UK Prescribing Information

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. *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. Acute pancreatitis has been observed in patients taking 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. Bullous pemphigoid has been observed in patients taking linagliptin. 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) or very rare (< 1/10,000). *Adverse reactions with linagliptin + metformin alone (as monocomponents or in combination):* Common: diarrhoea; nausea; lipase increased. Uncommon: nasopharyngitis; hypersensitivity; cough, decreased appetite; vomiting; rash; pruritus; amylase increased. Rare: pancreatitis; angioedema; urticaria; bullous pemphigoid. *Adverse reactions with metformin as monotherapy and that were not observed in patients receiving Jentadueto*: Very common: abdominal pain. Common: taste disturbance. Very rare: lactic acidosis; vitamin B_{12} deficiency; hepatitis; erythema. 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. *Adverse reaction observed in combination of Jentadueto with sulphonylurea:* Very common: hypoglycaemia. *Adverse reactions observed in combination of Jentadueto with insulin:* Uncommon: constipation; liver function disorders. 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** December 2019.

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).