EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

BYETTA

International non-proprietary name:

exenatide

Procedure No. EMEA/H/C/000698/II/0021

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

BYETTA contains exenatide, which is glucagon like peptide 1 analogue. BYETTA received a marketing authorisation in the EU on 20 November 2006 and is approved for the treatment of type 2 diabetes mellitus in combination with metformin, and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The currently approved indication is:
BYETTA is indicated for treatment of type 2 diabetes mellitus in combination with metformin, and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The purpose of the Type II variation is to include information concerning the use of exenatide with a thiazolidinedione (TZD). The following indication is proposed;

BYETTA is indicated for treatment of type 2 diabetes mellitus in combination with:
- *metformin*
- *sulphonylureas*
- *thiazolidinediones*
- *metformin and a sulphonylurea*
- *metformin and a thiazolidinedione*

in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

Additionally, amendments to the SmPC sections 4.2, 4.8 and 5.1 and the PL are proposed. Also Annex II has been updated to reflect the new version number of the Risk Management Plan (RMP).

The MAH has requested a waiver for the new indication in children. The PDCO has agreed with this waiver (decision 15 January 2010).

1.2. Non-clinical aspects

No non-clinical data or discussion was included in the dossier therefore MAH was requested to discuss the potential for pharmacological and/or toxicological interactions between exenatide and TZD, and justify the absence of non-clinical studies on the combination.

Potential for Pharmacokinetic Interaction
The MAH believes that based on the known clearance properties of exenatide (passive renal elimination) and TZDs (hepatic clearance), a metabolism-based interaction between these 2 agents is not probable. However, a possible pharmacokinetic interaction exists due to exenatide's known action of delaying gastric emptying, which has been shown to reduce the Cmax of concomitantly administered oral drugs without an accompanying change in AUC. Although no clinical or nonclinical pharmacokinetic studies have been conducted to evaluate the interaction of exenatide and concomitant TZDs, the long-term placebo controlled studies (GWAP and GWCG) provide an assessment of the efficacy and safety of these therapies. In Studies GWAP and GWCG, subjects with type 2 diabetes, inadequately controlled with optimally effective doses of TZDs alone, or TZDs and metformin, were randomly assigned to either placebo or exenatide treatment for 16 or 26 weeks, respectively. These studies (GWAP and GWCG) have shown that concomitant TZD usage results in an increase in efficacy, without any signs of additive safety concerns, which confirms a lack of clinically relevant pharmacokinetic interactions.

Potential for Pharmacological Interaction
Byetta and TZD produce their antihyperglycemic pharmacological actions by 2 distinctly different mechanisms of action. Byetta is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. Thiazolidinediones produce their antihyperglycemic pharmacological effect by improving sensitivity to insulin in peripheral tissues, especially adipose tissue, skeletal muscle, and the liver. TZDs are potent agonists for peroxisome proliferator-activated receptor-gamma (PPARγ). These receptors modulate the transcription of several insulin responsive genes involved in control of glucose

and lipid metabolism in adipose tissue, skeletal muscle, and the liver. There is no known overlap of these 2 pathways. Based on the divergence in the mechanisms of action of Byetta and TZDs, there appears to be minimal risk of pharmacological synergism/interaction; thus, nonclinical animal pharmacology studies on the combination of Byetta and TZDs are not warranted.

Potential for Toxicological Interaction
The target organs of toxicity for Byetta and TZDs have been well-characterized in the individual nonclinical toxicology programs for Byetta, rosiglitasone, and pioglitasone. There is no commonality of target organs identified for Byetta and the TZDs indicating a low potential for synergism/interaction. In nonclinical cardiovascular safety assessments of Byetta, there was no evidence of hERG blockade in vitro or of QT/QTc prolongation in monkeys, given single and repeated doses of 150 mcg/kg/day (482 times the human therapeutic exposure). No dose-limiting or target organ toxicity was noted in mice, rats, or monkeys at doses up to 760 mcg/kg/day (182 days), 250 mcg/kg/day (91 days), or 150 mcg/kg/day (273 days) (519, 130, and 482 times the human therapeutic exposure, respectively). In 24-month carcinogenicity studies in rats and mice, Byetta produced a weak signal for thyroid c-cell adenomas in female rats given 18, 70, or 250 mcg/kg/day (5, 22, and 130 times the human therapeutic exposure, respectively), but not in male rats or mice. Product labeling for the TZDs rosiglitazone and pioglitazone has reported heart enlargement at 5, 22, and 2 and 11, 1, and 2 times the human therapeutic exposure, respectively, in mice, rats, and dogs. Rosiglitazone produced adipose tissue hyperplasia and benign lipomas in 24-month carcinogenicity studies in mice and rats, respectively, at doses 2 times the human therapeutic exposure. Pioglitazone produced benign and malignant transitional cell tumors of the urinary bladder in male rats given the maximum recommended human dose on a mg/m2 basis for 24 months. No tumors were produced in mice given pioglitazone doses 11 times the human dose for 24 months. Based on the marked differences in the target organ toxicity profiles between Byetta and the TZDs, the potential for toxicological synergism/interaction resulting in reduction of previously determined, single agent no-observed adverse effect levels (NOAELs) appears to be low. Furthermore, no causes for significant toxicological concern were identified in clinical Studies GWAP and GWCG of the proposed combination. On this basis, and in agreement with ICH M3(R2) guidance on combination drug toxicity testing, nonclinical animal toxicology studies on the combination of Byetta and TZDs are not warranted.

It is endorsed by CHMP that there is no concern for any important pharmacological and/or toxicological interactions between exenatide and TZDs based on theoretical considerations and experimental data. The absence of combination studies is justified.

Ecotoxicity/environmental risk assessment
The MAH declared that exenatide, as a moderately sized peptide, is exempted from the environmental risk assessment requirement, according to Section 2 "Scope and Legal Basis" of the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) and that Eli Lilly and Company knows of no information that indicates a potential for significant impact on the environment from the use of exenatide.

This proposal has been endorsed by CHMP.

1.3. Clinical aspects

3.3.1. Clinical efficacy

Study Design

Study GWAP
This was a multicenter, randomized, double-blind, two-arm, parallel, placebo-controlled, outpatient trial. Patients randomized to exenatide therapy administered 5 µg study drug BID for the first 4 weeks of therapy, and then increased their dose to 10 µg BID for the remaining 12 weeks of therapy. Patients took their assigned study medication for a total of 16 weeks.
The *primary objective* was to test the hypothesis that glycemic control, as measured by change in HbA1c (%) from baseline to endpoint (Week 16, or early discontinuation), with exenatide (BID, before morning and evening meals) is superior to placebo (BID), in patients with type 2 diabetes and inadequate glycemic control taking thiazolidinediones (TZDs) alone or TZDs with metformin (Met).

Patients with type 2 diabetes aged between 21 and 75 years (inclusive), had been treated with TZDs alone (for at least 4 months prior to screening) or with TZDs and Met (for at least 30 days prior to screening), had an HbA1c between 7.1% and 10.0% (inclusive), had a body mass index (BMI) >25 kg/m2 and <45 kg/m2, and their body weight must have been stable for at least 3 months prior to screening.
The exclusion criteria included a clinically significant history of cardiac disease or presence of active cardiac disease within the year prior to inclusion in the study and□ a history of renal transplantation or were currently receiving renal dialysis or had serum creatinine ≥1.5 mg/dL (≥132 µmol/L) for males and≥1.2 mg/dL (≥110 µmol/L) for females.

The *minimum doses* for rosiglitazone were ≥4mg daily, for pioglitazone ≥ 30 mg daily. There was no required minimum dose for metformin. The proportion of patients treated with a combination of MET and TZD was 80%.

Study GWCG
This was a multicenter, double-blind, placebo-controlled, randomized, two-arm, parallel, outpatient trial designed to compare the effects of twice-daily (BID) exenatide plus oral antidiabetic (OAD) agents and placebo BID plus OAD with respect to glycemic control, as measured by HbA1c, in patients with type 2 diabetes who experienced inadequate glycemic control with TZD alone or TZD plus metformin. Patients were treated with study therapy (either exenatide plus OAD or placebo plus OAD) for 26 weeks, followed by an optional open-label extension period of a minimum of 12 weeks, during which all patients received exenatide BID plus OAD through to study completion.

Patients had type 2 diabetes, were at least 18 years of age, had been treated with TZDs alone (for at least 120 days prior to screening) or with TZDs and metformin (for at least 30 days prior to screening), had an HbA1c between 7.1% and 10.0% (inclusive), had a body mass index (BMI) 25 kg/m2 <BMI<45 kg/m2, and had stable body weight for at least 3 months prior to screening.
The exclusion criteria included a clinically significant history of cardiac disease, renal disease, liver disease, gastrointestinal disease, or oncolytic disease.
The *minimum doses* for rosiglitazone were ≥4mg daily, for pioglitazone ≥ 30 mg daily. There was no required minimum dose for metformin. The proportion of patients treated with a combination of MET and TZD was 95%.

Study GWBG
This was a multicentre, randomised, open-label, parallel-arm comparator study of out-patients with T2DM who were not adequately controlled using a combination of dual or triple OAD therapy. Patients were randomised to exenatide (5 µg twice daily [BID] for the first 4 weeks of therapy and then 10 µg BID, before the morning and evening meal) or insulin glargine ('treat to target' FPG ≤5.6 mmol/L once daily) in addition to their current OAD regimen. Patients who received exenatide during the study and completed 6 months of treatment were invited, at the discretion of the investigator, to enter an open-label extension period.

Patients included in the study presented with T2DM, had been treated with dual or triple OAD therapy at a stable dose for at least 3 months prior to randomisation and were at least 30 years of age. HbA1c values were between 7.5% and 10.0%, BMI was >27 kg/m2 and patients had at least one cardiovascular risk factor. Patients were excluded if they had a malignancy or had been in remission from a malignancy for less than 5 years, had Class III or IV cardiac disease, uncontrolled hypertension, a history of renal transplantation or dialysis, clinical signs or symptoms of liver disease, hamoglobinopathy, chronic anaemia, proliferative retinopathy or metabolic acidosis.

Table1 OADs at baseline

Parameter	Exenatide (N=118)	Insulin Glargine (N=116)	Total (N=234)
OADs administered at baseline [n (%)]			
2 OADs	69 (58.5)	68 (58.6)	137 (58.5)
3 OADs	48 (40.7)	47 (40.5)	95 (40.6)
Other [a]	1 (0.8)	1 (0.9)	2 (0.9)
OAD combination administered at baseline (n[%])			
Metformin / SU	50 (42.4)	49 (42.2)	99 (42.3)
Metformin / TZD	17 (14.4)	15 (12.9)	32 (13.7)
SU / TZD	2 (1.7)	4 (3.4)	6 (2.6)
Metformin / SU / TZD	48 (40.7)	47 (40.5)	95 (40.6)
Other [a]	1 (0.8)	1 (0.9)	2 (0.9)

Study GWAY

This was a randomized, open-label, comparator-controlled, three-arm, multicenter study. One hundred and forty-one subjects with inadequate glycemic control (HbA1c ≥6.8% and ≤10.0%), despite metformin treatment, were randomly assigned to receive exenatide, rosiglitazone, or exenatide plus rosiglitazone, in addition to their current dose of metformin. A subset (73) of these subjects participated in hyperglycemic and euglycemic clamp procedures.

The primary objective was to test the hypothesis that in patients with type 2 diabetes who had not achieved adequate glycemic control with metformin treatment, the addition of exenatide and rosiglitazone would provide superior beta-cell function as measured by the argininestimulated insulin incremental area under the curve (ASI-iAUC) during a hyperglycemic clamp test, than adding rosiglitazone alone after 20 weeks of treatment.

Rosiglitazone was uptitrated to the maximum recommended dose of 4 mg BID and exenatide to 10 µg BID. Metformin was continued at the same dose and frequency as in the pre-study setting.

The exclusion criteria included cardiac disease or presence of active cardiac disease within 1 year of screening, including myocardial infarction, clinically significant arrhythmia, unstable angina, moderate to severe congestive heart failure (New York Heart Association class III and higher), coronary artery bypass surgery or angioplasty. Patients with renal disease or with serum creatinine ≥1.5 mg/dL (males) or ≥1.4 mg/dL (females) were excluded.

Patient Disposition

Table 2. Summary of Reasons for Discontinuation for Studies Supporting the Proposed Indication

	H8O-MC-GWAP N=233		H8O-MC-GWBG N=235		H8O-MC-GWCG N=165		H8O-US-GWAY N=137	
Reason for Discontinuation n (%)	Exenatide N=121	Placebo N=112	Exenatide[1] N=118	Insulin Glargine N=117	Exenatide N=111	Placebo N=54	Exenatide[1] N=92	Rosiglitazone N=45
Adverse event	19 (15.7)	2 (1.8)	7 (5.9)	4 (3.4)	4 (3.6)	1 (1.9)	7 (7.6)	1 (2.2)
Entry criteria not met	0	0	1 (0.8)	2 (1.7)	0	1 (1.9)	0	0
Loss of glucose control	2 (1.7)	1 (0.9)	0	1 (0.9)	3 (2.7)	0	0	0
Personal conflict or other subject decision	5 (4.1)	8 (7.1)	8 (6.8)	2 (1.7)	2 (1.8)	1 (1.9)	6 (6.5)	4 (8.9)
Physician decision	2 (1.7)	1 (0.9)	2 (1.7)	2 (1.7)	2 (1.8)	0	2 (2.2)	0
Protocol completed	86 (71.1)	96 (85.7)	99 (83.9)	104 (88.9)	96 (86.5)	50 (92.6)	67 (72.8)	34 (75.6)
Protocol violation	5 (4.1)	4 (3.6)	1 (0.8)	1 (0.9)	2 (1.8)	0	7 (7.6)	3 (6.7)
Lost to follow-up	2 (1.7)	0	0	0	2 (1.8)	1 (1.9)	2 (2.2)	3 (6.7)
Sponsor's decision	0	0	0	0	0	0	1 (1.1)	0

[1]Column represents subjects who may have been treated with exenatide without TZD (GWAY), or with exenatide in addition to TZD and other OADs or with exenatide and OADs not including TZDs (GWBG).

In all studies, a greater proportion of subjects treated with exenatide than the other treatment(s) discontinued for any reason within a single study. In Study GWAP, more subjects discontinued due to adverse events in the exenatide treatment group (n=19 [15.7%]) compared to placebo (n=2 [1.8%]).

Baseline Demographics

Table 3 Demographics of Exenatide-Treated Subjects

Demographic Category	H8O-MC-GWAP (n=121)	H8O-MC-GWCG (n=111)	H8O-US-GWAY[1] (n=92)	H8O-BP-GWBG[1] (n=118)
Gender – n (%)				
n	121	111	92	118
Male	65 (53.7)	67 (60.4)	45 (48.91)	83 (70.3)
Female	56 (46.3)	44 (39.6)	47 (51.09)	35 (29.7)
Age (year)				
n	121	111	92	118
Mean (SD)	55.63 (10.76)	54.93(8.27)	55.78 (9.83)	56.8 (10.2)
Median	56.32	54.62	54.26	58.0
Minimum - Maximum	21.06–75.58	32.12-74.96	35.10-75.74	30.0–75.0
Age group (n [%])				
n	121	111	92	[1]
<65 years	98 (81.0)	97 (87.4)	73(79.3)	[1]
≥65 years	23 (19.0)	14 (12.6)	19 (20.7)	[1]
Race – n (%)				
n	121	111	92	118
Caucasian	103 (85.1)	63 (56.8)	61 (66.3)	110 (93.2)
African Descent	3 (2.5)	8 (7.2)	10 (10.9)	1 (0.8)
Hispanic	12 (9.9)	38 (34.2)	21 (22.8)	0
Native American	0	0	0	0
Asian	2 (1.7)	2 (1.8)	0	7 (5.9)
Other	1 (0.8)	0	0	0
Unknown	0	0	0	0
Duration of Diabetes (years)				
n	120	111	92	118
Mean (SD)	7.3 (4.94)	6.34 (4.21)	4.71 (3.65)	9.0 (4.6)
Median	6.0	5.00	4.00	8.5
Minimum – Maximum	1.0–23.0	1.00-25.00	0.17-22.0	0.9–22.8
HbA1c (%)				
n	121	111	92	118
Mean (SD)	7.9 (0.90)	8.22(0.92)	7.81(0.76)	8.65 (0.68)
Median	7.6	8.00	7.70	8.70
Minimum – Maximum	6.5–11.3	6.60-10.40	6.50-9.80	7.10–10.30
Body Weight (kg)				
n	121	111	92	118
Mean (SD)	97.53 (18.85)	94.53(17.78)	93.36 (15.33)	101.38 (19.81)
Median	98.2	93.40	92.05	97.05
Minimum – Maximum	54.0–145.7	65.00-142.00	57.0-130.9	65.50–179.00
BMI (kg/m²)				
n	121	111	92	118
Mean (SD)	34.00 (5.06)	33.54 (6.11)	32.62 (4.31)	34.6 (5.7)
Median	33.75	32.98	32.85	33.6
Minimum – Maximum	24.00–44.74	23.52-72.83	24.28-40.21	26.3–59.1
BMI Group (n [%])				
n	121	111	92	[2]
<30 kg/m²	32 (26.4%)	34(30.6)	31(33.7)	[2]
≥30 kg/m²	89 (73.6%)	77 (69.4)	61 (66.3)	[2]

Abbreviations: BMI = body mass index; CSR = clinical study report; HbA1c = hemoglobin A1c; ITT = intent-to-treat; n = number of subjects; SD = standard deviation.

[1] Column represents subjects who may have been treated with exenatide without TZD (GWAY), or with exenatide in addition to TZD and other OADs or with exenatide and OADs not including TZDs (GWBG).

[2] Not categorically presented for this study.

Study results

Table 4. Summary of Efficacy Results in Studies H8O-MC-GWAP, H8O-BP-GWBG, and H8O-MC-GWCG (ITT Subjects)

	Change From Baseline to Endpoint (LS Mean (SEM)[2])					
Treatment	**N**	**HbA1c (%)**	**N**	**Fasting Glucose (mmol/L)**	**N**	**Body Weight (kg)**
H8O-MC-GWAP (16 weeks)						
10 mcg Exenatide	117	-0.74 (0.09)*	114	-1.15 (0.19)*	121	-1.47 (0.30)*
Placebo	105	0.14 (0.10)	105	0.21 (0.21)	110	-0.02 (0.33)
LS Mean Difference ± SEM 95%		-0.88 (0.11)*		-1.36 (0.25)*		-1.45 (0.38)****
CI (E – P)[1]		(-1.100, -0.654)		(-1.843, -0.873)		(-2.208, -0.700)
H8O-BP-GWBG (26 Weeks)[3]						
10 mcg Exenatide	113	-1.18 (0.09)*	103	-2.12 (0.25)*	117	-2.49 (0.30)*
Insulin Glargine	111	-1.22 (0.09)*	101	-3.61 (0.25)*	114	2.90 (0.30)*
LS Mean Difference ± SEM 95%		0.04 (0.12)		1.49 (0.35)*		-5.39 (0.42)*
CI (E – I)[1]		(-0.20, 0.28)		(0.80, 2.18)		(-6.22, -4.57)
H8O-MC-GWCG (26 weeks)						
10 mcg Exenatide	110	-0.84 (0.20)*	103	-0.65 (0.46)	111	-1.43 (0.61)***
Placebo	54	-0.10 (0.23)	53	0.37 (0.52)	54	-0.75 (0.70)
LS Mean Difference ± SEM 95%		-0.74 (0.16)*		-1.02 (0.38)**		-0.69 (0.51)
CI (E – P)[1]		(-1.06,-0.41)		(-1.78, -0.26)		(-1.69, 0.31)

*p<0.001; **p=0.009; ***p=0.020; ****p=0.0002

[1] Method of analysis used across all trials was ANCOVA LOCF. Models were similar but not identical.

[2] CI (E-I) or (E-P) = the 2-sided, 95% CI for the LS mean difference between treatments (E-I) or (E-P).

[3] Subjects may have been treated with exenatide in addition to TZD and other OADs or with OADs not including TZDs (GWBG).

Table 5. Summary of Efficacy Results in Study H8O-US-GWAY (ITT Subjects)

	Exenatide (A)	Exenatide + Rosiglitazone (B)	Rosiglitazone (C)	A versus B p-value	A versus C p-value	B versus C p-value
HbA1c (%) n=133						
Baseline	7.79 ± 0.116	7.84 ± 0.115	7.93 ± 0.116			
20 weeks	6.96 ± 0.118*	6.55 ± 0.116*	6.90 ± 0.118*			
Change	-0.908 ± 0.118	-1.31 ± 0.116	-0.968 ± 0.118	0.016	0.720	0.039
Weight (kg) n=133						
Baseline	93.05 ± 2.39	93.76 ± 2.36	91.78 ± 2.39			
20 weeks	89.70 ± 0.547*	91.31 ± 0.538*	93.99 ± 0.547*			
Change	-2.82 ± 0.547	-1.21 ± 0.538	1.48 ± 0.547	0.038	<0.001	<0.001
Fasting glucose (mmol/L) n=132						
Baseline	8.42 ± 0.278	8.43 ± 0.271	8.48 ± 0.274			
20 weeks	6.98 ± 0.250*	6.84 ± 0.244*	6.63 ± 0.250*			
Change	-1.46 ± 0.250	-1.60 ± 0.244	-1.80 ± 0.250	0.693	0.331	0.555

Duration of treatment = 20 weeks
Footnote(s): *p<0.05 from baseline. Data are LS means ± SE.
[1] Analysis results based on MMRM.

Table 6. Summary of Subjects Achieving HbA1c Targets in Studies H8O-MC-GWAP and H8O-MC-GWCG (Per-Protocol Subjects)

Endpoint Efficacy Measure	Exenatide	Placebo	p-value[1]
Study H8O-MC-GWAP			
Number of Subjects	79	80	
Subjects with HbA1c ≤7%	49 (62.0%)	13 (16.2%)	<.0001 [2]
Number of Subjects	84	88	
Subjects with HbA1c ≤6.5%	25 (29.8%)	7 (8.0%)	.0002 [3]
Study H8O-MC-GWCG			
Number of Subjects	93	47	
Subjects with HbA1c ≤7%	46(49.5%)	18 (38.3%)	.181 [2]
Number of Subjects	98	49	
Subjects with HbA1c ≤6.5%	36 (36.7%)	7 (14.3%)	.005 [3]

[1] Statistical analysis used the Cochran-Mantel-Haenszel method.
[2] Analysis excluded subjects with baseline HbA1c ≤7%.
[3] Analysis excluded subjects with baseline HbA1c ≤6.5%.

Discussion of clinical efficacy

Studies GWAP and GWCG are considered as the pivotal trials for the current application. The study designs with placebo as control are considered as adequate. Study GWAP was also included in the initial MAA for Byetta.
The majority of the patients in these studies were treated with a combination of metformin and TZD at the time of inclusion in the studies and were considered as failures on this dual therapy. The number of patients on monotherapy with TZD was limited (n=33). However, considering the small target population for the TZD+exenatide combination, the very limited safety data presented (not showing any unexpected safety issues) was considered as acceptable. The dual therapy indication is therefore considered as approvable**.** Based on the demographic characteristics the study populations seem to be representative of the target population with approx. 7 years duration of the disease and HbA1c of around 8% at baseline. However, the number of patients older than 65 years is limited.

3.3.2. Clinical safety

Patient exposure

Table 7. Summary of Subject Exposures to Exenatide by Concomitant OAD Therapy in Studies H8O-MC-GWCG,H8O-BP-GWBG, H8O-MC-GWAP, and H8O-US-GWAY (Intent-to-Treat Subjects)

	Number of Subjects Exposed to Exenatide by Concomitant OAD				
Concomitant OAD	Study GWCG	Study GWBG	Study GWAP	Study GWAY	Total
TZD only	6	--	27	--	33
TZD + metformin	105	17	93	47	262
TZD + sulfonylurea	--	2	--	--	2
TZD + metformin + SU	--	48	1	--	49
Other (without TZD)	--	--	--	--	--
Metformin + SU	--	50	--	--	50
Repaglinide	--	1	--	--	1
None (exenatide only)	--	--	--	45	45
Total	111	118	121	92	442

Abbreviations: OAD = oral antidiabetic agent; SU = sulfonylurea; TZD = thiazolidinedione.

Of the 346 exenatide treated subjects who received TZD therapy, 125 (36%) had exposures 6 to <18 weeks, 180 (52%) had exposures 18 to <32 weeks, and 17 (5%) had exposures ≥32 weeks.

Adverse events

Gastrointestinal events, particularly nausea, were the most common adverse events reported during Studies GWAP, GWCG, GWBG, and GWAY.
The percentage of exenatide subjects reporting nausea in these studies was similar to that of exenatide-treated subjects in non-TZD studies. Among treatment-emergent adverse events occurring at ≥ 5% in the 4 core studies, oedema peripheral was notably higher than in the non-TZD studies. This adverse event is well recognized with TZD treatment but was not more frequent with combination exenatide and TZD (6%) than with placebo (11%). No treatment-emergent cases of pancreatitis were observed in the integrated studies database.
In the 4 core studies, cardiac disorders were reported by 1% of subjects receiving exenatide plus TZD (aortic valve sclerosis and tachycardia), 3% of subjects receiving insulin plus TZD (arrhythmia and cardiac failure), and no subjects receiving placebo and TZD.

Table 8. Summary (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence of at Least 5%who Received Exenatide Plus Thiazolidinedione (TZD) (Alone or in Combination with other Oral Antidiabetic Agents) in Studies GWAP, GWCG, GWBG, and GWAY Compared with Subjects Having Same Events in Long-Term, Controlled Exenatide Studies Presented in the Safety Update of Original BYETTA Marketing Authorization Application (Intent-to-Treat Population)

	Current Type II Variation[3]			Long-Term Exenatide Studies Presented in Safety Update[4]			
	All TZD + Exenatide Studies	Placebo-Controlled	Comparator-Controlled	Placebo-Controlled		Comparator-Controlled	
System Organ Class Preferred Term	Exenatide (N=346)	Placebo (N=211)	Insulin (N=68)	Exenatide (N=1084)	Placebo (N=595)	Exenatide (N=704)	Insulin (N=658)
Gastrointestinal disorders							
Nausea	120 (35%)	20 (9%)	3 (4%)	469 (43%)	106 (18%)	306 (43%)	67 (10%)
Vomiting	48 (14%)	1 (<1%)	3 (4%)	139 (13%)	19 (3%)	110 (16%)	33 (5%)
Diarrhoea	34 (10%)	6 (3%)	6 (9%)	141 (13%)	38 (6%)	60 (9%)	17 (3%)
Dyspepsia	26 (8%)	1 (<1%)	0 (0%)	64 (6%)	11 (2%)	20 (3%)	5 (1%)
Flatulence	18 (5%)	0 (0%)	1 (1%)	16 (1%)	6 (1%)	4 (1%)	1 (<1%)
General disorders and administrative site conditions							
Oedema peripheral	21 (6%)	23 (11%)	7 (10%)	21 (2%)	18 (3%)	3 (<1%)	5 (1%)
Infections and infestations							
Nasopharyngitis	34 (10%)	13 (6%)	15 (22%)	80 (7%)	48 (8%)	60 (9%)	58 (9%)
Nervous system disorders							
Headache	26 (8%)	10 (5%)	13 (19%)	89 (8%)	36 (6%)	56 (8%)	56 (9%)
Dizziness	16 (5%)	6 (3%)	1 (1%)	88 (8%)	32 (5%)	28 (4%)	19 (3%)

[1] Both datasets contain data from Study H8O-MC-GWAP.
[2] Data presented in the safety update, submitted during regulatory response to the original BYETTA marketing authorization application, comprised 35 integrated studies. Of these studies, 4 were placebo-controlled with treatment durations of 16 or 30 weeks, and 4 were active comparator-controlled studies with treatment durations of 16 to 52 weeks.
[3] MedDRA version 12.0.
[4] MedDRA version 8.0

More exenatide plus TZD-treated (9%) than placebo- (1%) or insulin-treated (4%) subjects discontinued from the 4 core studies because of adverse events. Among exenatide-treated patients,

nausea (17 of 32 exenatide-treated subjects) and vomiting (9 subjects) accounted for the majority of discontinuations.
The incidences of nausea and vomiting leading to withdrawal with exenatide plus TZD treatment were slightly higher in the 4 core studies (5% and 3%, respectively) than those of exenatide-treated subjects in the long-term, placebo- and comparator-controlled studies, including Study GWAP, presented in the original BYETTA MAA. In those long-term controlled studies, the percentage of subjects receiving exenatide who withdrew due to nausea or vomiting was 4% and 1%, respectively. However, the overall incidence of gastrointestinal adverse events leading to withdrawal for exenatide-treated subjects receiving TZD in the 4 core studies (8%) was not different from that observed for exenatide-treated subjects in the earlier, long-term studies in the BYETTA MAA (placebo-controlled, 5%; insulin-controlled, 6%). These results indicate that exenatide used together with a TZD does not result in qualitatively different gastrointestinal side effects compared with other exenatide/oral agent combinations.
Other events that led to discontinuation of exenatide-treated subjects were cough (moderate severity), injection site reaction (mild severity), chest pain (severe), breast cancer (severe), diarrhoea (mild severity), and acute renal failure (severe). Of these events, injection site reaction and diarrhoea were considered related to study treatment.

Serious adverse events and deaths

Of 346 exenatide-treated subjects in the 4 cores studies, 8 subjects (2%) experienced a serious adverse event. An additional exenatide-treated subject experienced hypoglycemia that was reported as serious in the clinical study report but was not captured as serious in the integrated dataset. All of these serious events were classified as serious because they were associated with hospitalization or were considered clinically relevant for another unspecified reason. In addition, all of the events, with the exception of a case of campylobacter infection and acute renal failure (both events reported by the same exenatide-treated subject), had resolved by the time of final reporting. Similar percentages of placebo- (2%) and insulin-treated (3%) subjects experienced a serious adverse event. The overall incidence of serious adverse events for exenatide-treated subjects receiving TZD in the 4 core studies was not different from that observed for exenatide-treated subjects in the earlier, long-term studies in the BYETTA MAA (placebo-controlled, 4%; insulin-controlled, 4%).
No serious cardiac disorders were reported for subjects receiving exenatide plus TZD in the 4 core studies. One other subject receiving exenatide without TZD experienced serious cardiac disorders (1, acute myocardial infarction; 1, supraventricular tachycardia). One subject receiving insulin plus TZD, metformin, and SU experienced serious cardiac failure.

Injection Site Reactions
The treatment-emergent adverse event data of the integrated studies database were searched for MedDRA preferred terms indicative of injection site reactions. No clinically meaningful differences in injection site reactions were observed between exenatide-treated subjects who received concomitant TZDs and exenatide-treated subjects who did not receive TZDs.

Pancreatitis
No treatment-emergent cases of pancreatitis were observed in the integrated studies database. To better understand the relationship between exenatide and pancreatitis described in some spontaneously reported cases, the MAH continues to pursue a drug safety program that includes thorough investigation of individual spontaneous case reports along with clinical and epidemiologic studies.

Acute Renal Failure
Two cases of acute renal failure were observed in the integrated studies database; however, neither was considered related to treatment. In Study GWBG, 1 exenatide-treated subject experienced the serious event of acute renal failure and withdrew from study because of this event. In Study GWAY, 1 TZD-treated subject experienced the serious event of acute renal failure and remained in study.
While no significant safety issues have been identified in relation to acute renal failure in the exenatide preclinical or clinical development programs, spontaneously-reported events of acute renal failure have occurred and the MAH continues to monitor these events.

Hypoglycemia

Hypoglycemia was reported in 11% and 7% of subjects taking TZDs who were treated with exenatide and placebo, respectively, in placebo-controlled studies. As with hypoglycemia reports in the original BYETTA MAA, hypoglycemia events among exenatide-treated subjects in the 4 core studies appeared to be related to concomitant use of SU. Twenty eight (54.9%) exenatide-treated subjects receiving

TZD in combination with SU reported hypoglycemic episodes. The incidence was substantially lower (12.5%) in subjects receiving exenatide in combination with TZD alone or TZD with metformin. The incidence of hypoglycemia was not notably different for subjects receiving exenatide plus TZD (6.1%) versus subjects receiving those agents and metformin (13.4%). Most hypoglycemic episodes were mild or moderate in intensity.
Eight subjects (5 exenatide, 3 insulin glargine) experienced severe hypoglycemia. Four of the exenatide-treated subjects were also receiving SU treatment.

Laboratory findings

Anti-exenatide antibodies were assessed at baseline and again at study termination or early discontinuation in Studies GWAP and GWAY. Of 115 subjects exposed to exenatide and assessed as to their antibody status in Study GWAP, 46 (40%) were treatment-emergent anti-exenatide antibody-positive and 69 (60%) were anti-exenatide antibody-negative at their last study visit. Subjects exposed to exenatide in Study GWAY had a similar incidence of treatment-emergent anti-exenatide antibody positivity.
Treatment-emergent adverse events potentially associated with immune responses were compared for exenatide, insulin, and placebo subjects in the 4 core studies. No clinically relevant differences in the incidence or types of potentially immune-related treatment emergent adverse events were observed between treatments.

Safety in special populations

Renal function
Subjects in the integrated studies database with mild (n= 86 exposed to exenatide) and moderate (n= 5 exposed to exenatide) renal impairment were retrospectively identified through a calculation of creatinine clearance using the Cockcroft-Gault formula. No subjects with severe renal impairment or end-stage renal disease participated in the studies that compose this database.
In all treatment groups (exenatide, exenatide plus TZD, placebo, and insulin) subjects with normal and mildly impaired renal function had similar incidences and types of treatment-emergent adverse events.
Age
Review of treatment-emergent adverse events by age subgroup (n= 63 for age: >=65 to <75 and n= 1 for age: >=75 exposed to exenatide, respectively) did not indicate any obvious age related difference.

Safety Considerations Related to Postmarketing Reports

Concomitant use of exenatide with TZD has been approved for use in some countries (US, 2006). Experience with this combination therapy has been recorded in the BYETTA Periodic Safety Updated Reports since 2006. No additional safety concerns have been identified for exenatide use in combination with TZD alone or in combination with other OADs. Consequently, no changes to current pharmacovigilance activities or plans outlined in the Risk Management Plan are needed for a treatment indication involving TZDs.

Additional data concerning safety in patients receiving triple therapy

With responses to RSI the MAH has provided, the integrated studies (H8OMC- GWAP, H8O-MC-GWAY, H8O-BP-GWBG, and H8O-MC-GWCG) safety data, for patients using triple therapy of exenatide in combination with TZD plus metformin. The results from these studies are summarized in the table below.

Table 9. Adverse Reactions Reported for Exenatide-treated Subjects in All Integrated Studies by TZD Use

Body System/Adverse Reaction Terms	All Integrated Studies[a] ITT Subjects Taking TZD + MET Only (n=262) Frequency of Occurrence Common	Very Common
Gastrointestinal Disorders		
Abdominal Distension[b]	X	
Abdominal Pain[b]	X	
Constipation[c]	X	
Diarrhoea[b]	X	
Dyspepsia[b]	X	
Flatulence[c]	X	
Gastrooesophageal Reflux Disease[b]	X	
Nausea[b]		X
Vomiting[b]		X
General Disorders and Administration Site Conditions		
Asthenia[b]	X	
Injection Site Haematoma[d]	X	
Nervous System Disorders		
Dizziness[b]	X	
Headache[b]	X	
Skin and Subcutaneous tissue Disorders		
Hyperhidrosis[b]	X	
Rash[c]	X	

Abbreviations: ITT= intent-to-treat; MET = metformin; TZD = thiazolidinediones.

[a] Includes Studies H8O-MC-GWAP, H8O-US-GWAY, H8O-BP-GWBG; H8O-MC-GWCG.

[b] Term identified in Table 1 Section 4.8 **Undesirable effects** of the SmPC

[c] Term identified in Spontaneous Reports section of Section 4.8 **Undesirable effects** of the SmPC

[d] Medical concept described in Injection Site Reactions section of Section 4.8 **Undesirable effects** of the SmPC .

Discussion on clinical safety

The safety assessment from the 4 safety studies included in the variation is limited to a total of 343 subjects for 19 weeks. As expected, GI adverse events were common in the exenatide treated patients. However, the combination with TZD did not seem to increase the incidence of GI symptoms compared to other exenatide combinations. Neither were there any signs of an increased risk of oedema when exenatide was added to TZD compared to placebo. No serious cardiac disorders, cases of treatment related renal failure or cases of pancreatitis were reported, but it should be remembered that only 17 patients had an exposure longer than 32 weeks. No deaths were reported during the 4 core studies.

Pooling data from the four studies may be an inappropriate way to describe the safety profile considering that the studies differed in their demographic data, inclusion/exclusion criteria, their dose regimes, and use of exenatide in combination with other antidiabetic drugs. The applicant was requested to present the safety profile for patients having received the triple therapy applied for without addition of any other antidiabetic drugs. Additionaly provided data in RSI revealed no new adverse event reactions, beyond those already reported for metformin plus sulfonylurea indication.

1.4. Risk Management Plan (RMP)

The MAH submitted an updated RMP (version 10) with responses to RSI. MAH included the use of exenatide with TZD as potentially missing data and has amended the RMP accordingly. THE CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

1.5. Changes to the Product Information

The MAH proposed to change the indication in section 4.1 of the SPC as follows: *"BYETTA is indicated for treatment of type 2 diabetes mellitus in combination with:*

- *metformin*
- *sulphonylureas*
- *thiazolidinediones*
- *metformin and a sulphonylurea*
- *metformin and a thiazolidinedione*

in patients who have not achieved adequate glycaemic control on maximally tolerated

doses of these oral therapies."
This was accepted by the CHMP.
As a result of the new indication further changes were made to sections 4.2, 4.8 and 5.1. The Package Leaflet has been updated accordingly.

1.6. Overall conclusions and Benefit-Risk Assessment

In support of the extension of indication 4 clinical studies were submitted. One (GWAP) out of these 4 studies has already been assessed in the initial MAA. At that time point, this trial was deemed sufficient to assess efficacy, but the study duration was considered insufficient by the CHMP to determine the safety of exenatide with TZD. A new study has now been completed (Study GWCG, 26 weeks duration), and data is also available from two other studies (GWBG and GWAY) in which some patients are exposed to exenatide and TZD.

The study design and study populations are basically considered as acceptable. However, the number of patients on monotherapy with TZD at the time of inclusion was limited (n=33) and these patients may not have been representative for the restricted EU monotherapy indication for TZDs. However, according to further analyses by the MAH, 21 of these patients may have been representative according to European standards.

Benefits

Concerning efficacy associated with the addition of exenatide to TZD + metformin, exenatide was superior to placebo and the treatment resulted in clinically relevant reductions of HbA1c in the pivotal studies GWAP and GWCG (mean reductions - 0.74 and -0.84 %, respectively). Furthermore, in study GWBG, exenatide was non-inferior to insulin glargine concerning reduction of HbA1c and in study GWAY, the addition of exenatide +rosiglitazone resulted in a more pronounced reduction of HbA1c compared to either of the drugs alone. Thus, a clinically relevant effect of the addition of exenatide to TZD + metformin is indicated by these results.

Risks

As mentioned above, the main reason why the combination of exenatide with a TZD was not approved at the time of MAA, was the limited data concerning safety (121 patients treated for 16 weeks). The exposure is now increased to 346 patients out of whom 125 had exposures 6 to 18 weeks, 180 had exposures 18 to 32 weeks, and 17 had exposures ≥32 weeks. Approximately 90 % of these patients were treated with exenatide+TZD+ one or more additional drugs (most often metformin). Concerning safety in these patients, as expected, GI adverse events were common in exenatide treated patients. However, the combination with TZD did not seem to increase the incidence of GI symptoms compared to other exenatide combinations. Neither were there any signs of an increased risk of oedema when exenatide was added to TZD compared to placebo. No serious cardiac disorders, cases of treatment related renal failure or cases of pancreatitis were reported, but it should be remembered that only 17 patients had an exposure longer than 32 weeks. No new adverse event reactions, beyond those already provided in the SmPC for the current metformin plus sulfonylurea indication, were identified by examination of the TZD data by itself.

The target population for dual therapy with TZD + exenatide (patients inadequately controlled by diet and exercise for which metformin is inappropriate because of contraindications or intolerance) is not the same as for triple therapy. Patients treated with TZD monotherapy due to intolerance to Met is not likely to differ from the population treated with dual therapy, Met+TZD, and for these patients efficacy and safety data could be extrapolated between populations.
The patients with contraindications to Met may on the other hand be a more vulnerable population including patients with renal/hepatic impairment and cardiac disease. However, considering the warnings and contraindications for TZD, only patients with renal impairment would be eligible for TZD monotherapy. Considering that exenatide is not recommended in patients with severe renal impairment, it is indeed agreed that the target population in Europe for the TZD+exenatide combination is likely to be small. Still, some reassurance concerning efficacy and safety is needed and it is questioned whether data from 21 representative patients is sufficient. Considering the target population (patients with mild/moderate renal impairment), the adverse events potentially expected could be oedema (fluid retention) and more pronounced gastrointestinal side effects (patients with moderate renal impairment have a 36% lower clearance of exenatide). Based on the results in study GWAP as well as on the analyses of TZD only users in all studies (presented in the MAHs response),

these potential issues were not confirmed. The safety profile in the dual therapy group was similar to the triple therapy group.

Concerning alternative add-on treatments for patients on TZD monotherapy, SU as an alternative treatment to exenatide can lead to hypoglycaemia and weight increase, although the long term experience of SU speaks in its favour. Insulin, on the other hand, should in general be avoided in combination with TZD due to the risk of fluid retention.

Balance

Submitted studies show that exenatide added to TZD with or without metformin, results in a clinically relevant glucose lowering effect without any new, unexpected safety concerns compared to previously approved combination indications. The benefit/risk balance is therefore considered as positive and the variation is approvable. Considering the small target population for the TZD+exenatide combination, the very limited safety data presented was considered as acceptable. The dual therapy indication is therefore considered as approvable.

2. Conclusion

On 24 June 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Package Leaflet and Annex II.