiative that operates independently of the regulatory activities of the Board of the PMPRB. The statements and opinions expressed in this NPDUIS report do not represent the official position of the PMPRB.

Parts of this study are based on information obtained from the BioPharm Insight[®] database, published by ©Infinata. The analyses, conclusions and/or statements in this NPDUIS report do not represent the position of ©Infinata.

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Executive Summary

The *New Drug Pipeline Monitor* (NDPM) provides information on drugs currently under development that may have an impact on future drug expenditures in Canada. This annual publication contains a select list of pipeline drugs in Phase III clinical trials or under review by the US Food and Drug Administration (FDA) that demonstrate the potential to have a significant clinical impact. The BioPharm Insight® database is the main data source for drug selection.

This is the seventh edition of the NDPM. It updates the pipeline list reported in the December 2014 edition and identifies additional drugs for this list, as of October 2015. This edition includes a summary of the status of all of the drugs identified in previous editions of the NDPM, along with a review of Canadian and international sales and prices of drugs that have subsequently been granted market authorization in Canada.

Key Findings

This edition of the NDPM identifies 10 new pipeline drugs, 5 of which are biologics. Of the 27 pipeline drugs identified in previous editions:

- 16 are retained in this edition of the NDPM, as they continue to satisfy the criteria for drug selection, 4 of which are biologics;
- 3 were removed from the list after being granted market authorization by Health Canada;
- 2 were removed from the list following an updated scientific assessment; and
- 6 were removed from the list, as there is no information on current clinical trials in Canada.

The current pipeline list features a total of 26 drugs, 9 of which are biologics.

To date, a total of 71 new drugs have been selected in the seven NDPM reports published since 2007, 20 of which subsequently received market authorization granted by Health Canada. These include the following recent top-selling and/or high-priced Canadian launches: aflibercept (Eylea, Zaltrap); ipilimumab (Yervoy); plerixafor (Mozobil); ticagrelor (Brilinta); eculizumab (Soliris); raltegravir (Isentress); and rivaroxaban (Xarelto).

Results based on data contained in IMS AG's MIDAS™ database (All rights reserved) suggest that the sales for these drugs were higher in foreign markets than in Canada in Q4-2014. Factors that may explain this include: higher relative price levels (especially in the United States), earlier market launches and/or increased market uptake for the new drugs in foreign countries. The foreign markets analyzed are the seven that the Patented Medicine Prices Review Board considers in reviewing the prices of patented drug products (PMPRB7): France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States.

The NDPM is an annual publication, with the next edition planned for 2016. Future editions will continue to monitor the pipeline list and identify new drugs to be featured in the NDPM.

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Introduction

This is the seventh edition of the *New Drug Pipeline Monitor* (NDPM), an annual publication that provides information on drugs currently under development that may have an impact on future drug expenditures in Canada. Each report contains a list of pipeline drugs identified as part of a search of the BioPharm Insight[®] database¹; a specialized database that provides information on over 21,000 drugs in clinical trials. The search is supported by a review of recent scientific literature.

Only drugs that meet a set of selection criteria are candidates for the NDPM. The selection criteria were prepared by Sintera Inc. for the Patented Medicine Prices Review Board (PMPRB) and were approved by the NPDUIIS Advisory Committee in 2006. This standardized approach has been consistently applied to all editions of the NDPM. The criteria include: the phase of development, the indication, the mechanism of action and the impact on clinical practice. A decision-tree algorithm was developed to ensure a consistent application of the criteria. The selection of pipeline drugs includes a broad representation across therapeutic areas. In addition, consideration is given to high-cost drugs and classes where a new drug could have a financial impact on budgets, along with classes with a high utilization share of generic drugs.

As in previous reports, this edition of the NDPM updates the status of pipeline drugs identified in prior publications. Some drugs were removed from the list either because the manufacturer received authorization to market the drug in Canada or because a scientific assessment no longer supports their retention on the pipeline list. Similarly, drugs were retained if ongoing trials supported the initial assessment for inclusion on the pipeline list.

The report is organized into three sections. Following an overview of the methodology and process for drug selection, Section 1 identifies the new pipeline drugs added to this edition of the NDPM; Section 2 provides status updates of the pipeline drugs identified in previous editions; and Section 3 reviews the past and current pipeline drugs.

Drug Selection – Methodology and Process

The main source of information for the NDPM is the BioPharm Insight[®] database, which tracks drugs from pre-clinical discovery through clinical trials to market launch and subsequent sales. The database is a comprehensive resource of investigational drugs and may contain more than 21,000 drugs at any one time. The database search capabilities allow drugs to be selected under various fields, including phase of development, therapeutic area, indication, drug mechanism, orphan drug, fast track and molecule type.

Four main criteria are used for selecting drugs in the pipeline:

Phase of Development

Only drugs in Phase III clinical trials or under review by the US Food and Drug Administration (FDA) are considered as potential candidates for the NDPM. Drugs reaching this stage are more likely to proceed to regulatory approval and marketing in the near future in Canada. Drugs in earlier phases of development may not necessarily progress beyond these stages.

Indication and Therapeutic Area

Drugs are considered to be potential candidates if they could be used to treat life-threatening conditions, conditions with unmet needs or rare diseases, or if they could potentially change clinical practice in a therapeutic area.

Drug Description

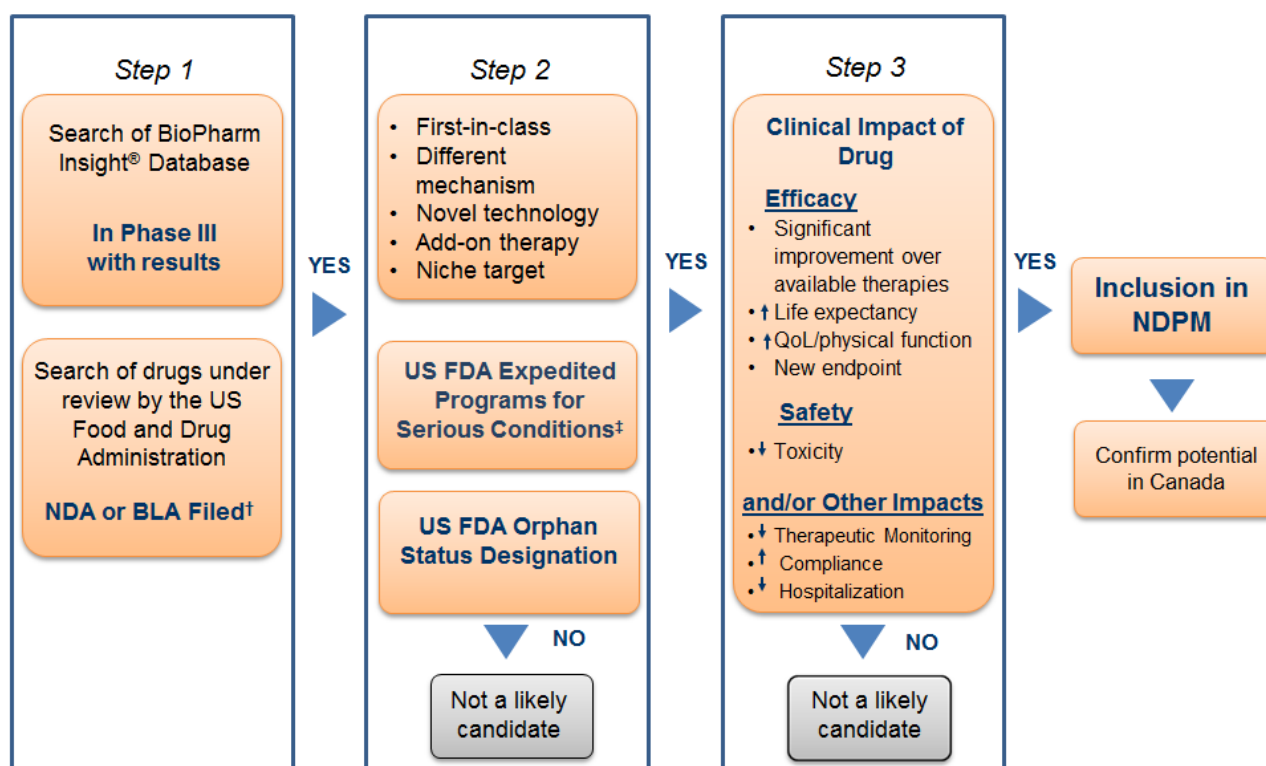
Drug description keywords that flag that a new drug could potentially change clinical practice include: first drug in a class, different mechanism of action, novel technology, add-on therapy, targeted niche, or an existing drug with a new indication.

Clinical and Other Impacts

Drugs must demonstrate the potential to have a significant clinical impact or a significant impact on other sectors of the health care system. Examples include: increased efficacy versus existing drugs; impacts on patient health, such as increased life expectancy or quality of life; new or redefined outcomes; or an improved safety profile.

An algorithm developed for selecting drugs is illustrated in Figure 1. The algorithm combines the search capabilities of the BioPharm Insight[®] database and the key criteria used to identify a potentially high-impact drug. Because the sources of information for this database are largely from the United States, additional sources are used to determine whether the new drugs are in development in Canada.

Figure 1. Algorithm for drug selection for the *New Drug Pipeline Monitor**



*Figure 1 is a modified version of the diagram presented in previous editions of the NDPM; it includes a search of drugs accepted in one or more US FDA expedited drug development programs for serious conditions.

† New Drug Application/Biologic License Application.

‡US FDA expedited drug development programs for serious conditions include: fast track designation, breakthrough therapy designation, accelerated approval pathway and priority review designation.

STEP 1

As a first step in identifying potential candidates for the NDPM, the BioPharm Insight® database is searched for drugs currently in Phase III clinical trials or under review by the FDA, with a New Drug Application (NDA) or Biologic License Application (BLA) filed. As Phase III trials may have just been initiated for some of the drugs, the search is further narrowed to focus solely on drugs with available Phase III results to allow for their scientific assessment.

Table 1 summarizes, by therapeutic area, the results of this first step in the search. The database profile for each of these drugs was reviewed, with particular attention given to the drug description field. Specific keywords were sought, such as first-in-class or different mechanism of action. If these keywords were identified, the next step was to determine the results, if any, of Phase III clinical trials. Under the development history field of the drug profile, details of the Phase III results were scanned to further validate drug characteristics, such as increased efficacy or safety. If this scan revealed a lack of effect or a safety issue, the drug was screened out.

Based on this selection process, a total of 1,037 drugs were identified in Phase III clinical trials, and 479 drugs were identified as currently under review by the US FDA. As reported in Table 1, these drugs cover a large spectrum of therapeutic areas.

**Table 1. Step 1 in the drug selection process:
Number of drugs in Phase III clinical trials or under review by the US Food and Drug Administration by therapeutic area**

Therapeutic area	In Phase III	NDA/BLA* filed
Cancer	229	37
Cardiovascular	82	28
Central nervous system	92	69
Dermatology	38	17
Eye and ear	41	15
Gastrointestinal	43	39
Genitourinary	32	24
Hematological	46	30
HIV infections	9	10
Hormonal system	79	33
Immune system	80	37
Infectious diseases	101	66
Musculoskeletal	59	12
Nephrology	14	5
Pain	57	37
Respiratory	35	20
Total†	1,037	479

* New Drug Application/Biologic License Application.
† The total reported for Phase III trials or NDA/BLA filed is not necessarily the sum of the number of drugs in each therapeutic class, as some drugs may belong to multiple therapeutic classes.
Source: BioPharm Insight®. Note that the database search for the new drugs added to the NDPM was completed as of June 17, 2015.

STEP 2

For the second step, drugs in Phase III clinical trials are screened by therapeutic area and indication. Drugs are considered as potential candidates for the NDPM if they have been accepted by the FDA in one or more of the four FDA expedited drug development programs for serious conditions: fast track designation, breakthrough therapy designation, accelerated approval and priority review designation. The FDA expedited drug development programs are intended to facilitate and expedite development and review of new drugs to address an unmet medical need in the treatment of a serious condition, including a life-threatening condition. In addition, drugs intended for the treatment of rare diseases and granted an orphan designation by the FDA are also considered as potential candidates for the NDPM.

For Phase III drugs that are neither in any of the FDA expedited drug development programs nor designated as orphan drugs, the drug profiles are searched for keywords relating to specific drug descriptions, such as first-in-class, different mechanism of action, novel technology, add-on therapy, targeted niche or existing drugs with a new indication. If the drugs have these key descriptors, Phase III results are scanned to further validate the drug characteristics identified in the profile, such as a significantly increased efficacy or increased safety.

Table 2 reports the drugs from Table 1 that were screened in as part of the second step in the selection process. Biologics are identified separately, as they tend to be high-cost drugs with the potential to impact drug expenditures. Of the 160 drugs screened in, 29 were biologics. In most therapeutic areas, one or more biologics were identified, with the greatest number selected for respiratory system (6) and central nervous system diseases (5). Similarly, for the therapeutic area of cancer, as well as cardiovascular diseases, 4 biologics in Phase III clinical trials or with a NDA/BLA filed were retained in this second step.

**Table 2. Step 2 in the drug selection process:
Number of drugs by therapeutic area, pharmaceutical and biologic**

Therapeutic area	In Phase III		NDA/BLA* filed	
	Pharmaceutical	Biologic	Pharmaceutical	Biologic
Cancer	—	3	3	1
Cardiovascular	27	3	5	1
Central nervous system	29	5	16	0
Dermatology	2	1	2	1
Eye and ear	15	2	4	0
Gastrointestinal	—	—	6	—
Genitourinary	—	—	1	—
Hematological	—	—	—	3
HIV infections	—	—	2	—
Hormonal system	—	—	6	2
Immune system	—	—	5	—
Infectious diseases	—	—	1	—
Musculoskeletal	—	1	1	—
Nephrology	—	—	—	—
Pain	—	—	2	—
Respiratory	2	3	2	3
Total	75	18	56	11
Total	160			

** New Drug Application/Biologic License Application.*
Source: BioPharm Insight®. Note that the database search for the new drugs added to the NDPM was completed as of June 17, 2015.

STEP 3

In the third step, the clinical impact of each drug is considered. Canadian sources are consulted to determine whether there is information on any Canadian development. This is followed by a scientific assessment of the identified drugs. If the preliminary Phase III results suggest a positive efficacy/safety impact, the drugs are then considered for inclusion in the NDPM.

The list of drugs reported in Table 2 was further narrowed by checking all drugs against Health Canada's Clinical Trials Database and the US National Institutes of Health (NIH) clinical trials registry to determine whether there was information on ongoing clinical trials in Canada. In previous editions of the NDPM, the primary source of information was the journal *Pharmacy Practice*, which no longer prepares a list of investigational drugs in Canada. To assess pipeline candidates that could be available in Canada, clinical trial sites information in the BioPharm Insight[®] database was consulted. In addition, the database of clinical trials in Canada, published on the Health Canada's website², was used as a source for information on current clinical trials in Canada. Since Health Canada's Clinical Trials Database lists trials that were authorized by Health Canada starting on April 1, 2013, before excluding a candidate, the clinical trials registry maintained by the NIH³ was also consulted to confirm whether Canada was listed as an investigating site.

The next step was a scientific assessment of this preliminary list. For this assessment, details of the Phase III results from the BioPharm Insight[®] drug profiles were reviewed, specifically looking for significant improvements in efficacy and safety outcomes. In addition, the MEDLINE[®] database was searched to determine how the drug was viewed in the published literature.

The final screening ensured that drugs from a diverse set of therapeutic classes were included in the pipeline list. New drugs entering a class with high utilization (e.g., cardiovascular) or costly drugs (e.g., cancer) are more likely to be featured in the NDPM, as these have the potential to impact drug expenditures. The same logic can be applied to drugs entering a therapeutic area with a high utilization of generic drugs.

1. New Drugs Added to the NDPM

Based on the drug selection process described in the previous section, 10 drugs were added to this edition of the NDPM, 5 of which are biologics. Table 3 lists these drugs, clearly identifies the ones that are biologics and provides information pertaining to the drug's trade name, company, therapeutic area and rationale for inclusion in the NDPM.

Table 3. Drugs added to the *New Drug Pipeline Monitor*

Drug (Trade name)* Company†	Therapeutic area (ATC‡) Indication	Rationale for inclusion in the NDPM
Cancer		
Blinatumomab (Blinicyto) Amgen Astellas BioPharma K.K.; Amgen, Inc.; Astellas Pharma Inc.; Lonza Group Ltd.; MedImmune, LLC	Cancer (L01) Leukemia <i>Biologic</i>	<ul style="list-style-type: none"> Received orphan drug designation and breakthrough therapy designation for acute lymphoblastic leukemia (ALL) and was granted accelerated approval by the FDA in December, 2014. A first-in-class bispecific T-cell engager (BiTE) antibody that may have the potential to selectively direct and activate the human immune system to act against cancer cells. In Phase III studies in Canada for ALL.⁴ Has demonstrated a favourable safety profile and promising results.⁵ Administered intravenously.
Nivolumab [§] (Opdivo) Bristol-Myers Squibb; Celgene Corporation; Celldex Therapeutics; Kyowa Hakko Kirin Pharma, Inc.; Novartis AG; Ono Pharmaceutical Co., Ltd.	Cancer (L01) Melanoma <i>Biologic</i>	<ul style="list-style-type: none"> Received orphan drug designation and breakthrough therapy designation for melanoma and was granted accelerated approval by the FDA in December 2014; in March 2015, the FDA approved its use for squamous non-small cell lung cancer (NSCLC). A programmed death-1 (PD-1) immune checkpoint inhibitor. In Phase III studies in Canada for various cancers, including melanoma.⁶ "Nivolumab led to a greater proportion of patients achieving an objective response and fewer toxic effects than with alternative available chemotherapy regimens for patients with advanced melanoma that has progressed after ipilimumab or ipilimumab and a BRAF inhibitor. Nivolumab represents a new treatment option with clinically meaningful durable objective responses in a population of high unmet need."⁷ Administered intravenously.
Olaparib (Lynparza) AstraZeneca PLC	Cancer (L01) Ovarian cancer	<ul style="list-style-type: none"> Received accelerated approval by the FDA in December 2014.⁸ A poly (ADP-ribose) polymerase (PARP) inhibitor and the first drug in its class approved in the US as a monotherapy for patients with gBRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.⁹ The FDA also approved a test called BRACAnalysis CDx specifically to identify women who may be candidates for treatment with Lynparza.

Drug (Trade name)* Company†	Therapeutic area (ATC‡) Indication	Rationale for inclusion in the NDPM
		<ul style="list-style-type: none"> The first 'personalized' therapy for patients with BRCA mutation-positive ovarian cancer.¹⁰ In Phase III studies in Canada for breast cancer¹¹, ovarian cancer^{12,13,14}, pancreatic cancer¹⁵ and prostate cancer.¹⁶ "Lynparza is an example of how a greater understanding of the underlying mechanisms of disease can lead to targeted, more personalized treatment."¹⁷ Administered orally.
Palbociclib (Ibrance) Onyx Pharmaceuticals, Inc.; Pfizer, Inc.	Cancer (L01) Breast cancer	<ul style="list-style-type: none"> Received FDA breakthrough therapy designation in April 2013, priority review designation in October 2014, and was granted FDA accelerated approval in February 2015. Selective inhibitor of cyclin-dependent kinase 4/6 (CDK4/6). Add-on drug: for use with letrozole (aromatase inhibitor). In Phase III studies in Canada for breast cancer.¹⁸ When palbociclib was combined with letrozole, patients experienced a significantly longer progression-free survival period (20.2 months.) vs. patients who received letrozole alone (10.2 months).¹⁹ Administered orally.
Cardiovascular		
Alirocumab (Praluent) Regeneron Pharmaceuticals, Inc.; Sanofi	Cardiovascular Hypercholesterolemia <i>Biologic</i>	<ul style="list-style-type: none"> Accepted for a priority review by FDA and approved in July 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low-density lipoprotein cholesterol (LDL-C). Ongoing trials, with results expected in 2017, are assessing cardiovascular outcomes and will provide a robust assessment of its long-term safety and efficacy profile. First-in-class of monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) and have a significant role in the regulation of LDL-C. In clinical studies in Canada.²⁰ Adding alirocumab to atorvastatin provided significantly greater low-density lipoprotein cholesterol (LDL-C) reductions vs. adding ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin, and enabled greater LDL-C goal achievement.^{21,22} Administered subcutaneously.
Central nervous system		
Valbenazine (NBI-98854) Mitsubishi Tanabe Pharma Corporation; Neurocrine Biosciences, Inc.	Central nervous system Tardive dyskinesia	<ul style="list-style-type: none"> Received breakthrough therapy designation by FDA in October 2014.²³ Highly-selective, vesicular monoamine transporter 2 (VMAT2) inhibitor that modulates dopamine release. In Phase III studies in Canada for tardive dyskinesia.²⁴

Drug (Trade name)* Company†	Therapeutic area (ATC‡) Indication	Rationale for inclusion in the NDPM
		<ul style="list-style-type: none"> • “The profound response in this Kinect 2 study demonstrates the potential of NBI-98854 as both a safe and highly effective treatment for patients suffering from tardive dyskinesia.”²⁵ • Administered orally.
Hematological		
Idarucizumab (Praxbind) Boehringer Ingelheim GmbH	Hematological, Various (V03) Coagulant <i>Biologic</i>	<ul style="list-style-type: none"> • Received breakthrough therapy designation by FDA in June 2014 and was granted accelerated approval in October 2015²⁶; filed with European Medicines Agency (EMA) and Health Canada.²⁷ • Humanized antibody fragment for use as a specific antidote for the anticoagulant effect of dabigatran. • In Phase III studies in Canada for uncontrolled bleeding.²⁸ • Administered intravenously.
Infections		
Solithromycin Cempra Pharmaceuticals, Inc.; Merck & Co., Inc.; Toyama Chemical Company Co. Ltd.	Infectious diseases Community-acquired pneumonia	<ul style="list-style-type: none"> • Filing with FDA expected mid-2016 for community-acquired bacterial pneumonia.²⁹ • A next-generation macrolide and first fluoroketolide with high potency against Gram-positive and Gram-negative bacteria commonly associated with community-acquired respiratory tract infections and skin and skin structure infections. • In Phase III studies in Canada for pneumonia.³⁰ • Shows a profile of activity similar to that of telithromycin, but <i>in vitro</i> data suggest a lower risk of hepatotoxicity, visual disturbance, and aggravation of myasthenia gravis due to reduced affinity for nicotinic receptors.³¹ • Administered orally and intravenously.
Respiratory		
Mepolizumab (Nucala) GlaxoSmithKline	Respiratory, Immune system (L04) Asthma <i>Biologic</i>	<ul style="list-style-type: none"> • Approved by FDA in November 2015 for add-on maintenance treatment of severe eosinophilic asthma. • A humanized monoclonal antibody that blocks interleukin-5 and reduces inflammatory mediators-producing white blood cell accumulation in the lungs. • In clinical studies in Canada for asthma.³² • A potentially important and well tolerated therapy in carefully selected populations of patients with asthma.³³ • Clinically significant reductions of asthma exacerbations with improvements in markers of asthma control.³⁴ • Administered subcutaneously and intravenously.

Drug (Trade name)* Company†	Therapeutic area (ATC‡) Indication	Rationale for inclusion in the NDPM
Miscellaneous		
Lumacaftor/ivacaftor combination (Orkambi) Vertex Pharmaceuticals, Inc.	Genetic diseases, Respiratory (R07) Cystic fibrosis (CF)	<ul style="list-style-type: none"> Received breakthrough therapy designation and orphan drug designation by FDA; approved by FDA in July 2015; has been submitted for approval by Health Canada.³⁵ Lumacaftor is a CF transmembrane conductance regulator (CFTR) corrector, designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the F508del CFTR. Ivacaftor is a CFTR potentiator (approved in Canada in 2012 as Kalydeco) designed to enhance the function of the CFTR protein once it reaches the cell surface. The first medicine designed to treat the underlying cause of cystic fibrosis in people who are homozygous for the F508del mutation in the CFTR gene (i.e., with two copies of the F508del mutation in the CFTR gene), the most common form of the disease. In Phase III studies in Canada for cystic fibrosis.³⁶ The rate of pulmonary exacerbations was 30–39% lower in combination groups than in the placebo group; the rate of events leading to hospitalization or the use of intravenous antibiotics was lower in the lumacaftor–ivacaftor groups as well.³⁷ Administered orally.
<p>* If the drug and trade name are the same, only one entry is made.</p> <p>† Companies “working on a drug” as defined by the BioPharm Insight® database. More than one company may develop and market a drug, and their relationship may be defined by a licensing agreement.</p> <p>‡ When listed in the WHO ATC/DDD Index.</p> <p>§ Nivolumab was approved by Health Canada on September 25, 2015.</p> <p>Source: BioPharm Insight®. Note that the database search for the new drugs added to the NDPM was completed as of June 17, 2015.</p>		

2. Status Update of Current NDPM Drugs

The previous edition of the NDPM (December 2014) featured a total of 27 pipeline drugs. This edition provides a status report for these drugs, as follows:

- 16 drugs are retained in this edition of the NDPM, as they continue to satisfy the criteria for drug selection, see Table 4;
- 3 drugs were removed from the NDPM after being granted market authorization by Health Canada, see Table 5;
- 2 drugs were removed from the NDPM, as current scientific assessments of the results of the Phase III clinical trials no longer support the potential for the drug to have a significant clinical impact, see Appendix A;
- 6 drugs were removed from the NDPM, as confirmation of current clinical trials in Canada could not be obtained, see Appendix B.

Table 4 lists the 16 drugs (including 4 biologics) from previous editions of the NDPM that remain as pipeline candidates, as they continue to satisfy the criteria for drug selection. A status update based on a review of the BioPharm Insight® database and recent scientific literature is provided, along with a rationale for retaining the drugs in the pipeline list. Other key resources consulted include Health Canada's Clinical Trials Database and the US National Institutes of Health (NIH) clinical trials registry.

Table 4. Drugs retained in the *New Drug Pipeline Monitor*

Drug* (Trade name) Company†	Therapeutic area (ATC‡) Indication	Update and rationale for retaining in the pipeline list
<i>ABT-199 (see Venetoclax below)</i>		
Ataluren (Translarna) Genzyme Corporation, a Sanofi Company; PTC Therapeutics, Inc.; Sanofi	Genetic diseases, Musculoskeletal system (M09) Cystic fibrosis; Duchenne muscular dystrophy	<p>Previous description:</p> <ul style="list-style-type: none"> • "Correction of the underlying gene effect is a particularly exciting prospect as a new therapy for cystic fibrosis."³⁸ • Approved conditionally in Europe in July 2014 for Duchenne muscular dystrophy.³⁹ • In Phase III studies in Canada for cystic fibrosis⁴⁰ and Duchenne muscular dystrophy.^{41,42} <p>Update</p> <ul style="list-style-type: none"> • Received orphan drug designation by the FDA in December 2014 for treatment of mucopolysaccharidosis type I. Previously granted FDA orphan drug designations for the following indications: cystic fibrosis resulting from a nonsense mutation (September 2004), Duchenne muscular dystrophy (January 2005), spinal muscular atrophy (March 2008). <p>Rationale: Current literature continues to suggest that ataluren is an important new therapy for cystic fibrosis and muscular dystrophy.</p>

Drug* (Trade name) Company†	Therapeutic area (ATC‡) Indication	Update and rationale for retaining in the pipeline list
Avatrombopag (also known as E5501) Eisai Co., Ltd.	Hematological Thrombocytopenia	<p>Previous description:</p> <ul style="list-style-type: none"> An oral, second-generation thrombopoietin receptor agonist that stimulates platelet production. <p>Update:</p> <ul style="list-style-type: none"> There is no new published data. Listed in Health Canada's Clinical Trials Database.^{43,44} <p>Rationale: Phase III studies are ongoing for avatrombopag as a treatment for thrombocytopenia and available information does not suggest any issues.</p>
Betrixaban Lee's Pharmaceutical Holdings Limited; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Portola Pharmaceuticals Inc.	Cardiovascular Stroke, thrombosis	<p>Previous description:</p> <ul style="list-style-type: none"> An oral, highly selective factor Xa inhibitor anticoagulant with distinct pharmacological characteristics, that offers convenience of once daily dosing, less drug interactions and may allow greater flexibility for use in patients with poor renal function. Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT00742859, a phase II study.⁴⁵ <p>Update:</p> <ul style="list-style-type: none"> The ongoing Phase III APEX Study is assessing betrixaban for both hospital and post-discharge prevention of venous thromboembolism, or blood clots, in acute medically ill patients. Preliminary data on efficacy trends and safety are positive.⁴⁶ <p>Rationale: Current literature continues to suggest that betrixaban may be an effective anticoagulant.</p>
Istradefylline (Nourist) Kyowa Hakko Kirin Pharma, Inc; Valeant Pharmaceuticals International, Inc.	Central nervous system Parkinson's disease	<p>Previous description:</p> <ul style="list-style-type: none"> First in a new class: selective adenosine A2A receptor antagonists. Data obtained from seven randomized controlled trials, including 2,205 patients, showed significant reductions in the daily off-time (primary outcome).⁴⁷ In Phase III studies in Canada for Parkinson's disease.⁴⁸ <p>Update:</p> <ul style="list-style-type: none"> A Phase III study of 308 patients showed that istradefylline treatment was well tolerated and produced a sustained reduction in off-time in levodopa-treated Parkinson's disease patients over a 52-week period.⁴⁹ <p>Rationale: Current literature continues to suggest that istradefylline may be a promising non-dopaminergic therapy for the treatment of Parkinson's disease.</p>
Ixekizumab Eli Lilly & Co.	Dermatology Psoriasis <i>Biologic</i>	<p>Previous description:</p> <ul style="list-style-type: none"> Interleukin-17A (IL-17A) inhibitor that represents a new therapeutic approach for patients with psoriasis. <p>Update:</p> <ul style="list-style-type: none"> Results from Phase III studies show greater efficacy of ixekizumab compared to etanercept, both given as a subcutaneous injection.⁵⁰ In Phase III studies in Canada for plaque psoriasis^{51,52} and ankylosing spondylitis.⁵³ <p>Rationale: Current literature continues to suggest that ixekizumab is an effective treatment for patients with psoriasis.</p>

Drug* (Trade name) Company†	Therapeutic area (ATC‡) Indication	Update and rationale for retaining in the pipeline list
Laquinimod (Nerventra) Active Biotech AB; Teva Pharmaceutical Industries Ltd.	Central nervous system (N07) Multiple sclerosis; Crohn's disease; Huntington's disease; lupus nephritis	<p>Previous description:</p> <ul style="list-style-type: none"> Novel once-daily, orally administered immunomodulatory compound with a favourable risk–benefit profile.⁵⁴ Phase II study in Crohn's has been published.⁵⁵ <p>Update:</p> <ul style="list-style-type: none"> In Phase III studies in Canada for multiple sclerosis⁵⁶, Crohn's disease^{57,58,59} and Huntington's disease.⁶⁰ <p>Rationale: Current literature continues to suggest that laquinimod may be a promising therapy for the treatment of relapsing–remitting multiple sclerosis and for Crohn's disease.</p>
Lebrikizumab Chugai Pharmaceutical Co., Ltd; Genentech, Inc.; Roche	Respiratory Asthma <i>Biologic</i>	<p>Previous description:</p> <ul style="list-style-type: none"> An anti-IL-13 monoclonal antibody for the treatment of asthma that demonstrates benefits in patients with poorly controlled asthma. In Phase III studies in Canada.^{61,62,63} <p>Update:</p> <ul style="list-style-type: none"> Data from two randomised placebo-controlled studies “extend, previously published results demonstrating the efficacy of lebrikizumab in improving rate of asthma exacerbations and lung function in patients with moderate-to-severe asthma who remain uncontrolled despite current standard-of-care treatment.”⁶⁴ It was granted orphan designation by FDA (March 2015) for treatment of idiopathic pulmonary fibrosis. <p>Rationale: Current literature continues to suggest that lebrikizumab may be a promising therapy for the treatment of asthma and other indications are also being explored.</p>
Mipomersen (Kynamro) Genzyme Corporation, a Sanofi Company; Isis Pharmaceuticals, Inc.	Cardiovascular (C10) Hypercholesterolemia	<p>Previous description:</p> <ul style="list-style-type: none"> An injectable (via subcutaneous route) second-generation 2'-O-methoxyethyl chimeric antisense oligonucleotide that reduces hepatic production of apolipoprotein B-100 (Apo B), the principal apolipoprotein of LDL and its metabolic precursor, VLDL, and is “effective for lowering Apo B-containing lipoproteins in patients with severe hypercholesterolemia.”⁶⁵ Approved in the US in 2013 for homozygous familial hypercholesterolemia (as an orphan indication). Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT00607373, a Phase III study.⁶⁶ <p>Update:</p> <ul style="list-style-type: none"> In a meta-analysis of all published randomized controlled trials comparing safety and efficacy of mipomersen with placebo in adults with dyslipidemia, “mipomersen resulted in a significant improvement in lipid parameters except for HDL-C and increased the risks of injection-site reactions, flu-like symptoms, and hepatic steatosis compared with placebo.”⁶⁷ <p>Rationale: Current literature continues to suggest that mipomersen may be an effective therapy for the treatment of hypercholesterolemia.</p>
Ocrelizumab	Musculoskeletal, Immune system	<p>Previous description:</p> <ul style="list-style-type: none"> A humanized monoclonal antibody that selectively targets the CD20-positive B-cells implicated in the inflammatory and neurodegenerative processes of MS.

Drug* (Trade name) Company†	Therapeutic area (ATC‡) Indication	Update and rationale for retaining in the pipeline list
Biogen Idec Inc.; Genentech, Inc.; Roche Holdings AG	Multiple sclerosis (MS) <i>Biologic</i>	<p>Update:</p> <ul style="list-style-type: none"> Results from two Phase III studies involving 1,656 relapsing MS patients (both relapsing–remitting and secondary progressive) randomized to either an ocrelizumab infusion every 6 months (600 mg) or Rebif 44 mcg three times a week showed that ocrelizumab significantly reduced relapse rates, new lesion formation on MRI and disability progression during the two years of the study compared to Rebif. A Phase III study of ocrelizumab in primary progressive MS is still underway.⁶⁸ Regulatory submissions in the US and Europe planned for early 2016.⁶⁹ Not listed in Health Canada's Clinical Trials Database but Canada is listed as one of the investigating sites for study NCT01412333, a Phase III study.⁷⁰ <p>Rationale: Current literature continues to suggest that ocrelizumab may be an effective treatment for multiple sclerosis.</p>
Ponesimod Actelion Pharmaceuticals Ltd; Roche	Immune system Multiple sclerosis (MS) and psoriasis	<p>Previous description:</p> <ul style="list-style-type: none"> Belongs to the class of sphingosine-1-phosphate receptor 1 (S1P1) modulators. Potential for once-a-day oral dosing, for multiple autoimmune disorders.⁷¹ "Significant clinical benefit was seen [with ponesimod for treatment of psoriasis] at week 16 that increased with maintenance therapy."⁷² <p>Update:</p> <ul style="list-style-type: none"> Phase III trials in MS were initiated in April 2015.⁷³ Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT02425644, a Phase III study.⁷⁴ <p>Rationale: Although current literature is limited, ponesimod may be an important therapy for multiple sclerosis and effective for treatment of psoriasis.</p>
Ranirestat (also known as AS3201) Dainippon Sumitomo Pharma Co. Ltd.; Eisai Co., Ltd.; Kyorin Pharmaceutical Co., Ltd	Pain Diabetic neuropathy	<p>Previous description:</p> <ul style="list-style-type: none"> An oral aldose reductase inhibitor (ARI) with a stronger and longer-acting inhibitory effect compared to other drugs (e.g., pregabalin (Lyrica)) used for managing diabetic neuropathy. <p>Update:</p> <ul style="list-style-type: none"> Still in Phase III trials. Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT00101426, a Phase III study.⁷⁵ <p>Rationale: There is no new published literature on ranirestat since the last update. As Phase III studies are ongoing, it is retained and will be monitored.</p>
Safinamide (Xadago) Meiji Seika Pharma Co., Ltd.; Merck Serono SA; Newron Pharmaceuticals; Zambon Group	Central nervous system Parkinson's disease (PD), epilepsy and restless leg syndrome	<p>Previous description:</p> <ul style="list-style-type: none"> An oral α-aminoamide derivative with both dopaminergic properties (highly selective and reversible inhibition of monoamine oxidase-B) and non-dopaminergic properties (selective sodium channel blockade and calcium channel modulation, with consequent inhibition of excessive glutamate release).⁷⁶ "In Phase III trials, safinamide has been found to be a useful adjunctive to dopamine agonists in early PD and has been shown to increase time without increasing troublesome dyskinesias when used as an adjunct to levodopa in patients with advanced PD."⁷⁷

Drug* (Trade name) Company†	Therapeutic area (ATC‡) Indication	Update and rationale for retaining in the pipeline list
		<ul style="list-style-type: none"> Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT00605683, a Phase III study.⁷⁸ <p>Update:</p> <ul style="list-style-type: none"> Approved in Europe (February 2015) as an add-on therapy to stable-dose levodopa, alone or in combination with other PD therapies in mid- to late-stage fluctuating PD patients; it has been filed in the US.⁷⁹ <p>Rationale: Current literature continues to suggest that safinamide may be an effective treatment for Parkinson's disease.</p>
Selexipag (Upravi) Actelion Pharmaceuticals Ltd; Nippon Shinyaku Co., Ltd	Cardiovascular Pulmonary arterial hypertension (PAH)	<p>Previous description:</p> <ul style="list-style-type: none"> An oral, selective prostacyclin (PGI₂) receptor (IP receptor) agonist. "The Phase III trial – GRIPHON – has a clinically relevant and highly robust primary end-point of time to first morbidity/mortality event and will provide vital information on the long-term effects of selexipag in patients with PAH."⁸⁰ Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT01106014, a Phase III study.⁸¹ <p>Update:</p> <ul style="list-style-type: none"> Filed in December 2014 with FDA for the treatment of pulmonary arterial hypertension.⁸² <p>Rationale: Current literature continues to suggest that selexipag may be an effective treatment for pulmonary arterial hypertension.</p>
Tanezumab Eli Lilly & Co.; Pfizer, Inc.	Pain <i>Biologic</i>	<p>Previous description:</p> <ul style="list-style-type: none"> A humanized monoclonal antibody, given by subcutaneous injection, that inhibits nerve growth factor and may have therapeutic benefit in patients with osteoarthritis (OA) who experience inadequate pain relief with nonsteroidal anti-inflammatory drugs (NSAIDs). <p>Update:</p> <ul style="list-style-type: none"> Tanezumab compared to NSAIDs and opioids showed greater efficacy in OA.⁸³ Also being evaluated in diabetic peripheral neuropathy⁸⁴ and pain from bone metastases.⁸⁵ In Phase III studies in Canada.⁸⁶ <p>Rationale: Current literature continues to suggest that tanezumab may be an effective treatment for pain management of OA.</p>
Vatalanib Bayer AG; Novartis AG	Cancer Colorectal cancer, pancreatic cancer	<p>Previous description:</p> <ul style="list-style-type: none"> Potentially first oral tyrosine kinase inhibitor to be used long-term in combination with standard chemotherapy for the treatment of patients with metastatic colorectal cancer. "Vatalanib was well tolerated as a second-line therapy and resulted in favourable 6-month survival rate in patients with metastatic pancreatic cancer, compared with historic controls."⁸⁷ <p>Update:</p> <ul style="list-style-type: none"> Not listed in Health Canada's Clinical Trials Database, but Canada is listed as one of the investigating sites for study NCT00056459, a Phase III study.⁸⁸

Drug* (Trade name) Company†	Therapeutic area (ATC‡) Indication	Update and rationale for retaining in the pipeline list
		Rationale: Current literature continues to suggest that vatalanib may be an effective treatment for pancreatic cancer.
Venetoclax (previously referred to as ABT-199) Abbott Laboratories; AbbVie; Genentech, Inc.; Roche Holdings AG	Cancer Leukemias	Previous description <ul style="list-style-type: none"> An oral selective B-cell lymphoma/leukemia 2 (BCL-2) inhibitor that is thought to impact tumour formation, tumour growth and resistance and appears to spare platelets while achieving potent anti-tumour activity.⁸⁹ Update <ul style="list-style-type: none"> Has been granted breakthrough therapy designation by the FDA for the treatment of chronic lymphocytic leukemia (CLL) in previously treated (relapsed/refractory) patients with the 17p deletion genetic mutation.⁹⁰ AbbVie plans to submit regulatory applications to the FDA and the European Medicines Agency (EMA) before the end of 2015. In clinical trials in Canada for chronic lymphocytic leukemia.⁹¹ Rationale: Current literature continues to suggest that venetoclax may be an effective treatment for chronic lymphocytic leukemia.
<p>* If the drug and trade name are the same, only one entry is made.</p> <p>† Companies "working on a drug" as defined by the BioPharm Insight® database. More than one company may develop and market a drug, and their relationship may be defined by a licensing agreement.</p> <p>‡ When listed in the WHO ATC/DDD Index.</p>		

Table 5 reports the three drugs (including one biologic) from the previous edition of the NDPM (December 2014) that were removed from this edition because they have received market authorization granted by Health Canada. The Notice of Compliance (NOC) date issued by Health Canada, as well as the date of first sale (if available), are provided in the table.

This table includes information on recommendations made by the Common Drug Review (CDR). The CDR conducts reviews of the clinical effectiveness and cost-effectiveness of drugs, as well as reviews of patient input for drugs, and provides formulary listing recommendations to public drug plans. The CDR is part of the Canadian Agency for Drugs and Technologies in Health (CADTH).

This table also reports on the status of price reviews by the Patented Medicine Prices Review Board (PMPRB). The PMPRB ensures that the prices of patented medicines sold in Canada are not excessive by reviewing the prices that patentees charge for each individual patented drug product to wholesalers, hospitals and pharmacies. Once a review is completed, the drug may be found to (i) be priced within the PMPRB Guidelines, (ii) exceed the Guidelines by an amount that does not trigger the investigation criteria, or (iii) exceed the Guidelines and become subject to an investigation.

Table 5. Drugs removed from the *New Drug Pipeline Monitor*: Market authorization granted by Health Canada

Drug (Trade name) Company	Indication	NOC date* Date of first sale†	Common Drug Review (CDR) recommendation‡	PMPRB review status
Abiglutide (Eperzan) GlaxoSmithKline Inc.	Type 2 diabetes mellitus ⁹² <i>Biologic</i>	NOC granted: 2015-07-15 Not marketed in Canada as of October 30, 2015	Not currently under review	Not currently under review
Nintedanib (Ofev) Boehringer Ingelheim (Canada) Ltd./Ltée	Idiopathic pulmonary fibrosis ⁹³	NOC granted: 2015-06-25 Date of first sale: 2015-06-29	List with clinical criteria and/or conditions (October 2015)	Under review
Sacubitril/valsartan (Entresto) Novartis Pharmaceuticals Canada Inc.	Heart failure	NOC granted: 2015-10-02 Not marketed in Canada as of October 30, 2015	Under review	Under review
<p>* A Notice of Compliance issued by Health Canada indicates that the drug product meets the regulatory requirements for use in humans or animals and that the product is approved for sale in Canada.</p> <p>† The date of first sale is as reported to the PMPRB. This date may precede the Health Canada NOC date, as a product may be sold under the Special Access Programme or the Clinical Trial Applications or it may be an Investigational New Drug.</p> <p>‡ CDR recommendations are made by the Canadian Drug Expert Committee (CDEC), an independent advisory body composed of individuals with expertise in drug therapy and drug evaluation. Submissions by manufacturers are voluntary, so recommendations may not be available for some drugs. The information on the current CDR status is available at: http://www.cadth.ca/en/products/cdr/.</p>				

3. Review of Past and Current NDPM Drugs

To date, a total of 71 new drugs have been selected in seven NDPM reports published since 2007. When they were selected, these drugs were either in Phase III clinical trials or under review by the US FDA, and demonstrated the potential to have a significant clinical impact. Of these:

- 10 (14%) are new drugs identified in this edition of the NDPM;
- 16 (23%) continue to satisfy the NDPM criteria for drug selection;
- 25 (35%) no longer satisfy the NDPM criteria for drug selection;
- 20 (28%) were subsequently granted market authorization by Health Canada.

The majority of the NDPM drugs (65%) continue to have promising scientific assessments (37%) or have already received market authorization by Health Canada (28%). However, a number of the drugs (35%) were removed from the NDPM either (i) because the scientific assessments no longer supported their retention or (ii) because there was no current information to indicate that these drugs were being investigated in clinical trials in Canada.

Table 6 lists the drugs that have subsequently received market authorization granted by Health Canada. Drugs with relatively high sales and/or prices are highlighted: aflibercept (Eylea, Zaltrap); ipilimumab (Yervoy); plerixafor (Mozobil); ticagrelor (Brilinta); eculizumab (Soliris); raltegravir (Isentress); and rivaroxaban (Xarelto).

The table indicates the current Common Drug Review recommendation, the PMPRB review status and the PMPRB Maximum Average Potential Price (MAPP). Using the MIDAS™ database for the fourth quarter of 2014 (Q4-2014), the table also provides an indication of the foreign price relative to the Canadian level (foreign-to-Canadian price ratio) as well as a measure of the market penetration for the molecule in Canada and in foreign markets (sales per 1 million people for the molecule).

The results suggest that the sales for the drugs with available data were higher in foreign markets than in Canada in Q4-2014. For instance, in the case of rivaroxaban (Xarelto), which is the top-selling drug in Q4-2014 amongst the 20 featured in the NDPM, the sales for 1 million people in foreign markets were \$1,188,374, which were higher than the Canadian sales of \$915,396. This drug, which is an antithrombotic agent (B01), is one of the earliest drugs featured in the NDPM; it received an NOC in 2008, and a subsequent recommendation from the CDR for listing with criteria/conditions.

Factors that may explain higher sales for the new drugs in foreign markets than in Canada include: higher relative price levels (especially in the United States), earlier market launches and/or increased market uptake for the new drugs in foreign countries. Higher sales in foreign markets, however, may suggest a potential for market growth in Canada.

A price analysis of the drugs with available foreign and Canadian prices in the MIDAS™ database indicates that manufacturer-level prices in foreign markets were above the Canadian levels for some of the drugs in the table. For instance, the median price for rivaroxaban (Xarelto) 20 mg film-coated tablets in foreign markets was 12% higher than in Canada, as indicated by a foreign-to-Canadian ratio of 1.12.

Note that some of the drugs may be available in the countries analyzed but may not have sales and pricing information available in IMS AG's MIDAS™ database. The results are reported only for drugs with available information in this database.

The Canadian and international prices reported in IMS AG's MIDAS™ database are manufacturer ex-factory prices and reflect all sales to the pharmacy sector. Market spot exchange rates were used to convert foreign currency prices into their Canadian dollar equivalents.

The foreign markets analyzed are the seven that the PMPRB considers in reviewing the prices of patented drug products (PMPRB7): France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States.

**Table 6. Past drugs identified in the *New Drug Pipeline Monitor* with market authorization granted by Health Canada
Sales and prices in Canada and foreign* markets, Q4-2014**

NDPM edition†	Drug (Trade Name) Company	ATC Therapeutic subgroup Indication	Notice of Compliance (NOC) date / Date of first sale	Common Drug Review (CDR) recommendation	PMPRB review status	PMPRB Maximum Average Potential Price (MAPP)	Foreign-to- Canadian price ratio‡	Sales§ per 1 million people for the molecule	
								Canada	Average in foreign markets
7 th	Nintedanib (Ofev)	Antineoplastic agents (L01)	NOC granted: June 25, 2015	List with clinical criteria and/or conditions (Oct. 2015)	Under review	—	—	—	\$37,607
	Boehringer Ingelheim (Canada) Ltd./Ltee	Idiopathic pulmonary fibrosis	Date of first sale: June 29, 2015						
7 th	Albiglutide (Eperzan)	Drugs used in diabetes (A10)	NOC granted: July 15, 2015	Not currently under review	Not yet sold	—	—	—	\$21,253
	GlaxoSmithKline Inc.	Type 2 diabetes mellitus <i>Biologic</i>	Not marketed in Canada as of Oct. 30, 2015						
6 th	Aflibercept (Eylea) Bayer Inc.	Aflibercept (Eylea): Ophthalmologicals (S01) Macular degeneration neovascular, age- related; macular edema secondary to central retinal vein occlusion; macular edema, diabetic	Aflibercept (Eylea): NOC granted: Nov. 8, 2013 Date of first sale: Dec. 23, 2013	Aflibercept (Eylea): List with conditions (Oct. 2014) List with clinical criteria and/or conditions (May 2015)	40 mg/mL Within Guidelines	40 mg/mL \$1,851.1629/mL	0.78 (40 mg/mL)	\$260,898**	\$822,165††

	(Zaltrap)	Aflibercept (Zaltrap): Antineoplastic agents (L01) Metastatic colorectal cancer <i>Biologic</i>	Aflibercept (Zaltrap): NOC granted: Feb. 12, 2014 Date of first sale: May 8, 2014	Aflibercept (Zaltrap): The pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee does not recommend funding aflibercept in combination with an irinotecan-fluoropyrimidine (FOLFIRI) based therapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen (Sept. 2014)	100 mg/vial Within Guidelines 200 mg/vial Within Guidelines	100 mg/vial \$500.0000/vial 200 mg/vial \$1,250.0000/vial			
6 th	Macitentan (Opsumit) Actelion Pharmaceuticals Ltd.	Antihypertensives (C02) Pulmonary arterial hypertension	NOC granted: Nov. 6, 2013 Date of first sale: Jan. 15, 2014	List with clinical criteria and/or conditions (Jan. 2015)	10 mg Within Guidelines	10 mg \$128.3572/tablet	1.14	\$22,917	\$58,768
6 th	Tofacitinib (Xeljanz) Pfizer Canada Inc.	Immunosuppressants (L04) Rheumatoid arthritis	NOC granted: Apr. 17, 2014 Date of first sale: June 6, 2014	List with criteria/condition (April 2015)	5 mg Within Guidelines	5 mg \$29.2945/tablet	1.69	\$14,054	\$297,356
5 th	Mirabegron (Myrbetriq) Astellas Pharma Canada Inc.	Urologicals (G04) Overactive bladder	NOC granted: Mar. 6, 2013 Date of first sale: Mar. 28, 2013	List with criteria/condition (Nov. 2014)	50 mg Within Guidelines 25 mg Within Guidelines	50 mg \$5.4990/tablet 25 mg \$2.1510/tablet	1.09 (50 mg)	\$66,988	\$128,114

5 th	Sacubitril/valsartan (Entresto) Novartis Pharmaceuticals Canada Inc	Agents acting on the renin-angiotensin system (C09) Heart failure	NOC granted: Oct. 2, 2015 Not marketed in Canada as of Oct. 30, 2015	Under review	Not currently under review	—	—	—	—
4 th	Pirfenidone (Esbriet) InterMune International AG; InterMune Canada Inc.; Hoffmann-La Roche Limited	Immunosuppressants (L04) Idiopathic pulmonary fibrosis	NOC granted: Oct. 1, 2012 Date of first sale: May 31, 2012	List with criteria/condition (April 2015)	267 mg Within Guidelines	267 mg \$15.8878/capsule	—	—	\$107,752
4 th	Retigabine or ezogabine (Potiga) GlaxoSmithKline Inc.	Antiepileptics (N03) Epilepsy	NOC granted: Oct. 18, 2012 Not marketed in Canada as of Oct. 30, 2015	Not currently under review	Not yet sold	—	—	—	\$1,508
4 th	Ipilimumab (Yervoy) Bristol-Myers Squibb	Antineoplastic agents (L01) Melanoma <i>Biologic</i>	NOC granted: Feb. 1, 2012 Date of first sale: Nov. 7, 2011	The pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee recommended funding conditional on the cost-effectiveness of ipilimumab being improved to an acceptable level (Apr. 2012)	5 mg/mL Within Guidelines	5 mg/mL \$627.1548/mL	1.30	\$279,738	\$522,354
4 th	Plerixafor (Mozobil) Genzyme Canada Inc.; Sanofi Aventis Canada Inc.	Immunostimulants (L03) Hematopoietic stem cell mobilization	NOC granted: Dec. 8, 2011 Date of first sale: Mar. 26, 2012	Do not list (Sept. 2012)	20 mg/mL Within Guidelines	20 mg/mL \$7,100.2321/mL	1.11	\$25,611	\$38,539

4 th	Telaprevir (Incivek) Vertex Pharmaceuticals (Canada) Incorporated	Antivirals for systemic use (J05) Hepatitis C	NOC granted: Aug. 16, 2011 Date of first sale: Oct. 3, 2011	List with criteria/conditions (June 2013)	375 mg Within Guidelines	375 mg \$71.7040/tablet	0.87	\$16,160	\$31,446
4 th	Ticagrelor (Brilinta) AstraZeneca	Antithrombotic agents (B01) Acute coronary syndromes	NOC granted: May 30, 2011 Date of first sale: June 1, 2011	Do not list (Dec. 2011)	90 mg Within Guidelines	90 mg \$1.4377/tablet	1.07	\$141,498	\$202,890
4 th	Vandetanib (Caprelsa) AstraZeneca	Antineoplastic agents (L01) Thyroid cancer	NOC granted: Jan. 12, 2012 Date of first sale: Feb. 23, 2012	Not currently under review	300 mg Does Not Trigger Investigation 100 mg Within Guidelines	300 mg \$189.4568/tablet 100 mg \$174.2366/tablet	1.25 (300 mg)	\$11,906	\$17,250
4 th	Perampanel (Fycompa) Eisai Ltd.	Antiepileptics (N03) Epilepsy	NOC granted: Apr. 4, 2013 Date of first sale: May 17, 2013	List with criteria/condition (Oct. 2013)	2 mg Within Guidelines 4 mg Within Guidelines 6 mg Within Guidelines 8 mg Within Guidelines	2 mg \$9.4500/tablet 4 mg \$9.4500/tablet 6 mg \$9.4500/tablet 8 mg \$9.4500/tablet	0.73 (2 mg)	\$15,237	\$18,159

					10 mg Within Guidelines	10 mg \$9.4500/tablet			
					12 mg Within Guidelines	12 mg \$10.9300/tablet			
3 rd	<p>Eculizumab (Soliris)</p> <p>Alexion Pharmaceuticals Inc.</p>	<p>Immunosuppressants (L04)</p> <p>Paroxysmal nocturnal hemoglobinuria; atypical hemolytic uremic syndrome</p> <p><i>Biologic</i></p>	<p>NOC granted: Jan. 28, 2009</p> <p>Date of first sale: May 25, 2009</p>	<p>Do not list (Feb. 2010)</p> <p>Do not list (July 2013)</p>	Notice of Hearing	—	—	—	\$417,041
3 rd	<p>Lapatinib (Tykerb)</p> <p>GlaxoSmithKline Inc.; Novartis Pharmaceuticals Canada Inc.</p>	<p>Antineoplastic agents (L01)</p> <p>Breast cancer</p>	<p>NOC granted: May 15, 2009</p> <p>Date of first sale: June 5, 2009</p>	The pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee does not recommend funding lapatinib in combination with letrozole in postmenopausal patients with hormone receptor positive, HER2 receptor positive metastatic breast cancer (July 2013)	250 mg Within Guidelines	250 mg \$27.0664/tablet	1.03	\$22,264	\$52,021
3 rd	<p>Raltegravir (Isentress)</p> <p>Merck Frosst Canada Ltd.</p>	<p>Antivirals for systemic use (J05)</p> <p>HIV-1 infection</p>	<p>NOC granted: Nov. 27, 2007</p> <p>Date of first sale: Nov. 28, 2007</p>	Do not list (June 2010)	<p>400 mg Within Guidelines</p> <p>100 mg Within Guidelines</p> <p>25 mg Within Guidelines</p>	<p>400 mg \$13.5000/tablet</p> <p>100 mg \$4.2033/tablet</p> <p>25 mg \$1.0509/tablet</p>	1.05 (400 mg)	\$361,760	\$443,287

3 rd	Rivaroxaban (Xarelto)	Antithrombotic agents (B01)	NOC granted: Sept. 15, 2008	List with clinical criteria/conditions (Dec. 2008)	20 mg Within Guidelines	20 mg \$3.2000/tablet			
	Bayer Inc.	Venous thromboembolic events; stroke; systemic embolism	Date of first sale: Sept. 16, 2008		15 mg Within Guidelines	15 mg \$2.8400/tablet	1.12 (20 mg)	\$915,396	\$1,188,374
					10 mg Voluntary Compliance Undertaking	10 mg \$8.9702/tablet			
3 rd	Sapropterin (Kuvan)	Alimentary tract and metabolism products(A16)	NOC granted: Apr. 30, 2010	Do not list (Jan. 2011)	100 mg Within Guidelines	100 mg \$34.8421/tablet	—	—	\$43,319
	Biomarin Pharmaceutical Inc.	Phenylketonuria	Date of first sale: July 5, 2010						
<p>Note: Some of the drugs may be available in the countries analyzed but may not have sales and pricing information available in IMS AG's MIDAS™ database. The results are reported only for drugs with available information in this database.</p> <p>* France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States (PMPRB7).</p> <p>† NDPM edition when the drug was removed from the pipeline list as it received market authorization from Health Canada.</p> <p>‡ At manufacturer levels. Results are restricted to the retail market (excluding hospital sales) and prescription bound products.</p> <p>§ In Canada, where available; otherwise, in the PMPRB7.</p> <p>** Sales for Eylea. Zaltrap has no available sales in the retail market in Canada, as reported by IMS AG's MIDAS™ database.</p> <p>††Sales for Eylea and Zaltrap combined.</p> <p>Source: MIDAS™ Database, October–December 2014, IMS AG All Rights Reserved</p>									

Appendix A: Drugs removed from the list due to scientific assessment

Table A identifies the two drugs from the previous edition of the NDPM (December 2014) that were removed from this edition, as current scientific assessments of the results of the Phase III clinical trials no longer support the potential for a significant clinical impact.

**Table A. Drugs removed from the *New Drug Pipeline Monitor*:
Current scientific assessment**

Drug (Trade name) Company	Therapeutic area Indication	Rationale for removal
Cethromycin (Restanza) Advanced Life Sciences, Inc.; Pfizer, Inc.	Infections Community-acquired pneumonia	Previous description: <ul style="list-style-type: none"> An oral antibiotic designed to overcome emerging bacterial resistance to macrolides and penicillins in the treatment of community-acquired pneumonia. Update: <ul style="list-style-type: none"> "...two studies did find significantly more adverse events with use of cethromycin as compared to clarithromycin and nemonoxacin when compared to levofloxacin."⁹⁴
NX-1207 Nymox Pharmaceutical Corporation; Recordati S.P.A.	Genitourinary Benign prostatic hyperplasia	Previous description: <ul style="list-style-type: none"> A first-in-class drug for the treatment of benign prostatic hyperplasia, a disorder that causes difficulties with urination associated with aging. Update: <ul style="list-style-type: none"> Phase III studies failed to meet primary endpoint.⁹⁵

Appendix B: Drugs removed from the list due to lack of evidence of ongoing clinical trials

Table B lists the six drugs from the previous edition of the NDPM (December 2014) that were removed in this edition, as there is no evidence that they are currently being investigated in clinical trials in Canada. Nevertheless, these drugs may receive market authorization in Canada in the future.

**Table B. Drugs removed from the *New Drug Pipeline Monitor*:
No evidence of ongoing clinical trials in Canada**

Drug (Trade name) Company	Therapeutic area Indication	Rationale for removal
Cetilistat (Cametor) Norgine BV; Takeda Pharmaceutical Company Limited	Gastrointestinal Obesity	<p>Previous description:</p> <ul style="list-style-type: none"> • Showed similar weight loss to that seen with orlistat (Xenical) but with up to 90% fewer severe gastrointestinal side effects.⁹⁶ • Approved in Japan (September 2013). • "Cetilistat showed mild to moderate adverse events, predominantly of gastrointestinal nature (steatorrhea), with an incidence lower than orlistat."⁹⁷ <p>Rationale for removal:</p> <ul style="list-style-type: none"> • Not listed in Health Canada's Clinical Trials Database. Canada's participation could not be confirmed in trials listed on www.clinicaltrials.gov.
DIMS 0150 (Kappaproct) InDex Pharmaceuticals AB	Immune System Ulcerative colitis	<p>Previous description:</p> <ul style="list-style-type: none"> • New class: Toll-like receptor 9 (TLR9) agonist that may be an effective, non-invasive treatment option for patients with severe ulcerative colitis who no longer respond to steroid therapy and whose only current alternative is surgical removal of the colon. <p>Rationale for removal:</p> <ul style="list-style-type: none"> • Not listed in Health Canada's Clinical Trials Database. Canada's participation could not be confirmed in trials listed on www.clinicaltrials.gov.
Lorcaserin hydrochloride (Belviq) Arena Pharmaceuticals, Inc.; CY Biotech Company Ltd.; Eisai Co., Ltd.; Ildong Pharmaceutical Co., Ltd.	Gastrointestinal Obesity	<p>Previous description:</p> <ul style="list-style-type: none"> • An oral, serotonin (5-hydroxy-tryptamine, 5-HT) 5-HT_{2C} receptor agonist that regulates food intake. • Approved in the US in 2012. <p>Rationale for removal:</p> <ul style="list-style-type: none"> • Not listed in Health Canada's Clinical Trials Database. Canada's participation could not be confirmed in trials listed on www.clinicaltrials.gov.
Rebamipide (Mucosta)	Eye and ear; gastrointestinal	<p>Previous description:</p> <ul style="list-style-type: none"> • An amino acid derivative of 2(1H)-quinolinone, used for mucosal protection, healing of gastroduodenal ulcers, and treatment of gastritis.

Drug (Trade name) Company	Therapeutic area Indication	Rationale for removal
Acucela, Inc.; Novartis AG; Otsuka Pharmaceutical Co., Ltd.	Dry eye syndrome	<ul style="list-style-type: none"> “The results of the study show that 2% rebamipide is effective in improving both the objective signs and subjective symptoms of dry eye patients for at least 52 weeks. In addition, 2% rebamipide treatment was generally well tolerated.”⁹⁸ <p>Rationale for removal:</p> <ul style="list-style-type: none"> Not listed in Health Canada’s Clinical Trials Database. Canada’s participation could not be confirmed in trials listed on www.clinicaltrials.gov.
Rigosertib sodium (Estybon) Baxter International, Inc.; Onconova Therapeutics, Inc.; SymBio Pharmaceuticals Limited	Cancer Solid and hematological cancers	<p>Previous description</p> <ul style="list-style-type: none"> New class: an inhibitor of the phosphoinositide 3-kinase and polo-like kinase pathways that induces mitotic arrest and apoptosis in neoplastic cells, while sparing normal cells. <p>Rationale for removal:</p> <ul style="list-style-type: none"> Not listed in Health Canada’s Clinical Trials Database. Canada’s participation could not be confirmed in trials listed on www.clinicaltrials.gov.
Sotatercept (ACE-011) Acceleron Pharma; Celgene Corporation	Cancer Anemia, bone cancer <i>Biologic</i>	<p>Previous description:</p> <ul style="list-style-type: none"> A protein therapeutic that increases red blood cell levels by targeting molecules in the TGF-β superfamily. Potential to stimulate bone formation: unmet medical need in treatment of bone loss. “Multiple doses of sotatercept plus thalidomide appear to be safe and generally well-tolerated in multiple myeloma patients.”⁹⁹ <p>Rationale for removal:</p> <ul style="list-style-type: none"> Not listed in Health Canada’s Clinical Trials Database. Canada’s participation could not be confirmed in trials listed on www.clinicaltrials.gov.

References

- ¹ BioPharm Insight® database. Available at: <http://www.infinata5.com/BioPharm/AccessPoint.aspx?action=Login.ShowLogin&datakey=BioPharm> (Search completed June 17, 2015)
- ² Health Canada. *Health Canada's Clinical Trials Database*. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>
- ³ U.S. National Institutes of Health clinical trials registry. Available at: <https://clinicaltrials.gov>
- ⁴ Control number 168103. *A phase 3, randomized, open label study investigating the efficacy of the BiTE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL)*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵ Buie LW, Pecoraro JJ, Horvat TZ, Daley RJ. *Blinatumomab: A first-in-class bispecific T-cell engager for precursor B-cell acute lymphoblastic leukemia*. Ann Pharmacother. 2015; Jun 3. pii: 1060028015588555. [Epub ahead of print].
- ⁶ Control number 181446. *A phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage iiib/c or stage iv melanoma in subjects who are at high risk for recurrence*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁷ Weber JS, D'Angelo SP, Minor D, et al. *Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial*. Lancet Oncol. 2015;16(4):375-84.
- ⁸ FDA News Release. *FDA approves Lynparza to treat advanced ovarian cancer*. 2014. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427554.htm>.
- ⁹ Bixel K, Hays JL. *Olaparib in the management of ovarian cancer*. Pharmgenomics Pers Med. 2015;8:127-35.
- ¹⁰ Lheureux S, Bowering V, Karakasis K, Oza AM. *Safety evaluation of olaparib for treating ovarian cancer*. Expert Opin Drug Saf. 2015;14(8):1305-16.
- ¹¹ Control number 171119. *A randomised, double-blind, parallel group, placebo-controlled multi-centre phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ¹² Control number 179853. *A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying germline BRCA1/2 mutations*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.

-
- ¹³ Control number 165198. *A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ¹⁴ Control number 164991. *A phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ¹⁵ Control number 177620. *A phase III, randomised, double blind, placebo controlled, multicentre study of maintenance olaparib monotherapy in patients with GBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ¹⁶ Control number 175751. *A randomised, double-blind, placebo-controlled, multicentre phase II study to compare the efficacy, safety and tolerability of olaparib versus placebo when given in addition to abiraterone treatment in patients with metastatic castrate-resistant prostate cancer who have received prior chemotherapy containing docetaxel.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ¹⁷ FDA News Release. *FDA approves Lynparza to treat advanced ovarian cancer.* 2014. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427554.htm>.
- ¹⁸ Control number 179041. *Phase III study evaluating palbociclib (PD-0332991), a cyclin-dependent kinase (CDK) 4/6 inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ¹⁹ Finn RS, Crown JP, Lang I, et al. *The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.* *Lancet Oncol.* 2015;16(1):25-35.
- ²⁰ Control number 167403. *A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of an every four weeks treatment regimen of alirocumab in patients with primary hypercholesterolemia.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ²¹ Bays H, Gaudet D, Weiss R, et al. *Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial.* *J Clin Endocrinol Metab.* 2015;jc20151520. [Epub ahead of print]
- ²² Robinson JG, Farnier M, Krempf M, et al; ODYSSEY LONG TERM Investigators. *Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.* *N Engl J Med.* 2015;372(16):1489-99.
- ²³ Müller T. *Valbenazine granted breakthrough drug status for treating tardive dyskinesia.* *Expert Opin Investig Drugs.* 2015;24(6):737-42.
- ²⁴ Control number 179790. *A phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study to assess the efficacy, safety, and tolerability of nbi-98854 for the treatment of tardive dyskinesia.* Health Canada's Clinical Trials Database. Available at <http://www.hc-sc.gc.ca/dhp->

mps/prodpharma/databasdonclin/index-eng.php.

- ²⁵ News Release. *Neurocrine announces positive results of VMAT2 inhibitor NBI-98854 in Kinect 2 study*, 2014. Available at: <http://www.prnewswire.com/news-releases/neurocrine-announces-positive-results-of-vmat2-inhibitor-nbi-98854-in-kinect-2-study-238945761.html>.
- ²⁶ FDA News Release. *FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa*. October 16, 2015. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm>
- ²⁷ News Release. *Boehringer Ingelheim submits applications for approval of idarucizumab*, specific reversal agent to dabigatran etexilate (Pradaxa®), to EMA, FDA and Health Canada*. March 3, 2015. Available at: http://www.boehringer-ingelheim.ca/en/news/press_releases/2015/3Mar2015111.html.
- ²⁸ Control number 173990. *A phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ²⁹ News Release. *Cempra completes patient enrollment of Solitaire-IV phase 3 clinical trial*. July 7, 2015. Available at: <http://investor.cempra.com/releasedetail.cfm?ReleaseID=920866>.
- ³⁰ Control number 170088. *A randomized, double-blind, multi-center study to evaluate the efficacy and safety of intravenous to oral solithromycin (CEM-101) compared to intravenous to oral moxifloxacin in the treatment of adult patients with community-acquired bacterial pneumonia*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ³¹ Van Bambeke F. *Renaissance of antibiotics against difficult infections: Focus on oritavancin and new ketolides and quinolones*. Ann Med. 2014;46(7):512-29.
- ³² Control number 178258. *A randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ³³ Walsh GM. *Mepolizumab-based therapy in asthma: an update*. Curr Opin Allergy Clin Immunol. 2015;15(4):392-6.
- ³⁴ Ortega HG, Liu MC, Pavord ID, et al.; MENSA Investigators. *Mepolizumab treatment in patients with severe eosinophilic asthma*. N Engl J Med. 2014;371(13):1198-207.
- ³⁵ Drug Development Technology. *Orkambi (lumacaftor/ivacaftor) for the treatment of cystic fibrosis (CF), United States of America*. Available at: <http://www.drugdevelopment-technology.com/projects/orkambi-lumacaftor-ivacaftor-cystic-fibrosis/>
- ³⁶ Control number 163367. *A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508DEL-CFTR mutation*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>
- ³⁷ Wainwright CE, Elborn JS, Ramsey BW, et al.; TRAFFIC Study Group; TRANSPORT Study Group. *Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR*. N Engl J Med.

2015; Jul 16;373(3):220-31.

- ³⁸ Jones AM, Helm JM. *Emerging treatments in cystic fibrosis*. *Drugs*. 2009;69(14):1903-10.
- ³⁹ PTC Therapeutics, Inc. (PTCT) receives conditional approval in the European Union for Translarna™ for the treatment of nonsense mutation Duchenne muscular dystrophy. News Release, August 4, 2014. Available at: <http://ir.ptcbio.com/releasedetail.cfm?ReleaseID=863914>.
- ⁴⁰ Control number 175879. *A phase 3 efficacy and safety study of ataluren (PTC124 ®) in patients with nonsense mutation cystic fibrosis*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁴¹ Control number 164252. *A phase 3 efficacy and safety study of ataluren (PTC124) in patients with nonsense mutation dystrophinopathy*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁴² Control number 175873. *A phase 3 extension study of ataluren (PTC124) in patients with nonsense mutation dystrophinopathy*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁴³ Control number 170972. *A randomized, global, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-daily oral avatrombopag for the treatment of adults with thrombocytopenia associated with liver disease prior to an elective procedure*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁴⁴ Control number 170968. *A randomized, global, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-daily oral avatrombopag for the treatment of adults with thrombocytopenia associated with liver disease prior to an elective procedure*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁴⁵ NCT00742859. *A phase 2, randomized, parallel group, dose finding, multicenter, multinational study of the safety, tolerability and pilot efficacy of three blinded doses of the oral Factor Xa inhibitor betrixaban compared with open label dose-adjusted warfarin in patients with non-valvular atrial fibrillation (EXPLORE Xa)*. Available at: www.clinicaltrials.gov.
- ⁴⁶ Press release. *Portola's factor Xa inhibitor betrixaban successfully passes futility analysis in phase 3 APEX study; trial continues as planned and remains on track for enrollment completion by year-end*. February 5, 2015. Available at: <http://www.marketwatch.com/story/portolas-factor-xa-inhibitor-betrixaban-successfully-passes-futility-analysis-in-phase-3-apex-study-trial-continues-as-planned-and-remains-on-track-for-enrollment-completion-by-year-end-2015-02-05>.
- ⁴⁷ Tao Y, Liang G. *Efficacy of adenosine A2A receptor antagonist istradefylline as augmentation for Parkinson's disease: A meta-analysis of randomized controlled trials*. *Cell Biochem Biophys*. 2015;71(1):57-62.
- ⁴⁸ Control number 169689. *A phase 3, 12-week, double-blind, placebo-controlled, randomized, multicenter study to evaluate the efficacy of oral istradefylline 20 and 40 mg/day as treatment for subjects with moderate to severe Parkinson's disease*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.

-
- ⁴⁹ Kondo T, Mizuno Y; Japanese Istradefylline Study Group. *A long-term study of istradefylline safety and efficacy in patients with Parkinson disease*. Clin Neuropharmacol. 2015;38(2):41-6.
- ⁵⁰ Griffiths CE, Reich K, Lebwohl M, et al; UNCOVER-2; UNCOVER-3 investigators. *Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials*. Lancet. 2015; Jun 9. pii: S0140-6736(15)60125-8.
- ⁵¹ Control number 162961. *A multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of LY2439821 to etanercept and placebo in patients with moderate-to-severe plaque psoriasis*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵² Control number 184282. *A multicenter, randomized, double-blind study comparing the efficacy and safety of ixekizumab dosing regimens in patients with moderate-to-severe plaque psoriasis*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵³ Control number 163730. *A multicenter, randomized, double-blind, active and placebo-controlled 16-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in patients with active ankylosing spondylitis*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵⁴ Thöne J, Ellrichmann G. *Oral available agents in the treatment of relapsing remitting multiple sclerosis: an overview of merits and pitfalls*. Drug Healthc Patient Saf. 2013;5:37-47.
- ⁵⁵ D'Haens G, Sandborn WJ, Colombel JF, et al.; on behalf of the Laquinimod for Crohn's Disease Investigators. *A phase II study of laquinimod in Crohn's disease*. Gut. 2015;64(8):1227-35.
- ⁵⁶ Control number 178380. *A multinational, multicenter, randomized, double blind, parallel group, placebo controlled study to evaluate the efficacy, safety, and tolerability of once daily oral administration of laquinimod (0.6 or 1.5 mg) in patients with primary progressive multiple sclerosis (PPMS)*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵⁷ Control number 171526. *A phase III, open-label induction and maintenance study in active moderate to severe Crohn's disease patients*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵⁸ Control number 171534. *A phase III, randomized, double blind, placebo controlled 52 week maintenance of remission study of laquinimod in Crohn's disease patients*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁵⁹ Control number 171267. *A phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability of laquinimod in active moderate to severe Crohn's disease patients*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁶⁰ Control number 176036. *A multicenter, multinational, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of laquinimod (0.5, 1.0 and 1.5 mg/day) as treatment in patients with Huntington's disease*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.

-
- ⁶¹ Control number 165969. *A phase III, randomized, double-blind, placebo-controlled study to assess the efficacy and safety, and tolerability of lebrikizumab in adolescent patients with uncontrolled asthma who are inhaled corticosteroids and a second controller medication.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁶² Control number 166218. *A phase III, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lebrikizumab in patients with uncontrolled asthma who are on inhaled corticosteroids and a second controller medication.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁶³ Control number 182779. *A phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma.* Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁶⁴ Hanania NA, Noonan M, Corren J, et al. *Lebrikizumab in moderate-to-severe asthma: pooled data from two randomized placebo-controlled studies.* *Thorax*. 2015;70(8):748-56.
- ⁶⁵ Li N, Li Q, Tian XQ, et al. *Mipomersen is a promising therapy in the management of hypercholesterolemia: a meta-analysis of randomized controlled trials.* *Am J Cardiovasc Drugs*. 2014; 14(5):367-76.
- ⁶⁶ NCT00607373. *A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of mipomersen as add-on therapy in homozygous familial hypercholesterolemia subjects.* Available at: www.clinicaltrials.gov.
- ⁶⁷ Panta R, Dahal K, Kunwar S. *Efficacy and safety of mipomersen in treatment of dyslipidemia: a meta-analysis of randomized controlled trials.* *J Clin Lipidol*. 2015;9(2):217-25.
- ⁶⁸ Virtual MS Center. *A drug similar to rituximab will soon be available to people with MS.* July 2, 2015. Available at: <http://www.healthcarejourney.com/physician-blog/a-drug-similar-to-rituximab-will-soon-be-available-to-people-with-ms>.
- ⁶⁹ Roche Investor Update. *Roche's ocrelizumab significantly reduced both relapses and disability progression versus interferon beta-1a (Rebif®) in two Phase III studies in multiple sclerosis.* June 30, 2015. Available at: <http://www.roche.com/investors/updates/inv-update-2015-06-30b.htm>.
- ⁷⁰ NCT01412333. *A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis.* Available at: www.clinicaltrials.gov.
- ⁷¹ Brossard P, Derendorf H, Xu J, et al. *Pharmacokinetics and pharmacodynamics of ponesimod, a selective S1P1 receptor modulator, in the first-in-human study.* *Br J Clin Pharmacol*. 2013;76(6):888-96.
- ⁷² Vaclavkova A, Chimenti S, Arenberger P, et al. *Oral ponesimod in patients with chronic plaque psoriasis: a randomised, double-blind, placebo-controlled phase 2 trial.* *Lancet*. 2014;384(9959):2036-45.
- ⁷³ FierceBiotech. *Actelion launches Phase III MS test for ponesimod.* April 16, 2015. Available at: <http://www.fiercebiotech.com/story/actelion-launches-phase-iii-ms-test-ponesimod/2015-04-16>.
- ⁷⁴ NCT02425644. *Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple*

-
- sclerosis. Available at: www.clinicaltrials.gov.
- ⁷⁵ NCT00101426. *Safety and efficacy trial of ranirestat (AS-3201) in patients with diabetic sensorimotor polyneuropathy*. Available at: www.clinicaltrials.gov.
- ⁷⁶ Deeks ED. *Safinamide: first global approval*. *Drugs*. 2015;75(6):705-11.
- ⁷⁷ Kandadai RM, Jabeen SA, Kanikannan MA, Borgohain R. *Safinamide for the treatment of Parkinson's disease*. *Expert Rev Clin Pharmacol*. 2014;7(6):747-59.
- ⁷⁸ NCT00605683. *A Phase III, double-blind, placebo-controlled randomised trial to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of safinamide, as add-on therapy, in subjects with early idiopathic Parkinson's disease treated with a stable dose of a single dopamine agonist*. Available at: www.clinicaltrials.gov.
- ⁷⁹ Deeks ED. *Safinamide: first global approval*. *Drugs*. 2015;75(6):705-11.
- ⁸⁰ Sitbon O, Morrell N. *Pathways in pulmonary arterial hypertension: the future is here*. *Eur Respir Rev*. 2012;21(126):321-7.
- ⁸¹ NCT01106014. *A multicenter, double-blind, placebo-controlled phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension*. Available at: www.clinicaltrials.gov.
- ⁸² News release. *Actelion's NDA for selexipag (Uptravi) accepted by the FDA*. March 3, 2015. Available at: http://www.drugs.com/nda/uptravi_150303.html.
- ⁸³ Schnitzer TJ, Marks JA. *A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee*. *Osteoarthritis Cartilage*. 2015;23 Suppl 1:S8-17.
- ⁸⁴ Bramson C, Herrmann DN, Carey W, et al. *Exploring the role of tanezumab as a novel treatment for the relief of neuropathic pain*. *Pain Med*. 2015;16(6):1163-76.
- ⁸⁵ Sopata M, Katz N, Carey W, et al. *Efficacy and safety of tanezumab in the treatment of pain from bone metastases*. *Pain*. 2015 Apr 25. [Epub ahead of print]
- ⁸⁶ Control number 185218. *A phase 3, randomized, double-blind, placebo and active-controlled, multicenter, parallel-group study of the analgesic efficacy and safety of tanezumab in adult subjects with chronic low back pain*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁸⁷ Dragovich T, Laheru D, Dayyani F, et al. *Phase II trial of vatalanib in patients with advanced or metastatic pancreatic adenocarcinoma after first-line gemcitabine therapy (PCRT O4-001)*. *Cancer Chemother Pharmacol*. 2014;74(2):379-87.
- ⁸⁸ NCT00056459. *A randomized, double-blind, placebo-controlled, phase III study in patients with metastatic adenocarcinoma of the colon or rectum who are receiving first-line chemotherapy with oxaliplatin/5-fluorouracil/leucovorin with PTK787/ZK 222584 or placebo*. Available at: www.clinicaltrials.gov.
- ⁸⁹ Davids MS, Letai A. *ABT-199: taking dead aim at BCL-2*. *Cancer Cell*. 2013;23(2):139-41.

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- ⁹⁰ Press release. *Investigational medicine venetoclax receives breakthrough therapy designation in relapsed or refractory chronic lymphocytic leukemia in previously treated patients with the 17P deletion genetic mutation*. May 6, 2015. Available at: <http://abbvie.mediaroom.com/2015-05-06-Investigational-Medicine-Venetoclax-Receives-Breakthrough-Therapy-Designation-in-Relapsed-or-Refractory-Chronic-Lymphocytic-Leukemia-in-Previously-Treated-Patients-with-the-17p-Deletion-Genetic-Mutation>.
- ⁹¹ Control number 166664. *A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed or refractory chronic lymphocytic leukemia harboring the 17P deletion*. Health Canada's Clinical Trials Database. Available at: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>.
- ⁹² Product monograph accessible at: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>.
- ⁹³ Product monograph accessible at: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>.
- ⁹⁴ Pakhale S, Mulpuru S, Verheij TJ, et al. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev*. 2014. Oct 9;10:CD002109.
- ⁹⁵ News release. *Phase 3 studies for new drug for benign prostatic hypertrophy fail*. December 1, 2014. Available at: <http://www.innovationbreakdownbook.com/blog/2014/11/5/phase-3-studies-of-new-drug-for-benign-prostatic-hypertrophy-fails>.
- ⁹⁶ Kopelman P, Groot Gde H, Rissanen A, et al. *Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: comparison with orlistat (Xenical)*. *Obesity* (Silver Spring). 2010;18(1):108-15.
- ⁹⁷ Gras J. *Cetilistat for the treatment of obesity*. *Drugs Today (Barc)*. 2013;49(12):755-9.
- ⁹⁸ Kinoshita S, Awamura S, Nakamichi N, Suzuki H, et al; Rebamipide Ophthalmic Suspension Long-term Study Group. *A multicenter, open-label, 52-week study of 2% rebamipide (OPC-12759) ophthalmic suspension in patients with dry eye*. *Am J Ophthalmol*. 2014;157(3):576-83.e1.
- ⁹⁹ Abdulkadyrov KM, Salogub GN, Khuazheva NK, et al. *Sotatercept in patients with osteolytic lesions of multiple myeloma*. *Br J Haematol*. 2014;165(6):814-23.