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Sitagliptin/pioglitazone for type 2 diabetes mellitus – monotherapy or add-on therapy

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Sitagliptin/pioglitazone for type 2 diabetes mellitus – monotherapy or add-on therapy

Target group

- Type 2 diabetes mellitus: uncontrolled on metformin and pioglitazone or metformin and sitagliptin – monotherapy or add-on therapy to metformin.

Technology description

Sitagliptin/pioglitazone (MK-0431C; MK-431C) is a fixed dose combination of sitagliptin, DPP-4 inhibitor, and pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist. It is intended to substitute sitagliptin or pioglitazone, or to be used as an add-on to metformin, for the treatment of patients with type 2 diabetes who are uncontrolled on metformin in combination with pioglitazone or sitagliptin. In phase III clinical trials, sitagliptin was administered orally at 100mg once daily and pioglitazone was administered orally at 15mg to 45mg once daily.

Sitagliptin and pioglitazone are available for clinical use in the UK as separate agents, and as fixed dose combinations with metformin. A fixed-dose combination of pioglitazone/glimepiride for the treatment of type 2 diabetes mellitus has also been registered in the EU. Fixed dose combinations of pioglitazone/alogliptin and sitagliptin /simvastatin are in phase III clinical trials for treatment of type 2 diabetes mellitus.

Innovation and/or advantages

If licensed, sitagliptin/pioglitazone may offer an additional treatment option for people with poorly controlled hyperglycaemia.

Developer

Merck Sharp & Dohme Limited (MSD).

Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

NHS or Government priority area

This topic is relevant to the National Service Framework for Diabetes (2007).

Relevant guidance

- NICE Technology Appraisals. Liraglutide for the treatment of type 2 diabetes. 2010[1].
- NICE Technology Appraisals. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. 2008[2].
- NICE Technology Appraisals. Guidance on the use of long-acting insulin analogues for the treatment of diabetes - Insulin glargine. 2002[3].
- NICE Clinical Guideline. Type 2 diabetes: the management of type 2 diabetes. 2009[4].
- NICE Clinical Guideline. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. 2007[5].
- National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). 2008[6].
- Clinical Knowledge Summaries. Diabetes type 2. Blood glucose management. 2007[7].
- International Diabetes Federation. Global guideline for type 2 diabetes. 2005[8].

Clinical need and burden of disease

The prevalence of diabetes in the UK is increasing, but not accurately known, and varies with factors such as the mix of ethnic groups and degree of social deprivation[6]. In England and Wales the prevalence of diabetes (diagnosed and undiagnosed) in adults is estimated to fall between 5% and 12%[9]. In 2010 around 3.3 million people above the age of 16 years were living with diabetes (diagnosed and undiagnosed) in England and Wales[9], with more than 85% of them having type 2 diabetes[6]. It is accepted that a high proportion of people with diabetes are undiagnosed.

An estimated 4.2% of deaths in men and 7.7% of deaths in women in the UK can be attributed to diabetes[6]. These are likely to be underestimates as death registrations for vascular events such as stroke and myocardial infarction (MI) frequently under record the underlying causative disease[6]. Life expectancy is reduced by up to 10 years in people with diabetes[10]. Cardiovascular disease is the most common complication of type 2 diabetes and is the greatest cause of morbidity and premature death in this patient group, accounting for around 60% of all deaths from diabetes[11]. Other long-term complications associated with diabetes include: nephropathy, retinopathy and neuropathy, leading respectively to renal failure, reduced vision or blindness, and foot ulceration and amputation.

Existing comparators and treatments

Current treatment options include[4,6]:

- Oral anti-diabetes drugs (alone or in combination)
  - Metformin.
  - Sulfonylureas: gliclazide, glibenclamide, glipizide, tolbutamide, glimepiride.
  - Alpha-glucosidase inhibitors: acarbose.
  - Thiazolidinediones (glitazones): rosiglitazone (EMA suspended marketing authorisation in September 2010), pioglitazone.
  - DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin.
- Injectable drugs
  - Exenatide (twice daily SC).
  - Liraglutide (once daily SC).
  - Insulin (human or analogue).

Current practice is that treatment should aim to achieve the target glycated haemoglobin (HbA1c) level of 6.5% for first 2 treatment steps, or 7.5% if further treatment steps are required or where there is severe risk of hypoglycaemia.

Efficacy and safety

Trial	NCT00397631; pioglitazone with sitagliptin or placebo; phase III.	NCT01028391; pioglitazone with sitagliptin or placebo, plus metformin if required; phase III extension.
Sponsor	Merck.	Merck.
Status	Trial complete but unpublished.	Trial complete but unpublished.
Source of information	Trial registry[12].	Trial registry[13].
Location	EU, USA and other countries.	EU, USA and other countries.
Design	Randomised, active-controlled.	Extension study.
Participants and schedule	n=520; adults; type 2 diabetes; HbA1c 8%-12%; not on antihyperglycaemic therapy (oral or insulin); managed with diet and exercise alone. Randomised to receive co-administration	n=317; adults; type 2 diabetes; completed NCT00397631; ≥75% compliance with study treatment protocol. Continued on treatment as randomised

	of pioglitazone 30mg and sitagliptin 100mg once daily, or pioglitazone 30mg and placebo once daily.	in NCT00397631, but dose of piaglitazone increased to 45mg once daily in both arms. Patients not meeting specific glycaemic goals received metformin at dose determined by investigator.
Follow-up	Active treatment period 24 weeks.	Additional 30 weeks.
Primary outcome	HbA1c.	HbA1c.
Secondary outcomes	Fasting plasma glucose (FPG) and 2-hour post prandial glucose (PPG) level.	FPG
Key results	At week 24 for sitagliptin/pioglitazone and pioglitazone/placebo respectively: change from baseline HbA1c (%), -2.38 (95% CI -2.55 to -2.21) vs -1.49 (95% CI -1.66 to -1.32); change from baseline FPG (mg/dL), -63 (95% CI -68.3 to -57.6) vs -40.2 (95% CI -45.6 to -34.8); change from baseline 2-hour PPG (mg/dL), -113.6 (95% CI -122.4 to -104.8) vs -68.9 (95% CI -77.8 to -60).	At week 54 for sitagliptin/pioglitazone and pioglitazone/placebo respectively: change from baseline HbA1c, -2.37 (95% CI -2.54 to -2.19) vs -1.86 (95% CI -2.04 to -1.68); change from baseline FPG, -61.3 (95% CI -66.7 to -55.9) vs -52.8 (95% CI -58.4 to -47.2).
Adverse effects (AEs)	Non serious AEs (infections and infestations, nervous system disorders) reported in 8%. Serious AEs affected 3% of participants receiving sitagliptin/pioglitazone and 2% of those receiving pioglitazone/placebo. Gastrointestinal, ear and labyrinth, psychiatric and skin disorders more frequent in sitagliptin/pioglitazone arm, whereas vascular and nervous system disorders more frequent in pioglitazone/placebo arm.	Non serious AEs (infections and infestations) reported in 5%. Serious AEs affected 3% of participants receiving sitagliptin/pioglitazone and 2% of those receiving pioglitazone /placebo. Cardiac disorders more frequent in sitagliptin/pioglitazone arm.

Trial	NCT00722371; pioglitazone and sitagliptin as combination therapy or monotherapy; phase III.
Sponsor	Merck.
Status	Ongoing.
Source of information	Trial registry[14].
Location	EU, USA and other countries.
Design	Randomised, active-controlled.
Participants and schedule	n=1,295; adults; type 2 diabetes; treatment naïve. Randomised to receive sitagliptin 100mg once daily as monotherapy, or pioglitazone 15mg, 30mg, or 45mg once daily as monotherapy or co-administered with sitagliptin 100mg once daily.
Follow-up	Active treatment period 54 weeks.
Primary outcome	HbA1c at week 24.
Secondary outcomes	HbA1c at week 54; FPG and 2-hour PPG level at week 24 and 54.
Expected reporting date	Study expected to complete March 2011.

Estimated cost and cost impact

The cost of fixed dose combination of sitagliptin and pioglitazone is not yet known. Their cost as separate agents are [15]:

Drug	Dose	Annual cost
Sitagliptin (Januvia; MSD)	100mg once daily	£432
Pioglitazone (Actos; Takeda)	15mg to 45mg once daily	£185-£480

Claimed or potential impact – speculative

Patients

- ☐ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ None identified

Services

- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use
- ☐ Other:
- ☑ None identified

Costs

- ☐ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☐ New costs:
- ☐ Savings:
- ☑ Other: uncertain unit cost compared to separate agents.

Other issues

- ☐ Clinical uncertainty or other research question identified:
- ☑ None identified

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