BYDUREON® (exenatide) 2MG POWDER AND SOLVENT FOR PROLONGED-RELEASE SUSPENSION FOR INJECTION

BYETTA® (exenatide) 5 MICROGRAMS AND 10 MICROGRAMS SOLUTION FOR INJECTION, PREFILLED PEN

Please note this is a combined PI for BYDUREON and BYETTA; Consult individual Summaries of Product Characteristics before prescribing

USES:

For Bydureon and Byetta: Treatment of type 2 diabetes mellitus in combination with metformin, sulphonylurea, thiazolidinedione, or combinations of metformin and sulphonylurea or metformin and thiazolidinedione, in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

For Byetta only: Byetta is also indicated 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:

Bydureon: Powder and solvent for prolonged-release suspension for injection containing 2mg exenatide.

Byetta: Solution for injection in prefilled pen. Each dose contains 5μg exenatide in 20μL, or 10μg exenatide in 40μL.

DOSAGE AND ADMINISTRATION:

For Bydureon and Byetta: Administer as subcutaneous injection in the thigh, abdomen, or back of upper arm. Hepatic impairment: No dose adjustment required. Children and adolescents: Safety and efficacy not established in patients below 18 years of age.

For Bydureon only: The recommended dose is 2mg exenatide once weekly, on the same day each week, at any time of day, with or without meals. Administer immediately after suspension of powder in the solvent. If dose is missed, administer as soon as practical, then resume once weekly dosing schedule. Two injections should not be given on the same day. Bydureon is for self-administration, appropriate training is recommended. When Bydureon is added to existing metformin and/or thiazolidinedione, the current dose of these oral therapies can be continued. Increased risk of hypoglycaemia when Bydureon is added to sulphonylurea. Consider reduction in dose of sulphonylurea to reduce the risk of hypoglycaemia. Blood glucose self-monitoring may be necessary to adjust the dose of sulphonylurea. Patients switching from Byetta to Bydureon may experience transient elevations in blood glucose concentrations, which generally improve within first 2 weeks after therapy initiation. If a different antidiabetic treatment is started after the discontinuation of Bydureon, consideration should be given to the prolonged release of Bydureon. Elderly: No dose adjustment required for Bydureon. Very limited clinical experience in ages>75 years. Consideration should be given to the patient’s renal function. Renal impairment: No dose adjustment required for patients with mild renal impairment (creatinine clearance (CrCl) 50-80 ml/min). Bydureon is not recommended in patients with moderate (CrCl 30-50ml/min) or severe renal impairment (CrCl<30 ml/min) or end-stage renal disease.

For Byetta only: Initiate at 5μg exenatide per dose, administered twice daily (BID) for at least one month. The dose can then be increased to 10μg BID. Doses higher than 10μg BID is not recommended. Administer within the 60 minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). Do not administer after a meal. If injection missed, continue treatment with the next scheduled dose. Administer Byetta and basal insulin as 2 separate injections. When Byetta is added to existing metformin and/or pioglitazone therapy, continue current doses of these agents as no increased risk of hypoglycaemia anticipated. On addition of Byetta to sulphonylurea or basal
insulin, consider reduction in dose of sulphonylurea or basal insulin to reduce risk of hypoglycaemia. Blood glucose self-monitoring may be necessary to adjust dose of sulphonylurea or basal insulin. **Elderly:** use with caution, proceed conservatively with dose escalation from 5µg to 10µg in >70 years. Very limited clinical experience in ages >75 years. **Renal impairment:** No dose adjustment required for patients with mild renal impairment (creatinine clearance (CrCl) 50-80 ml/min). Dose escalation from 5µg to 10µg should proceed conservatively in moderate renal impairment (CrCl 30-50ml/min). Not recommended in patients with severe renal impairment (CrCl<30 ml/min) or end-stage renal disease.

**CONTRAINDICATIONS:**  
*For Bydureon and Byetta:* Hypersensitivity to the active substance or to any of the excipients.

**WARNINGS AND PRECAUTIONS:**  
*For Bydureon and Byetta:* **General:** The concurrent use of Bydureon and Byetta has not been studied and is not recommended. Not to be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Must not be administered by intravenous or intramuscular injection. **Renal impairment:** Uncommon, spontaneously reported events of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring haemodialysis. Some occurred in patients experiencing events that may affect hydration and/or receiving medicinal products known to affect renal function/hydration status, including angiotensin converting enzyme inhibitors, angiotensin-II antagonists, non-steroidal anti-inflammatory medicinal products and diuretics. Reversibility observed with supportive treatment and discontinuation of potentially causative medicinal products, including exenatide. **Severe gastrointestinal disease:** Not recommended. **Acute pancreatitis:** Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. Spontaneously reported events of acute pancreatitis. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. Inform patients of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis suspected, discontinue use; if acute pancreatitis is confirmed, Byetta/Bydureon should not be restarted. Caution should be exercised in patients with a history of pancreatitis. **Rapid weight loss:** Rapid weight loss at a rate of >1.5kg per week has been reported with exenatide, which may have harmful consequences, e.g. cholelithiasis.  
*For Bydureon only:* **Discontinuation of treatment:** The effect of Bydureon may continue as plasma levels of exenatide decline over 10 weeks. Choice of other medicinal products and dose selection should be considered accordingly until exenatide levels decline. **Concomitant medicinal products:** Concurrent use of Bydureon with insulin, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied.  
*For Byetta only:* **Concomitant medicinal products:** Concurrent use of Byetta with meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied and cannot be recommended. Use with caution and follow closely in patients receiving oral medicinal products that require rapid gastrointestinal absorption, that have a narrow therapeutic ratio or that require careful monitoring. **Patients with BMI ≤25:** limited experience. **Excipients:** Contains metacresol, may cause allergic reactions.

**DRUG INTERACTIONS:**  
*For Bydureon and Byetta:* **Warfarin and cumarol derivatives:** Increased INR (International normalised ratio) spontaneously reported during concomitant use. INR should be closely monitored during initiation of Bydureon or Byetta and during dose increase of Byetta. **HMG CoA reductase inhibitors:** Concomitant use with exenatide was not
associated with consistent changes in lipid profiles. However lipid profiles should be monitored regularly with Byetta and as appropriate with Bydureon.

For Bydureon only: No dose adjustment required for medicinal products sensitive to delayed gastric emptying.

For Byetta only: May reduce the extent and rate of absorption of other oral agents and thus these agents may need to be administered at a separate time. Consult SmPC for further details.

PREGNANCY AND LACTATION:

For Bydureon only: Women of childbearing potential should use contraception during treatment with Bydureon. Discontinue at least 3 months before trying to get pregnant. Avoid use during pregnancy and breast-feeding.

For Byetta only: Discontinue if trying to become pregnant. Avoid use during pregnancy and breast-feeding.

UNDESIRABLE EFFECTS: Consult SmPC for full list of side effects.

For Bydureon and Byetta: Very common (≥1/10): Diarrhoea, nausea. Common (≥1/100 to <1/10): Decreased appetite, dizziness, headache, abdominal distention, constipation, flatulence, abdominal pain, dyspepsia, gastroesophageal reflux disease, pruritus and/or urticaria, asthenia. Uncommon (≥1/1000 to <1/100): Dehydration (generally associated with nausea, vomiting and/or diarrhoea), somnolence, eructation, altered renal function (including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine). Rare (≥1/10,000 to <1/1000): Anaphylactic reaction. Frequency not known: Acute pancreatitis, angioneurotic oedema, macular and papular rash, INR ratio increased with concomitant warfarin use (some reports associated with bleeding). Patients may develop anti-exenatide antibodies following treatment with Bydureon or Byetta. These patients tend to have more injection site reactions (e.g. skin redness, itching).

For Bydureon only: Very common (≥1/10): Hypoglycaemia (with sulphonylurea). Common (≥1/100 to <1/10): Vomiting, injection site pruritus, fatigue, injection site erythema. Uncommon (≥1/1000 to <1/100): Intestinal obstruction, injection site rash. Frequency not known (cannot be estimated from available data): Injection site abscesses and cellulitis. Small subcutaneous injection site nodules observed very frequently, consistent with the known properties of PLGA polymer microsphere formulations.

For Byetta only: Very common (≥1/10): Hypoglycaemia (with a sulphonylurea or metformin and sulphonylurea), vomiting. Common (≥1/100 to <1/10): Hyperhidrosis, feeling jittery. Uncommon (≥1/1000 to <1/100): injection site reactions, weight decreased. Rare (≥1/10,000 to <1/1000): Intestinal obstruction.

Legal category: For Bydureon and Byetta: POM.

Marketing authorisation number: Bydureon: EU/1/11/696/001 (single dose kit) and EU/1/11/696/003 (pre-filled pen) Byetta: 5μg - EU/1/06/362/001 and 10μg - EU/1/06/362/003.

Presentation & basic NHS price: Bydureon: 4 x 1 single-dose weekly kit or 4 x 1 pre-filled pen £73.36. Byetta: £68.24 per pack of 5μg (1 pen), £68.24 per pack of 10μg (1 pen).

Further information is available from: AstraZeneca AB, SE-151 85 Södertälje, Sweden. [BYDUREON] and [BYETTA] are trademarks of the AstraZeneca group of companies.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to AstraZeneca on 0800 783 0033.
FORXIGA®▼ 5MG & 10MG FILM-COATED TABLETS (dapagliflozin)

PRESENTING INFORMATION. Consult Summary of Product Characteristics before prescribing.

**Presentation:** 5mg or 10mg dapagliflozin (as propanediol monohydrate) film-coated tablets.

**Indications:** Adults 18 years and older: For patients with type 2 diabetes mellitus to improve glycaemic control: as monotherapy when diet and exercise alone do not provide adequate glycaemic control and use of metformin is considered inappropriate due to intolerance, or in combination with other glucose lowering drugs including insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

**Dosage:** Adults: 10mg once daily as monotherapy and add-on combination therapy with other glucose lowering drugs including insulin. Forxiga can be taken at any time of the day with or without food. Consider a lower dose of insulin or insulin secretagogues such as a sulphonylurea when used in combination with dapagliflozin to reduce the risk of hypoglycaemia. Children and adolescents: <18 years: Safety and efficacy not yet established. Elderly: ≥65 years: No dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. ≥75 years: Not recommended. Mild renal impairment: No dosage adjustment. Moderate & severe renal impairment: Not recommended. Severe hepatic impairment: Starting dose of 5mg is recommended, if well tolerated, dose may be increased to 10mg.

**Contraindications:** Hypersensitivity to dapagliflozin, or excipients. Warnings and precautions: Not to be used in patients with type 1 diabetes mellitus or for diabetic ketoacidosis. Dapagliflozin is not recommended in patients concomitantly treated with pioglitazone and has not been studied with GLP-1 analogues. Use in patients with renal impairment: Not recommended in moderate to severe renal impairment (CrCl <60ml/min or eGFR <60ml/min/1.73m²). Renal function monitoring is recommended: prior to initiation of dapagliflozin and at least yearly thereafter; prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter; for renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl <60ml/min or eGFR< 60ml/min/1.73m², treatment should be discontinued. Use in patients with hepatic impairment: Exposure is increased in patients with severe hepatic impairment. Use in patients at risk of volume depletion, hypotension and/or electrolyte imbalances: Dapagliflozin is associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations. Not recommended in patients receiving loop diuretics or who are volume depleted. Exercise caution in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients. Careful monitoring of volume status and electrolytes is recommended in conditions leading to volume depletion, such as acute gastrointestinal illness. In volume depleted patients temporary interruption of dapagliflozin is recommended until volume depletion is corrected. Urinary tract infections: Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Elderly patients: Elderly patients are more likely to have impaired renal function, be treated with medicines such as anti-hypertensives or diuretics, and be at a greater risk of volume depletion. Cardiac failure: Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV. Elevated haematocrit: Caution in patients with elevated haematocrit. Urine laboratory assessments: Patients will test positive for glucose in the urine due to mechanism of action. Lactose: Not recommended in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.
**Drug interactions:** Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Consider a lower dose of insulin or insulin seoretagogue in combination with dapagliflozin to reduce the risk of hypoglycaemia. Dapagliflozin has a low potential for other interactions with commonly used agents in patients with type 2 diabetes. 

**Pregnancy and lactation:** Do not use during pregnancy or breast-feeding. 

**Undesirable events:** Refer to SmPC for complete information on side effects. Very common (≥1/10): Hypoglycaemia (when used with SU or insulin). Common (≥1/100 to <1/10): Vulvovaginitis, balanitis and related genital infections, urinary tract infection, dizziness, back pain, dysuria, polyuria, haematocrit increased, creatinine renal clearance decreased, dyslipidaemia. 


CV 14 0176

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to AstraZeneca on 0800 783 0033.