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Pasireotide Long-Acting Repeatable (Signifor) for acromegaly – first and second line

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Pasireotide Long-Acting Repeatable (Signifor) for acromegaly – first and second line

Target group

- Acromegaly: *de novo*, persistent or recurrent – first or second line treatment.

Background

Acromegaly is a rare, serious condition characterised by excessive production of growth hormone (GH) caused by GH-secreting somatotroph pituitary adenomas in more than 90% of cases[1]. GH induces the synthesis of insulin-like growth factor I (IGF-I) in the liver. Elevated levels of IGF-I and GH cause metabolic dysfunction and somatic growth, including bone growth and organ enlargement, resulting in significant morbidity and mortality[6]. Due to insidious onset and slow progression, acromegaly is often diagnosed years after onset which has implications for disease prognosis. Clinical characteristics of the disease include broadened extremities and facial features, thickened soft tissue, mandibular overgrowth and maxillary widening, as well as other rheumatologic, cardiovascular, respiratory and metabolic manifestations such as diabetes mellitus, hypertension and congestive heart failure[5]. GH-secreting adenomas occurring in young patients before the closure of the epiphyseal bone result in accelerated growth and gigantism.

Technology description

Pasireotide long-acting repeatable (LAR) (SOM230, Signifor) is a novel multireceptor ligand somatostatin (sst) analogue with a high affinity binding profile for sst_1, sst_2, sst_3 and sst_5 receptor subtypes, mimicing the action of natural sst. Receptor subtypes sst_2 and sst_5 are expressed in 90% of GH-secreting pituitary tumours and once activated signal the pituitary gland to suppress GH secretion[1]. Pasireotide LAR also exhibits antiangiogenic activity (inhibiting vascular endothelial growth factor [VEGF] secretion) and works to reduce both the incidence and volume of pituitary tumours[2]. Pasireotide LAR is intended to treat acromegaly first or second line and is administered as an intramuscular (IM) depot injection. In trials it has been administered at a dose of between 20 and 60mg every 28 days.

Pasireotide LAR is in phase III clinical trials for Cushing's disease, gastro-entero-pancreatic neuroendocrine tumours and post-pancreatectomy complications, and is in phase II trials for meningioma.

Innovation and/or advantages

If licensed, pasireotide LAR offers an additional long-acting treatment option for acromegaly patients requiring somatostatin analogue therapy.

Developer

Novartis Pharmaceuticals Ltd.

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 Long Term Conditions (2005).

Relevant guidance

- The Acromegaly Consensus Group. Guidelines for acromegaly management: an update. 2009[3].
- American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly. 2004[4].

Clinical need and burden of disease

Acromegaly is a rare disease with an estimated 3,000 UK patients[5] and prevalence of 1.2 per 10,000 population in the EU[6] with an annual incidence of 3-4 per million. However, the clinical diagnosis of acromegaly is often missed so these figures may underestimate the frequency of the disease. It is most often diagnosed in adults between the ages of 30 and 50. Active acromegaly is associated with significant morbidity and a 2 or 3-fold increased mortality compared to the general population[7], with death predominantly attributable to vascular and respiratory disease. The increased mortality associated with acromegaly can be diminished if treatment is successful in reducing GH hypersecretion to less than 2-2.5mg/L[6].

Existing comparators and treatments

Current treatments are aimed at correcting or preventing tumour compression by excising the disease-causing lesion and reducing GH and IGF-I levels. Trans-sphenoidal surgery is considered first line treatment and has an overall remission rate of 55-70%[6]. Other treatments used first or second line include pharmacological treatment and/or radiotherapy[3]. Radiotherapy is successful in lowering GH levels and controlling tumour growth but has several limitations including a long lag time to clinical effect and hypopituitarism.

Because of the limitations of surgery and radiotherapy, pharmacological therapy is necessary for a significant number of patients[3] and may be categorised into three treatment options:

- Somatostatin analogues – octreotide and slow release depot preparations of octreotide such as sandostatin LAR.
- GH receptor antagonists – pegvisomant.
- Dopamine agonists – bromocriptine and cabergoline.

Efficacy and safety

Trial	NCT00088582, CSOM230B2201; pasireotide vs octreotide; phase II.	NCT00171730, CSOM230B2201E1; pasireotide vs octreotide; phase II extension of NCT00088582.
Sponsor	Novartis.	Novartis.
Status	Completed.	Ongoing.
Source of information	Trial registry[8], publication[9].	Trial registry[10].
Location	EU (inc UK), USA.	EU (inc UK), USA and Switzerland.
Design	Randomised, active-controlled, open-label.	Uncontrolled, open-label.
Participants and schedule	n=62; adults; acromegaly due to pituitary adenoma. All patients received octreotide 100µg subcutaneous (SC) three times daily for 28 days, then pasireotide 200µg, 400µg and 600µg SC (28 days on each dose level) twice daily, in a random order.	n=30; adults; acromegaly due to pituitary adenoma, completed NCT00088582 in which they achieved biochemical control with no serious adverse effects. Patients received minimum dose of pasireotide at which biochemical response was demonstrated.

Follow-up	Active treatment period of 3 months.	Primary outcome measured every 4 weeks; 3 month follow up intervals.
Primary outcome	GH and IGF-I blood concentrations.	GH and IGF-I blood concentrations.
Secondary outcomes	Safety and efficacy.	Safety and efficacy.
Key results	Reduction in GH and IGF-I levels observed at 28 days and 3 months demonstrated by full or partial biochemical response (19% and 27% of patients respectively). Mean change in GH at day 28, -1.5µg/L (95% CI -4.4 to 1.5); at month 3, -2.1µg/L (95% CI -4.7 to 0.5). No clear dose related relationship. 39% of patients achieved ≥20% reduction in pituitary tumour volume (mean percentage reduction, 14.5 ± 2.5% SE). Patients reported improved acromegaly symptom scores by month 3.	-
Expected reporting date	-	Dec 2010.
Adverse effects (AEs)	75% of patients experienced suspected drug-related AE. Most common AEs: nausea (25%), diarrhoea (21%), abdominal pain (11%), flatulence (10%) and increased blood glucose levels (6%).	-

Trial	NCT00600886, CSOM230C2305; pasireotide LAR vs octreotide LAR; phase III.	NCT01137682, CSOM230C2402, EUDRACT 2009-016722-13; pasireotide LAR vs octreotide LAR or lanreotide autogel (ATG); phase III.
Sponsor	Novartis.	Novartis.
Status	Ongoing.	Ongoing.
Source of information	Trial registry[11], manufacturer.	Trial registry[12], manufacturer.
Location	EU (inc UK), USA, Canada and other countries.	EU (inc UK), USA, Canada and other countries.
Design	Randomised, active-controlled.	Randomised, active-controlled.
Participants and schedule	n=330; adults; acromegaly; no previous medical treatment. Randomised to pasireotide LAR 40mg or Sandostatin LAR (octreotide) 20mg.	n=186; adults; inadequately controlled acromegaly (GH mean concentration >2.5µg/L, IGF-I >1.3 µg/L). Randomised to pasireotide LAR 40mg, or 60mg; octreotide LAR 30mg; or lanreotide ATG 120mg every 28 days.
Follow-up	Active treatment period 1 year.	Active treatment period 24 weeks.
Primary outcome	GH and IGF-I blood concentrations.	GH and IGF-I blood concentrations.
Secondary outcomes	Tumour volume; normalisation of IGF-I levels; mean reductions in GH and IGF-I; health related quality of life.	GH and IGF-I blood concentrations at 12 weeks; tumour volume.
Expected reporting date	Nov 2010.	May 2012.

Estimated cost and cost impact

The cost of pasireotide is not yet known for this indication. The costs of other selected acromegaly treatments are[13]:

Drug	Dose	Period: 28 days
Octreotide	100µg SC injection three times a day.	£548.52
Octreotide LAR (Sandostatin LAR)	20mg IM injection once every 28 days.	£705.50
Lanreotide ATG	60mg SC injection once every 28 days for somatostatin analogue naive patients.	£551.00
Pegvisomant	80mg loading dose, then 10mg/day.	£1400.00 (excluding loading dose).

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: long-acting depot formulation.
- ☐ 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 existing therapies.

Other issues

- ☑ Clinical uncertainty or other research question identified:
  No clinical trials identified for patients with uncontrolled acromegaly that directly compare pasireotide with pegvisomant.
- ☐ None identified

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