Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Title of paper:	**Sitagliptin as the preferred choice DPP-4 inhibitor**		
Meeting date:	June 2022		
Agenda item:	To be completed by APC secretary	**Attachment(s):**	APC preferred choice T2DM rationale document
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Paper type			
For:	Approval		

Executive Summary: *(provide a short description of the subject matter and draw attention to the issues / facts and the proposal)*

The patent for Sitagliptin will expire in September 2022, with generic equivalents projected to become available late 2022.
This change is projected to create an annual windfall of £1.1m per year across Surrey Heartlands. This is based on activity levels between April-Jun 2021, on the assumption of an 80% price reduction for the generic equivalent. This price reduction is based on knowledge of average price reductions of between 70-90% six months post-patent expiry.

Our current preferred choices for DPP-4 inhibitor in Surrey Heartlands are alogliptin and sitagliptin.

- Allogliptin is currently the most cost-effective option, but only contributes 6% to DPP prescribing. It is NOT licensed in monotherapy

  The EXAMINE trial (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) also found a non-significant trend towards heart failure hospitalisation. This makes it a less favourable option in patients with heart failure compared to Sitagliptin and Linagliptin which have been found to have a neutral effect on risk of heart failure (1).

- Sitagliptin is the second most prescribed DPP-4 inhibitor, making up 43% of all prescribing (either alone or as a combination product), 0.7% of this is brand prescribing. However, Sitagliptin can be used as an alternative in patients with mild, moderate and severe renal impairment with appropriate dose reductions.

Standard dosing of Sitagliptin is 100mg daily when GFR ≥ 45mL/min (6).

- Dosing adjustments made to Sitagliptin in renal impairment (6):
- Moderate renal impairment (GFR ≥ 30 to < 45 mL/min): 50mg once daily
- Severe renal impairment (GFR ≥ 15 to <30 mL/min): 25mg once daily
- End-stage renal disease (ESRD) (GFR < 15 mL/min), including haemodialysis or peritoneal dialysis: 25 mg once daily.

If sitagliptin was preferentially prescribed instead of linagliptin, we could generate approximate savings of £1 million per year in Primary Care.

- Linagliptin is the most frequently prescribed DPP-4 inhibitor across Surrey Heartlands, making up 47% of all DPP-4 inhibitor prescribing (either alone or in combination with another antihyperglycemic).

  It is not expected to become available as a generic until the end of 2026.

  As linagliptin is hepatically metabolised it is a potential option for patients severely renally impaired only when other classes of antihyperglycemic drugs are not clinically appropriate as no dose adjustment is required.

- Saxagliptin and combinations contribute to approximately 2.4% of DPP-4 prescribing.
- Vildagliptin, with combination formulations are less than 1.6% DPP-4 inhibitor prescribing and comes off-patent in September 2022, Vildagliptin also requires liver enzyme monitoring as it is associated with rare cases of hepatic dysfunction, so cannot be used in patients with hepatic impairment (2) unlike the other DPP-4 inhibitors.

Four large, placebo-controlled trials evaluating Mortality and Cardiovascular (CV) outcomes with the DPP-4 inhibitors found no significant differences in the incidence of Major Adverse CV events with DPP-4 inhibitors compared to placebo. However, hospitalisation due to heart failure was significantly higher in Saxagliptin treated patients compared to placebo, hence Saxagliptin is not recommended in patients with T2DM and high risk of HF (1). Vildagliptin had no significant effect on left ventricular ejection fraction but led to an increase in left ventricular volumes (1).
DPP-4 inhibitors have been found to have good safety and tolerability in patients with impaired kidney function (5).

There are no significant differences reported between DPP-4 inhibitors with respect to blood glucose-lowering efficacy against other oral antihyperglycemic treatments within current systematic review evidence, or in one RCT head-to-head comparison of Sitagliptin and Saxagliptin. There have been no direct comparison studies between all DPP-4 inhibitors (3).

NICE guidance on the management of type 2 Diabetes (NG 28) has been published (update March 2022) with SGLT-2 inhibitors now being recommended for most patients due to their cardioprotective benefits, hence initiation of DPP-4 inhibitors will decrease. For patients where a DPP-4 inhibitor is considered appropriate, NICE recommends that DPP-4 inhibitor selection should be based on the lowest acquisition cost. (3,4). In future new patients initiated on a DPP-4 inhibitor should be prescribed sitagliptin. Consideration could be given to switching patients (where capacity allows) who are receiving other DPP-4 inhibitors to sitagliptin in cohorts of patients where an SGLT-2 inhibitor is contra-indicated / not tolerated and patient's do not wish to progress to injectable therapy. This will deliver wider savings than the projected savings of £1.1 million/year.

We propose Sitagliptin to be the DPP-4 inhibitor of choice across Surrey Heartlands, when clinically indicated. Any cost saving generated from this change in therapeutic preferred choice will support funding of other high-cost therapies in diabetes such as the use of SGLT-2 inhibitors, due to their cardiovascular and renal benefits together with the increased use real time or flash continuous glucose monitoring.

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(1) Consentino F, Grant PJ, Aboyans V et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular disease developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). European Heart Journal 2020; 41: 255-323. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD | European Heart Journal | Oxford Academic (oup.com)

(2) Novartis Pharmaceuticals Limited. Galvus 50mg tablets SmPC. 2020. Available from: Galvus 50 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

(3) MTRAC Commissioning support for DPP-4 inhibitors (Gliptins) for the treatment of type 2 diabetes. June 2019. Microsoft Word - MTRAC DPP-4i update guidance final v.2 (centreformedicinesoptimisation.co.uk)

(4) Type 2 diabetes in adults: management. NG28 NICE Dec 2015 updated March 2022

(5) Gallwitz. Clinical Use of DPP-4 inhibitors. Front. Endocrinol 2019; 10: 389 https://doi.org/10.3389/fendo.2019.00389

(6) Merck Sharp and Dohme Limited. Januvia 25mg film coated tablets SmPC.2022. Available from : JANUVIA 25mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Summary: *(What is the APC being asked to do and why)*

The APC is being asked to approve the change to the preferred choice of DPP-4 inhibitor being Sitagliptin alone when the use of a DPP-4 is clinically indicated. All other DPP-4 inhibitors are recommended to have their Traffic Light Status changed to “Do not initiate in new patients”

This change is being requested because Sitagliptin is coming off-patent and will be available generically in late 2022, producing significant cost-savings, which can be reinvested elsewhere.

The PAD document for preferred choices has been amended for review to reflect this change in preferred choice.

Accompanying papers (please list):

- APC preferred choice T2DM rationale document (amended for uploading to PAD if proposal agreed)