Octreotide

Section: 18. Medicines for endocrine disorders > 18.8. Medicines for disorders of the pituitary hormone system

ATC codes: H01CB02

Indication	Acromegaly or pituitary gigantism ICD11 code: 5A60.0
INN	Octreotide
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IM:** 20 mg in vial (modified-release, as acetate) plus diluent **Parenteral > General injections > SC:** 0.05 mg per mL in 1 mL vial (immediate-release, as acetate) ; 0.1 mg per mL in 1 mL vial (immediate-release, as acetate) ; 0.5 mg per mL in 1 mL vial (immediate-release, as acetate)
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Octreotide
DrugBank	Octreotide

Expert Committee recommendation

The Committee noted that pituitary adenomas were relatively common but usually non-malignant. About 10% of clinically identified adenomas are associated with excessive growth hormone secretion and are responsible for acromegaly and gigantism. The Committee noted that trans-sphenoidal surgery to remove the adenoma was the treatment of first choice for this condition but accepted that pharmacological treatment with somatostatin analogues was an effective alternative in situations where surgery is not effective, possible or available. The Committee wished to highlight that the application did not adequately elaborate on the evidence identified to describe the benefits and harms of somatostatin analogues in the treatment of acromegaly and gigantism. The Committee noted that several studies support the benefits of optimal hormonal control (by means of surgery and/or pharmacological intervention) in reducing mortality rates in patients with acromegaly. The Committee also noted evidence of the effectiveness of somatostatin analogues in normalizing growth hormone and IGF-1 levels. The Committee considered that the frequency of adverse effects associated with somatostatin analogues was relatively high, and that the burden of treatment was considerable. However, given the reported mortality benefit, the Committee considered the overall benefit-to-harm profile to be favourable for the intervention. The Committee noted that there appeared to be no differences in efficacy between lanreotide and octreotide, however no head-to-head studies had been conducted. The Committee also noted that no comparative cost–effectiveness data were available, but lanreotide was reported to be more expensive than octreotide in most settings reported in the application. Based on these considerations, the Expert Committee recommended the inclusion of octreotide immediate-release and modified-release injections on the complementary list of the EML for use in the

management of acromegaly and gigantism in adults with growth hormone-producing pituitary adenomas. The Committee did not recommend the inclusion of lanreotide depot injection either as an individual medicine or as a therapeutic alternative to octreotide, because it was not shown to be superior to octreotide, is more expensive and, unlike octreotide, generic forms are not widely available.

Background

Lanreotide and octreotide have not previously been considered for the inclusion on the Model Lists for the management of gigantism and acromegaly in adults with growth hormone-producing tumours. The EML does not currently include any medicines for this indication.

Public health relevance

Pituitary adenomas are relatively common tumours found in the pituitary gland. They are detected in about 10% of unselected pituitary samples during autopsies and in magnetic resonance imaging scans of healthy individuals at a similar rate. The prevalence is about 50 cases per million population with an annual incidence of new diagnoses of about 3–4 per million. However, not all these tumours cause noticeable symptoms. Clinical studies have shown that the overall prevalence of pituitary adenomas is about 1 in 1420 individuals, with 10% of these tumours secreting growth hormone (1). Most patients with pituitary adenomas experience symptoms due to excessive growth hormone secretion, resulting in acromegaly or gigantism. In addition, symptoms may arise from the size of the tumour itself, such as visual field defects, hypopituitarism, cranial nerve palsy and headache. Symptomatic patients are the primary target for treatment with medications, such as octreotide or lanreotide, if surgery fails to control the symptoms (2–5). Clinical complications of acromegaly include musculoskeletal abnormalities, hypopituitarism, sleep apnoea, cardiovascular abnormalities, reproductive system abnormalities and colon neoplasms. Risk factors for cardiovascular disease and diabetes have also been reported. Mortality is also two- to three-fold higher than the general population (6). Trans-sphenoidal surgery is the primary treatment for pituitary tumours and offer a chance for cure. Even if a complete cure is not achieved, surgery can significantly reduce growth hormone levels and improve clinical symptoms. The success of the surgery depends on factors such as tumour size and baseline growth hormone levels, with better outcomes seen in smaller tumours and lower growth hormone levels. Maintaining growth hormone levels lower than 2 ng/mL after surgery can reduce mortality and reverse much of the associated morbidity. Relapses occur in about 5% of patients who initially achieve growth hormone levels lower than 2 ng/mL, but in fewer than 2% when the threshold is 1 ng/mL The risks of surgery for small tumours are minimal when performed by experienced pituitary neurosurgeons. However, larger tumours have a higher risk of complications such as cerebrospinal fluid leak, meningitis and permanent diabetes insipidus (2–5). About one third of patients have microadenomas, of whom 20–40% do not respond to surgery. Among patients with macroadenomas, surgical control rates are even lower, with 50–75% of patients not achieving successful outcomes. For patients who are not effectively treated through surgery, medical therapy is the next option. Somatostatin receptor ligands such as lanreotide and octreotide are the primary medications used in such cases and can achieve hormonal control in about 30–40% of patients (2–5,7) In many low-income countries, access to specialized pituitary neurosurgeons is limited. A survey conducted in 2018 showed that 16% of these countries did not have any practicing neurosurgeons at all (8). In such situations, medical treatment with somatostatin receptor ligands may be the primary and most effective form of treatment, rather than a secondary option after surgery.

Benefits

Hormonal control, by surgical and/or pharmacological means, has been associated with lower rates of morbidity and mortality in patients with acromegaly. An analysis of three multicentre clinical trials investigated the biochemical efficacy of long-acting lanreotide in patients with acromegaly previously untreated with somatostatin analogues (9). Efficacy endpoints were normalized insulin-like growth factor-1 (IGF-1) levels, and growth hormone < 2.5 ng/mL + normalized IGF-1 at study end/last value available. Pooled analyses found that in patients treated with lanreotide, 42% achieved normalized IGF-1 levels (46% post-surgery and 40% de novo) and 35% achieved growth hormone plus IGF-1 control (39% post-surgery and 33% de novo). A 2018 systematic review and meta-

analysis of 26 observational studies (10 770 participants) compared acromegaly mortality rates with those of the general population (10). Of note, somatostatin analogues were introduced for treatment of acromegaly in the 1980s. From 17 studies published before 2008, the standardized mortality ratio (SMR) for patients with acromegaly was significantly higher than in the general population (1.76, 95% confidence interval (CI) 1.52 to 2.04). From nine studies published after 2008, no significant difference was found between patients with acromegaly and the general population (SMR 1.35, 95% CI 0.99 to 1.85). From six studies in which somatostatin analogues were used as adjuvant treatment to surgery and/or radiotherapy, mortality was not increased in acromegaly patients (SMR 0.98, 95% CI 0.83 to 1.15), while studies that investigated only patients treated with surgery and/or radiotherapy, mortality in acromegaly patients was significantly higher (SMR 2.11, 95% CI 1.54 to 2.91). An analysis of clinically available somatostatin analogue formulations for the treatment of acromegaly investigated the relative efficacy of lanreotide and octreotide preparations and concluded that lanreotide depot and octreotide long-acting formulations were equivalent in the control of symptoms and biochemical markets in patients with acromegaly (11). The application stated that due to the rarity of gigantism cases, evidence was derived from uncontrolled reports or case series, but it did not reference or elaborate these data.

Harms

Gastrointestinal symptoms such as diarrhoea, bloating, nausea and abdominal discomfort occur in 50–75% of patients receiving somatostatin analogues. Hepatobiliary disorders (e.g. cholelithiasis, gallstones and biliary sludge) and injection-site reactions have also been reported frequently (12–15). A study of patient reported outcome data from 105 patients with acromegaly treated with somatostatin analogues in routine clinical practice found that more than 80% reported experiencing joint pain, forgetfulness and memory loss, soft tissue swelling, and fatigue/weakness (16).

Cost / cost effectiveness

The prices for somatostatin analogues vary considerably across countries and settings. Representative retail costs for lanreotide depot injection and octreotide long-acting injection from different countries, as reported in the application, are shown in Table 26 (refer TRS 1049). The application stated that cost–effectiveness studies comparing the two medicines have not been conducted. The application described the costs associated with managing the complications of untreated acromegaly (e.g. cardiovascular disease, diabetes, musculoskeletal effects) as being considerable, although cost differentials were not assessed.

WHO guidelines

WHO guidelines for the treatment of pituitary adenomas, acromegaly and gigantism are not currently available.

Availability

The application highlighted that the availability of expert pituitary neurosurgeons in many low-income countries is limited, with a 2018 survey showing that 16% of such countries have no practising neurosurgeon at all (8). In such circumstances, medical treatment with somatostatin analogues may be the only effective treatment and would be considered the primary treatment rather than a secondary treatment. Lanreotide and octreotide have wide regulatory approval and are available globally. Generic brands of octreotide are reported to be available in some markets. Octreotide, and to a lesser extent lanreotide, is included on multiple national essential medicines lists, including in low- and middle-income countries.

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