Non-Interventional Study Report

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Version	1
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Monitoring of Compliance with Exenatide Prescribing Guidelines in Canada
Drug Utilisation Study of BYETTA in Canada for 2011-2014

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
MAH	Marketing authorisation holder
DUS	Drug utilisation study
OAD	Oral antidiabetic drug
SAE	Serious adverse event
TZD	Thiazolidinediones

RESPONSIBLE PARTIES

Name	Professional Title	Role in Study	Affiliation	Email Address
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STUDY REPORT SUMMARY (ABSTRACT)

Study Description

BYETTA (exenatide BID) post launch utilisation was investigated based on retrospective data analysis of IMS Brogan Canada prescription database documented between May 2011 and May 2014. A total of 1,027 unique patients treated with BYETTA were included in the study. During the three-year period post launch, the majority of patients (97%) were treated with BYETTA in accordance with the Canadian Product Monograph, while off-label behaviour mostly in conjunction with basal insulins was identified. Only <5 paediatric patients (<0.49%) were receiving BYETTA during the analysis period.

AMENDMENT HISTORY

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
Not applicable		

MILESTONES

Date	Milestone
May 31, 2013	Years 1-2 data collection period completed
May 31, 2014	Year 3 data collection period completed

1. BACKGROUND AND RATIONALE

1.1 Background

BYETTA (exenatide BID) 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). BYETTA should be initiated at 5 µg per dose administered twice daily (BID) in patients with type 2 diabetes mellitus who are already receiving metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. Based on clinical response, the dose of BYETTA can be increased to 10 µg BID after 1 month of therapy to further improve glycemic control, as tolerated. The maximum dose is 10 µg BID. If no improvement in blood glucose control is seen after 3-4 months, alternative therapies should be considered.

During Health Canada's review of the marketing authorisation application of BYETTA, Eli Lilly (the original MAH for BYETTA) provided a commitment to monitor the off-label use and compliance to the Product Monograph of BYETTA prescriptions through a post-launch drug 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 labelling 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.

The indications for use of BYETTA in Canada are:

Add-on to metformin and/or sulfonylurea:
BYETTA® (exenatide) injection is indicated in combination with metformin, and/or a 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.

Add-on to insulin glargine:
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.

The contraindications for BYETTA in Canada are:

- BYETTA is contraindicated in patients with known hypersensitivity to this product or any of its components.

- 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.

Further information regarding the background, pharmacological class, properties, the mechanism of action of BYETTA and the most up-to-date information on its safety profile can be found in the approved Canadian Product Monograph.

1.2 Rationale

The study was undertaken in order to characterise the post-launch use of BYETTA in Canada and evaluate the compliance with the approved Canadian Product Monograph.

2. OBJECTIVES

IMS Brogan has been contracted to conduct a drug utilisation study (DUS) to assess BYETTA use and adherence to the Canadian indications and clinical use recommendations since its launch in the Canadian market.

2.1 Primary Objective

To evaluate BYETTA use outside labelling indications in Canada.

2.2 Secondary Objective

To assess the concomitant use of BYETTA with either thiazolidinediones (TZD) or insulin.

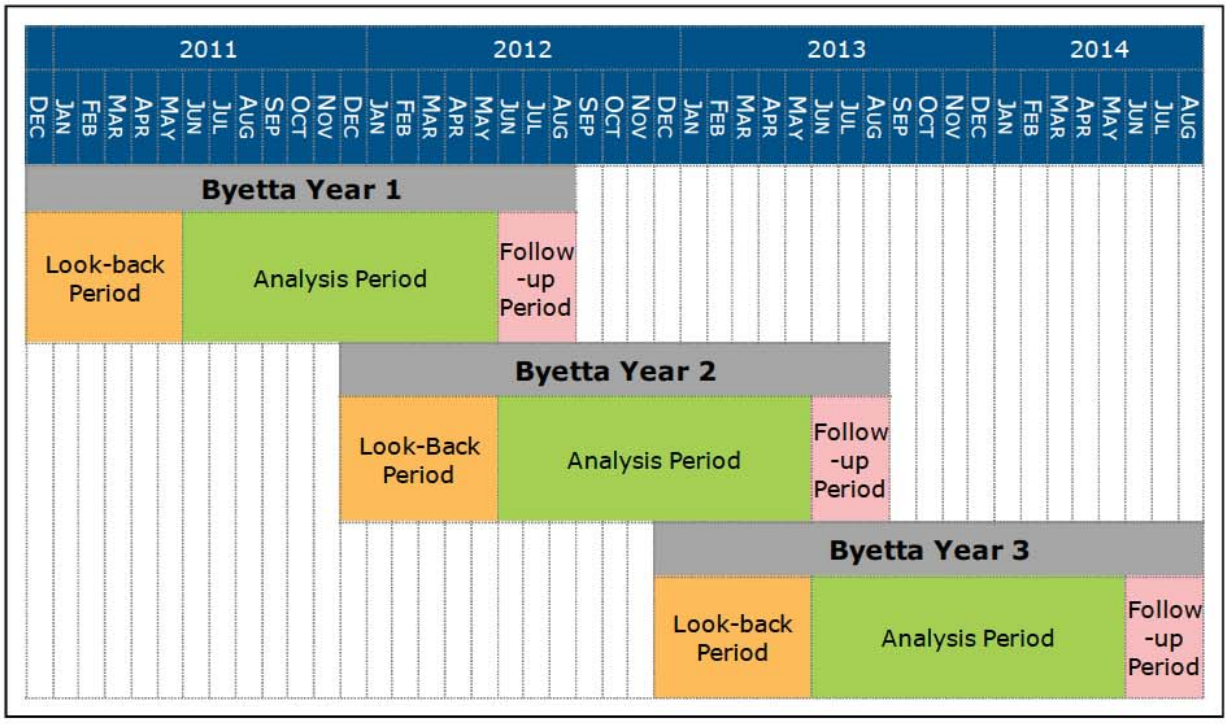
3. METHODOLOGY

3.1 Study Design – General Aspects

The study was designed as a retrospective cohort study utilising data from the Canadian IMS Brogan's Longitudinal Patient Data assets (LRx). De-identified patient level prescription information was used to evaluate adherence to the labelling recommendations for BYETTA use in Canada. Patient records were selected for the study if patients were prescribed BYETTA in the analysis period (June 2011 to May 2014). Concomitant medications at the time the Byetta was prescribed and during the entire study period were investigated. The

analysis was conducted for Years 1, 2 and 3 post BYETTA launch (2011-2014) allowing for an analysis of trends in BYETTA use over time, as shown in Figure 1.

Figure 1 Three 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

3.2 Data Source

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 1 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%

MAT: Moving Annual Total (12 months of data based on the current month)

3.3 Study Population

IMS data in Canada does not contain diagnosis code, therefore, indication for usage was inferred from pattern of drug treatment. We assume that of patients identified through prescription of BYETTA, most were type 2 diabetes since the majority of the patients used BYETTA concomitantly with oral anti-diabetic medications, and were an adult (≥ 18 years of age) at the time of the BYETTA was prescribed. The eligible patients were all Canadian patients treated with BYETTA with a record in LRx from June 01, 2011 to May 30, 2014. Patients from 10 provinces were included in the study.

3.4 Inclusion Criteria

All patients in the LRx database who have been prescribed BYETTA in Canada during the analysis period were included in the study.

3.5 Exclusion Criteria

Exclusion criteria were required since the pharmacy data (LRx) is driven through data entry at the individual stores. Criteria were used to exclude patients and/or transactions where there were entry mistakes or which had place-holder information that wasn't accurate. The exclusion criteria were established to ensure a consistent record for patients in the study sample.

Table 2 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 >208 prescriptions of any antidiabetic drug per year	This is to eliminate pharmacist error
Min Rx Criteria	Patients with <6 prescriptions of any antidiabetic drug per year	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	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 otherwise included multiple times in the data
Analysis Period	Patients without any Rx in the Analysis Period	Patients who do not have a prescription in the analysis period cannot be included as they do not have any prescriptions to analyze
12 Month Gap	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 otherwise counted multiple times in the data set
6-month look back data	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	All patients without 3 month follow-up data	Ensures patients therapy can be appropriately classified as add-on or switch

4. VARIABLES AND MEASUREMENTS

Prescription patterns, transitional or concomitant use of BYETTA with other anti-diabetic drugs were identified and defined based on the rules described in this section.

4.1 BYETTA prescription

The study was based on a 'Look-Back,' 'Analysis' and 'Follow-Up' period. Patient records were selected for the study if they were treated with a BYETTA prescription in the analysis period.

The 'Look-back' period was 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.

4.2 Adherence to the BYETTA indication

The primary outcome of interest was the off-label use of BYETTA in Canada. Business rules were developed according to the Canadian Product Monograph for BYETTA and are outlined in the study protocol version 6 to identify patients with off-label use of BYETTA (Table 3). The study protocol version 6 was submitted to Health Canada in May 2013. The Business rules were prioritized to ensure the appropriate classification of each patient. Therefore patients were classified based on the highest rank business rule. For example, if a patient received scripts of BYETTA add-on to both metformin and other insulin during the analysis period, they were classified as "inferred on-label" as they have a script for metformin and therefore are classified by business rules 1 and 2. Three patients cohorts were defined by the business rules: Inferred On-label, Off-label and Inferred-Off-label (Table 3).

Table 3 Business rules applied to classify patients as "on-label" vs. "off-label"

Priority	Business Rules	Cohort Description	Inferred Adherence
1	Concomitant use of* BYETTA with metformin (met) and/or sulfonylurea (SU) OR Concomitant use of BYETTA with insulin glargine	Met and/or SU or insulin glargine is prescribed with BYETTA	Inferred On-label
2	Evidence of** BYETTA and metformin and/or sulfonylurea OR Evidence of BYETTA and insulin glargine	Met and/or SU or insulin glargine 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	Geriatric Patients	Patients over the age of 64 (>64)	
11	All other combinations	All other combinations	

Note 1: Where a patient fell into multiple categories, their classification defaulted to the higher priority (pediatric and geriatric patients [#9 and #10] were flagged regardless of the priority they fall into)
* "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

4.3 Other Variables and Covariates

4.3.1 Transition vs concomitancy

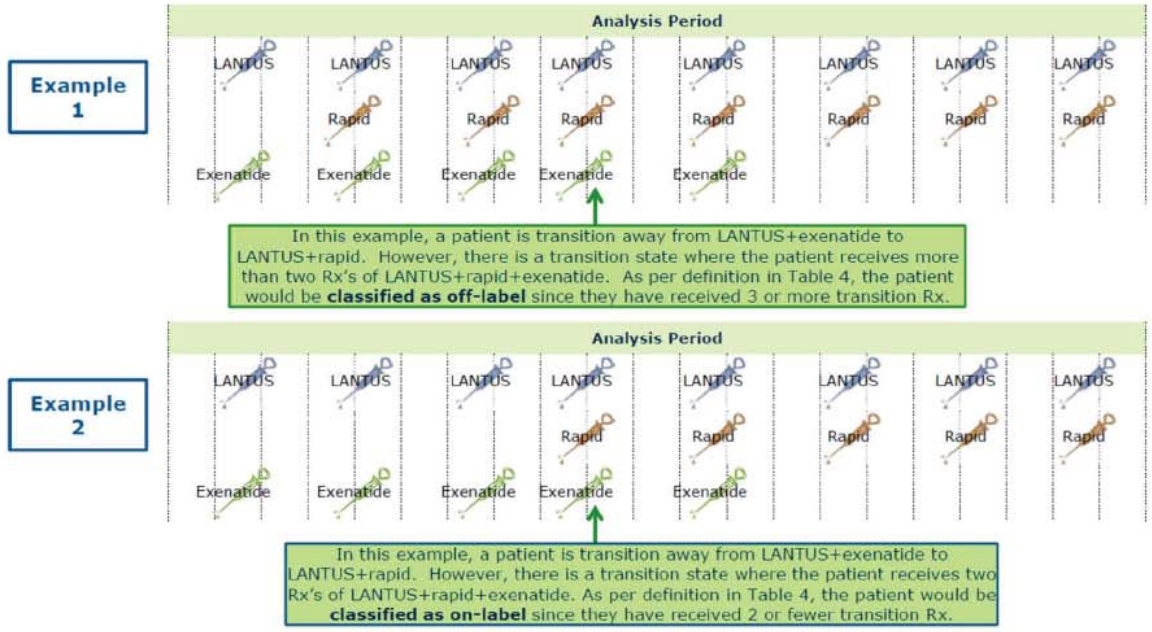
To further investigate patterns and drug classes of concomitancy, additional business rules were developed during the data analysis to separate concomitancy from transition according to a prescription history during the indexed study period (3 years).

Table 4 Rules for classification of transition and concomitancy

Cohort	Description	Interpretation
No following scripts	Following the first instance, drug X and exenatide are not seen concomitantly	Transitional patient
<3 following scripts	Drug X and exenatide are used concomitantly for less than 3 scripts	Transitional patient
≥3 following scripts	Drug X and exenatide are used concomitantly for 3 or more scripts	Concomitant patient
Multiple concomitant starts	Patients have multiple instances of Drug X and exenatide concomitancy in their treatment history	Concomitant patient

Drug X = rapid insulin, premix insulin, or VICTOZA (three separate analyses).

Figure 2 Distinguishing between add-on and switch therapies



4.3.2 Other anti-diabetic drugs than exenatide

Other classes of anti-diabetic drugs in addition to exenatide were included in the study and are listed in Table 5. This table was updated compared with the original study protocol version 6 in order to include the up-to-date availability of diabetes medications in Canada (specifically, canagliflozin [INVOKANA] was added to the list).

Table 5 Diabetes Medications Tracked for BYETTA patients

Category	Product Group	Product
Insulin	Analog Premix Insulin	Humalog Mix, NovoMix
	Human Premix Insulin	Lilly Human Premix, NNCI Human Premix
	insulin glargine	insulin glargine
	Levemir	Levemir
	Human Basal Insulin	Novolin NPH, Humulin N
	Analog Rapid Insulin	Apidra, Humalog, NovoRapid

	Human Rapid Insulin	Humulin R, Novolin Toronto
OAD	Metformin	Metformin and all generics
	Sulfonylurea (SU)	Diamicron / Diamicron MR, Gliclazide, Glimepiride/ Amaryl, Glyburide
	Thiazolidinedione (TZD)	Avandamet, Avandaryl, Actos, Avandia, Generic Pioglitazone
	DPP4s	Januvia, Janumet, Onglyza, Komboglyze*, Trajenta, Jentadueto*
	Prandase	Prandase
	PPG Regulators	GlucoNorm, Starliz, Generic Repaglinide
	SGLT-2	Invokana
GLP-1	Victoza	Victoza

5. STATISTICAL ANALYSIS

This was a retrospective cohort study, with no hypothesis test. Number and proportion of patients were classified in each patient cohort of "inferred on-label", "off-label" and "inferred off-label"; data were described by study year and gender. Overall off-label use was calculated. Concomitant use of BYETTA with insulin or TZD was further studied.

Data on age and gender were obtained based on records documented in the prescription database when a patient initiating a treatment with BYETTA. The patterns and drug classes of concomitant medications were studied and described for each of the three patient cohorts.

6. RESULTS

6.1 Study Participation

A total of 2093 patient records with prescriptions for BYETTA were initially selected for inclusion in the analysis. Of those, 35 patients were excluded for lacking a consistent year of birth, province, or gender; 213 patients were excluded for inconsistent reporting at stores; 740 patients were excluded for having <6 prescriptions for anti-diabetic medications per year; 3 patients were excluded for a gap of >12 month between their antidiabetic therapy prescriptions, and 75 patients were excluded for lacking any prescriptions in the analysed period. The final number of unique patients eligible for the data analysis was 1027 (Figure 3).

Figure 3 Patient attrition based on the exclusion criteria

Criteria and Conditions	# of Patients	% of Patients
Initial Patients with BYETTA Rx Selected	**2,093**	**100%**
Demographic Criteria Patients without a consistent year of birth, province, or gender	*(35)*	*(2%)*
Constant Store Criteria Patients at stores with inconsistent reporting after May 2011	*(213)*	*(10%)*
Max Rx Criteria Patients with >208 anti-diabetic Rx/year	*(0)*	*(0%)*
Min Rx Criteria Patients with <6 anti-diabetic Rx/year	*(740)*	*(35%)*
Consistent Patients Patients without any prior Rx at a store	*(0)*	*(0%)*
6 Months Look Back data Patients without 6 months of data prior to first BYETTA script	*(0)*	*(0%)*
3 Months Follow Up Data Patients without 3 months of follow-up data	*(0)*	*(0%)*
12 Month Gap Patients with a year gap between diabetes Rx	*(3)*	*(0%)*
Analysis Period Patients without any Rx in the selection period	*(75)*	*(4%)*
Final Patient Cohort *(Used in the Analysis)*	**1,027**	**49%**

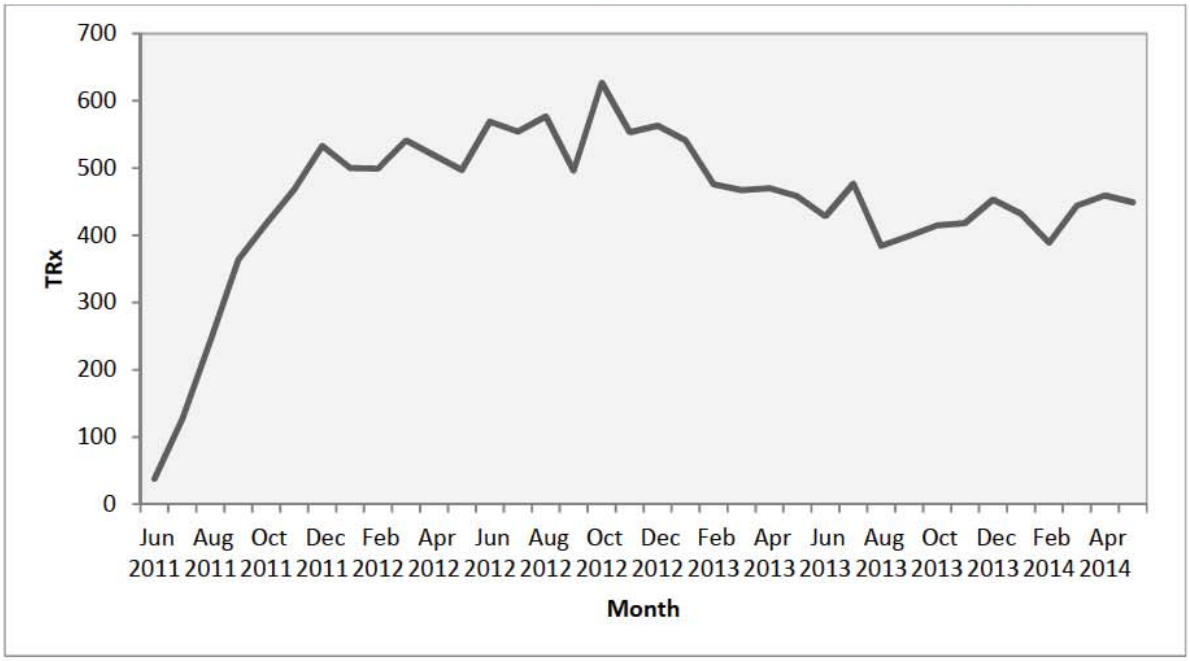
Patient Sample – Carried forward for analysis

6.2 Main Results

6.2.1 BYETTA use

The number of BYETTA prescriptions increased slowly during the first 6 months after launch but then remained relatively stable during Years 2 and 3 of the study (Figure 4). The total number of unique patients receiving BYETTA was 1027.

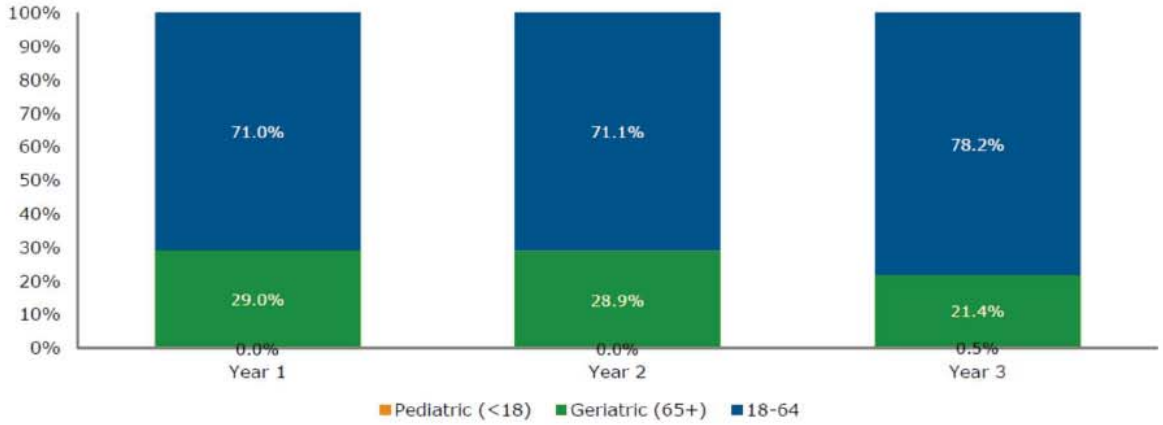
Figure 4 Total number of BYETTA prescriptions (June 2011 – August 2014)



6.2.2 Demographic and other subject characteristics

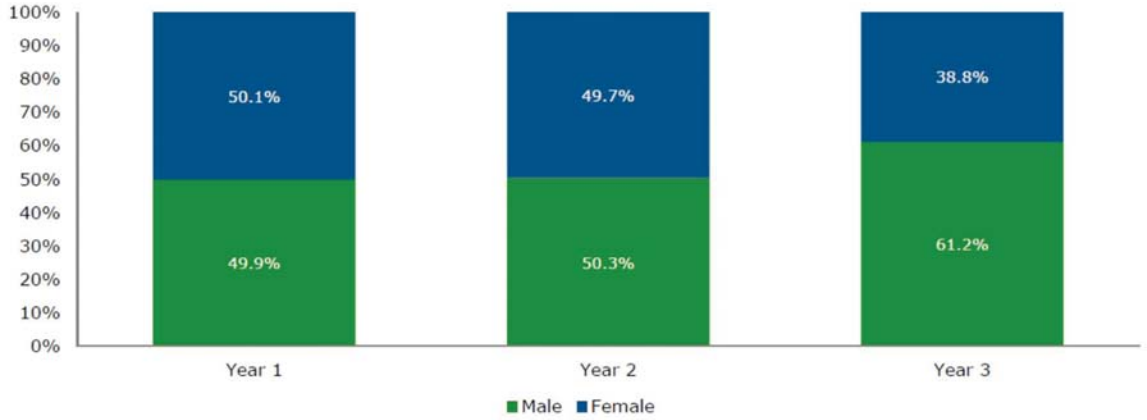
Of the 1027 BYETTA patients included in the study, 72% were between the ages of 18 and 64 years. Figure 5 shows the distribution of age by study year. Over the 3 years less than 5 patients were under 18 (more precise number cannot be provided due to privacy concerns). All paediatric patients received exenatide therapy in year 3. The distribution of age by study year is summarised in Figure 5.

Figure 5 BYETTA Patients by Age



The proportions of male and female patients treated with BYETTA were close to 50% during the first two years of the study, with an increase in the proportion of male patients in the third year (Figure 6). Over the 3 years there were a total of 537 males (52%) and 490 females (48%).

Figure 6 BYETTA Patients by Gender

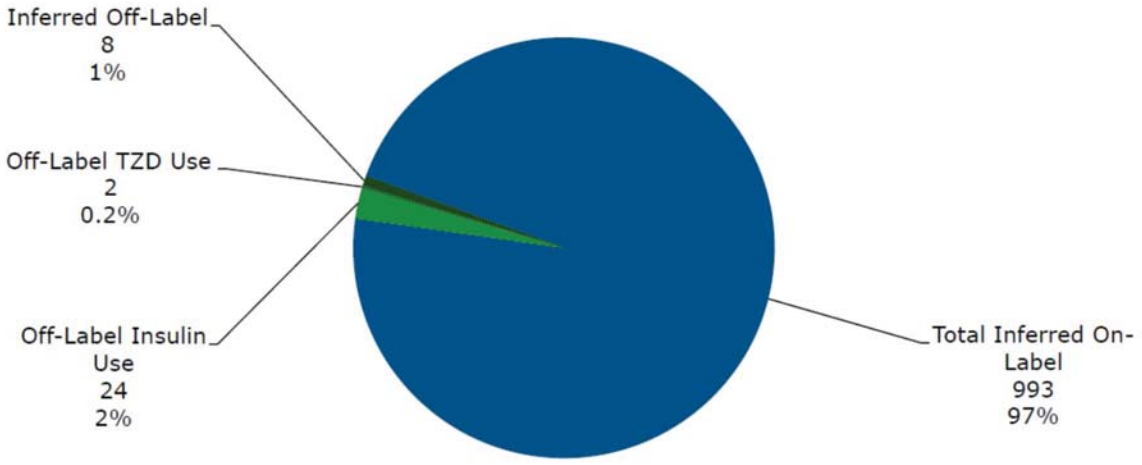


6.2.3 Overall Inferred Label Results

Based on the analysis of data from Years 1 through 3, approximately 97% (993) of patients are classified as 'inferred on-label' (Business rules priority 1 or 2) (Figure 7).

The remaining 3% (34) were considered as off-label or inferred 'off-label'. Approximately 2% of patients were classified as using off-label insulin (LEVEMIR and/or human basal insulin), 0.2% as off-label TZD use, whereas 1% were classified as inferred off-label use due to evidence of BYETTA use with any other OAD or any other insulin (Figure 7).

Figure 7 3 Year Total: BYETTA Label Results



The usage of BYETTA with particular antidiabetic medications is presented in Figure 8 and Tables 6-8 below. The majority of patients were using BYETTA with metformin and/or insulin glargine, in accordance with the product monograph. Insulin glargine, LEVEMIR, and basal insulins have accounted for 56% of combined total usage.

The proportions of patients for all inferred label categories remained stable throughout the duration of the study, with a modest increase in Year 3 in the off-label TZD use category (2.5% vs. 0.2% for Year 3 and Years 1-2, respectively).

Table 6 BYETTA Patients by Indication (Years 1-2)

Indication	Male		Female		Total	
	# of Patients	% of Patients	# of Patients	% of Patients	# of Patients	% of Patients
Inferred On-Label	423	97.2%	415	94.7%	838	96.2%
Off-Label Insulin Use	8	1.8%	15	3.4%	23	2.6%
Off-Label TZD Use	2*	0.5%	2*	0.5%	2*	0.2%
Inferred Off-Label	2*	0.5%	6	1.4%	8	0.9%
Total	436	100.0%	437	100.0%	873	100.0%

*Patient counts of <5 have been confidentialized to 2
**Table includes all patients over the age of 18

Table 7 BYETTA Patients by Indication (Year 3)

Indication	Male		Female		Total	
	# of Patients	% of Patients	# of Patients	% of Patients	# of Patients	% of Patients
Inferred On-Label	324	96.1%	254	93.7%	578	95.4%
Off-Label Insulin Use	2*	0.6%	9	3.3%	11	1.8%
Off-Label TZD Use	9	2.7%	6	2.2%	15	2.5%
Inferred Off-Label	2*	0.6%	2	0.7%	2*	0.3%

Total	336	100.0%	270	100.0%	606	100.0%

*Patient counts of <5 have been confidentialized to 2
**Table includes all patients over the age of 18

Table 8 BYETTA Patients by Indication (Years 1-3)

Indication	Male		Female		Total	
	# of Patients	% of Patients	# of Patients	% of Patients	# of Patients	% of Patients
Inferred On-Label	523	97.2%	470	95.7%	993	96.5%
Off-Label Insulin Use	11	2.0%	13	2.6%	24	2.3%
Off-Label TZD Use	2*	0.4%	2*	0.4%	2*	0.4%
Inferred Off-Label	2*	0.4%	6	1.2%	8	0.8%
Total	537	100.0%	490	100.0%	1,027	100.0%

*Patient counts of <5 have been confidentialized to 2
**Table includes all patients over the age of 18

6.2.4 Concomitant anti-diabetic medications use with BYETTA

The proportion of patients by concomitant therapy is summarized in Table 9. The majority of patients were using BYETTA with metformin (82%) and/or SU (39%) or BYETTA with insulin glargine (LANTUS) (32%), in accordance with the Product Monograph.

Off-label use of BYETTA was rare accounting for only 3% (n=34) of all patients treated with BYETTA; most instances (2%) were in conjunction with LEVEMIR, human basal and rapid insulins.

As highlighted in Table 9, among 993 unique patients of inferred on-label use of BYETTA, 87% of the patients had recorded insulin use at any time point of the study period. For use of insulin, thirty-three of the inferred on-label patients used insulin glargine, 23% used basal insulins (LEVEMIR and human basal), 27% of patients reported use of rapid insulin and only 4% of patients demonstrating use of premix insulin. The rapid insulin use was seldom observed alone among BYETTA users. Further data analysis revealed that 94% of the patients taking rapid insulin also had a record of other insulin use, 54% of the patients had a record of

insulin glargine and 40% a record of other basal insulin. TZD scripts were identified in 48 (4.8%) patients in the BYETTA on-label category (Table 9).

The proportion of all BYETTA patients by on-label and off-label behaviour is further characterised in Figure 8. Overall, among 1027 BYETTA patients, 664 (65%) patients were inferred on-label and did not use any concomitant medication considered off-label. Twenty three percent of patients (233) were inferred on-label and demonstrated other off-label medication use but in combination with basal insulin. A small proportion of BYETTA patients were inferred on-label (9%, n=96) and demonstrated use of off-label medication but not in conjunction with basal insulin. Only 3% of patients (n= 34) were treated with BYETTA off-label without any on-label behaviour.

Figure 8 3 Year Total: BYETTA Label Results

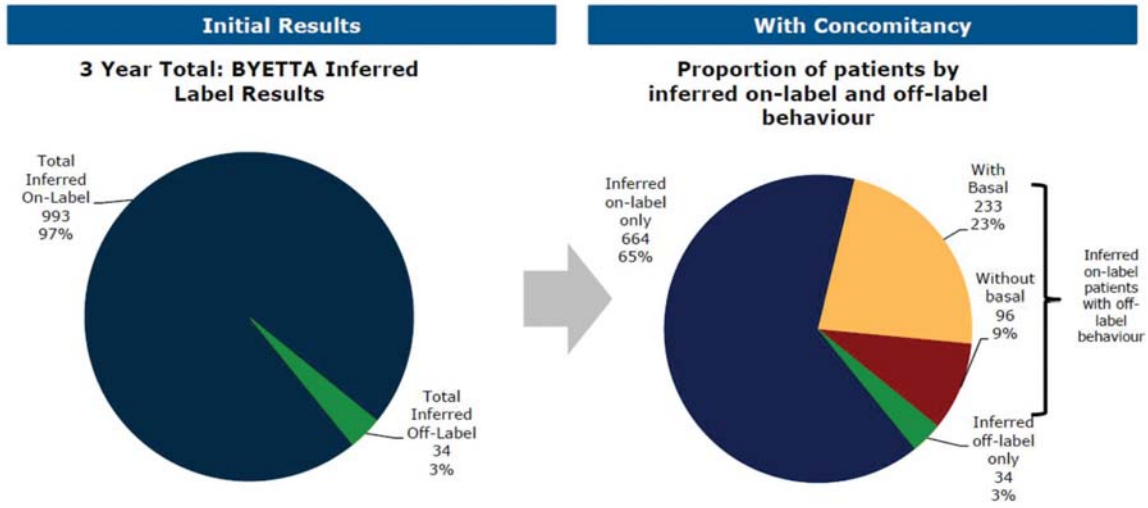


Table 9 Concomitant medications with BYETTA by inferred label categories (Year 1 to Year 3).

Concomitant Products	All Patients (>18 yrs)		Inferred On-Label		Inferred Off-label		Off-label Insulin Use		Off-label TZD Use	
	N	%	N	%	N	%	N	%	N	%
Metformin	838	81.7	838	84.5%	0	0.0%	0	0.0%	0	0.0%
SU	405	39.5%	405	40.8%	0	0.0%	0	0.0%	0	0.0%
TZD	50	4.9%	48	4.8%	0	0.0%	0	0.0%	2	100.0%

Other Oral Anti-diabetic drugs	177	17.3%	171	17.2%	2	25.0%	2	8.3%	2	100.0%
LANTUS	331	32.3%	331	33.4%	0	0.0%	0	0.0%	0	0.0%
LEVEMIR	126	12.3%	114	11.5%	0	0.0%	12	50.0%	0	0.0%
Human Basal	127	12.4%	115	11.6%	0	0.0%	12	50.0%	0	0.0%
Rapid Insulin	285	27.8%	267	26.9%	0	0.0%	18	75.0%	0	0.0%
Premix Insulin	40	3.9%	37	3.7%	0	25.0%	2	8.3%	0	0.0%
Monotherapy	92	9.0%	89	9.0%	2		0			
VICTOZA	99	10%	91	9.2%	8		0			
Total Unique Patients	**1,027**	**100.0%**	**993**	**100.0%**	**8**	**100.0%**	**24**	**100.0%**	**2**	**100.0%**

Note: Double counting of patients occurred as some patients receive more than one product with their exenatide or they change their therapy but continue on exenatide. Exenatide Rapid/Premix/VICTOZA transitional patients with <3 script overlap were not counted as concomitant. Patient counts of <5 have been confidentialized to 2.

7. DISCUSSION & CONCLUSION

7.1 Discussion

Of the 1027 unique patients included in the analysis, less than 5 patients were <18 years of age (actual number not available due to privacy rules). The majority of patients (72%) were between 18 and 64 years of age, with the proportions of male and female patients close to 50% for Years 1 and 2, with a slight increase in male patients during Year 3.

The off-label use of BYETTA was identified in 3% of the patients, with two thirds of the off-label BYETTA users were concomitantly using BYETTA with LEVEMIR and human basal insulins. The majority of patients using BYETTA can be considered on-label (97%); metformin and sulfonylurea were the most common anti-diabetic drugs concomitantly prescribed with BYETTA.

In those patients taking BYETTA on-label (i.e., inferred on-label category) some off-label behaviour was also observed for about one third of the patients. Most of the off-label behaviour (n=233) was identified as being associated with basal insulin use (i.e., LEVEMIR and/or other basal). The high proportion of patients who were prescribed basal insulin likely indicates uncontrolled hyperglycaemia based on oral anti-diabetic therapy alone. BYETTA is indicated for these patients. In a very small number of inferred on-label patients (n=96) off label medication was not associated with basal insulin use. Given that these 96 patients were

also receiving on-label treatment with their BYETTA, the addition of more anti-diabetic medications, whether off-label or not, likely indicates more severe diabetes and possibly uncontrolled hyperglycaemia.

Although LEVEMIR is not listed as a permitted combination in the Product Monograph for BYETTA, certain prescribers may prefer LEVEMIR over insulin glargine and combine it with BYETTA without understanding that LEVEMIR is not specifically mentioned in the Product Monograph for BYETTA.

Monotherapy with BYETTA was observed in 1% of patients (92). With some other newer antidiabetic agents, monotherapy may reflect their use for non-approved indications such as weight loss. No data is available to explain the use of exenatide in this fashion, although the intention for usage as weight-reducing treatment cannot be excluded.

No pharmacological basis is evident to suggest an explanation for combining BYETTA and VICTOZA.

7.2 Conclusions

- The majority of patients were treated with BYETTA in accordance with the Canadian Product Monograph
- One third of patients in the inferred on-label category displayed some off-label behaviour at certain time points, mainly in conjunction with basal insulin
- BYETTA usage in paediatric patients was extremely limited