Multidisciplinary management of type 2 diabetes:
Practical considerations in diagnosis, care planning and treatment selection

Case study*

Tailoring type 2 diabetes therapy to minimise hypoglycaemia risk

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***Fictitious case, created for illustrative purposes only by a healthcare professional**

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Prescribing information and adverse event reporting information can be found at the end of this case study.
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Presentation details

- MB* is a 63-year-old Caucasian married man who works as a warehouse assistant
- He was diagnosed with type 2 diabetes (T2D) 5 years ago
- His glycaemic control was initially good on metformin alone, but over the past two years his HbA_{1c} level has started to rise
  - His GP initiated gliclazide 80 mg twice daily (b.d.), and 6 months ago escalated the dose to 160 mg b.d.

***Fictitious case, created for illustrative purposes only**

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Go to **Initial assessment (i)**

Initial assessment (i)

- MB was recently admitted to hospital with hypoglycaemia
  - Due to staffing pressures at work, he had skipped lunch and was then assigned a heavy manual task
  - His colleagues found him slumped on some pallets, unconscious, and an ambulance was called
  - At the time of admission, his blood glucose level was 2.6 mmol/L
- MB is concerned about recurrence of hypoglycaemia, as he often needs to operate a forklift at work. He fears he may lose his job
  - After his hospital admission, MB has stopped taking his gliclazide and now wishes to explore alternative glucose-lowering therapies to use while continuing to take metformin

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Go to **Initial assessment (ii)**

Initial assessment (ii)

- At his last clinic visit, before hospitalisation, MB's test results were as follows:

- His current medication regimen is:

HbA_{1c}	52 mmol/mol (6.9%)
Estimated glomerular filtration rate (eGFR)	58 mL/min/1.73 m^2
Blood pressure	138/76 mmHg
BMI	29 kg/m^2

Metformin (glucose-lowering medication for T2D)	1000 mg twice daily (b.d.)
Gliclazide (glucose-lowering medication for T2D)	160 mg b.d. (he hasn't taken this since his hospital admission)
Atorvastatin (for primary prevention of a cardiovascular [CV] event based on his CV disease risk)	20 mg once daily (o.d.)
Lisinopril (he has a history of hypertension)	10 mg o.d.

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Go to **Considerations for management (i)**

Considerations for management (i)

- When thinking about taking the next step after maximum tolerated dose of metformin, NICE advises considering dual therapy with[1]:
  - Metformin and a DPP-4i; metformin and pioglitazone; metformin and an SGLT-2i; or metformin and an SU (this last option has already been tried and failed for this patient)
- The healthcare professional (HCP) should consider the following patient characteristics:
  - Age[2], sex[3], ethnicity[4], faith[4], beliefs[4], occupation[5], driving[5], health literacy[6], and dexterity[7]
- Additionally, the following factors must also be taken into consideration:
  - BMI[2], renal function[8], hepatic function[8], heart failure[8], comorbidities[8], polypharmacy[9], drug interactions[9], and drug intolerance[1]

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Go to **Considerations for management (ii)**

DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; SU, sulphonylurea

Considerations for management (ii)

- MB has mild to moderate impairment of his renal function, and he is overweight. His options were considered as follows:
  - A dipeptidyl peptidase 4 (DPP-4) inhibitor:
    - Impedes the enzyme DPP-4, which is involved in the inactivation of the incretin hormones GLP-1 and GIP that play important roles in the physiological regulation of glucose homeostasis[10]
    - Low risk of hypoglycaemia[8]
    - Weight neutral[8]
    - Can be used without dose adjustment in mild renal impairment (eGFR >50 mL/min/1.73min^2).[11–15] Linagliptin can be used at all stages of renal impairment without needing dose adjustment[11]

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Go to **Considerations for management (iii)**

GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide; eGFR, estimated glomerular filtration rate

Considerations for management (iii)

- Thiazolidinedione:
  - Reduces insulin resistance and improves insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPARγ) and promoting differentiation of fat cells[10]
  - Low risk of hypoglycaemia[8]
  - May cause fluid retention, which may exacerbate or precipitate heart failure[16]
    - MB is at higher risk of heart failure due to his type 2 diabetes and history of hypertension[17]
- A sodium–glucose co-transporter 2 (SGLT2) inhibitor:*
  - Improves glycaemic control by reducing renal glucose absorption, leading to excretion of excess glucose in the urine. In addition, they increase the excretion of sodium, resulting in osmotic diuresis and reduced intravascular volume[10]
  - Low risk of hypoglycaemia[8]
  - Can provide some weight loss[8]
  - These agents should not be initiated when eGFR is <60 mL/min/1.73 m^2 [18–20]

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Go to **Considerations for management (iv)**

eGFR, estimated glomerular filtration rate
*SGLT2 inhibitors are not licensed for weight loss

Considerations for management (iv)

- A glucagon-like peptide 1 (GLP-1) receptor agonist:*
  - Activates GLP-1 receptor, mimics action of GLP-1 to enhance prandial insulin secretion, reduces prandial glucagon secretion, delays gastric emptying and exerts satiety effect[10]
  - Low risk of hypoglycaemia[8]
  - Can provide some weight loss[8]
  - NICE does not recommend use of GLP-1 receptor agonists as a second-line blood-glucose lowering option[1]
- Insulin
  - Used as a direct substitute for the body's own insulin. It is available in three injectable forms – animal, human and analogue – with a range of rates of action[21]
  - Risk of hypoglycaemia and weight gain[8]
  - NICE does not recommend use of insulin as a second-line blood-glucose lowering option[1]

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Go to **Considerations for management (v)**

*GLP-1 receptor agonists are not licensed for weight loss

Considerations for management (v)

- After discussion with MB, his GP recommended a DPP-4 inhibitor as MB preferred to avoid an injectable option if possible
- The GP also advised MB that if the medication was tolerated and effective, he could switch to a combination tablet (DPP-4 inhibitor plus metformin) to reduce his pill burden[22]
- MB was reminded of the importance of adhering to diet and lifestyle as part of his diabetes management plan[1] and counselled on potential side effects for his new therapy regimen, including how to recognise symptoms of pancreatitis should this occur while taking a DPP-4 inhibitor[8]
- The GP reminded MB that if he suffered a further episode of severe hypoglycaemia within 12 months of his recent episode, this must be reported to the Driver and Vehicle Licensing Authority[23]

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Go to **Follow-up**

Follow-up

- At MB's 3-month review, his HbA_{1c} was 57 mmol/mol (7.4%), which the GP and patient both agreed was acceptable
- His weight had decreased somewhat since stopping gliclazide therapy
- He had no more hypoglycaemic episodes and felt confident when driving at work

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Go to **Clinical implications**

Clinical implications

- Fear of hypoglycaemia can compromise glycaemic control in people with T2D[24]
- Hypoglycaemia can lead to defensive behaviour changes, such as reducing or stopping medication, excessive blood glucose monitoring or overeating[24]
- There is a wide range of medications available as add-on to metformin[1,8]
- HCPs should consider hypoglycaemia risk, weight gain and renal function when prescribing[1,8]
- Both the NICE guidelines and the ADA/EASD position statement highlight the need for individualisation of therapy in T2D and the need to modify HbA_{1c} targets in circumstances such as comorbidities and reduced life expectancy[1,8]

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References

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Prescribing information PI

Prescribing information (i)

TRAJENTA® (linagliptin) 5 mg film-coated tablets

Film-coated tablets containing 5 mg linagliptin. **Indication:** Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Dose and Administration:** 5 mg once daily. If added to metformin, the dose of metformin should be maintained and linagliptin administered concomitantly. When used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia. Renal impairment: no dose adjustment required. Hepatic impairment: pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. Elderly: no dose adjustment is necessary based on age however, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population. Paediatric population: the safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. Take the tablets with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as possible but a double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin; a dose reduction of the sulphonylurea or insulin may be considered. Acute pancreatitis: In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Bullous pemphigoid: If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interactions:** Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates. The risk for clinically meaningful interactions by other medicinal products on linagliptin is low and in clinical studies linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, warfarin, digoxin or oral contraceptives (please refer to Summary of Product Characteristics for information on clinical data). **Fertility, pregnancy and lactation:** Avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for linagliptin. **Undesirable effects:** Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies (frequencies identified from pooled analysis of placebo-controlled studies) in clinical trial and from post-marketing experience. The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data). Very common: hypoglycaemia (combination with/add-on to metformin and sulphonylurea). Common: lipase increased (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin; combination with/add-on to metformin and empagliflozin). Uncommon: nasopharyngitis (monotherapy; combination with/add-on to metformin; combination with/add-on to insulin); hypersensitivity e.g. bronchial hyperreactivity (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); cough (monotherapy; combination with/add-on to metformin; combination with/add-on to insulin); pancreatitis (combination with/add-on to insulin); constipation (combination with/add-on to insulin); rash (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin). Rare: angioedema (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); urticaria (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (monotherapy). Not known: nasopharyngitis (combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); hypersensitivity e.g. bronchial hyperreactivity (combination with/add-on to metformin and empagliflozin); cough (combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); pancreatitis (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); bullous pemphigoid (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (combination with/add-on to insulin). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 28 tablets £33.26. **Legal category:** POM. **MA number:** EU/1/11/707/003. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** April 2017.

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 Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

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Prescribing information (ii)

JENTADUETO® (linagliptin and metformin hydrochloride)

Film-coated tablets containing 2.5 mg linagliptin and 850 mg metformin hydrochloride or 2.5 mg linagliptin and 1,000 mg metformin hydrochloride. **Indication:** Jentadueto is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control: in patients inadequately controlled on their maximally tolerated dose of metformin alone; in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products; in patients already being treated with the combination of linagliptin and metformin as separate tablets. **Dose and Administration:** *Adults with normal renal function (glomerular filtration rate (GFR) ≥ 90 ml/min):* The dose should be individualised based on the patient's current regimen, effectiveness and tolerability, not exceeding the maximum recommended daily dose of 5 mg linagliptin plus 2,000 mg metformin hydrochloride. *Patients inadequately controlled on maximal tolerated dose of metformin monotherapy*: the usual starting dose should provide linagliptin 2.5 mg twice daily (5 mg total daily dose) plus the current metformin dose. *Patients switching from co-administration of linagliptin and metformin:* Initiate at the dose of linagliptin and metformin already being taken. *Patients inadequately controlled on dual combination of the maximal tolerated dose of metformin and a sulphonylurea:* The dose should provide linagliptin 2.5 mg twice daily (5 mg total daily dose) and a metformin dose similar to the dose already being taken. When linagliptin plus metformin hydrochloride is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia. *Patients inadequately controlled on dual combination with insulin and the maximal tolerated dose of metformin:* The dose should provide linagliptin 2.5 mg twice daily (5 mg total daily dose) and a metformin dose similar to the dose already being taken. When linagliptin plus metformin hydrochloride is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia. *Elderly:* As metformin is excreted by the kidney, use with caution as age increases. Monitoring of renal function is necessary. Exercise caution in patients 80 years and older as clinical experience in this age group is limited. *Renal impairment:* Assess GFR before initiating treatment and at least annually thereafter, or more frequently (e.g. every 3−6 months) in patients at an increased risk of further progression of renal impairment and in the elderly. Review factors that may increase lactic acidosis risk before considering initiation in patients with GFR < 60 ml/min. If no adequate strength of Jentadueto is available, use individual monocomponents instead of the fixed dose combination. For full details prescribers should consult the Summary of Product Characteristics. *Hepatic impairment:* Not recommended. Clinical experience in patients with hepatic impairment is lacking. *Paediatric population:* Safety and efficacy in children and adolescents (aged 0 to 18 years) have not been established. No data are available. *Taking Jentadueto:* To be taken twice daily with meals. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet. If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time (the missed dose should be skipped). **Contraindications:** Hypersensitivity to the active substances or to any of the excipients; any acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis); diabetic pre-coma; severe renal failure (GFR < 30 ml/min); acute conditions with the potential to alter renal function such as dehydration, severe infection, shock; disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock; hepatic impairment, acute alcohol intoxication, alcoholism. **Warnings and Precautions:** Should not be used in patients with type 1 diabetes. Caution is advised when Jentadueto is used in combination with a sulphonylurea and/or insulin due to increased incidence of hypoglycaemia. Acute worsening of renal function causes metformin accumulation and increases the risk of lactic acidosis. Temporarily discontinue treatment in case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake). Initiate products that can acutely impair renal function (e.g. antihypertensives, diuretics and non-steroidal anti-inflammatory drugs (NSAIDs)) with caution. Inform patients and/or care givers of the risk of lactic acidosis. If lactic acidosis is suspected the patient should stop taking Jentadueto and seek immediate medical attention. Intravascular administration of iodinated contrast agents may result in metformin accumulation and increased risk of lactic acidosis. Discontinue treatment prior to or at the time of the imaging procedure. Restart after at least 48 hours, provided that renal function is re-evaluated and found to be stable. Assess GFR before initiating treatment and regularly thereafter (see Dose and Administration). Temporarily discontinue treatment in the presence of conditions that alter renal function. Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure use Jentadueto with regular monitoring of cardiac and renal function. Discontinue treatment at the time of surgery under general, spinal or epidural anaesthesia. Restart therapy no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function is re-evaluated and found to be stable. A patient with previously well controlled type 2 diabetes on Jentadueto who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. If acidosis of either form occurs, stop treatment immediately and initiate other appropriate corrective measures. There have been spontaneously reported adverse reactions of acute pancreatitis with linagliptin. If pancreatitis is suspected, Jentadueto should be discontinued; if confirmed, treatment should not be restarted. Patients should be informed of the characteristic symptoms of acute pancreatitis. Exercise caution in patients with a history of pancreatitis. If bullous pemphigoid is suspected, Jentadueto should be discontinued. **Interactions:** *Combination requiring precautions for use:* glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics. More frequent blood glucose monitoring should be performed, especially at the beginning of treatment with such medicinal products. If necessary, adjust the dose of Jentadueto during therapy with the other medicinal product and on its discontinuation; products which may increase the risk of lactic acidosis e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics. Monitor renal function closely when starting or using such products; Organic cation transporter 1 (OCT1) and OCT2 inhibitors/inducers such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib and olaparib. Use caution, especially in patients with renal impairment. Consider dose adjustment if needed. *Concomitant use not recommended:* Alcohol; iodinated contrast agents. **Fertility, pregnancy and lactation:** Jentadueto should not be used during pregnancy. If the patient plans to become pregnant, or if pregnancy occurs, discontinue treatment and switch to insulin treatment as soon as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Jentadueto therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. The effect of Jentadueto on human fertility has not been studied. **Undesirable effects:** Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Adverse reactions reported with linagliptin + metformin alone or as add-on to other background anti-diabetic therapies: *Adverse reactions with linagliptin + metformin:* Common: diarrhoea; lipase increased. Uncommon: nasopharyngitis; hypersensitivity; cough, decreased appetite; nausea; vomiting; rash; pruritus; blood amylase increased. Rare: angioedema; urticaria. Not known: pancreatitis; bullous pemphigoid. *Adverse reactions with linagliptin + metformin + sulphonylurea:* Very common: Hypoglycaemia. Common: lipase increased. Uncommon: hypersensitivity; diarrhoea; nausea; vomiting; rash; pruritus; blood amylase increased. Rare: angioedema; urticaria. Not known: nasopharyngitis; cough; decreased appetite; pancreatitis; bullous pemphigoid. *Adverse reactions with linagliptin + metformin + insulin:* Common: nausea; lipase increased. Uncommon: nasopharyngitis; hypersensitivity; cough; diarrhoea; pancreatitis; constipation; liver function disorders; rash; pruritus. Rare: angioedema; urticaria. Not known: decreased appetite; vomiting; bullous pemphigoid; blood amylase increased. *Adverse reactions with linagliptin + metformin + empagliflozin:* Common: lipase increased. Uncommon: vomiting; rash; blood amylase increased. Rare: angioedema; urticaria. Not known: nasopharyngitis; hypersensitivity; cough; decreased appetite; diarrhoea; nausea; pancreatitis; pruritus; bullous pemphigoid. *Additional information on individual components:* Adverse reactions previously reported with one of the individual active substances may be potential adverse reactions with Jentadueto, even if not observed in clinical trials. *Metformin:* Known adverse reactions that were not reported in patients who received Jentadueto. Very common: abdominal pain. Common: taste disturbance. Very rare: lactic acidosis; vitamin B12 deficiency; hepatitis; skin reactions. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** *2.5 mg/850 mg* 56 tablets £33.26; *2.5 mg/1,000 mg* 56 tablets £33.26. **Legal category:** POM. **MA numbers:** 2.5 mg/850 mg (56 tablets) EU/1/12/780/005; 2.5 mg/1,000 mg (56 tablets) EU/1/12/780/019. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** June 2017.

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