PROTOCOL
FOR
PRESCRIBING EXENATIDE (BYDUREON) 2 mg for Once Weekly Subcutaneous Injection

This document should be read in conjunction with the current Summary of Product Characteristics
http://www.medicines.org.uk/

1. Approved Indication	Treatment of Type 2 diabetes mellitus in combination with metformin and/or a sulphonylurea in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. Note: Exenatide once weekly is **NOT** currently licensed for use in combination with insulin and so is not indicated for use within this protocol.
2. Therapeutic use & Background	Exenatide is a glucagon-like-peptide-1 (GLP-1) receptor agonist. It works by binding to the GLP-1 receptor to increase insulin secretion, suppress glucagon secretion, and slow gastric emptying. Once weekly Exenatide has been reviewed by NICE (TA248, February 2012):- ▪ Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5% [59 mmol/mol] or other higher level agreed with the individual), and the person has: o body mass index (BMI) ≥ 35 kg/m^2 in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight **or** o BMI < 35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. ▪ Treatment with prolonged-release exenatide in a triple therapy regimen should only be continued as described if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] and a weight loss of at least 3% of initial body weight at 6 months). ▪ Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes only if: o the person is intolerant of either metformin **or** a sulphonylurea, or a treatment with metformin **or** a sulphonylurea is contraindicated, **and** o the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, **or** a treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated. ▪ Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] at 6 months). **Exenatide once weekly may be initiated in Powys by GP's who are experienced in the treatment of Diabetes Mellitus and who currently initiate insulin. Treatment should be restricted to patients who fit the NICE guidance above.** **It should be noted that the administration device for this preparation is very different to other GLP1 or insulin devices and this lack of familiarity should be considered when choosing this agent.**
3. Contraindications / Special Warnings	Hypersensitivity to the active substance or to any of the excipients. Exenatide once weekly should not be used in patients with:- • Type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

	• Type 2 diabetes mellitus patients who require insulin therapy due to ß–cell failure. • End-stage renal disease or severe renal impairment (creatinine clearance <30ml/min). • Severe gastro-intestinal disease including gastroparesis, due to gastrointestinal adverse effects. • Pregnancy and breast feeding.
4. Cautions	Intravenous or intramuscular injection of exenatide once weekly is not recommended. The experience in patients with a BMI ≤25 is limited. Clinical experience in patients >75 years old is limited. Patients switching from exenatide twice daily to once weekly may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

5. Typical Dosage Regimen (Adults)	The normal dose is 2mg exenatide once weekly.
	
	The dose should be administered on the same day each week.
	
	Exenatide once weekly can be administered at any time of the day, with or without meals.
	
	If a dose is missed, it should be administered as soon as practical. Thereafter, patients can resume their once weekly dosing schedule. Two injections should not be given on the same day.
	
	Each dose should be administered as a subcutaneous injection in the abdomen, thigh or exceptionally the back of the upper arm.
	
	• **Elderly:** No dose adjustment is required based on age. However, as renal function generally declines with age, consideration should be given to the patient's renal function. The clinical experience in patients >75 years old is very limited.
	• **Renal Impairment:**
	  ○ No dosage adjustment is necessary in patients with mild renal impairment (creatinine clearance (GFR) 50 – 80ml/min)
	  ○ Experience in patients with creatinine clearance <50ml/min is very limited and therefore use is not recommended and the twice daily preparation may be more appropriate.

6.Drug Interactions For a comprehensive list consult the BNF or SPC	The effect of exenatide once weekly in slowing gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Patients receiving medicinal products which have either a narrow therapeutic ratio or those which require careful clinical monitoring (including warfarin) should be followed closely. If such medicines need to be administered with food, patients should be advised to, if possible, take them with a meal when exenatide once weekly is not administered. • **Metformin**: When adding exenatide once weekly to existing metformin therapy, the current dose of metformin can be continued, as no increased risk of hypoglycaemia is anticipated compared to metformin alone. • **Sulphonylureas**: Increased risk of hypoglycaemia. Consider a reduction in the dose of sulphonylurea. Blood glucose monitoring may be required initially. • **Thiazolidinediones (glitazones)**: Limited experience exists for the combination with exenatide once weekly and the combination should not be used under this protocol. • Oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as **antibiotics or oral contraceptives**, should be taken at least 1 hour before exenatide injection according to the manufacturers. • **Gastroresistant formulations** (**e.g. enteric coated, proton pump inhibitors**) 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 once weekly injection.

<table>
<tr><td></td><td>

Digoxin: No clinically relevant effects were noted on the maximum blood concentrations obtained or overall patient drug exposure, although there was a 2 hour delay in reaching the maximum concentration when administered 30 minutes after exenatide once weekly. It is however advisable to monitor digoxin concentrations in patients considered to be at high risk of digoxin toxicity.
Although not considered clinically significant, changes in lipid profiles may occur with concomitant use of exenatide once weekly and statins. Lipid profiles should be monitored regularly.
Warfarin: Increased INR has been reported during concomitant use of warfarin and exenatide once weekly. The INR should be closely monitored during initiation and dose increase of exenatide once weekly therapy in patients on warfarin and/or coumarol derivatives.

</td></tr>
<tr><td>7.
Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult SPC or BNF</td><td>
Adverse reaction frequency are classified using the following convention:
Very common (≥ 10%), common (≥ 1% and < 10%); uncommon (≥ 0.1% and < 1%).
<table>
<tr><th>Clinical condition</th><th>Management</th></tr>
<tr><td>GI: Nausea, vomiting and diarrhoea (very common)
Constipation, abdominal pain or distension, dyspepsia (common)</td><td>May diminish after a few days or weeks on continued treatment. Could try short course anti-emetic but if no improvement stop the anti-emetic. Reassess after a few weeks.
It is worth checking that exenatide once weekly is being used correctly and recommending smaller meal portion sizes.</td></tr>
<tr><td>CNS: Headache, dizziness (common)</td><td></td></tr>
<tr><td>Respiratory: Nasopharyngitis (common)</td><td></td></tr>
<tr><td>Metabolic: Hypoglycaemia</td><td>Especially in combination with sulphonylureas. May require blood glucose monitoring initially.</td></tr>
<tr><td>Other: Pancreatitis (rare)</td><td>Discontinue exenatide once weekly immediately and discuss with Specialist</td></tr>
<tr><td>Other: Altered renal function (incidence not known)</td><td>Significant change – review treatment</td></tr>
</table>

Small subcutaneous injection site nodules can form due to the polymer microspheres contained within product. Individual nodules should resolve over a period of 4 to 8 week. It is therefore possible for a patient to have up to 8 nodules, in the injection area, at any one time of varying sizes.

The patient should be advised to report any of the following signs or symptoms without delay: Symptoms of acute pancreatitis (persistent, severe abdominal pain)

Exenatide once weekly is a black triangle drug (at the time of writing)

<u>Any adverse reaction</u> to a black triangle drug should be reported to the CHM via the ‘yellow card’ scheme.
</td></tr>
<tr><td>8.
Baseline investigations</td><td>Baseline bodyweight and HBA1c. Waist circumference measurement can be useful.</td></tr>
</table>

9. Monitoring

Daily blood glucose monitoring is not routinely required but for patients taking a sulphonylurea, where a dose adjustment of the sulphonylurea may be necessary, it may be appropriate for patients initiating Exenatide once weekly to monitor their blood glucose on a daily basis for the first 2 months.

Monitoring	Frequency	Results	Action
HbA1c	**Every 3 months for the first 6 months then every 6 months**	At 6 months: at least a 1% reduction	*Review treatment if this is not achieved*
Bodyweight		At 6 months: At least a 3% reduction	*Review treatment if this is not achieved*
Blood Pressure			*Review treatment or refer if there are any significant changes*
U&Es, eGFR		Significant change	

10. Pharmaceutical aspects

Exenatide once weekly is presented as a kit containing a powder for reconstitution, plus solvent in a pre-filled syringe. Full instructions are provided on how to reconstitute the powder and prepare the injection for use; however appropriate training is recommended before administering the product. A different site of injection should be used each week.

Store in a refrigerator (2^{o}C – 8^{o}C). Do not freeze. Shelf life 2 years.
Store away from the freezer compartment.

The kit may be kept for up to 4 weeks below 30^{o}C prior to use
Store in the original package in order to protect from light.

Once reconstituted the suspension must be injected immediately.

11. Contact information

Diabetes Specialist Nurses:-

- **South – Jenny Jarvis - 01874 615637**
- **Mid – Patricia Powell - 01597 828717**
- **North – Sally Ann Jones - 01686 617360**

12. Criteria for shared care for non-initiating GP's

Prescribing responsibility will only be transferred when

- Treatment is for a specified indication and duration.
- Treatment has been initiated and established by the secondary care specialist.
- The patient's initial reaction to and progress on the drug is satisfactory.
- The GP has agreed in writing in each individual case that shared care is appropriate.
- The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.

13. Responsibilities of initiating prescriber

- Initiate treatment.
- Undertake baseline monitoring.
- Dose adjustments.
- Monitor patient's initial reaction to and progress on the drug.
- Ensure that the patient has an adequate supply of medication.
- Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug.

For Secondary Care providers operating under shared care - provide GP with

- Diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review.
- Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient *or* inform GP if the patient does not attend appointment
- Advice on when to stop this drug.

Provide patient with relevant drug information and instruction:(if appropriate refer to the Diabetes Specialist Nurse or suitably trained Practice Nurse):

- On safe injection technique, reconstitution and preparation of the injection, blood glucose monitoring, the symptoms of hypoglycaemia and treatment.
- Dosing instructions – to be injected once weekly on the same day each week.
- If experiencing nausea, changing the injection timing may be an option.
- Supply an exenatide once weekly information pack
- Discuss driving and the need to inform the DVLA and their insurance company.
- Discuss risks of pancreatitis including symptoms and importance of stopping if this occurs.
- Issue monitoring booklet if necessary.

	• Enable informed consent to therapy
14. Responsibilities of Primary Care	• Prescribe exenatide once weekly as part of the shared care agreement. • To monitor and prescribe according to the monitoring table. • To ensure that the monitoring and dosage record is kept up to date. • If operating under shared care advise the Specialist if the patient does not attend for appropriate monitoring. • Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary. • Monitor the general health of the patient. • Stop treatment on the advice of the specialist. • Ensure no drug interactions with other medicines.
15. Responsibilities of patients	• Monitor blood glucose levels if requested. • To attend hospital and GP clinic appointments, bring monitoring booklet if supplied. • Failure to attend could result in medication being stopped. • To report adverse effects to their specialist or GP.
16. Additional Responsibilities	Responsibilities of all prescribers: Any serious reaction to an established drug should be reported to CHM
17. Supporting documentation	Include patient information leaflet if available
18. Patient monitoring booklet	Include patient information leaflet if available
19.GP letter	Attached below
20.Guideline date.	01 January 2012
21. Guideline review date	01 January 2014 – or in light of new NICE guidance

Shared care agreement – next page

Shared Care Agreement Form if Prescribing Exenatide Once Weekly under Shared Care

Consultant request

Dear Dr ***IMPORTANT: ACTION NEEDED**

Patient name:
Date of birth:
Diagnosis:

This patient is suitable for treatment with Exenatide Once Weekly for the treatment of *(insert indication)*

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by Trust / LHB / AWMSG). I am therefore requesting your agreement to share the care of this patient.

Treatment was started on (*insert date started*) (*insert dose*)

If you are in agreement, please undertake monitoring and treatment from *(insert date*)
NB: date must be at least 1 month from initiation of treatment).

Baseline tests: *(insert information)*

Next review with this department: *(add date)*
You will be sent a written summary within 14 days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking exenatide once weekly.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

Signature

Consultant name

GP Response

Dear Dr

Patient *(Insert Patients name)*

Identifier *(Insert Patient Date of birth/address)*

I have received your request for shared care of this patient who has been advised to start Exenatide Once Weekly

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient.

GP signature Date

GP address/practice stamp