Coventry & Warwickshire

Area Prescribing Committee

Drug Positioning Statement	DPS001
Exenatide (Byetta®▼) [Treatment of Type 2 Diabetes]	Aug 2014

VERDICT

Coventry & Warwickshire APC recommends that exenatide (Byetta ®▼) is used in line with current NICE C87G on the management of Type 2 diabetes within its licensed indications. *Prescribers should refer to the APC's GLP-1 drugs comparison chart (DCC02) for information on the alternatives available including data on safety and cost*

Specialist Drug List status: Specialist Advised (SA)

Summary notes[1,2,3,4]

INDICATION:

Exenatide (Byetta®) is a Glucagon like peptide – 1 (GLP-1) analogue licensed for the treatment of Type 2 diabetes mellitus in combination with:
- metformin
- sulfonylureas
- thiazolidinediones
- metformin and a sulfonylurea
- metformin and a thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. **Exenatide has also had a licence extension for use as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.**

PRESENTATION:

Byetta 5 and 10 micrograms solution for injection, pre-filled pen.

DOSE: Byetta therapy should be initiated at 5 microgram exenatide per dose, administered twice daily for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 microgram to further improve glycaemic control. Doses higher than 10 microgram twice daily are not recommended.

Byetta can be administered at any time within the 60-minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). Byetta **should not** be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose.

COST COMPARISON:

Drug and dosage [2]	Cost (30 days)
Exenatide 5 or 10micrograms twice daily	£68.24
Exenatide 2mg once weekly	£73.36
Liraglutide 1.2 mg to 1.8mg once daily	£78.48-£117.72
Lixisenatide 10micrograms 14 days increasing to 20 micrograms once daily	£54.14 (20micrograms daily is also £54.14)

STORAGE: Before use - store in a refrigerator, in use - store below 25°C without needle attached; Shelf life for pen in use: 30 days

Drug profile [5&6]

- Reduces HbA1c from baseline by 0.8 – 0.9%
- The recent marketing authorisation for twice daily exenatide (Byetta) as an adjunctive therapy to basal insulin, with or without metformin and/or pioglitazone was based on a randomised, double-blind, 30-week, phase III trial [5](n = 261). This found that adding twice-daily exenatide to basal insulin therapy with insulin glargine improved HbA_{1c} levels in patients with sub-optimally controlled type 2 diabetes. The reduction of HbA_{1c} level from baseline at week 30 was 1.74% in the exenatide plus glargine group and 1.04% in the placebo plus glargine group ($p < 0.001$). The addition of exenatide did not lead to more hypoglycaemia but was associated with more gastro-intestinal side effects. A total of 9% of the exenatide recipients withdrew due to adverse events compared to 1% of the placebo group ($p < 0.010$). The authors note that the study was short term, hence the long-term efficacy and safety of adding twice-daily exenatide to insulin glargine is not known. The study used a disease-oriented outcome (HbA_{1c}) and no data are available on quality of life or cardiovascular events.
- Promotes weight loss.
- Nausea and vomiting are common side effects. Not recommended in patients with severe GI disease.
- Does not require continual dose titration.
- No data available on sustainability of HbA1c reduction.
- No morbidity or mortality outcome data currently available.
- Blood glucose monitoring is not essential for exenatide (However monitoring may still be part of patient's overall care plan).
- Suspected adverse reaction reports of necrotising and haemorrhagic pancreatitis have been received in association with exenatide. Some of these reports had a fatal outcome. If pancreatitis is diagnosed, exenatide should be permanently discontinued[6].

Drug profile (Continued)

- Reports of renal impairment, including acute renal failure and worsened chronic renal failure have also been received. Exenatide is not recommended for use in patients with end stage renal disease or severe renal impairment[6]. In patients with moderate renal impairment, dose escalation from 5 µg to 10 µg should proceed conservatively. No dosage adjustment is required with age or hepatic impairment.
- For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before exenatide injection. Gastro-resistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 hour before or more than 4 hours after exenatide injection.

Current place in therapy [7-10]

NICE[7]

NICE clinical guideline 87 recommends a third-line position for exenatide (in addition to metformin and a sulfonylurea) in patients with:

-BMI > 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific problems associated with high body weight, or

-BMI < 35.0kg/m2 and where therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities. Those who may lose their job as a result of moving onto insulin therapy, *e.g.* Group 2 (LGV or PCV) drivers may be considered suitable for exenatide. However the DVLA require that such patients are individually assessed and therefore patients must inform them appropriately if initiated on exenatide**.**

A positive opinion has been received by the Committee for Medicinal Products for Human Use (CHMP) of exenatide in combination with insulin[3] and the license has now been extended to this combination. Following a consultation, NICE has decided to update Clinical Guideline 87. Exenatide in combination with basal insulin for the treatment of type 2 diabetes is under consideration to be included in the guideline update.

SMC[8, 9]

Exenatide is accepted for restricted use for the treatment of Type 2 diabetes mellitus in combination with metformin and a thiazolidinedione as a third-line pre-insulin treatment option. Exenatide has previously been accepted by SMC for restricted use for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulfonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. In a third review exenatide was accepted for use as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults with type 2 diabetes who have not achieved adequate glycaemic control with these agents. In the pivotal phase lll study, addition of exenatide to basal insulin in combination with other anti-diabetic agents was associated with a clinically significant reduction in HbA1c of -0.7% compared with placebo, with 60% of patients achieving a target HbA1c level ≤7.0%.

MTRAC[11]

Exenatide treatment should be initiated in secondary care by diabetologists, who can assess the need for this treatment. It is then suitable for continued prescribing in primary care. There are no outcome data on the effect of exenatide on morbidity or mortality.

Summary

The evidence for the efficacy of exenatide was considered to be relatively strong, based on RCTs which have shown that exenatide reduces HbA1c levels to a greater extent than placebo. Two open label comparator studies found exenatide to be non inferior to insulin glargine or biphasic insulin aspartame in reducing HbA1c levels. In the trials, up to 57% of exenatide–treated patients reported at least one episode of nausea. There are no outcome data on the effect of exenatide on morbidity or mortality. As twice-daily exenatide has recently received a license for use as adjunctive therapy to **basal insulin** with or without metformin and/or pioglitazone, commissioners and local specialists would need to identify those patients for whom such a regimen might be appropriate.

References

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