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UPDATE ON TYPE 2 DIABETES MELLITUS

- **Type 2 diabetes mellitus, which results in increased morbidity and mortality, continues to increase globally**
- **Initial management consists of lifestyle modification and glucose-lowering therapy; metformin is recommended as the drug of first choice**
- **Addition of one or two more hypoglycaemic agents to metformin monotherapy is normally required in order to maintain glycaemic control over time**
- **Optimal management involves prevention of complications and treatment of co-morbidities, in addition to control of hyperglycaemia**

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterised by chronic hyperglycaemia due to deficiency in the secretion and/or function of insulin (i.e. insulin resistance).[1,2] Both the incidence and prevalence of T2DM are increasing worldwide, particularly in developing countries, in conjunction with increased obesity rates and westernisation of lifestyle.[3,4] **T2DM is known to be associated with a reduced life expectancy and increased morbidity**.[3] Although cardiovascular disease (CVD) is the commonest cause of mortality and morbidity, T2DM is also associated with an increased risk of other diseases including cancer, chronic liver disease, cognitive decline and accelerated arthritis, in addition to the microvascular and macrovascular complications.[2,4] Therefore T2DM management places a significant burden of care on each country's health system.[4]

Currently there are thought to be >190,000 cases of T2DM in Ireland;[5] however, this is likely to be an underestimate, since early diagnosis is often difficult.[6] Moreover, a recent review reported a significant increase in the prevalence of diagnosed diabetes in Ireland from 2.2 % in 1998 to 5.2 % in 2015.[4] **The National Clinical Programme for Diabetes** has recommended "integrated" care for T2DM, whereby healthcare professionals work together in primary and secondary care to take joint responsibility for patients with T2DM on a proactive basis.[6] This bulletin will outline the general guidance for care of patients with T2DM, from the recently published ICGP **Practical guide to integrated type 2 diabetes care**[6], and will provide an update on current pharmacotherapy options in the management of T2DM.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

T2DM is characterised by insulin resistance and a loss of insulin-producing capacity in the pancreas. Insulin resistance is the initial state, which the pancreas copes with by increasing production of insulin from the beta cells.[7] Over time however, pancreatic insulin production falls. It is generally accepted that **by the time T2DM is diagnosed, the pancreas has lost half of its insulin-producing capacity**.[8] Persistent hyperglycaemia is associated with metabolic changes which result in damage to both small (microvascular) and large (macrovascular) blood vessels.[2,9,10]

Both genetic and acquired / environmental factors play an important role in the development of T2DM;[1] **it is thought that genetic factors primarily affect beta-cell function whereas acquired / environmental factors are mainly responsible for the insulin resistance seen in T2DM**.[11] There is a strong hereditary (multigenic) component to the disease; T2DM is more common in certain ethnic groups (e.g. people of African, African-Caribbean and South Asian family origin), and various genes have been identified as conferring increased risk of developing T2DM.[1,9]

Acquired / environmental risk factors include obesity, physical inactivity, dyslipidaemia, existing CVD, or long-term corticosteroid use.[6] It is thought that these social, behavioural and environmental risk factors unmask the effects of genetic susceptibility which results in the development of T2DM.[12]

DIAGNOSIS

The classic symptoms of T2DM are polyuria and polydipsia. However, these may not be present in the early stages of the disease and the diagnosis may only be made when a T2DM- related complication occurs.[3,5] Early identification of T2DM may reduce the development of complications; therefore **it is recommended to test for T2DM in asymptomatic patients who have high risk factors**. The WHO recommends the options listed in Figure 1 for diagnosing T2DM.

Figure 1: Criteria for diagnosis of T2DM*[3,6]

Symptoms of diabetes plus random plasma glucose concentration ≥11.1mmol/L

or

Fasting plasma glucose ≥7.0mmol/L

or

2-hour plasma glucose ≥11.1mmol/L during a 75 gram Oral Glucose Tolerance Test

or

$HbA1_c$ ≥48mmol/mol (>6.5%)

*in the absence of unequivocal hyperglycaemia, the result should be confirmed by repeat testing on a different day

$HbA1_c$ is useful as it reflects chronic hyperglycaemia, with less day-to-day biological variability compared with plasma glucose levels.[13] However **a normal HbA1c does not rule out a T2DM diagnosis**, because the $HbA1_c$ level can be influenced by a variety of blood conditions including haemoglobinopathies, haemolytic anaemia and other types of anaemia.[13] Plasma glucose criteria should be used to diagnose T2DM in these conditions.[6]

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

T2DM is a chronic metabolic condition requiring long-term management. **The aims of treatment are to (1) control hyperglycaemia and (2) manage complications and co-morbidities**.[9] Individualisation of therapy is key to the successful control of T2DM, depending on the status of the patient.[6,14] An **integrated care model** is now recommended in Ireland; this includes the GP and practice nurse (the primary care givers to the patient with T2DM), the "integrated care" diabetes nurse specialist (acting as liaison between primary and secondary care) and the diabetologist, community dietitian, ophthalmologist and podiatrist as appropriate for the individual patient's needs.[6] A **practice-based diabetes register** is recommended to facilitate the provision of quality integrated care for the T2DM patient.

LIFESTYLE INTERVENTIONS

Diet, exercise and education remain the foundation of any T2DM programme.[2] Studies have shown that patients' knowledge about diabetes and their general health literacy affect their adherence to self-management of T2DM.[15] **Non-adherence, especially in the first year after diagnosis, has been shown to increase the incidence of complications** and to result in higher health expenditure.[16] Education should include the nature of T2DM, its potential complications, the importance of lifestyle interventions (weight control, dietary advice (including alcohol), smoking cessation, regular exercise, foot care) and how to self-manage the disease and medication(s).[2,6]

As part of structured education on diabetes in Ireland, several interactive group courses are run, in various venues throughout the country, for patients with newly diagnosed and ongoing T2DM.[17] Further information is available at the end of this bulletin [see **Useful Resources** section].

PHARMACOLOGICAL MANAGEMENT

Pharmacotherapy is indicated when lifestyle interventions alone are not effective (or are judged to be unlikely to be effective) in controlling hyperglycaemia.[2] **Factors to be considered in determining glycaemic goals include duration of T2DM, life expectancy, existing complications, and/or co-morbidities and psychosocial factors** (e.g. resources, available support systems).[18]

Table 1 outlines the most commonly used hypoglycaemic agents.

Table 1: Most commonly used hypoglycaemic agents for Type 2 Diabetes Mellitus[19-36]

Class (medicines)	Mode of Action [route*]	Undesirable Effects / Special Precautions for the class include*
BIGUANIDES • metformin	↓ rate of hepatic glucose production; ↑insulin sensitivity; ↑glycogen storage in skeletal muscle which → ↓ blood glucose [oral]	Nausea, flatulence, diarrhoea (see dose instructions); ↓ vitamin B12. C/I in patients with CrCl <30ml/min. Use with care in presence of dehydration due to ↑ risk of lactic acidosis.
SULFONYLUREAS (SU) • glimepiride • gliclazide • glibenclamide	Stimulate insulin release from pancreas ("insulin secretagogue") [oral]	Risk of hypoglycaemia and weight gain. Use with caution in patients with ↓ renal or ↓ hepatic function (↑ risk of hypoglycaemia).
DPP-4 INHIBITORS • linagliptin • saxagliptin • sitagliptin • vildagliptin	↑ plasma levels of active GIP and GLP-1 which → ↑ secretion of insulin ("insulin secretagogue") [oral]	Risk of hypoglycaemia when used in combination with SU and/or insulin. Associated with development of acute pancreatitis. Use with caution in patients with past history of pancreatitis.
THIAZOLIDINEDIONES • pioglitazone	Act as insulin sensitisers which → ↑ insulin-mediated glucose uptake into muscle and adipose tissues [oral]	Fluid retention and ↑ weight; URTI; fractures. Cases of bladder cancer have been reported. C/I in patients with heart failure. LFTs should be checked periodically.
GLP-1 RECEPTOR AGONISTS • exenatide • liraglutide • dulaglutide**	Stimulates glucose-dependent insulin secretion from the pancreas; ↓ inappropriate glucagon secretion; slows passage of food through GI tract. [S/C]	GI reactions including nausea, vomiting, diarrhoea; injection site reactions; risk of hypoglycaemia when used in combination with SU and/or insulin. Associated with development of acute pancreatitis. Use with caution in patients with past history of pancreatitis.
SGLT2 INHIBITORS** • canagliflozin • dapagliflozin • empagliflozin	↓ reabsorption of filtered glucose in kidneys and ↓ renal threshold of glucose which → ↑ urinary glucose excretion (and osmotic diuresis) [oral]	Volume depletion; thirst; constipation (some agents); nausea; GU infections; hypotension; ↓ CrCl / GFR; dyslipidaemia. Risk of hypoglycaemia when used in combination with SU and/or insulin. Not to be initiated if CrCl<60ml/min. Use with caution in older age groups. Potential risk of toe amputation in patients with high CVD risk has been reported and may be a class effect.

*full prescribing information, including dosage, is contained in the **Summary of Product Characteristics** (SmPC) for each medicine.
** medicines that are subject to additional monitoring [▼] to allow early identification of new safety information.
C/I=contraindicated; CrCl=creatinine clearance; CVD=cardiovascular disease; DPP4=dipeptidyl peptidase-4 inhibitor; GI=gastrointestinal; GFR=glomerular filtration rate; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; GU=genitourinary; LFTs=liver function tests; URTI= upper respiratory tract infection; S/C= subcutaneous; SGLT=sodium-glucose co-transport.

Other hypoglycaemic therapies: the **meglitinides**, repaglinide and nateglinide, act as secretagogues (similar to sulphonylurea) to reduce post-prandial hyperglycaemia; they may also cause hypoglycaemia and weight gain.[37,38] **Acarbose** inhibits alpha-glucosidase; it may cause significant GI upset but no hypoglycaemia.[6,39] **Insulin therapy** is recommended in patients failing to achieve adequate glycaemic control with other therapies.[3] Insulin initiation is usually carried out in a diabetic day care centre, although it may also be undertaken at primary care level when the integrated T2DM team, including diabetes nurse specialists, is in place.[6] Further details on the role of insulin therapy are available in the ICGP guide to integrated T2DM care (**www.icgp.ie**).[6]

Choice of hypoglycaemic therapy: Metformin monotherapy remains the hypoglycaemic therapy of first choice for T2DM, based on its glucose-lowering efficacy, safety profile, weight neutrality and reasonable cost in comparison with other agents (Table 1).[40,41] A recent safety review has confirmed that it is safe for use in patients with creatinine clearance ≥30ml/min.[35] **If diet and metformin (at maximum dose) fail to provide adequate control after 3 to 4 months, combination therapy with another agent should be instituted**; triple therapy may be required to maintain glycaemic control over time. A recent meta-analysis (n=301 randomised controlled trials (RCTs) involving all classes of hypoglycaemic agents) showed that metformin was associated with lower or similar $HbA1_c$ levels compared with all other drug classes given as monotherapy, while all drugs were estimated to be effective when added to metformin.[42] Although no significant differences in terms of deaths from CVD were noted between the 9 drug classes in this meta-analysis, these findings must be viewed with caution because only a minority of studies included this as an outcome. CV benefit has been recorded with use of liraglutide and empagliflozin in patients at high CV risk ; however follow-up time for each placebo-controlled RCT was short (median 3.8 and 3.1 years).[41,43,44] Therefore the **choice of agent(s) for combination therapy should be determined by suitability for the individual patient's needs**, in terms of mechanism of action and safety profile (see Table 1).[45]

COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

Patients with T2DM are at increased risk of CVD, blindness, end-stage renal disease resulting in transplantation and dialysis, and non-traumatic lower limb amputations.[2,6] A vital goal of treatment is to prevent or delay the onset of these complications by early detection and prompt intervention of risk factors.[3,6] Table 2 outlines the T2DM-related macrovascular and microvascular complications and their risk factors.

Table 2: T2DM-related vascular complications[2,3,6]

Macrovascular disease		Microvascular disease	
Complications • cerebrovascular disease • peripheral arterial disease • ischaemic heart disease	**Risk factors include:** glycaemic control, smoking hyperlipidaemia, hypertension, albuminuria	**Complications** • retinopathy • nephropathy • neuropathy	**Risk factors include:** glycaemic control, duration of T2DM, hypertension

In terms of **glycaemic control**: a level of **$HbA1_c$ <53mmol/mol (<7.0%)** is the agreed target which has been shown to reduce the risk of T2DM complications (especially microvascular disease); therefore this should be the treatment goal.[6,18] However, **less stringent glycaemic control** (HbA1c <58mmol/mol; <8.0%) **may be acceptable for some patients**, such as older patients or those with advanced complications or co-morbidities or where hypoglycaemia is a risk, or in the absence of adequate social support systems.[18] In contrast, newly diagnosed / younger patients with T2DM may tolerate more stringent controls ($HbA1_c$ <48mmol/mol; <6.5%).[6,7,9]

MACROVASCULAR DISEASE

CVD is responsible for 50% of the mortality and a vast amount of morbidity in T2DM.[7] However, recent data from the Framingham Heart Study have shown that patients with T2DM remain inadequately managed with regard to CVD risk factors.[46] A full CVD history should be taken at diagnosis and a CVD risk score (using a validated risk assessment chart) and ECG undertaken annually for all patients without overt CVD.[6]

Lifestyle modifications: There is strong evidence to support the efficacy of **smoking cessation, weight loss, dietary modification (to reduce saturated fats and increase fibre) and exercise (moderate / vigorous physical activity >150 minutes/week)** in preventing / minimising CVD in patients with T2DM.[7] These interventions should be included as part of the integrated care of T2DM.[6]

Hypertension is a risk factor for both T2DM-related macrovascular and microvascular complications; however > 60% of newly diagnosed T2DM patients are found to have hypertension.[7] Guidelines recommend measurement of blood pressure (BP) at least annually and at every visit if found to be above the **recommended target BP (<140mmHg systolic; <80mmHg diastolic)**. Lower BP levels may be appropriate for individuals especially in the presence of existing CVD, while less stringent BP control may be warranted for some patients (e.g. those at risk of falls or drug toxicity, or with reduced renal function).[6,13] If antihypertensive therapy is required to achieve target BP, the regimen should include either an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in view of their reno-protective effects.[7,13]

Lipid abnormalities: Lipids should be checked annually; the primary target for therapy is LDL-C.[13] Statin therapy is recommended for T2DM patients >40 years to achieve either a target of LDL-C level of ≤ 2.5 mmol/L (if no CVD) or ≤ 1.8mmol/L in the presence of CVD or at least a 50% reduction of LDL-C at maximum statin therapy.[7] Ezetimibe may be added to statin therapy, or used instead, if the patient is statin-intolerant. Fibrate therapy may be required to treat high triglycerides in the presence of well controlled T2DM.[6]

Other therapies: Aspirin has been shown to reduce CVD events in patients with known CVD, but there is conflicting evidence regarding its benefit / risk as primary prevention.[13] Low dose aspirin (75-150mg/day) is recommended for all T2DM patients with known CVD but is not recommended routinely for those with low CVD risk, in view of the risk of GI bleeding.[6,9] Clopidogrel (75mg/day) should only be used in the presence of aspirin toxicity or allergy.[6,47]

MICROVASCULAR DISEASE

T2DM is a chronic progressive disease therefore **microvascular disease is related to the duration of disease and the level of glycaemic control**.[10] Management involves (1) primary prevention in terms of modifiable risk factors, including optimal glycaemic control (Table 2) and (2) secondary prevention to ensure early diagnosis and intervention of overt microvascular disease.[10]

Retinopathy is the commonest complication of T2DM; it is estimated that **>10% of patients have some evidence of retinopathy at diagnosis**.[3,10] In addition to management of all the other risk factors, all T2DM patients should have a retinal screening examination performed at diagnosis and at least annually thereafter; specialist referral is needed for new vessel formation or macular disease.[3,8] The **Diabetic RetinaScreen** service is now available for all diabetic patients in Ireland [see "**Useful Resources**" section below].

Neuropathy: the most frequently occurring neuropathy in T2DM is **diabetic peripheral sensorimotor polyneuropathy (DPN)**; it can lead to foot problems and troublesome pain / paraesthesia.[3,10] All T2DM patients should be examined for evidence of DPN and peripheral arterial disease (PAD) at diagnosis and have feet classified; they should have a formal footcare assessment at least annually thereafter.[48] **All potential non-diabetic causes of neuropathy should be ruled out** and/or managed if present (including vitamin B12 deficiency, excessive alcohol intake, hypothyroidism, renal disease).[3,6,10] [see "**Useful Resources**" section below]

Table 3 outlines the approach to managing DPN in clinical practice.

Table 3: Management of T2DM-related DPN complications[6,10,48-51]

Problem	Recommended management*
Foot disease	Regular foot review (by primary care team and podiatrist); education in footcare (e.g. foot hygiene; correct footwear etc.). Specialist referral for active foot disease
Painful DPN	Check vitamin B12 and folate levels and treat if levels are low. Prescribe amitriptyline / pregabalin / duloxetine monotherapy (titrate dose to patient response) X 4 to 6 mths. If no response, switch / combine therapy (do **not** combine amitriptyline and duloxetine because of the risk of serotonin syndrome) X 4 to 6 mths. Specialist referral if lack of response or if DPN is severe

*all non-diabetic causes of neuropathy should be ruled out / managed if present.

Autonomic neuropathy: **Erectile dysfunction (ED)** may affect up to 50% of males with T2DM.[6] Male patients should be asked about ED at diagnosis and annually and other causes ruled out / treated. PDE5 therapy / vacuum devices may be needed if lifestyle interventions are not effective or if ED is associated with severe stress.[3,6] GI or bladder problems or orthostatic hypotension occur more rarely.

Nephropathy: Microalbuminuria is the earliest indicator of nephropathy in T2DM.[10] It is thought to reflect subclinical vascular damage and studies have shown that **microalbuminuria is predictive of CVD, CV mortality and all-cause mortality in T2DM**.[6] All patients should have (1) serum creatinine and urinary albumin/creatinine ratio (ACR) measured and (2) eGFR estimated at diagnosis and annually.[3,6] **If microalbuminuria is detected**, (ACR ratio ≥2.5mg/mmol [male]; ≥3.5mg/mmol [female] = 30-300mg urinary albumin/24 hours), **treatment with ACEI / ARB** should be instituted if eGFR is ≥60ml/min/1.73m^2. Specialist referral is recommended if there is uncertainty about the cause of the renal abnormality or when eGFR is <30ml/min/1.73m^2.[6]

USEFUL RESOURCES FOR TYPE 2 DIABETES MELLITUS

A Practical Guide to Integrated Type 2 Diabetes Care (ICGP) 2016. Comprehensive guide to all aspects of care for the patient with T2DM in Ireland. Available for download at: **www.icgp.ie**

Several education courses for patients are provided by the HSE as part of structured education in diabetes:
X-PERT Course for T2DM. Dietitian-led [6 x 2.5 hours] to improve knowledge and increase skills needed to look after T2DM
CODE. *Diabetes Ireland's* group education programme [~ 3 x 2 hour sessions], run by community dietitian / diabetes nurse
DESMOND [**D**iabetes **E**ducation and **S**elf-**M**anagement for **O**ngoing and **N**ewly **D**iagnosed [T2DM patients] ~ 6 hours in total.
For further information (and to book a course) check out: **www.hse.ie/eng/health/hl/living/diabetes/Diabetes_Courses/**

Diabetic RetinaScreen. National screening programme which provides free retinal examinations to all patients >12 years old with diabetes. For further information (and to register a patient) check out: **www.diabeticretinascreen.ie**

The National Model of Care for the Diabetic Foot. Provides guidance on foot care management in T2DM base on category of risk. *Available from:* **www.hse.ie/eng/about/Who/clinical/natclinprog/diabetesprogramme/modelofcarediabetes.pdf**

Type 2 diabetes in adults: management. The National Institute for Care and Health Excellence (NICE), UK (July 2016 update). Available for download at: **www.nice.org.uk/guidance/ng28**

American Diabetes Association: standards of care. Check out: **http://professional.diabetes.org/content/clinical-practice-recommendations**

List of references available on request. Date of preparation: March 2017

References: UPDATE ON TYPE 2 DIABETES MELLITUS 2017 VOL 23 NO. 1

1. Polonsky S. the past 200 years in diabetes. NEJM 2012; 367: 1332-40

2. Inzucchi S. et al, Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care 2012 Jun; 35 (6): 1364-1379. https://doi.org/10.2337/dc12-0413

3. Global guidelines for type 2 diabetes. International Diabetes Federation Clinical Guidelines Taskforce, Brussels, 2012. http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes. Accessed 16th January 2017

4. Tracey M et al. Epidemiology of diabetes and complications among adults in the Republic of Ireland 1998-2015: a systematic review and meta-analysis. BMC Public Health 2016; 16:132. DOI 10.1186/s12889-016-2818-2

5. Diabetes Prevalence in Ireland. Diabetes Ireland. Available online at: www.diabetes.ie/about-us/diabetes-in-ireland/. Accessed 22 March 2017.

6. A practical guide to integrated type 2 diabetes care (ICGP) 2016. Available online at: www.icgp.ie (search for diabetes). Accessed 16th January 2017

7. Lars Ryden et al, ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal, doi:10.1093/eurheartj/eht108

8. Johnston R et al, Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment 2017; 21 (2) DOI 10.3310/hta21020.

9. Type 2 diabetes in adults: management. The National Institute for Care and Health Excellence (NICE), UK (July 2016 update). Available online at: https://www.nice.org.uk/guidance/ng28. Accessed 16th January 2017

10. Valencia W, Florez H, How to prevent the microvascular complications of type 2 diabetes beyond glucose control. BMJ 2017;356: i6505.doi 10.1136/bmj16505

11. Alsahli M and Gerich J, Abnormalities of insulin secretion and B-cell defects in type 2 diabetes *in* Textbook of Diabetes 4th Edition. Editors: Holt R, Cockram

C, Flyvbjerg A, Goldstein B. Publishers Wiley-Blackwell. UK, 2010. Chapter 10 pp. 160-173

12. Reinehr T, type 2 diabetes mellitus in children and adolescents. World J diabetes 2013; 4: 270-81

13. FOX C et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015; 38: 1777-1803.

14. Wei W ET AL, a real world study of treatment patterns and outcomes in US managed-care patients with type 2 diabetes initiating injectable therapies. Diabetes Obes Metab 2017; 1-12

15. Nam S et al, barriers to diabetes management: patient and provider factors. Diabetes Research and Clinical Practice 2011; 93:1-9

16. Fukuda H and Mizobe M, Impact of nonadherence on complication risks and healthcare costs in patients newly-diagnosed with diabetes. Diabetes Research and Clinical Practice 2017; 123: 55-62

17. Diabetes education courses, provided by the HSE on a regional basis. Available to book at: http://www.hse.ie/eng/health/hl/living/diabetes/Diabetes_Courses/. Accessed 18th January 2017

18. Ismail-Beigi F, glycemic management of type 2 diabetes mellitus. NEJM 2012; 366: 1319-27

19. Glucophage® (metformin) Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 3rd February 2017

20. Glibenclamide Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 3rd February 2017

21. Amaryl® (glimepiride) Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 3rd February 2017

22. Diamicron® (gliclazide) Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 3rd February 2017

23. Trajenta® (LINAGLIPTIN). Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

24. Onglyza® (saxagliptin). Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 20th March 2017

25. Januvia® (sitagliptin) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

26. Galvus® (vildagliptin) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

27. Actos® (pioglitazone) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

28. Trulicity® (dulaglutide) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

29. Victoza® (liralgutide) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

30. Byetta® (exenatide) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 6th February 2017

31. Forxiga® (dapaglifozin) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

32. Jardiance® (empagliflozin) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

33. Invokana® (canagliflozin) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 2rd February 2017

34. Assessment report for GLP-1 based therapies Review under Article 5(3) of Regulation (EC) No 726/2004 Procedure no: EMEA/H/A-5(3)/1369. [EMA/474117/2013, 25 July 2013] Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/08/WC500147026.pdf. Accessed 18th January 2017

35. Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function. Recommendations for patients with kidney impairment updated in product information. EMA 14 October 2016 (EMA/603690/2016). Available online at www.ema.europa.eu. ACCESSED 2O MARCH 2017.

36. SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information: Diabetes patients reminded of importance

of preventative foot care. EMA, 24 February 2017 (EMA/118223/2017). Available online at www.ema.europa.eu. Accessed 28 Feb. 2017.

37. Novonorm® (repaglinide) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 6th March 2017

38. Starlix® (nateglinide) Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 6th March 2017

39. Glucobay® (acarbose) Summary of Product Characteristics . Available online at: www.hpra.ie. Accessed 6th March 2017

40. Qaseem A et al, oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. ANN INTERN MED 2017 doi:10.7326/M16-1860

41. Reusch J and Manson J, management of type 2 diabetes in 2017: getting to goal. Jama 2017; 317: 1015-6

42. PALMER C et al, comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with T2DM: a meta-analysis. JAMA 2016; 316: 313-324

43. Marso S et al, Liraglutide and cardiovascular outcomes in type 2 diabetes. NEJM 2016; 375:1834-44.

44. Zinman B et al, Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. NEJM 2015; 373: 2117-28

45. NIHR signal: nine different drug classes reviewed for T2DM. available online AT: https://discover.dc.nihr.ac.uk/portal/article/4000572/nine-different-drug-classes-reviewed-for-type-2-diabetes. Accessed 8 march 2017

46. Fox C et al. Cardiovascular disease risk factors, T2DM and the Framingham Heart Study, Trends Cardiovasc. Med 2010; 20: 90-5

47. Plavix ® (clopidogrel). Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 16th March 2017

48. Model of care for the diabetic foot. National Diabetes Programme Clinical Strategy and Programmes Directorate, 2011. Available online at: http://www.hse.ie/eng/about/Who/clinical/natclinprog/diabetesprogramme/modelofcarediabetes.pdf. Accessed 22 March 2017

49. Lyrica® (pregaba lin) Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 16th March 2017

50. Amitriptyline 25 mg Film-Coated Tablets. Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 16th March 2017

51. Cymbalta® (duloxetine) Summary of Product Characteristics. Available online at: www.medicines.ie. Accessed 16th March 2017