1. Monitoring of Compliance with Exenatide Prescribing Guidelines in Canada

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3. Monitoring of Compliance with Exenatide Prescribing Guidelines in Canada Study Protocol

3.1 Rationale

Exenatide is an injectable glucagon-like peptide 1 (GLP-1) receptor agonist approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) by the United States and Europe. Byetta (exenatide twice daily) is administered as a subcutaneous injection within 1 hour before the two main meals of the day, approximately 6 hours or more apart. Treatment is typically initiated at 5 mcg per dose, twice daily, and may be increased to 10 mcg twice daily based on the patient's clinical response.

During Health Canada's review of the marketing authorisation application of exenatide, Lilly provided a commitment to monitor the off-label use and compliance to the Summary of Product Characteristics (SPC) of exenatide prescriptions through a post-launch utilization study. Specifically, Health Canada requested that:

> *The RMP should be revised to include a post-marketing study conducted on exenatide use and adherence to labeling recommendations in Canada, similar to the drug utilization study requested by the EU Regulatory authority that is currently ongoing in various EU countries. Since preliminary information has already indicated off label use of exenatide with either TZD or insulin in the EU, the need for further study and/or additional risk management actions with these products should be specifically addressed.*

Table 1: Canadian Byetta Indication

Byetta Monograph
Indication and Clinical Use:
BYETTA is indicated in combination with metformin and/or sulfonylurea to improve glycemic control in patients with type 2 diabetes mellitus, when maximally tolerated doses of these oral therapies in addition to diet and exercise do not provide adequate glycemic control.
BYETTA is indicated in combination with insulin glargine (with or without metformin) to improve glycemic control in patients with type 2 diabetes mellitus when insulin glargine (with or without metformin) in addition to diet and exercise, does not provide adequate glycemic control
Contraindication:
BYETTA should not be used in the pediatric patient population.

BYETTA should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min), including patients receiving dialysis
BYETTA is contraindicated in patients with diabetic ketoacidosis, diabetic coma/precoma or type 1 diabetes mellitus.

Source: Byetta Drug Product Monograph, Canadian Pharmacists Association, online version, April 2011.

3.2 Objectives

IMS Brogan will conduct a study to assess Byetta use and adherence to the Canadian indications and clinical use recommendations since its launch in the Canadian market.

3.2.1 Primary Objectives

To evaluate exenatide use outside labeling indications in Canada.

3.2.2 Secondary Objective

To assess the concomitant use of exenatide with either thiazolinediones (TZDs) or insulin.

3.3 Data Source

The proposed study will utilize data from the IMS Brogan's Longitudinal Patient Data assets (LRx). LRx tracks the prescription activity of anonymized patients over time (longitudinally), with records dating back to 2004. Collection of prescriptions that include anonymized patient data from approximately 4,000 pharmacies nationwide enables visibility to all payer types and is ideally suited to provide insights into chronic, retail-based markets. LRx data is un-projected and is based on a large sample (~75% coverage nationally, see table 1). By tracking patient prescription history, LRx goes beyond measuring prescription volumes to tracking real-world behaviour and use.

Table 2: Coverage of LifeLink (LRx) Patient Longitudinal Database

Region	**% Coverage** *As a % of projected Rx volume in CompuScript – MAT Dec 2011*
Total Canada	**74.6%**
British Columbia	66.4%
Alberta	68.8%

Saskatchewan	71.9%
Manitoba	79.6%
Ontario	75.8%
Quebec	76.7%
New Brunswick	95.7%
Nova Scotia	67.2%
Newfoundland / PEI	53.1%

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3.4 Study Overview

3.4.1 *Assumptions*

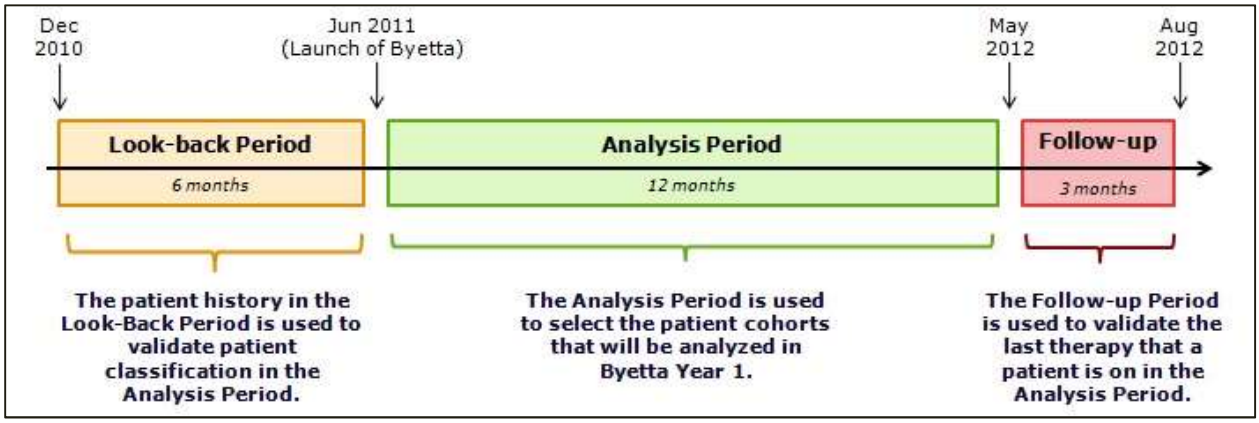
IMS data in Canada does not contain diagnosis codes, therefore disease indications will be inferred from pattern of drug treatment. We assume that pattern of drug treatment predicts indication and identifies Type 2 diabetes patients. For example, a patient who receives no OADs prior to insulin treatment would be classified as Type 1 Diabetes, while a patient who receives an OAD at any point in time would be classified as Type 2 Diabetes. We also assume the molecules used in the Diabetes market definition are used exclusively for diabetes treatment and we will not consider off-label use (e.g.. metformin for treatment of polycystic ovary syndrome. This use is expected to be very small.).

3.4.2 Study Design

This will be a retrospective database study using IMS Brogan's LRx dataset, in which de-identified patient level prescription information will be used to evaluate adherence to the labeling recommendations for exenatide use in Canada. The study will be based on a 'Look-Back,' 'Analysis' and 'Follow-Up' period as shown in figure 1. Patients will be selected for the study if they are receiving a Byetta prescription in the 12 month analysis period.

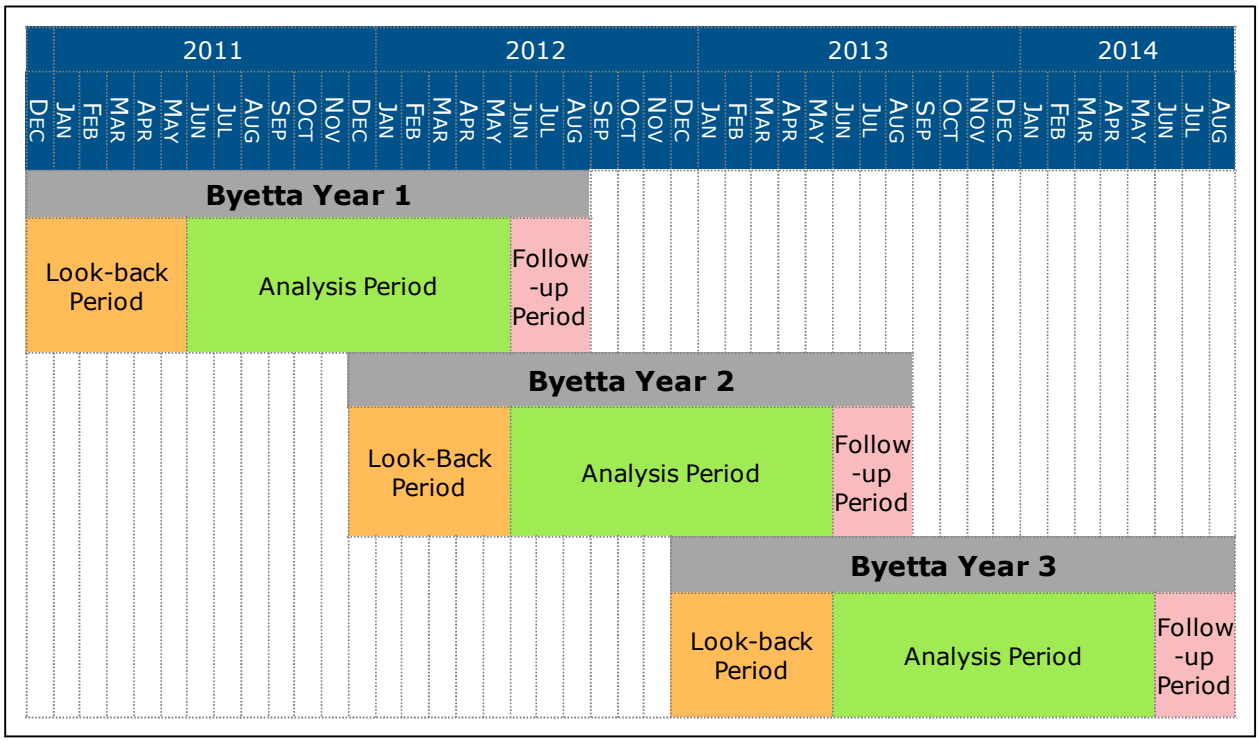
The 'Look-back' period is used to ensure that each patient within the analysis period has at least 6 months of data prior to first Byetta script. This eligibility period ensures that a patient whose first Byetta script occurs at the start of the analysis period can be classified appropriately and that they are present in the database prior to the first script. Similarly, the 'Follow-up' period is used to ensure that each patient has at least 3 months of data following the last script within the analysis period. This ensures that the duration of therapy for a patient who receives their last script at the end of the analysis period is accounted for and can have their therapy appropriately classified, specifically around the concomitant use of Byetta with insulin or TZDs.

Figure 1: Study periods proposed for analysis of Byetta use in the 1st year post launch



In addition to the study period proposed in figure 1, the analysis will be conducted for Year 1, 2 and 3 post Byetta launch allowing for an analysis of trends in Byetta use over time, as shown in figure 2. Study 1* will provide results on Year 1 and 2 and would commence at the availability of Aug 2013 data. Study 2** will provide Year 3 results and would commence at the availability of Aug 2014 data.

Figure 2: Three proposed analysis periods for study post Byetta Launch



Note: *Implies that the look-back period and the follow-up period are at least 6 months and 3 months for each patient, respectively.*

Note: *Month 1 = Date of First Byetta Sale = June 2011*

**Study 1: All Byetta prescriptions in the database in months 0-24, post launch*

*** Study 2: All Byetta prescriptions in the database in months 25-36, post launch*

3.4.3 Study Population

Inclusion/Exclusion Criteria:

All patients in the LRx database who have been prescribed Byetta in Canada during the analysis period will be included in the study. Patients with inconsistent records and/or insufficient data, as shown in table 3, will be omitted to restrict the analysis to a consistent and robust patient sample.

Exclusion criteria are required since the pharmacy data (LRx) is driven through data entry at the individual stores. The criteria are used to filter out transactions that either have entry mistakes or have place-holder information that is not accurate. The exclusion criteria are established to ensure a consistent record for patients in the study sample. Inclusion and exclusion criteria may be modified during the initial stages of the project.

Table 3: Exclusion criteria applied to remove patients with inconsistent Rx history

Criteria	Conditions for Exclusion	Rationale
Demographic Criteria	Patients without a consistent year of birth, province, or gender	Patients without a consistent demographic record of gender, year of birth and province are not reliable due to inconsistencies
Constant Store Criteria	Patients at stores with inconsistent reporting after May 2011	Stores with inconsistent recorded information will not have accurate information on what prescriptions a patient received
Max Rx Criteria	Patients with more than 208 Rx/year	This is to eliminate pharmacist error
Min Rx Criteria	Patients with fewer than 6 Rx	Patient with less than 6 prescriptions are excluded because there is the potential for including the same patient multiple times as occasionally patients fill prescriptions at different pharmacies when traveling or for convenience
Consistent Patients	Remove patients without any prior Rx at a store	Removing patients without any other prior prescriptions at a store also eliminates patients who have changed pharmacies and may be included multiple times in the data
Analysis Period	Remove patients without any	Patients who do not have a prescription

	Rx in the Analysis Period	in the analysis period cannot be included as they do not have any prescriptions to analyze
12 Month Gap	Remove patients with a year gap between Diabetes Rx	Patients with a year gap between diabetes prescriptions are likely to have filled prescriptions at an alternative pharmacy and could be counted multiple times in the data set
6-month look back data	Remove patients without 6 months of data prior to first Byetta script	Ensures all patients are present in the dataset and have a consistent record for analysis
3-month Follow-up data	Remove all patients without 3 month follow-up data	Ensures patients therapy can be appropriately classified as add-on or switch

To identify other diabetes therapies for the selected patients, prescriptions for product groups in table 2 will also be tracked for selected patients

Table 4: Diabetes therapies tracked for Byetta patients

Category	Product Group	Product
Insulin	**Premix Human**	Lilly Human Premix, NNCI Human Premix
	Premix Analog	Humalog Mix, NovoMix
	Basal Human	Novolin NPH, Humulin N
	Basal Analog	Lantus, Levemir
	Rapid Human	Humulin R, Novolin Toronto
	Rapid Analog	Apidra, Humalog, NovoRapid
OAD	**Metformin**	Metformin
	Sulfonylurea (SU)	Diamicron / Diamicron MR, Gliclazide, Glimepiride/ Amaryl, Glyburide
	Thiazolidinedione (TZD)	Avandamet, Avandaryl, Actos, Avandia, Generic Pioglitazone
	PPG Regulators	GlucoNorm, Starliz, Generic Repaglinide
	DPP4	Januvia, Onglyza, Janumet, Trajenta

	Prandase	Prandase
GLP1	**GLP1**	Victoza, Byetta

3.4.4 Study Outcomes and Definitions

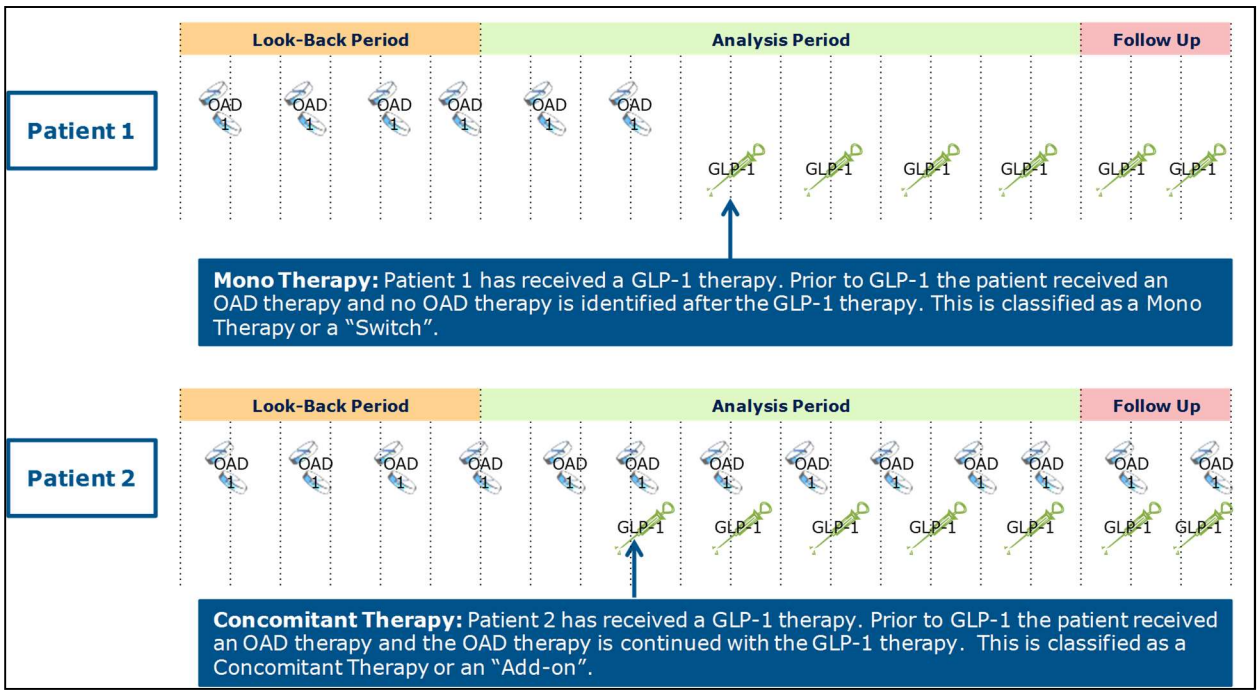
The primary outcome of interest is the off label use of Byetta in Canada.

A patient's therapy type will be inferred by identifying if a patient switches between, or adds on to therapies, as shown in figure 3.

Mono Therapy is defined as a patient receiving a specific therapy (Therapy 1) prior to a different therapy (Therapy 2) where Therapy 1 is not detected after Therapy 2 initiation. Mono therapy for this study, refers to a patient received a prescription for only one product at a given time.

Concomitant Therapy is defined as a patient receiving a specific therapy (Therapy 1) prior to a different therapy (Therapy 2) where Therapy 1 is detected after Therapy 2 initiation.

Figure 3: Distinguishing between add-on and switch therapies



Patients will be selected for the study if they receive a Byetta script anytime during the analysis period and if they met the inclusion criteria. To identify on-label vs. off-label use, patient history will then be used to classify patients as "inferred on-label" if they also received Metformin and/or SU or Lantus during the study (Business rules 1 and 2 in Table 5).

All other patients that do not meet the criteria for use of Byetta with metformin and/or SU or Lantus will be classified as "inferred off-label". The group of patients classified as "inferred off-label" will then be further classified to gain a better understanding of the trends in "inferred off-label" use of Byetta (Business rules 3-10 in Table 5).

The Business rules described in Table 5 are prioritized to ensure the appropriate classification of each patient. Therefore patients will be classified based on the highest rank business rule. For example, if a patient receives scripts for both Metformin and other insulin during the analysis period, they will be classified as "inferred on-label" as they have a script for metformin and therefore are classified by business rules 1 and 2

Note: The patient classification categories ('Inferred Adherence Label') can be modified in the initial phase of the project.

Table 5: Business rules applied to classify patients as "on-label" vs. "off-label"

(The business rules have been structured to align with the Canada monograph for Byetta indication and clinical use (see Table 1) and will be finalized upon study initiation).

Rank	Business Rules	Cohort Description	Inferred Adherence Label
1	Concomitant use of***** Byetta with metformin (met) and/or sulfonylurea (SU), **OR** Concomitant use of Byetta with Lantus	Met and/or SU or Lantus is prescribed with Byetta	Inferred On-label
2	Evidence of****** Byetta and metformin and/or sulfonylurea **OR** Evidence of Byetta and Lantus	Met and/or SU or Lantus is not prescribed with Byetta, but both appear in the analysis period	Inferred On-label
3	Evidence of Byetta and Levemir	Levemir is prescribed in the analysis period	Off-Label Insulin Use
4	Evidence of Byetta and Human Basal Insulin	Human basal insulin is prescribed in the analysis period	
5	Evidence of Byetta and thiazolidinedione (TZD)	TZD is prescribed in the analysis period	Off-Label OAD Use

6	Byetta Alone	No other products prescribed in the analysis period	Inferred Off-label
7	Evidence of Byetta and all other insulin	Other insulin is prescribed in the analysis period	
8	Evidence of Byetta and all other OADs	Other OADs are prescribed in the analysis period	
9	Pediatric Patients	Patient is under the age of 18 (<18)	
10	All other combinations	All other combinations	

Note: *Evidence of Diabetic ketoacidosis, diabetic coma/precoma and end stage renal disease cannot be inferred from the dataset; therefore we will not be able to identify these patients as a separate group*

***** *"Concomitant use of…" refers to continued use of Byetta and other product*

****** *"Evidence of…" refers to anytime within the study period including look-back or look forward periods*

3.4.5 Sample Size

All patients in the LRx database who have been prescribed Byetta in Canada during an analysis period and met the inclusion criteria will be included in the study. In similar studies in this market ~500,000 patient records have passed selection criteria for inclusion to a study sample. However the anticipated use of Byetta amongst this patient population in the first year of marketing in Canada is unknown at the present time and is projected to be modest. Upon initiation of the study, IMS Brogan will analyze the dataset to identify the number of patients available for study (the number of patients on Byetta in the analysis period). The number of Byetta patients is expected to rise in each year analyzed.

To allow for sufficient patients for a robust analysis, we will perform the first study 2 years after Byetta's launch in Canada, analyzing the two years separately (see figure 2). The analysis will be repeated in the subsequent year, to capture additional Byetta patients and identify shifts in Byetta usage.

3.4.6 Analysis Plan

The data extracted will be analyzed to complete the following 3 tables requested for each study year. The results will be provided as percent of patients who are "inferred on-label" and patients who are "inferred off-label", stratified by gender. Any off-label use in the pediatric population will be described (by gender and concomitant use).Results for the first report (year 1 and year 2 data) will be available in Q4 of 2013 and results for year 3 data will be available in Q4 of 2014.

Table 6: Indications for patients prescribed Byetta

(Patients over the age of 18)

Indication	Male		Female	
	# of Patients	% of Patients	# of Patients	% of Patients
Inferred On-Label				
Off-Label Insulin Use				
Off-Label OAD Use				
Off-Label				

Table 7: Byetta Concomitant medications

Concomitant medications	All Patients (>17 yrs) N (%)	Inferred On-Label N (%)	Inferred off-label (all combinations) N (%)	Off-Label Insulin Use N (%)	Off-Label OAD Use N (%)	Off-Label N (%)
Oral anti-glycaemics						
Metformin						
SU						
TZD						
Others						
Insulin						

3.4.7 Limitations

Based on restrictions in Canada, diagnosis can only be inferred. Therefore on-label and off-label use is an estimation based on the applied rules. The off-label use is likely over-estimated as the rules to include a patient in on-label and stringent and all other patients are considered off-label.

Counter indications such as diabetic ketoacidosis, diabetic coma/precoma and end-stage renal failure cannot be inferred from the data source. Therefore, these patients will not be identified in the study.

There is differing amount of information for each patient due to the fixed time frame of the analysis. Since each patient will have a different index date the amount of data will differ for those patients who initiate Byetta at the start of the analysis period compared to patients who initiate Byetta at the end of the analysis

period. This is ensures we have as much data available as possible for each patient so they can be classified appropriately

3.4.8 Adverse Events

Given the retrospective nature of this study (ie use of existing data), no AE data will be collected or reported from this study.

3.5 Dissemination Plan

This study will be used for regulatory purposes and dissemination.

The results may be presented at one or more scientific conferences. In addition, the results may be published in a relevant journal. However, IMS Brogan must be sourced as the supplier of the data and must provide written consent prior to publication or presentation.

4 References

N/A