COST-EFFECTIVENESS OF PASIREOTIDE LONG-ACTING RELEASE IN ACROMEGALY – SYSTEMATIC LITERATURE REVIEW

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INTRODUCTION

Acromegaly is a rare, chronic disease characterized by the excessive production of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1), primarily due to benign pituitary tumors. Its worldwide prevalence ranges from 1 in 7,500 to 1 in 35,800, with an annual incidence between 1 in 91,000 and 1 in 526,000[1]. Clinical manifestations include enlarged hands and feet, joint pain, and facial changes, alongside serious complications affecting cardiovascular, respiratory, and metabolic systems.

The main treatment goals are to stabilize and reduce tumor size, control hormone secretion (GH < 1.0 µg/L, IGF-1 within normal limits), alleviate symptoms, and minimize complications[2]. Surgical resection is the first-line treatment, while medical therapy and radiotherapy serve as alternatives for patients ineligible for surgery or with inadequate responses. Current treatments include first generation somatostatin receptor ligands (FGSRL), GH receptor antagonists, and dopamine agonists[3].

Biochemical control (normalisation of both GH and IGF-1 levels), is the primary treatment objective for patients with acromegaly; however, over 40% of patients treated with FGSRL do not achieve or sustain biochemical control[2,3].

In the EMA territory, pasireotide is indicated as a 2nd line medical treatment for adult patients with acromegaly who failed or are not candidates to surgery and who are inadequately controlled on treatment with another FGSRL[4].

OBJECTIVE

The aim of this study is to systematically determine the cost-effectiveness of pasireotide (PAS) long-acting release (LAR) in the treatment of acromegaly, given the conflicting reports in the literature regarding its economic viability. Previous studies have presented varying conclusions, with some indicating favorable cost-effectiveness while others suggest limited economic benefits. Additionally, the quality and objectivity of these studies differ significantly, leading to uncertainty in clinical decision-making.

This study aims to provide a robust and objective assessment of the cost-effectiveness of PAS LAR, thereby contributing valuable insights to the ongoing discourse in the literature and guiding healthcare professionals in their treatment choices.

METHODS

Systematic literature review

In May 2024, a systematic search of multiple databases was conducted to identify relevant literature published between January 2009 and April 2024. The databases searched included: 1. Medline in Process (via PubMed) 2. Medline (via the OVID platform) 3. Embase (via the OVID platform) 4. Web of Science 5. Centre for Reviews and Dissemination (CRD), York.

The search strategy was meticulously designed to capture a wide array of studies pertinent to the study population, interventions, and economic evaluations associated with acromegaly.

STUDY POPULATION

The search for literature pertaining to the study population was guided by established medical terminology and included the following keywords: "acromegaly," "growth hormone excess," "somatotropinoma," and "growth hormone-secreting pituitary adenoma." These terms were combined using the Boolean operator OR to ensure a comprehensive retrieval of relevant studies.

INTERVENTION

For the intervention component, the search strategy included terms such as "Pasireotide," "SOM-230," and the trade name "Signifor." These keywords were also linked with the Boolean operator OR to encompass all relevant studies regarding these specific interventions.

STUDY DESIGN

To address the economic aspects of the interventions, a targeted search was conducted using a variety of keywords related to economic evaluations. The following terms were utilized: "Costs," "Cost Analysis," "Cost Comparison," "Affordability," "Affordabilities," "Cost-Minimization," "Pricing," "Cost Measures," "Cost Utility Analysis," "Benefit," "Marginal Analysis," "Cost-Benefit," and "Economic." These terms were employed in various combinations, connected by both AND and OR operators, to ensure a thorough exploration of the economic literature.

### Quality assessment of evidence

Selected studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Tool to assess methodological quality[5].

The JBI Critical Appraisal Tool evaluates the methodological quality of research studies. It systematically assesses key aspects such as research question clarity and methodological appropriateness, ensuring high-quality evidence for systematic reviews and economic analyses. The tool aligns with NICE guidelines, enhancing its credibility in health research.

RESULTS

Out of the 160 records identified, six unique cost-effectiveness studies were deemed eligible for inclusion. Among these six selected full texts—comprising three research papers and three conference abstracts—there were two cost-utility studies and four cost-effectiveness studies. Each study addresses the costs associated with second line (or combined 1st and 2nd line) treatment for acromegaly in patients who have had an inadequate response to surgery or for whom surgery is not a viable option. All selected texts adopt the perspective of healthcare payers, with five of them incorporating incremental analysis. The time horizon for cost-effectiveness and utility analyses is set to a lifelong duration, while the budget impact analysis spans a maximum of five years. Notably, the selected analyses originate from five different countries: Brazil (2), France, Spain, Sweden, and Finland.
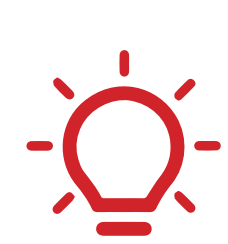
Brue et al. 2021 and Peral et al. 2019 presented a pronounced difference in generated QALY between PAS LAR and PEG. Brue et al. 2021 reported 13.56 QALY for PAS LAR vs 16.44 for PEG and 16.80 for PEG+FGSRL Peral et al. 2020 reported 10.81 for PAS vs 14.51 for PEG. Leonart et al. 2020, the only study based on published and transparent SLR and meta-analysis, reported similar QALY gains for PAS LAR and PEG.

CONCLUSIONS

- SLR revealed three cost-effectiveness studies published in full text and three published as an abstract only.
- Results were conflicting, especially regarding health benefits and cost-effectiveness of PAS LAR compared to PEG.
- For studies published in full texts serious limitations were found regarding Brue et al. (2021) and Peral et al. (2020) as revealed by the JBI tool and detailed evaluation.

Table 1. Inclusion and exclusion criteria for cost-effectiveness SLR of pasireotide long-acting release in acromegaly

TLR criteria	Inclusion criteria	Exclusion criteria
Study population	Adult patients with acromegaly who failed or are not candidates for surgery and who are inadequately controlled on treatment with another FGSRL (indication for pasireotide LAR approved by EMA)	Patients with Cushing disease, corticotropin-induced adrenocortical hyperplasia, or pituitary ACTH hypersecretion
Study design	Full and partial economic analyses	None
Interventions	Pasireotide LAR	None
Comparators	No restrictions	None
Language	English	Journal articles not available in English
Country	No limit	None
Time limits	2009 onwards	Publications prior to 2009

Key: LAR, Long-Acting Release; FGSRL, First-Generation Somatistatin Receptor Ligands; ACTH, adrenocorticotropic hormone; EMA, European Medicin Agency

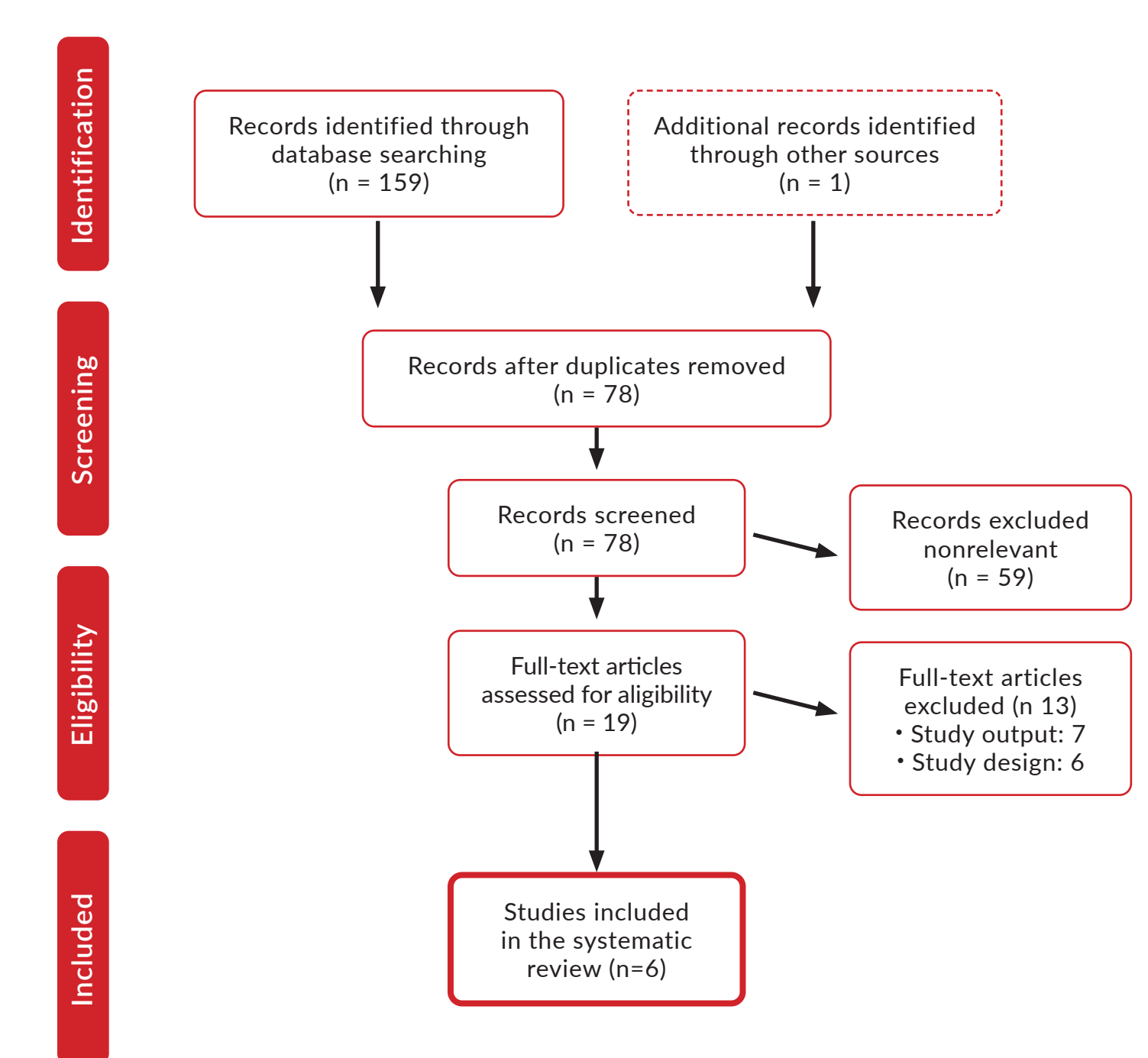### Figure 1. PRISMA flow diagram for systematic literature review

Table 2. Main characteristics and results of the included studies

Characteristic	Brue et al. (2021)[6]	Leonart et al. (2021)[7]	Peral et al. (2020)[8]	Hahl et al. (2015)[9]	Carlqvist et al. (2016)[10]	Paiva et al. (2023)[11]
Country	France	Brazil	Spain	Finland	Sweden	Brazil
Study type	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis
Population	Acromegaly patients not controlled on first-line FGSRL	Acromegaly patients who have failed surgery	Acromegaly patients not controlled on first-line FGSRL	Acromegaly patients with inadequate biochemical control	Acromegaly patients not controlled on first-line FGSRL	Acromegaly patients not controlled on first-line FGSRL
Interventions	• PAS LAR • PEG • PEG + FGSRL	Treatment strategies including first line FGSRL plus second line therapy with the following alternatives: • PAS LAR • PEG • PEG + LAN • PEG + OCT	• FGSRL (OCT or LAN) • PAS LAR • PEG	• PAS LAR, • PEG+ FGSRL	• Continued use of FGSRL • PAS LAR	• PAS LAR, • Maximum doses of FGSRL (OCT pr LAN) • PEG • PEG+ FGSRL
Outcomes	ICER: • PAS LAR vs FGSRL 562,463€ per QALY; • PEG vs FGSRL 171,332€ per QALY; • PEG + FGSRL versus FGSRL 186,242€ per	ICER: • Strategies dominated: PEG + OCT; PEG • LAN vs no 2nd line treatment: 28,389 US$ per QALY • PAS LAR vs LAN: 77,313 US$ per QALY • PEG + LAN vs PAS: 1,133,358 US$ per QALY	ICER: • PEG vs FGSRL: 85,869 € per QALY • PAS LAR vs FGSRL: 551,405 € per QALY	ICER: • PAS LAR dominant vs PEG+FGSRL treatment strategy (lower costs and higher QALY gain of PAS LAR)	ICER: • PAS LAR vs FGSRL: 670 000 SEK per QALY	ICER: • PAS LAR vs OCT R$150,051 per QALY • PAS LAR vs LAN R$159,143 per QALY • PAS LAR dominant vs PEG and PEG + LAN (lower costs and higher QALY gain of PAS LAR) • PAS LAR vs PEG + OCT: less costly and less effective

Key: ICER, Incremental Cost-Effectiveness Ratio; QALY, Quality-Adjusted Life Years; PAS LAR, Pasireotide Long-Acting Release; PEG, Pegvisomant; FGSRL, First-Generation Somatistatin Receptor Ligands; LAN, Lanreotide; OCT, Octreotide; SEK, Swedish Korona; R$, Brazilian Real; US$, United States Dollar

Table 3. JBI assessment of identified studies

Question	Brue et al. (2021)[15]	Leonart et al. (2021)[16]	Peral et al. (2020)[14]	Hahl et al. (2015)[18]	Carlqvist et al. (2016)[18]	Paiva et al. (2023)[18]
Is there a well-defined question?	➕	➕	➕	➕	➕	➕
Is there a comprehensive description of alternatives?	➕	➕	➕	➕	➕	➕
Are all important and relevant costs and outcomes for each alternative identified?	➕	➕	➕	➕	❓	➕
Has clinical effectiveness been established?	➕	❓	❓	➕	➕	➕
Are costs and outcomes measured accurately?	➖	➕	❓	➕	❓	❓
Are costs and outcomes valued credibly?	➕	➕	➖	➕	➕	➕
Are costs and outcomes adjusted for differential timing?	➕	➕	➕	❓	➕	❓
Is there an incremental analysis of costs and consequences?	➕	➕	➕	➕	➕	➕
Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	➕	➕	➕	❓	➕	❓
Does the study include all issues of concern to users?	❓	➕	❓	➕	➕	➕
Are the results generalizable to the setting of interest in the review?	❓	➕	❓	❓	❓	➕

Table 4. Methodological quality of identified studies

Question	Brue et al. (2021)[15]	Leonart et al. (2021)[16]	Peral et al. (2020)[14]	Hahl et al. (2015)[18]	Carlqvist et al. (2016)[18]	Paiva et al. (2023)[18]
Detailed methodology description?	NO	Yes, including: SLR / Risk of bias / ITC / Limitations	NO			
Serious methodological flaws	Yes (different follow-up, endpoint-definitions*)	NO	YES (PICO violated**)	Conference abstracts without detailed methodology description. Could not be appraised as full text publications.		
Transparent cost and efficacy inputs?	YES	YES	YES for costs/NO for health effects			
Systematic studies selection?	NO	YES based on SLR and meta-analysis: Leonart et al. 2018***	NO			
Sponsored?	Pfizer	Independent Researchers	Pfizer			

Key: SLR, Systematic Literature Review; ITC, Indirect Treatment Comparison; PICO, Population, Intervention, Comparator, Outcome
*for PAS: IGF-1 controlled at 24 weeks, for PEG IGF-1 controlled at any time between baseline and week 36; for PEG per-protocol results used instead of Intention to treat (ITT)
**PICO violation: PEG efficacy assessed with IGF-1 control, PAS with GH and IGF-1 control
***Leonart et al. 2018 established relative treatment effect between PAS LAR and PEG for the 1st line medical treatment of acromegaly. In Leonart et al 2020 it was assumed that this relative effect can be transferred to 2nd line setting.

The cost-effectiveness analysis by Leonart et al. (2021) was preceded by comprehensive clinical and economic systematic literature reviews (SLRs) to ensure a robust foundation. The study adhered to recognized HTA guidelines and best practice standards, addressing many of the limitations noted in Peral et al. (2020) and Brue et al. (2021). Its health outcomes align with real-world evidence (RWE), making it a credible and independent evaluation of cost-effectiveness for acromegaly treatments.

- Leonart 2021 is so far the only transparent and credible CE analysis published for 2nd line acromegaly pharmacological treatment
- PAS LAR offers comparable health benefits to PEG+FGSRL and PEG monotherapy at lower therapy cost
- with PAS LAR generating additional QALY, cost-effectiveness vs. SRL depends on the adopted willingness-to-pay threshold

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