1. **Title page**

Application for inclusion of Octreotide LAR and Lanreotide In the WHO Model Lists of Essential Medicines (2023) for Adults

Submitted by:
Mark E. Molitch, M.D.
Division of Endocrinology, Metabolism and Molecular Medicine
Northwestern University Feinberg School of Medicine

Co-authors
Jean-Pierre Chanoine, MD, FRCPC (Academic)
Clinical Professor of Pediatrics
Secretary General of Global Pediatric Endocrinology and Diabetes
Endocrinology and Diabetes Unit K4-206
British Columbia Children's Hospital
4480 Oak Street
Vancouver BC V6H 3V4
Canada
Email: jchanoine@cw.bc.ca; jpc1010vancouver@gmail.com

Sallianne Kavanagh MPharm, MRPharmS
Clinical Pharmacist
Department of Pharmacy, University of Huddersfield
Huddersfield, HD1 3DH, United Kingdom
Email: S.Kavanagh@hud.ac.uk

Contact:
Mark E. Molitch, M.D.
Professor Emeritus
Division of Endocrinology, Metabolism and Molecular Medicine
Northwestern University Feinberg School of Medicine
645 N. Michigan Avenue, Suite 530
Chicago, IL 60611
USA

Email: molitch@northwestern.edu
Phone 1 – 708-280-6848

1. Summary statement of the proposal for inclusion, change or deletion

This proposal requests inclusion of octreotide LAR and lanreotide for the management of patients with growth hormone producing tumors, with the clinical consequences of gigantism and acromegaly. The listing is being sought for the complementary list for EML.

Octreotide LAR and lanreotide are generally used for the treatment of patients with acromegaly who are not cured by transsphenoidal surgery. However, they also offer a safe and affordable first line of treatment in countries where surgery is not routinely available. This submission is particularly relevant to medical care in low- and middle-income countries where neurosurgery, the first line treatment for pituitary disease, may not be available or may not have the same positive outcomes compared to centers where a high number of surgeries is performed (see below). While these tumors are relatively rare, they are associated with significant morbidity/mortality and a medial approach can be life-saving while avoiding the risks and potential morbidity associated with suboptimal pituitary surgery.

The inclusion of these medicines is requested only for the EML. Indeed, EMLc focuses on children up to the age of 12 years and acromegaly/gigantism are extremely rare in younger children.

Context

- *Non-communicable diseases*

Endocrinology is a subspecialty of medicine that focuses on the diagnosis and treatment of patients with diseases of the endocrine system. These conditions are part of the non-communicable diseases (NCD) group.

Acromegaly and Gigantism

Acromegaly and gigantism are due to the excessive secretion of the hormone, growth hormone (GH), from pituitary tumors (1-7). Gigantism is the development of excessive height due to the excessive GH secretion occurring in children and adolescents prior to the closure of the epiphyses (the growth plates at the ends of bones) that occurs at the end of puberty. Acromegaly is due to the excessive GH secretion that occurs following this closure of the epiphyses.

GH-secreting tumors comprise about 10% of clinically identified pituitary adenomas (1-2). The prevalence is about 50 case per million population with an annual incidence of new diagnoses of about 3-4 per million. About two-thirds of GH-secreting tumors are > 10 mm in maximum diameter (macroadenomas) and the remainder < 10 mm in maximum diameter; malignant GH-secreting tumors are very rare (1-7).

GH secretion is regulated by the hypothalamus, which produces a stimulating hormone, GH-releasing hormone (GHRH) and an inhibitory hormone, somatostatin. Most of the biologic actions of GH occur via the stimulation of the production of insulin-like growth factor 1 (IGF-1) from the liver and locally in bone and other tissues. Almost all cases of acromegaly/gigantism are due to pituitary adenomas that arise spontaneously; several mutations in genes associated with the regulation of GH secretion have been described that result in tumor formation. Less than 100 cases have been reported in which the acromegaly/gigantism is due to a tumor producing GHRH (3-6).

Excess GH/IGF-1 may cause considerable morbidity, including hypertension, diabetes, heart disease, progressive arthritis, sleep apnea, muscle weakness, overgrowth of facial features and appendages, and colonic neoplasia (3-7). As noted above, when the GH excess starts before epiphysial closure at puberty, gigantism may result. Mortality is also increased 2 – 3 fold over the general population (3-7). Morbidity and mortality are related to the amount of hormone as well as the duration of disease and can be greatly ameliorated by early diagnosis and treatment that normalizes GH and IGF-1 levels. The approximately two-thirds of tumors that are macroadenomas can continue to grow and cause mass effects, such as visual field defects due to optic chiasm compression, hypopituitarism, cranial nerve palsies, and headaches.

Acromegaly/Gigantism are diagnosed biochemically, with the finding of elevated IGF-1 levels and elevated GH levels which cannot be suppressed by hyperglycemia using an oral glucose tolerance test (3-6). Following the biochemical confirmation, an MRI or CT scan is done to delineate the size and invasiveness of the tumor. If the tumor abuts the optic chiasm, then visual field ophthalmologic testing is done to determine if there are vision defects (3-6).

The goals of treatment are (1) elimination of effects due to the mass of the tumor (hypopituitarism, visual field defects, etc.); (2) reduction of elevated GH levels and IGF-I levels to normal; (3) amelioration of the end-organ effects of the elevated GH levels; (4) avoidance of damage to remaining normal hypothalamic or pituitary function; (5) minimizing other potential adverse effects of therapy (3-6).

The considerations below reflect published guidelines. As usual, these guidelines are written by experts living in high resource settings. There are to our knowledge no guidelines for patients living in low resource settings where surgery and radiotherapy are not available or are provided in a suboptimal manner because of the lack of infrastructure or expertise.

Transsphenoidal surgery is the first line treatment (see Figure) and offers the patient a chance for cure. Even when "cure" is not achieved, surgery may effect a significant reduction in GH levels and considerable amelioration of clinical symptoms. As would be expected, the smaller the tumor and the lower the basal GH levels, the better the surgical result. Using the criteria of postoperative, glucose-suppressed GH levels less than 1 ng/ml with a conventional RIA or 0.4 ng/ml with the newer two-site assays and normal IGF-I levels (age-adjusted), "cure" rates of 60% to 80% can be expected for intrasellar lesions and 25% to 50% for larger tumors when the operation is performed by experienced neurosurgeons (3-6). However, studies have shown that the increased mortality can be reduced to normal and much of the morbidity reversed when GH levels are maintained below 2 ng/ml (RIA) (3-6). Relapses occur in about 5% of patients who initially achieve glucose-suppressed GH levels of less than 2 ng/ml but < 2% when 1 ng/ml is used. With microadenomas, the risks of surgery are very small when surgery is performed by experienced pituitary neurosurgeons. The complication rates are higher for larger tumors, with risks for CSF leak, meningitis, and permanent DI. Loss of one or more anterior pituitary hormones occurs in 5 - 10% of patients. Rarely, patients with very large tumors may need craniotomy and a subfrontal lobe approach (3-6).

Medical therapy is generally reserved for patients who fail to achieve GH levels < 2 ng/ml (RIA) and normal IGF-I levels with surgery (3-6). Given the surgical control rates noted above, medical therapy is generally needed in 20-40% for those with microadenomas and 50-75% of those with macroadenomas.

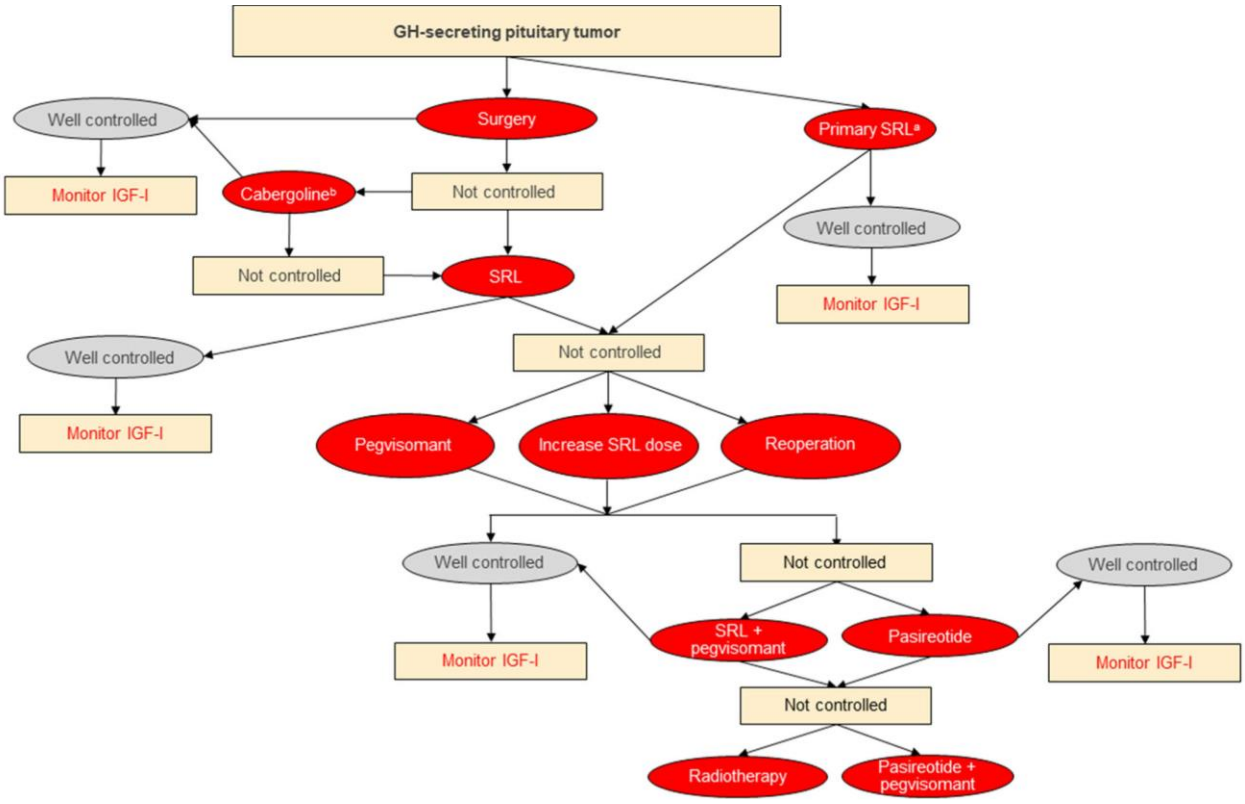

Figure: Multidisciplinary management of acromegaly (from Ref 5)

Medical therapy may be used alone or may be given following irradiation while awaiting the effects of the irradiation. A select group of patients may also be considered for primary medical therapy: (1) those who are medically unable to undergo surgery; and (2) those who have tumors that extend into the cavernous sinus and thus not curable by surgery and who do not have a visual field deficit. In this second group, somatostatin analogs often cause a 10 – 50% shrinkage of the tumor and growth during such treatment occurs in <2% of patients. Radiotherapy is usually reserved for patients whose GH/IGF-1 levels and tumors are not controlled by medical therapy and surgery but may also be given with medical therapy if surgery is not successful (3-6).

Somatostatin receptor ligand (also referred to as somatostatin analogs) treatment results in substantial reductions of GH and IGF-I in 90% of patients; in 30-40% of patients, GH levels can be reduced to < 1 ng/ml and IGF-I levels can be brought into the normal range (3-6). Two long-acting preparations of SRLs are the ones currently used in most patients. Octreotide-LAR and Lanreotide Depot are given monthly, intramuscularly, the doses given adjusted depending upon the GH and IGF-1 responses. MRI scans have demonstrated 10-50% tumor size reduction as a result of therapy with SRLs in about 30-50% of patients when used adjunctively following surgery (3-6). In patients who respond but do not normalize GH and IGF-1 levels with these drugs, the addition of cabergoline is often helpful (3-8). Side effects include mild abdominal bloating, nausea, moderate diarrhea, steatorrhea, and gastritis. Cholelithiasis and gall bladder sludge due to poor gall bladder contractility occur in up to 25% of patients but cholecystitis occurs in less than 1% of patients and is treated by laparoscopic cholecystectomy rather than stopping the drug if the patient is having a good GH/IGF-1 response.

The somatostatin receptor ligands, octreotide LAR and lanreotide Depot, are the mainstays of medical therapy. Other therapies are used much less frequently because of much higher costs and are used when treatment with the SRLs is not satisfactory. These other therapies include pasireotide, a newer SRL with activity against the somatostatin 5 receptor, which has somewhat better results than octreotide or lanreotide in normalizing GH/IGF-1 levels but has an increased risk for hyperglycemia (6), and pegvisomant, a GH-receptor antagonist which can lower IGF-1 levels but has no effect on GH levels or tumor growth (5,6). Cabergoline, is often added to somatostatin receptor ligands to aid in hormone reduction (8).

3. Consultation with WHO technical departments

To our knowledge, there is no WHO department with guidelines for acromegaly of gigantism.

4. Other organizations consulted and/or supporting the submission

This application is supported by several key organizations and stakeholders (see letters of support).
International Society of Endocrinology
Endocrine Society
Pituitary Society

The **International Society of Endocrinology (ISE)** represents the global endocrine community through its members and partners; national and regional organizations of clinicians, researchers, academics, nurses, dietitians and other allied health professionals active in the field of endocrinology. It collaborates with over 80 national and regional societies, comprising more than 50.000 health professionals globally. ISE promotes the dissemination of the latest scientific discoveries and clinical translations of such discoveries through a biennial international meeting and other meetings all over the world. The ISE has developed new diverse training and education opportunities for the community of endocrinologists around the world, including a continue medical education program which aims to help foster the globalization and inter-regional development of existing national meetings by offering ISE supported Symposia and travel fellowships to member societies all over the world and an online portal – the ISE Global Education Hub that gathers and blends educational content from ISE's own and supported meetings. The portal serves as a year-round virtual community and single-entry point for online educational resources in endocrinology.

The **Endocrine Society** is an international organization of over 18,000 endocrinologists that includes clinicians and basic scientists. It promotes breakthroughs in scientific discovery and medical care through publishing in its peer-reviewed journals, hosting an annual scientific meeting, creating resources and educational materials to help clinicians and investigators accelerate the pace of scientific discovery and translation of the latest science into clinical care, advocating for appropriate support and policies that benefit healthcare providers and patients, and educating the public about hormones and the roles that endocrine scientists and clinicians play in achieving optimal public health. The Endocrine Society publishes Clinical Guidelines for clinical care.

The **Pituitary Society** is an international organization of endocrinologists, neurosurgeons and others interested in pituitary disease and includes clinicians and basic scientists. The Society is dedicated to furthering the understanding of diseases of the pituitary gland. The Society sponsors educational conferences highlighting new advances in research and clinical care of pituitary diseases, provides information to the public about pituitary diseases, publishes a peer-reviewed journal that focuses on

pituitary disease, and publishes Clinical Guidelines for clinical care, including one on the management of patients with prolactinomas.

5. Key information for the proposed medicines International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International non-proprietary name (INN): Octreotide
Anatomical therapeutic chemical (ATC): HO1CB02

INN: Lanreotide
ATC: H01CB03

Dosage form(s) and strength(s) of the proposed medicine(s)
Octreotide LAR is available as single-use kits containing a 6-mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2 mL of diluent, one vial adapter, and one sterile 1½" 19 gauge safety injection needle. For prolonged storage, it should be stored at refrigerated temperatures between 2°C to 8°C (36°F to 46°F) and protected from light until the time of use. The kit should remain at room temperature for 30 to 60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

Lanreotide Depot is supplied in strengths of 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 in single, sterile, prefilled, ready-to-use, polypropylene syringes fitted with an automatic safety system, a bromobutyl rubber plunger stopper and a 20 mm needle covered by a plastic cap. The prefilled syringes should be stored at refrigerated temperatures between 2°C to 8°C (36°F to 46°F) and protect from light until use.

Indications (ICD 10 classification):
E22.0: Acromegaly and pituitary gigantism

Suggested wording
Octreotide and Lanreotide are indicated for the management of benign (rarely malignant) tumors of the pituitary. The medical management is most often performed by endocrinologists. Our group is submitting 3 applications relevant to tumors of the endocrine system.
These medicines could conceivably be included in Section 18 (18. MEDICINES FOR ENDOCRINE DISORDERS) or 8 (8. IMMUNOMODULATORS AND ANTINEOPLASTICS
When available, we have found that octreotide 20 mg and lanreotide 90 mg were the most common forms.

Complementary list	
Octreotide LAR	20 mg vial Acromegaly and pituitary gigantism
Lanreotide	90 mg prefilled syringe Acromegaly and pituitary gigantism

6. Proposal for an individual medicine or representative of pharmacological class/therapeutic group whether listing is requested as an individual medicine or as representative of a pharmacological class.

This application concerns octreotide LAR and lanreotide Depot as individual medicines.

7. Information supporting the public health relevance.

Pituitary adenomas are common. Ten per cent of unselected pituitaries examined at autopsy contain pituitary adenomas and MRI scans of normal volunteers show a similar proportion (1). Clearly, not all such tumors become clinically manifest. Clinical case-finding studies have shown an overall prevalence of pituitary adenoma of 1/1420 persons with 10% of these being GH-secreting (1). The great majority of patients are symptomatic from either the effects of the GH oversecretion causing acromegaly/gigantism or tumor size (see above) and these symptomatic patients are the target population for treatment with octreotide or lanreotide if they are not controlled by surgery (3-6). As noted above, about 1/3 of patients have microadenomas and 20-40% of those are not controlled by surgery and the 2/3 with macroadenomas have even lower control rates, with 50 – 75% not being controlled by surgery. Those not controlled by surgery are treated medically, with SRLs being the mainstay of medical therapy with hormonal control being achieved in 30-40% of patients (3-7).

In a cost analysis study using data from two major United States commercial claims databases, Broder et al noted that of 2,171 unique continuously-enrolled (for 1 year) acromegaly patients, complications related to acromegaly were common, with musculoskeletal abnormalities in 25.6 % (556) of patients, hypopituitarism in 16.6 % (361), sleep apnea in 11.5 % (249), cardiovascular abnormalities in 10.3 % (224), reproductive system abnormalities in 9.3 % (201), and colon neoplasms in 6.6 % (143) (11). Cardiovascular risk factors were present in 47.6 % (1,033) of patients: 31.0 % (673) had hypertension, 19.8 % (430) had hypertriglyceridemia, and 17.5 % (379) had diabetes (11). Seventeen percent of patients (373) had at least one inpatient hospitalization and 22.9 % (498) had at least one emergency department visit during the study year (11). During the same period, patients had a mean of 16.1 physician office visits (SD: 14.9; median: 12). Medical costs were primarily associated with non-emergency department outpatient services (mean: $12,268; SD: $21,185) and inpatient hospitalization (mean: $5,213; SD: $18,611) (11). Thus, control of the GH oversecretion and acromegaly is very important.

A very important point is that the numbers given above for control of pituitary tumor GH-secretion by neurosurgery are those of expert pituitary neurosurgeons. In fact, in many low-income countries the availability of such surgeons is quite limited, with one 2018 survey showing that 16% of such countries have no practicing neurosurgeon at all (12). In such circumstances, medical treatment with SRLs may be the only effective treatment and would be considered primary treatment rather than secondary treatment.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

<u>Diagnosis</u>

The diagnosis is made by finding elevated serum IGF-1 levels (age-adjusted) and failure to suppress GH levels to < 1 ng/mL during an oral glucose tolerance test. Magnetic resonance imaging (MRI) provides

considerably more anatomic detail than computed tomography (CT) and is used to determine tumor size, invasiveness of adjacent structures, and suitability for surgical removal.

Dosage Regimen

Octreotide LAR. A dose of 20 mg injected intramuscularly once monthly is usually the initial dose. The dose is adjusted upwards or downwards every 2-3 months depending upon the GH and IGF-1 responses. Most patients respond within 2-3 months, if they are going to respond (3-6). Doses higher than 30 mg per month are usually not used. Alternatives for patients who have only partial responses are: (1) addition of cabergoline; (2) switch to or addition of pegvisomant; (3) switch to pasireotide; (4) consider additional surgery; (5) consider irradiation. The dose should be administered by a nurse experienced in handling this medication.

Lanreotide Depot. A dose of 90 mg injected deep subcutaneously once monthly is usually the initial dose. The dose is adjusted upwards or downwards every 2-3 months depending upon the GH and IGF-1 responses. Most patients respond within 2-3 months, if they are going to respond (3-6). Doses higher than 120 mg per month are usually not used. Alternatives for patients who have only partial responses are: (1) addition of cabergoline; (2) switch to or addition of pegvisomant; (3) switch to pasireotide; (4) consider additional surgery; (5) consider irradiation. Although the package insert states that the dose should be administered by a nurse experienced in handling this medication, experience has shown that the dose can be self-administered or administered by a friend/family member after teaching (4).

Treatment Duration

Patients can be continued on octreotide LAR or lanreotide depot indefinitely. However, after 1-2 years of treatment, clinicians may try to taper the dose of the drug and if GH/IGF-1 levels are maintained in the normal range at the lowest doses, a lengthening of the time interval between doses can be tried (4,6). After 1-2 years of control that has been maintained at the lowest doses at extended intervals, about 20% of patients can be successfully withdrawn from these medications (9,10).

Current Guidelines

We are unaware of any WHO guidelines for the treatment of acromegaly or gigantism.

Guidelines from international organizations have been published by the American Academy of Clinical Endocrinologists (AACE) (3), by the Endocrine Society (4) and the Pituitary Society (5,6). The discussions above about choice of initial therapy (medical vs. surgical and octreotide vs. lanreotide) are discussed in all three guidelines and their recommendations coincide with what is recommended here. In general, there is little difference between octreotide LAR and lanreotide depot with respect to efficacy and safety.

Requirements and Monitoring

Doses are adjusted based upon periodic monitoring of GH and IGF-1 levels, initially every 1-2 months and then every 3-6 months for the first 1-2 years. Once IGF-1 levels have normalized and GH levels brought to < 1.0 ng/mL, they need to be checked only every 6 – 12 months. Escape from the suppressive effect of these drugs is very rare. Because of the multiple organ systems involved in

patients with acromegaly, the medical management of most patients is done by endocrinologists. Patients should be referred for neurosurgery only after consultation with an experienced endocrinologist. If surgery is performed, it should be carried out only by a neurosurgeon with expertise in pituitary surgery and who carries out a high volume of such surgeries to insure effectiveness and low adverse effects.

Core vs. Complementary List

We request inclusion of octreotide and lanreotide in the complementary list of essential medicines, as they are the most efficacious of medical therapies in controlling IGF-1 and GH levels and improving the long-term morbidity and mortality of acromegaly but likely will be prescribed by specialists in tertiary care settings.

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

Many studies have now shown that hormonal control can substantially reduce the morbidity and mortality of acromegaly. There have been several long-term single center studies documenting this (13-17) as well as meta-analyses (18-20). In a meta-analysis, Bolli et al compared the standardized mortality ratios (SMR) between studies reporting outcomes after surgery plus radiotherapy to studies reporting outcomes after the addition of SRLs to the therapeutic armamentarium, finding a reduction in SMR from 2.11 to 0.98 (20). Because gigantism is extremely rare, evidence-based treatment recommendations are only sustained by very small uncontrolled single or series reports.

As noted above, somatostatin receptor ligands are the mainstay of therapy. Various studies have shown that biochemical control can be achieved in 30-55% of patients when these drugs are used in patients not controlled by surgery (5,6). There are no head-to-head studies comparing octreotide LAR to lanreotide depot but analyses have shown them to have comparable efficacy (21). In patients who are inadequately controlled by these drugs when given every 4 weeks in conventional doses, the doses can be increased further or the dose frequency decreased (22.23). Pasireotide, a newer somatostatin receptor ligands with activity against the somatostatin 5 receptor, has been shown in prospective studies, to be better at normalizing IGF-1 levels than either octreotide LAR or lanreotide depot (24,25). Colao et al. showed that in pasireotide LAR and octreotide LAR patients, respectively, 38.6% and 23.6% (P = .002) of participants achieved normal IGF-1 levels in a prospective, head-to-head study (24). Gadelha et al showed that 14.6% of patients not controlled by octreotide LAR or lanreotide depot could then be controlled by pasireotide (25). In the U.S., an oral octreotide preparation became available in 2020; in patients previously controlled by octreotide LAR or lanreotide depot 65% in one study (26) and 64.3% in a second study (27).
Cabergoline, a dopamine receptor agonist used primarily for the treatment of patients with prolactinomas, has also been used in patients with acromegaly. A meta-analysis showed that 34% of patients not controlled by surgery could achieve biochemical control with cabergoline with it being most effect in patients with only modest elevations of GH and IGF-1 (8). However, the response is lost in some patients over time so that in one study only 21% of patients were controlled after 18 months of treatment (28). Cabergoline has been found to be useful when combined with other agents. The meta-analysis of Sandret et al. showed that 52% of patients uncontrolled with somatostatin receptor ligands then obtained control when cabergoline was added (8). Thus, it is used primarily in patients with mild elevations of GH/IGF-1 that persist postoperatively and as an add-on to somatostatin receptor ligands to achieve additional hormone lowering.

Pegvisomant is a GH receptor antagonist and so has no direct action on the GH-secreting tumor. It is given by daily injection. Although the initial trials showed that normalization of IGF-1 levels could be achieved in 95% of patients (29), more recent studies showed control in 75.4% of patients. (30). Additional studies have shown that weekly injections of pegvisomant added to monthly injections of somatostatin receptor ligands can result in control of IGF-1 levels in 96% of patients (31). Compared to somatostatin receptor ligands, it is more likely to achieve better improvement in glucose tolerance and may be preferred as medical therapy in patients with preexisting diabetes mellitus (5). Liver function tests need to be monitored, as significant elevations occur in 3.1% of patients as well as MRI scans, as tumor size increases in 7.1% of patients (30). Pegvisomant is generally used as second line therapy when control is not achieved with maximal doses of somatostatin (3-7).

In summary, somatostatin receptor ligands are regarded as the first line of medical therapy in patients who fail surgical control or in whom surgery cannot be done either because of the unavailability of expert pituitary surgeons or when there are medical contraindications to surgery. Although cabergoline can be used for patients with very modest persistent GH/IGF-1 elevations, there is a substantial loss of control over time. Cabergoline is mostly used as an add-on to somatostatin receptor ligands and this combination is sufficiently effective that the more expensive options of switching to pasireotide or pegvisomant are less often done. In addition to costs, the substantial worsening of glucose tolerance and preexisting diabetes has made pasireotide a less optimal therapy. Because of the lack of direct tumor effect, abnormal liver function tests, and costs, pegvisomant is also relegated to second line medical therapy. For patients not controlled by the combination of somatostatin receptor ligands and cabergoline, switching to pasireotide or switching to/adding pegvisomant are additional options.

10. Review of harms and toxicity: summary of evidence of safety

Injectable SRLs are generally well-tolerated. Gastrointestinal symptoms such as diarrhea, bloating, nausea and abdominal discomfort are the most common adverse effects occurring in 50-75% of patients but these generally decrease in severity over the first several months of treatment (32-35). Gallbladder stones and sludge occur in about 25% of subjects treated with SRLs but the stones are usually asymptomatic. One study showed that only 4% of subjects with gallstone disease had biochemical evidence of cholestasis (36). The general recommendation is to not do gall bladder radiologic/ultrasound studies unless the patient appears to have symptomatic cholecystitis (4). Injection site reactions are common but generally well-tolerated (36).

11. Summary of available data on comparative cost and cost-effectiveness of the medicines.

In the U.S. and most countries around the world, neither drug is generic. In the U.S., the retail cost for octreotide LAR is $4360 per 20 mg injection given monthly (Source: Epocrates 12/06/22). The retail cost in the U.S. for lanreotide depot is $8029 per 90 mg injection given monthly (Source: Epocrates 12/06/22).

Costs for such injections in representative LIMC are (in US$):
Brazil: $1200 for octreotide LAR and $800 for lanreotide depot
India: $213 for octreotide LAR and $267 for lanreotide depot. From a different source, we obtained octreotide LAR 628 USD (10 mg)
Argentina: 1100 USD for Octreotide and 2260 USD for lanreotide (120 mg)
Mexico: 1293 USD for Lanreotide (for 120 mg)

Neither drug is available in Bolivia.

No cost-effectiveness studies have been carried out comparing these two drugs but studies comparing the drugs in their ability to normalize/control GH and IGF-1 levels have shown that they are about the same (21). There are no studies comparing the long-term cost-effectiveness of using SRLs vs. no control of GH/IGF-1 levels in patients not controlled by surgery. The complications of acromegaly (heart disease, diabetes, hypertension, arthritis – see above) will continue and worsen if treatment is not instituted with the attendant costs. As noted by Holdaway et al., hypertension, present in 32% before treatment fell to 22% if GH levels were < 2 ng/mL in follow-up but 43% if GH levels were > 2 ng/mL in follow-up; similar changes were found for diabetes – 18% pretreatment, 7% if GH < 2 ng/mL and 17% if GH > 2 ng/mL in follow-up; for ischemic heart disease – 19% pretreatment, 7% if GH < 2 ng/mL and 15% if GH > 2 ng/mL in follow-up; and for arthritis 41% pretreatment, 25% if GH < 2ng/mL and 37% if GH > 2 ng/mL in follow-up (13). The differential in costs for treatment of these complications were not done but obviously would be considerable Furthermore, the mortality will remain more than two-fold increased if SRLs are not used to control hormone levels postoperatively (19).

12. Summary of regulatory status and market availability of the medicines

U.S. Food and Drug Administration (FDA):
Octreotide LAR 10, 20, 30 mg and Lanreotide 60, 90 120 mg are on the
Approved Drug Product List – Orange Book,
Accessed November 19, 2021

European Medicines Agency (EMA):
Octreotide LAR 10, 20, 30 mg and Lanreotide 60, 90 120 mg are on the List of Nationally Approved Medicinal Products.
Accessed November 19, 2021

Australian Government, Department of Health, Therapeutic Good Administration:
Octreotide LAR 10, 20, 30 mg and Lanreotide 60, 90 120 mg are on the Australian Register of Therapeutic Goods (ARTG) List.
Accessed November 19, 2021

Health Canada:
Octreotide LAR 10, 20, 30 mg and Lanreotide 60, 90 120 mg are on their Drug Product List of approved medications.
Accessed November 6, 2021

Japanese Pharmaceuticals and Medical Devices Agency:
Octreotide LAR 10, 20, 30 and Lanreotide are included in the list of approved medicines.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia)

Octreotide LAR and Lanreotide Depot are included in the United States Pharmacopoeia.

	International Pharmacopoeia	United States Pharmacopoeia	European Pharmacopoeia	British Pharmacopoeia
Octreotide	No	Yes	Yes	Yes
Lanreotide	No	Yes	No	No

14. References

1. Molitch ME. Diagnosis and treatment of pituitary adenomas. JAMA. 2017;317:516-524. doi: 10.1001/jama.2016.19699
2. Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med 2020;382:937-950. doi: 10.1056/NEJMra1810772
3. Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK; American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011;17(Suppl 4):1-44. doi: 10.4158/ep.17.s4.1
4. Katznelson L, Laws ER Jr, Murad MH, Melmed S, Molitch ME, Utz A, Wass JAH. Acromegaly: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014;99:3933-3951. Doi: 10.1210/jc.2014-2700
5. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, et al. Multidisciplinary management of acromegaly: A consensus. Rev Endocr Metab Disord. 2020 Dec;21(4):667-678. doi: 10.1007/s11154-020-09588-z
6. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, Molitch ME, et al. A Pituitary Society Update to Acromegaly management guidelines. Pituitary 2021;24:1–13. doi: 10.1007/s11102-020-01091-7
7. Gadelha MR, Kasuki L, Lim DST, Fleseriu M. Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr Rev 2019;40(1):268-332. doi: 10.1210/er.2018-00115
8. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a metaanalysis. J Clin Endocrinol Metab. 2011;96(5):1327–35. doi: 10.1210/jc.2010-2443
9. Ronchi CL, Rizzo E, Lania AG, Pivonello R, Grottoli S, Colao A et al. Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal. Eur J Endocrinol 2008;158(1):19-25. doi: 10.1530/EJE-07-0488
10. Ramírez C, Vargas G, González B, Grossman A, Rábago J, Sosa E, et al. Discontinuation of octreotide LAR after long term, successful treatment of patients with acromegaly: is it worth trying? Eur J Endocrinol 2012;166(1):21-6. doi: 10.1530/EJE-11-0738
11. Broder MS, Neary MP, Chang E, Cherepanov C, Katznelson L. Treatments, complications, and healthcare utilization associated with acromegaly: a study in two large United States databases. Pituitary 2014;17(4):333-41. doi: 10.1007/s11102-013-0506-0
12. Punchak M, Mukhopadhyay S, Sachdev S et al. Neurosurgical care: availability and access in low-income and middle-income countries. World Neurosurg 2018;112:e240-e254. doi: 10.1016/j.wneu.2018.01.029
13. Holdaway IM, Rajasoorya CR, Gamble GD, Stewart AW. Long-term treatment outcome in acromegaly. Growth Horm IGF Res 2003;13(4):185-92. doi: 10.1016/s1096-6374(03)00030-3
14. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab. 2004;89:667–674. doi: 10.1210/jc.2003-031199
15. Swearingen B, Barker FG 2nd, Katznelson L, Biller BM, Grinspoon S, Klibanski A, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab. 1998;83(10):3419-26. doi: 10.1210/jcem.83.10.5222

16. Sughrue ME, Chang EF, Gabriel RA, Aghi MK, Blevins LS. Excess mortality for patients with residual disease following resection of pituitary adenomas. Pituitary. 2011;14:276–383. doi: 10.1007/s11102-011-0308-1
17. Mercado M, Gonzalez B, Vargas G, Ramirez C, Espinosa de los Monteros AL, Sosa E et al. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab 2014;99(12):4438-46. doi: 10.1210/jc.2014-2670
18. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol. 2008;159:89–95. doi: 10.1530/EJE-08-0267
19. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP. Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab. 2008;93:61–67. doi: 10.1210/jc.2007-1191
20. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS . Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur J Endocrinol 2018;179(1):59–71. doi: 10.1530/EJE-18-0255
21. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab 2008;93(8):2957-68. doi: 10.1210/jc.2008-0027
22. Giustina A, Bonadonna S, Bugari G, Colao A, Cozzi R, Cannavo S, et al. High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial. Eur J Endocrinol 2009;161(2):331–8. doi: 10.1530/EJE-09-0372
23. Giustina A, Mazziotti G, Cannavò S, Castello R, Arnaldi G, Bugari G, et al. High-dose and high-frequency lanreotide Autogel in acromegaly: a randomized,multicenter study. J Clin Endocrinol Metab. 2017;102(7):2454–64. doi: 10.1210/jc.2017-00142
24. Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014;99(3):791–9. doi: 10.1210/jc.2013-2480
25. Gadelha MR, Bronstein MD, Brue T, Coculescu M, Fleseriu M, Guitelman M, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2(11):875–84. doi: 10.1016/S2213-8587(14)70169-X
26. Melmed S, Popovic V, Bidlingmaier M, Mercado M, van der Lely AJ, Biermasz N et al (2015) Safety and efficacy of oral octreotide in acromegaly: results of a multicenter phase III trial. J Clin Endocrinol Metab 100(4):1699–1708. doi: 10.1210/jc.2014-4113
27. Samson SL, Nachtigall LB, Fleseriu M, Gordon MB, Bolanowski M, Labadzhyan A, et al. Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide therapy. J Clin Endocrinol Metab 2020;105(10):e3785-3797. doi: 10.1210/clinem/dgaa526
28. Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Khandji AG, Post KD. Cabergoline therapy of growth hormone & growth hormone/prolactin secreting pituitary tumors. Pituitary. 2004;7:21–30. doi: 10.1023/b:pitu.0000044630.83354.f0

29. Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342:1171–1177. doi: 10.1056/NEJM200004203421604
30. Fleseriu M, Führer-Sakel D, van der Lely AJ, De Marinis L, Brue T, van der Lans-Bussemaker J,et al. More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY. Eur J Endocrinol. 2021 Aug 27;185(4):525-538. doi: 10.1530/EJE-21-0239
31. Bonert V, Mirocha J, Carmichael J, Yuen KCJ, Araki T, Melmed S (2020) Cost-effectiveness and efficacy of a novel combination regimen in acromegaly: a prospective, randomized trial. J Clin Endocrinol Metab. 105(9):3236–3245. doi: 10.1210/clinem/dgaa444
32. Chanson P, Boerlin V, Ajzenberg C, Bachelot Y, Benito P, Bringer J et al. Comparison of octreotide acetate LAR and lanreotide SR in patients with acromegaly. Clin Endocrinol 2000;53 (5), 577-586. doi: 10.1046/j.1365-2265.2000.01134.x
33. Mercado M, Borges F, Bouterfa H, Chang T-C, Chervin A, Farrall AJ, et al. A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. Clin Endocrinol 2007;66(6):859-68. doi: 10.1111/j.1365-2265.2007.02825.x
34. Geer EB, Sisco J, Adelman DT, Ludlam WH, Haviv A, Liu S et al. Patient reported outcome data from acromegaly patients treated with injectable somatostatin receptor ligands (SRLs) in routine clinical practice. BMC Endocrine Disorders 2020 20:117. doi: 10.1186/s12902-020-00595-4
35. Fleseriu M, Molitch M, Dreval A, Biermasz NR, Gordon MB, Crosby RD, et al. Disease and treatment-related burden in patients with acromegaly who are biochemically controlled on injectable somatostatin receptor ligands. Front Endocrinol 2021; doi: 10.3389/fendo.2021.627711
36. Attanasio R, Mainolfi A, Grimaldi F, et al. Somatostatin analogs and gallstones: a retrospective survey on a large series of acromegalic patients. J Endocrinol Invest. 2008;31:704–710. doi: 10.1007/BF03346419