NHS Circular:
MSAN (2023) 12

Chief Medical Officer Directorate
Pharmacy and Medicines Division

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Riaghaltas na h-Alba
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12 July 2023

Medicine Supply Alert Notice

GLP-1 receptor agonists used in the management of type 2 diabetes

Priority: Level 3*
Valid until: mid-2024

Issue

1. There are very limited, intermittent supplies of all glucagon-like peptide-1 receptor agonists (GLP-1 RAs) licensed in the management of Type 2 Diabetes Mellitus (T2DM).
2. Supply is not expected to return to normal until at least mid-2024.
3. The supply issues have been caused by an increase in demand for these products for licensed and off-label indications.
4. Please refer to the Specialist Pharmacists Service (SPS) Tool for Medicines Shortages for an up-to-date supply stock situation and clinical guidance on alternative treatment options (see paragraph 24 for further information).

Advice and Actions

5. Actions for healthcare professionals until supply issues have resolved:
   - **GLP-1 RAs should only be prescribed for their licensed indication.**
   - Avoid initiating new people with type 2 diabetes on GLP-1 RAs for the duration of the GLP1-RA national shortage. There is a flow chart of page 5 to help with selecting an alternative.
   - Review the need for prescribing a GLP-1 RA agent and stop treatment if no longer required due to not achieving desired clinical effect as per NICE CG28.
   - Avoid switching between brands of GLP-1 RAs, including between injectable and oral forms. The flow chart of page 5 provides a range of options.
   - Where a higher dose preparation of GLP-1 RA is not available, do not substitute by doubling up a lower dose preparation. The flow chart on page 5 provides a range of options.
   - Where GLP-1 RA therapy is not available, proactively identify patients established on the affected preparation and consider prioritising for review based on the clinical criteria set out in paragraphs 10-12.
   - Where an alternative glucose lowering therapy needs to be considered, use the principles of shared decision making as per NICE guidelines in conjunction with the **Additional Information** section that follows.
   - Where there is reduced access to GLP-1 RAs, support people with type 2 diabetes to access to structured education and weight management programmes where available.
   - Order stocks sensibly in line with demand during this time, limiting prescribing to minimise risk to the supply chain whilst acknowledging the needs of the patient.

***https://www.nss.nhs.scot/media/1842/medicine-supply-alert-notices-definitions-of-classifications-21-october-2019.pdf**

Additional Information

6. This guidance aims to support healthcare professionals in choosing suitable alternative glucose lowering therapies to GLP1 RAs during this period of national shortage. The advice in Annex 1 should be used in conjunction with NICE NG28 Type 2 Diabetes in Adults: choosing medicines.
7. When prescribing an alternative class of glucose lowering therapy, healthcare professionals are advised to use medicines across the class evenly to mitigate the potential for further national shortages.
8. This guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual, in consultation with them and their carers or guardians.
9. Clinical supervision is essential for switching between a GLP1-RA and any other treatment for diabetes to avoid detrimental glycaemic events.

Clinical Review

10. In most cases, the need to consider alternative glucose lowering therapy will arise when a person with T2DM established on GLP-1 RA therapy is unable to source their regular prescription.
11. Should a particular preparation of GLP-1 RA be unavailable, clinical teams may want to proactively identify people with T2DM established on that preparation to help planning. The Scottish Therapeutics Utility (STU) can identify patients who may be suitable for SGLT2's/ GLP1's and therefore may be suitable to convert people to SGLT2's where appropriate.
12. Consider prioritising review for people with T2DM on the affected GLP-1 RA preparation where:
    - HbA1c greater than 86mmol/mol in the previous 3 to 6 months. The Scottish Therapeutics Utility (STU) can help prioritise individuals by higher HBA1C for review.
    - HbA1c greater than 86mmol/mol prior to starting the GLP1-RA. STU can help prioritise individuals by higher HBA1C for review.
    - HbA1c not recorded in the previous 6 months.
    - Urine albumin creatinine ratio (uACR) greater than 30mg/mmol.
    - Self-monitoring glucose readings (or Continuous Glucose Monitoring, where available) are persistently above individualised target range.

Clinical Information

When is a GLP-1 RA normally recommended?

13. If triple therapy with metformin hydrochloride and two other oral drugs is tried and is not effective, or is not tolerated or contra-indicated, a GLP-1 RA may be considered as part of a triple therapy regimen by switching one of the other drugs for a GLP-1 RA.
14. These should only be considered for patients who have:
    - a BMI of 35 kg/m2 or above (adjusted for ethnicity) and who also have specific psychological or medical problems associated with obesity; or
    - a BMI lower than 35 kg/m2 and for whom insulin therapy would have significant occupational implications or if the weight loss associated with GLP-1 RAs would benefit other significant obesity related comorbidities.

15. GLP-1 RA therapies with proven cardiovascular benefit (such as liraglutide) should be considered in patients with established cardiovascular disease.
16. After six months, the GLP-1 RAs should be reviewed and only continued if there has been a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body-weight).
17. Insulin should only be prescribed in combination with a GLP-1 RA under specialist care advice and with ongoing support from a consultant-led multidisciplinary team.
18. The SPS Medicines Supply Tool will be updated for stock position of all GLP1 RAs
19. The SPS website will have a dedicated GLP1 RA page; all healthcare professionals can register to access this tool and instructions to do so are detailed in paragraphs 23-26 below:
    - Medicines Supply Tool – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice

20. Please refer to the links below for further information:
    - NICE NG197 Shared Decision Making
    - For all individual GLP1-RA preparations Summary of Product Characteristics Home - electronic medicines compendium (emc)
    - NICE NG28 Type 2 Diabetes in Adults: choosing medicines. Type 2 diabetes | Treatment summaries | BNF | NICE
    - The Scottish Government Effective Prescribing and Therapeutics Diabetes Prescribing Strategy.

21. **Please also review the information contained in the Annexe section of this MSAN**.
22. Clinical Expertise sought from Hannah Beba[1], Ketan Dhatariya[2], Jane Diggle[3], Clare Hambling[4], Nicola Milne[5], Philip Newland-Jones[6].
    1. Consultant Pharmacist, Diabetes, Primary Care Diabetes Society
    2. Consultant in Diabetes & Endocrinology and Chair, Association of British Clinical Diabetologists
    3. Diabetes Advance Nurse Practitioner and Co-Vice Chair Primary Care Diabetes Society
    4. General Practitioner and Chair, Primary Care Diabetes Society
    5. Diabetes Specialist Nurse, Primary Care Diabetes Society
    6. Consultant Pharmacist, Diabetes & Endocrinology, University Hospital Southampton NHSFT

22. Full guidance to be published by the above group; link will be supplied on the SPS Tool once available.

Specialist Pharmacy Service (SPS) website

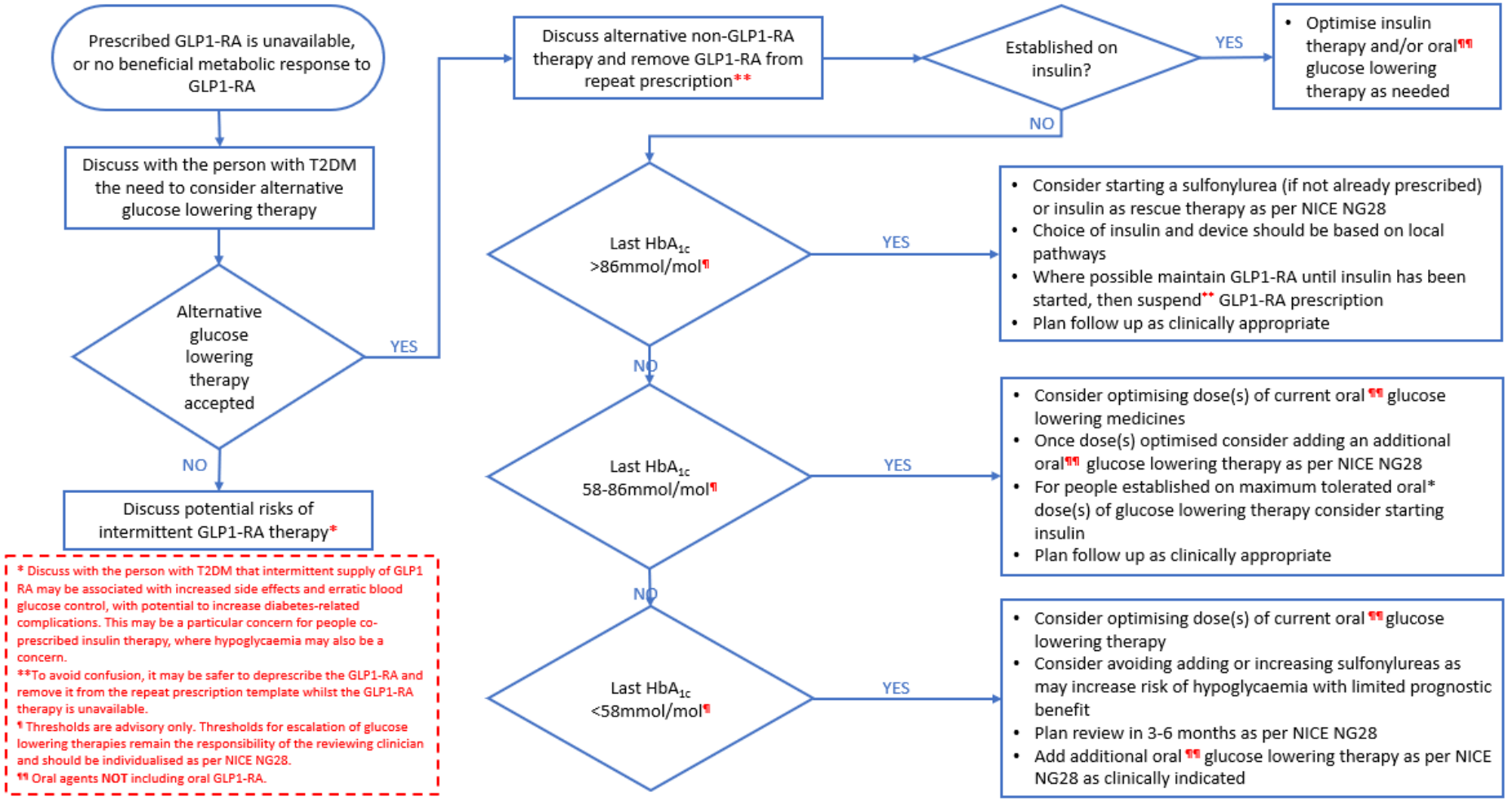
23. The UK Department of Health and Social Care (DHSC) in conjunction with SPS have launched an online Medicines Supply Tool, which provides up to date information about medicine supply issues.
24. To access the online Medicines Supply Tool you need to register with the SPS website. Registration for access to the website is available to UK healthcare professionals and organisations providing NHS healthcare. The tool is located under the Tools tab and then click on the Medicines Supply option.

25. We encourage prescribers, pharmacy professionals, and pharmacy procurement leads in Scotland to register with the SPS website and use its Medicine Supply Tool in order to stay up to date concerning medicines supply disruptions.
26. Please be aware that while medicines supply issues will appear on the SPS website, some of the recommended actions may not always be appropriate / relevant within the Scottish context.

Enquiries

27. Enquiries from Health Boards or healthcare professionals should be directed in the first instance to PharmacyTeam@gov.scot (primary care) or NSS.NHSSMedicineShortages@nhs.scot (secondary care).

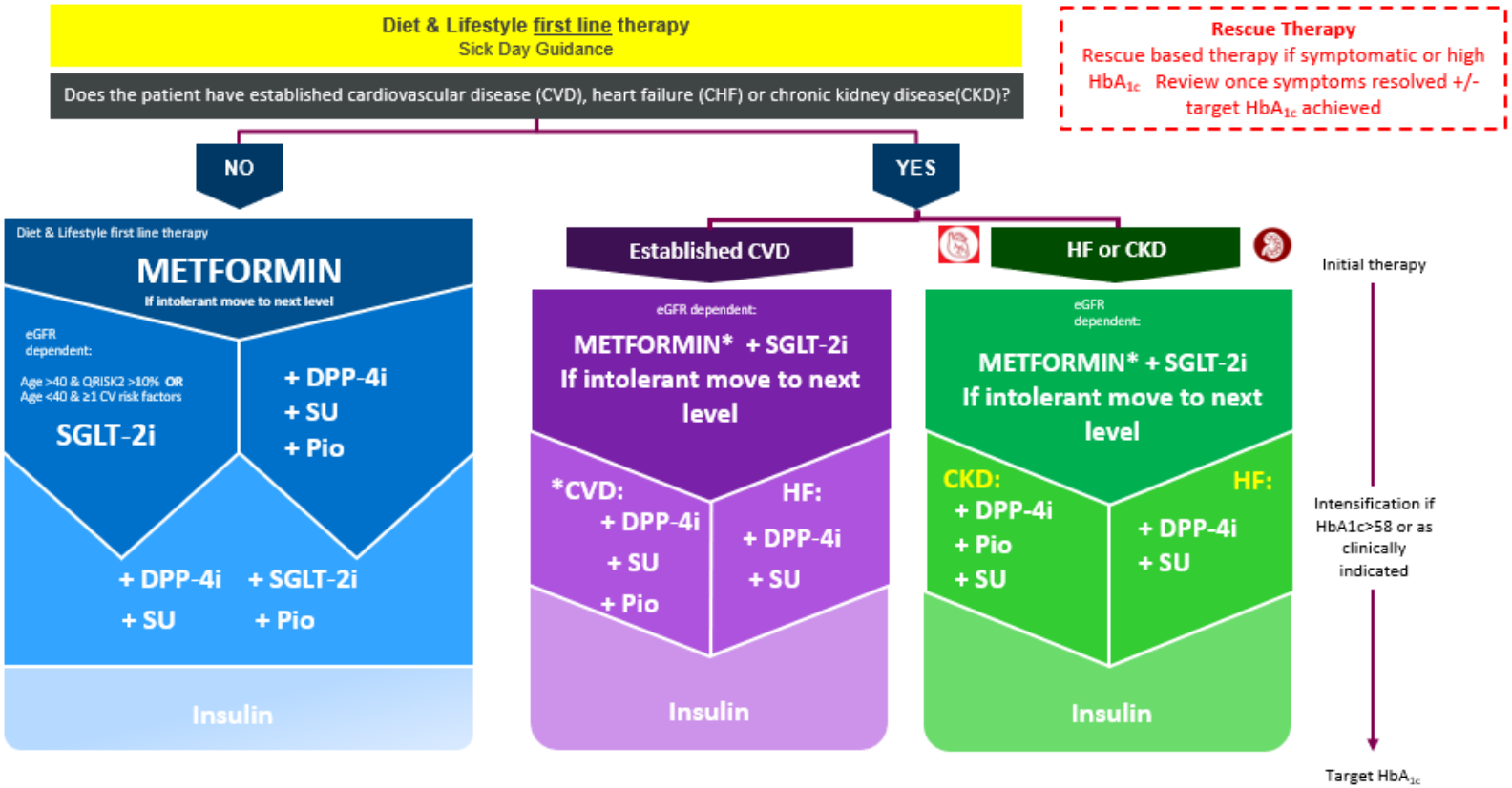
Annex 1: Selecting Alternative Glucose Lowering Therapy for People with T2DM when GLP1-RAs are unavailable



Note: Symptomatic hyperglycaemia may indicate clinical need for insulin therapy. If in doubt, discuss with specialist clinician. Symptoms of hyperglycaemia include polyuria, polydipsia, weight loss and fatigue. Think 4Ts – Thirst, Toilet, Thinner, Tired.

Annex 2: Quick reference guide for selecting oral antidiabetic therapy

Based on NICE NG28, adapted with permission from the North West London Diabetes Glycaemic Management Guideline



*** When initiating metformin**	Consider 2 weeks of monotherapy before initiating another agent to assess for gastrointestinal side-effects
When initiating a SGLT-2i	Consider a 25% dose reduction in any concomitant SU or Basal insulin & monitor for evidence of hypoglycaemia. If prescribing for Heart Failure (HF) or Chronic Kidney Disease (CKD) ensure licensed product is used.
Definitions	DPP-4i (Dipeptidyl Peptidase-4 Inhibitor), SGLT-2i (Sodium Glucose Co-Transporter-2 Inhibitor), SU (Sulfonylurea), Pio (Pioglitazone)
***CVD**	**Cardiovascular Disease in the ABSENCE of Heart Failure (HF). DO NOT** use Pio (Pioglitazone) if evidence of HF.

Annex 3: Oral Glucose Lowering Therapies by Class

Class	Biguanides	Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2iY "Gliflozins"	Di—tidyl Peptidase 4 Inhibitors (DDP4i) - "Gliptins"	Sulfonylureas	Thiazolidinedione
Medicine	Metformin	Canagliflozin, dapagliflozin, empaglifiozin and ertugllflozin	Alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin	Gliclazide, glipizide, glimepiride, glibenclamide and tolbutamide	Pioglitazone
When best to use	• Ensure metformin is taken with food. If gastrointestinal side effects develop consider switching to modified release • If hypoglycaemia a concern • People concerned about weight gain and wanting an agent that offers some weight loss/weight neutrality	• If hypoglycaemia is a concern • If the person is at high cardiovascular risk • Established heart failure or chronic kidney disease (CKD) consider a SGLT2i licensed for these indications in addition to diabetes • People concerned about weight gain and wanting an agent that offers some weight loss/weight neutrality	• If hypoglycaemia is a concern	• In people with high HbA1c as rescue therapy • Symptomatic hyperglycaemia	• Fatty liver disease • If people have deranged lipid profile it can increase HDL and lower LDL/TG • If hypoglycaemia is a concern • Can be continued in renal impairment
When to be cautious/not used	• If eGFR<45ml/min review dose and stop if eGFR <30ml/min/1.73m^2	• If high HbA1c >86mmol/mol • History of DKA • If renal function is <45ml/min then the SGLT2i will have minimal effect on blood glucose however effects for heart failure and CKD remain • Elderly, risk of volume depletion • History of recurrent urinary tract infection/urosepsis/genital infections • Use "Medication Sick Day" guidance • Preconception/pregnancy • Risk of hypoglycaemia if concomitant use with sulfonylurea or basal insulin therapy. Consider reducing dose of sulfonylurea or insulin (c. 25% insulin dose reduction)	• Dose adjustments required (except linagliptin). See BNF for dosing instructions by product and eGFR • Avoid in patients with a history of pancreatitis • Avoid saxagliptin in heart failure • Preconception/ pregnancy	• Consider alternatives in occupations where hypoglycaemia is likely to cause issues • Use cautious dosing and slower titrations in people with renal impairment • In the elderly where hypoglycaemia may be more concerning (set higher HbA1c targets and titrate cautiously with appropriate monitoring) • Preconception/ pregnancy	• Oedema or heart failure • Low bone mineral density (incl. post-menopausal women) • Avoid if current or history of bladder cancer or unexplained haematuria • Be aware of weight gain (lower doses can be used where this is more of an issue) • Significant liver impairment • Preconception/ pregnancy
HbA1c drop	1-2% (11-22mmol/mol)	1-1.5% (11-17mmol/mol)	0.5-0.8% (6-9mmol/mol)	1-2% (11-22mmol/mol)	0.5-1.4% (5-15 mmol/mol)
For further information please refer to NICE guidelines, British National Formulary and the Electronic Medicines Cornpendium					

Annex 4 : GLP-1 RAs affected

GLP-1 RA	Brand and formulation	Indication	Ability to uplift
Semaglutide	Ozmepic ® 0.25 mg solution for injection in pre-filled pen Ozmepic ® 0.5mg solution for injection in pre-filled pen Ozmepic ® 1mg solution for injection in pre-filled pen	Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control	Unable to uplift
Semaglutide	Rybelsus 3mg tablets Rybelsus 7mg tablets Rybelsus 14mg tablets	Oral GLP-1 RA licensed for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes.	Unable to uplift
Dulaglutide	Trulicity® 0.75 mg solution for injection in pre-filled pen Trulicity® 1.5 mg solution for injection in pre-filled pen Trulicity® 3 mg solution for injection in pre-filled pen Trulicity® 4.5 mg solution for injection in pre-filled pen	Type 2 diabetes mellitus as monotherapy (if metformin inappropriate)	Unable to uplift
		Type 2 diabetes mellitus in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control	
Liraglutide	Victoza® 6mg/ml solution for injection in prefilled pen	Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs, (including insulin) if existing treatment fails to achieve adequate glycaemic control	Unable to uplift
	Saxenda® 6mg/ml solution for injection in prefilled pen	Adjunct in weight management [in conjunction with dietary measures and increased physical activity in individuals with a body mass index (BMI) of 30 kg/m2 or more, or in individuals with a BMI of 27 kg/m2 or more in the presence of at least one weight-related co-morbidity]	

Exenatide	Byetta® 5micrograms/0.02ml solution for injection 1.2ml pre-filled pens Byetta® 10micrograms/0.04ml solution for injection 1.2ml pre-filled pens	Type 2 diabetes mellitus in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control	Unable to uplift
	Bydureon® 2mg/0.85ml prolonged-release suspension for injection 1.2ml pre-filled pens		

Source: BNF