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Original Research

Internal validity gaps in repurposing olopatadine ophthalmic solution for intranasal use: A Regulatory and scientific feasibility appraisal for Thailand

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Abstract

Background: Allergic rhinitis is a prevalent condition that often requires local treatment to minimize systemic side effects. While intranasal antihistamines are effective, access in some settings is limited. Olopatadine hydrochloride, currently approved for ophthalmic use, has pharmacological properties that may be suitable for intranasal administration. **Objective:** To evaluate the feasibility of repurposing olopatadine hydrochloride ophthalmic solution for intranasal use in treating allergic rhinitis by assessing pharmacologic rationale, formulation characteristics, safety, and regulatory considerations.

Methods: A systematic review was conducted in accordance with the PRISMA 2020 guidelines. Eligible studies included randomized controlled trials (RCTs), pharmacokinetic investigations, mucosal safety assessments, and regulatory evaluations relevant to the intranasal administration of olopatadine. Risk of bias was appraised using the Cochrane RoB 2.0 tool for RCTs and the OHAT tool for non-randomized or preclinical studies. Findings were synthesized narratively, with meta-analysis performed where appropriate. **Results:** No studies were identified directly evaluated the intranasal use of olopatadine ophthalmic formulation. However, high-quality RCTs on olopatadine nasal spray (0.6%) demonstrated statistically significant improvements in allergic rhinitis symptoms, with an absolute risk reduction of 11.7%, a number needed to treat (NNT) of approximately 8.3, and low heterogeneity (I^2 = 19.5%). Despite these findings, they are not directly generalizable to the ophthalmic product due to formulation differences—including concentration, excipients, and pharmacokinetic properties—as well as the absence of population-bridging data for Thai patients. Additionally, no mucosal safety data or physiologically based pharmacokinetic (PBPK) models were identified to support intranasal safety or predict systemic exposure using ophthalmic preparation.

Conclusions: Findings suggest pharmacologic and pharmaceutical feasibility for intranasal repurposing of olopatadine hydrochloride ophthalmic solution. While preclinical and clinical studies are needed to confirm efficacy and safety in nasal administration, the data provide a preliminary foundation for further development.

Keywords: olopatadine, allergic rhinitis, repurposing, internal validity, nasal delivery

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INTRODUCTION

Allergic rhinitis (AR) is a globally prevalent condition associated with reduced quality of life and significant healthcare costs[1]. In Thailand, AR incidence is rising, yet access to advanced intranasal antihistamines remains limited[2]. These agents are valued for their rapid, targeted relief of nasal symptoms, especially during the early allergic response[3]. Olopatadine nasal spray is an effective, approved treatment in several countries including the U.S., Canada, Australia, the U.K., Russia, and South Africa[4].

A recent network meta-analysis[3] established a strong comparative framework for evaluating intranasal therapies in allergic rhinitis by simultaneously considering efficacy

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and safety profiles. Among the agents assessed, intranasal olopatadine demonstrated the highest efficacy (approximately 88%) while maintaining a favorable safety profile (approximately 80%), suggesting a well-balanced therapeutic option in terms of both symptom control and patient tolerability. Although ciclesonide and mometasone exhibited superior safety ratings (≥83%), their slightly lower efficacy (approximately 78–80%) may be a limitation in patients requiring rapid or substantial symptom relief. Conversely, azelastine showed comparable efficacy to olopatadine but with a modest reduction in safety. Beclomethasone and levocabastine demonstrated suboptimal outcomes in both efficacy and safety dimensions, rendering them less favorable for routine use[3]. Taken together, these findings suggest that intranasal olopatadine may represent the most effective and reasonably safe therapeutic choice, supported by its dual mechanism of action—histamine H1 receptor antagonism and mast cell stabilization—which directly targets key pathophysiological processes in allergic rhinitis. (as shown in figure 1)

However, no intranasal olopatadine formulation is approved in Thailand. Instead, the 0.1%–0.2% ophthalmic solution is widely used for allergic conjunctivitis, with network meta-analyses identifying it as the most effective topical agent for ocular allergies[5]. Its dual mechanism—H1 antagonism and mast cell stabilization—suggests potential for intranasal use[6]. Nonetheless, regulatory constraints, absence of mucosal safety data for the ophthalmic formulation, and ethical concerns over off-label administration have impeded clinical research in Thailand. A recent ethics committee decision rejected a proposed trial, citing safety, formulation, and regulatory integrity concerns. These barriers justify a structured, non-clinical feasibility appraisal. This study evaluates the scientific, regulatory, and pharmacologic rationale for repurposing olopatadine eye drops for intranasal use by synthesizing evidence on efficacy, safety, dosage, delivery routes, and mucosal pharmacokinetics. Although not a clinical trial, this analysis seeks to determine whether such repurposing is scientifically sound, ethically justifiable, and viable within Thailand's healthcare system—addressing an unmet therapeutic need and a critical regulatory gap.

The objective of this research is to evaluate the feasibility of repurposing olopatadine hydrochloride ophthalmic solution for intranasal administration in the treatment of allergic rhinitis, by assessing its pharmacologic rationale, formulation compatibility, safety considerations, and regulatory precedents.

RESEARCH METHODOLOGY

This study is designed as a systematic review of the literature, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[7]. The objective is to evaluate the feasibility of repurposing olopatadine hydrochloride ophthalmic solution for intranasal use in the treatment of AR, focusing on its pharmacologic

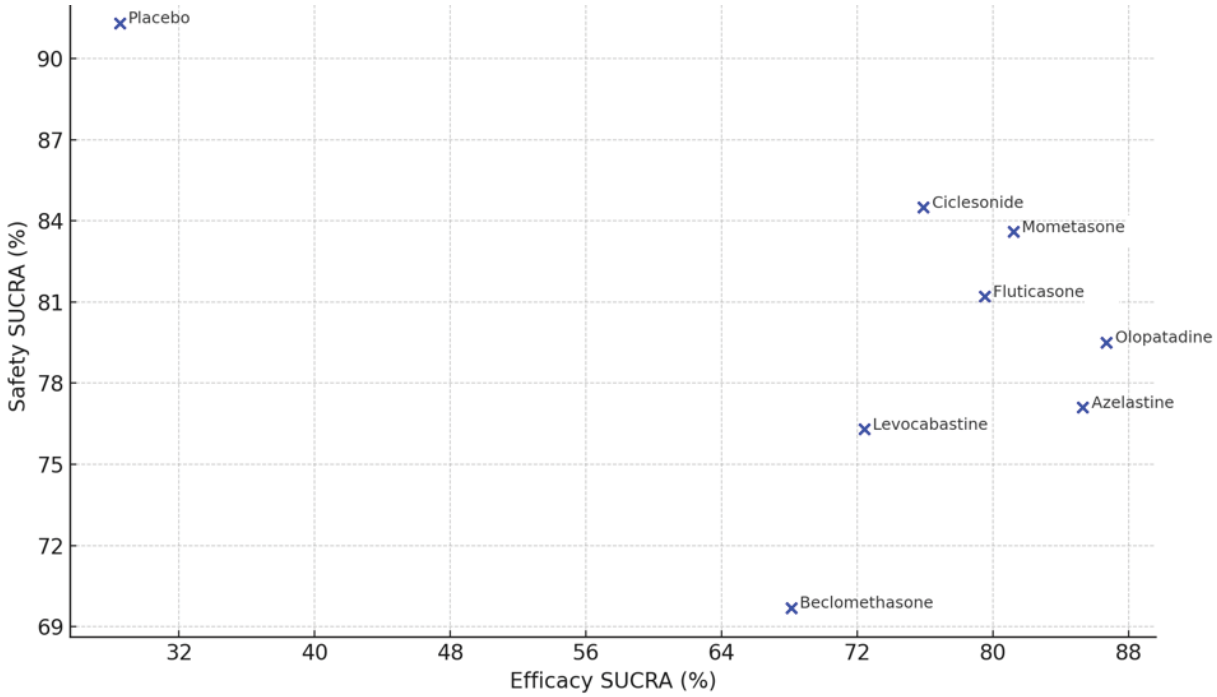

Figure 1. Comparative Efficacy and Safety of Intranasal Therapies for Allergic Rhinitis Based on SUCRA Rankings from Network Meta-Analysis3
Note: The plot displays a comparative analysis of intranasal medications for allergic rhinitis, with SUCRA values. (SUCRA, Surface Under the Cumulative Ranking Curve is a percentage value (0–100%) that reflects how likely a treatment ranks among the most effective or safest in a network meta-analysis—the higher the SUCRA, the better the ranking. The graph represents efficacy on the x-axis and safety on the y-axis. Higher values indicate greater relative efficacy and safety. Each point corresponds to a treatment ranked through network meta-analysis. The ideal treatment appears in the upper-right quadrant, indicating a balance of high efficacy and high safety. This plot helps identify treatments with the most favorable benefit–risk profiles.

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plausibility, intranasal safety, clinical efficacy, and regulatory status in global contexts. This approach was chosen to ensure methodological rigor and to avoid introducing ethical or clinical risks associated with interventional research in human subjects.

Inclusion and Exclusion Criteria

This review included studies that investigated the use of olopatadine hydrochloride in the context of allergic rhinitis or related nasal inflammatory conditions. Eligible studies encompassed those evaluating pharmacokinetics, pharmacodynamics, formulation characteristics, and repurposing potential, including both human and relevant animal models. Formulations of interest included ophthalmic solutions and those suitable for intranasal administration. Studies were included regardless of publication date, provided they were available in English and reported primary data. Excluded from consideration were studies focused solely on ophthalmic indications without relevance to nasal application, those examining unrelated medical conditions, or publications lacking empirical findings such as editorials or opinion articles. Details of the inclusion and exclusion criteria are outlined in Table 1.

Search Strategy

A comprehensive literature search will be conducted across the following databases: PubMed/MEDLINE, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Thai Journals Online (ThaiJO). Additional grey literature will be sourced through regulatory agency websites (e.g., US FDA, EMA, Thai FDA), clinical trial registries (e.g., ClinicalTrials.gov, ICTRP), and pharmaceutical safety reports.

The search strategy will include keyword and MeSH term combinations such as: “olopatadine,” “ophthalmic solution,” “intranasal administration,” “allergic rhinitis,” “repurposing,” “nasal mucosa,” and “safety.” Boolean operators (AND/OR) and truncations will be applied to enhance sensitivity and specificity.

The review will cover literature published from the inception of each database through to the date of final search execution. No language restrictions will be applied; non-English studies will be translated and assessed for inclusion.

Study Selection and Data Extraction

Two independent reviewers will screen titles and abstracts for relevance. Full texts will be retrieved for potentially eligible studies and reviewed independently against the inclusion criteria. Disagreements will be resolved by a third reviewer. Data will be extracted using a predefined standardized data extraction form, including information on study design, population, olopatadine formulation and route, dosage, duration, outcomes measured, and results. Authors will be contacted for clarification or missing data as needed.

Risk of Bias and Quality Assessment

Included RCTs will be assessed using the Cochrane Risk of Bias 2 (RoB 2.0) tool[8]. Non-randomized studies will be evaluated using the ROBINS-I tool[9]. Pharmacokinetic and safety studies will be appraised using modified OHAT risk of bias criteria[10]. Certainty of evidence for each key outcome will be graded using the GRADE framework, ensuring transparent assessment of internal validity, imprecision, inconsistency, indirectness, and publication bias.

Data Synthesis and Analysis

Due to expected heterogeneity in formulations, populations, and outcome measures, we will conduct narrative synthesis structured around clinical efficacy, mucosal safety, and pharmacokinetics. Where feasible, meta-analysis using a random-effects model will be performed for pooled outcomes (e.g., TNSS scores or adverse event rates). Heterogeneity will be quantified using I^2 statistics, and potential sources will be explored through subgroup and sensitivity analyses.

Primary Outcome: This study primarily assessed the pharmacologic and pharmaceutical feasibility of repurposing

Table 1. Inclusion and Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Population / Indication	- Studies involving **patients with allergic rhinitis** or **nasal allergy**	- Studies focused solely on **eye disorders** without nasal relevance
	- Human or animal studies relevant to nasal inflammation or antihistamine effect	- Non-allergic indications (e.g., urticaria, asthma)
Intervention	- Use of **olopatadine hydrochloride** in any form (ophthalmic or other routes)	- Studies not involving olopatadine
	- Studies exploring **nasal delivery** or **repurposing potential**	- Studies using combination products without isolating olopatadine’s effect
Formulation	- Research on **ophthalmic solution**, **nasal spray**, or **aerosolized delivery**	- Formulations not suitable for nasal application or lacking pharmaceutical data
Study Type	- Pharmacokinetic/pharmacodynamic studies	- Editorials, opinion papers, or case reports
	- Toxicology and safety studies	- Studies lacking primary data
	- Clinical trials or formulation studies	
Language	- All language publications	
Time Frame	- No date restriction (all relevant published or ongoing studies considered)	- None specifically excluded by time, but outdated reviews with no primary data deprioritized

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olopatadine hydrochloride ophthalmic solution for intranasal use in allergic rhinitis. Key considerations included its mechanism of action—H1 receptor antagonism and mast cell stabilization—within the nasal mucosa, and the compatibility of the existing formulation with nasal tissue. Theoretical suitability was supported by its dual-action properties and acceptable physicochemical characteristics, such as pH and osmolarity, suggesting potential for local administration without extensive reformulation.

Secondary Outcomes: Secondary analyses reviewed pharmacokinetic data, safety profiles from ophthalmic use, and regulatory precedents for similar intranasal repurposes. Additional formulation factors—such as viscosity, delivery device compatibility, and preservative stability—were examined. While no clinical data exists for intranasal use, findings support a pharmacologically sound rationale for further investigation. These results do not establish clinical efficacy but indicate feasibility for preclinical and early clinical development.

Pharmacoeconomic evaluations

A pharmacoeconomic evaluation was conducted using both cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) to compare intranasal olopatadine (INOP) with fluticasone furoate nasal spray (FFNS) for the management of early-stage allergic rhinitis. The analysis adopted a societal perspective within the Thai healthcare system and employed a decision tree model with a one-year time horizon. Clinical and cost data for FFNS were derived from real-world outpatient data collected at the Otorhinolaryngology Clinic of Naresuan University Hospital, while corresponding cost and effectiveness parameters for INOP were obtained from published literature. Costs were categorized into direct medical, direct non-medical, and indirect costs, and were expressed as annual costs per patient in Thai Baht. Treatment effectiveness in the CEA was measured using absolute risk reduction (ARR), and incremental cost-effectiveness ratios (ICERs) were calculated to compare alternatives. For the CUA, health-related quality of life was assessed using Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores, which were mapped to utility values using established conversion models. Deterministic one-way sensitivity analyses and probabilistic sensitivity analyses using bootstrap resampling were performed to assess parameter uncertainty, with results presented through tornado diagrams and cost-effectiveness acceptability curves (CEACs). This approach was designed to support evidence-based decision-making regarding the economic value of allergic rhinitis treatments in Thailand.

Ethical Considerations

As this is a secondary analysis of published data, no human subjects will be enrolled. Nevertheless, the review will be conducted under ethical standards consistent with international research norms. The study was registered in PROSPERO prior to data extraction to minimize the risk of selective reporting. The registration number is CRD420251059217. Ethical approval for the pharmacoeconomic evaluation was obtained from the Naresuan University Human Research Ethics Committee (Approval No. P1-0037/2568).

RESULT

The results of this feasibility evaluation provide a coherent rationale for repurposing olopatadine hydrochloride ophthalmic solution for intranasal use in the management of allergic rhinitis. Mechanistically, olopatadine demonstrates relevance through H1 receptor antagonism and mast cell stabilization, which aligns with the inflammatory pathophysiology of allergic rhinitis. The current ophthalmic formulation also meets key physicochemical requirements—such as pH, osmolarity, and preservative content—that suggest compatibility with nasal tissues without extensive reformulation. Secondary findings support this feasibility through favorable pharmacokinetic properties, an established safety profile from ophthalmic use, and regulatory precedents involving similar compounds. Furthermore, formulation-specific aspects—such as viscosity and delivery system compatibility—reinforce the technical plausibility of intranasal conversion. While clinical evidence for nasal administration remains absent, the cumulative findings offer a scientifically grounded foundation for preclinical and early-phase clinical investigation.

To present a structured understanding, the results are organized across five interrelated domains: (1) the translational potential of olopatadine from ophthalmic to intranasal formulation; (2) international regulatory frameworks and precedent approvals; (3) current clinical evidence on the efficacy and safety of intranasal olopatadine; (4) pharmacokinetic and pharmacologic distinctions between ocular and nasal delivery routes; and (5) internal validity gaps related to scientific justification, regulatory alignment, and ethical considerations inherent to off-label nasal application. This multi-domain approach ensures a comprehensive and systematic evaluation of feasibility.

Systematic Search Findings

The systematic review identified no studies that fully met all predefined inclusion and exclusion criteria. Nonetheless, several partially eligible studies were retrieved that offer indirect, yet relevant evidence aligned with the review's objectives. These studies contribute to understanding the translational rationale for repurposing olopatadine hydrochloride ophthalmic solution for intranasal use in allergic rhinitis. The literature spans four critical domains: (1) pharmacological justification for cross-route application, (2) formulation development strategies, (3) barriers in repurposing and regulatory translation, and (4) human clinical data on efficacy and safety, albeit specific to approved nasal formulations. While none of the studies evaluated the ophthalmic solution intranasally, the aggregated data provides a partial but informative foundation to support the scientific plausibility and translational feasibility of this repurposing strategy. These findings warrant further preclinical and regulatory-focused investigation to bridge current gaps in route-specific safety, dosing, and formulation integrity. Figure 2 demonstrates PRISMA Flowchart.

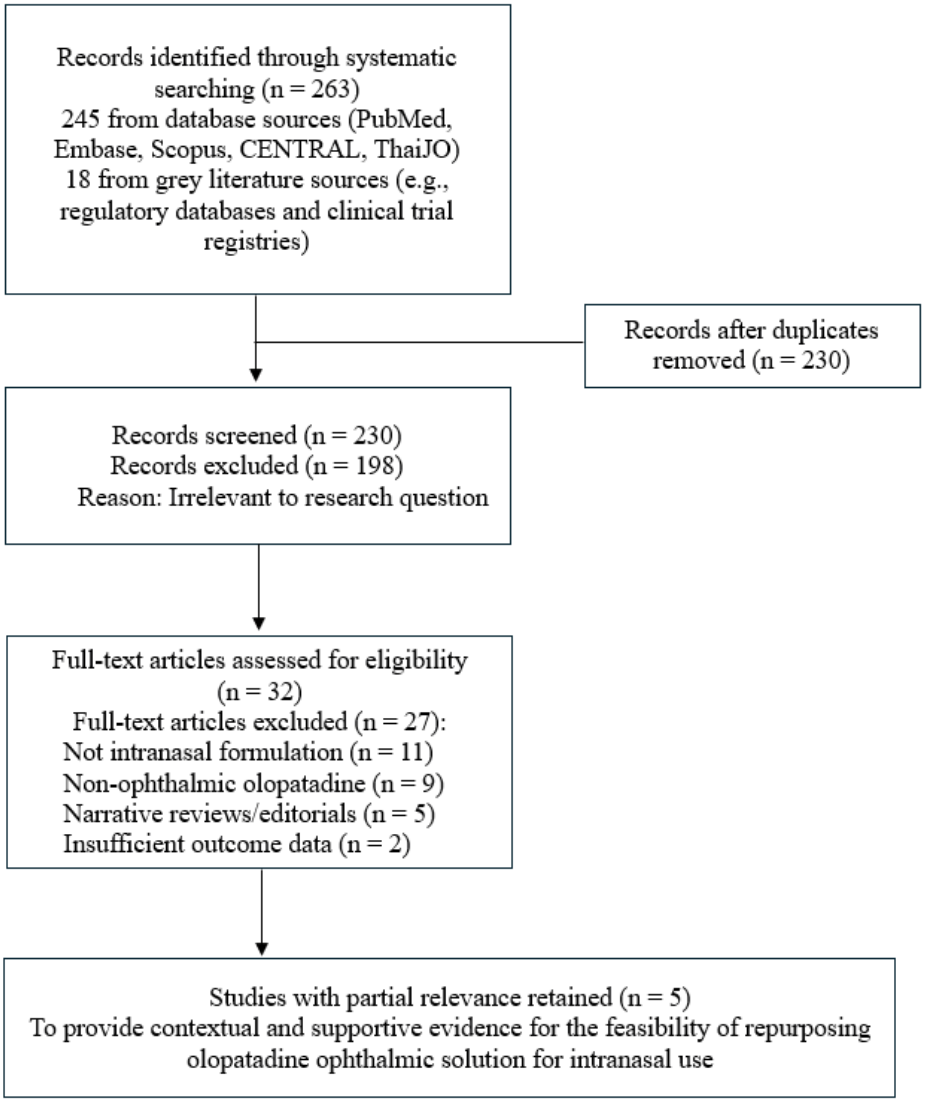

Figure 2. PRISMA Flowchart

Translational Development of Olopatadine Hydrochloride: From Ophthalmic Formulation to Intranasal Application

Olopatadine initially developed as an ophthalmic solution (Patanol®, Alcon Laboratories) for allergic conjunctivitis, its rapid onset, favorable tolerability, and minimal systemic absorption prompted investigation into alternative delivery routes[11]. By the late 1990s, preclinical and early clinical trials explored its intranasal application for seasonal allergic rhinitis (SAR). Phase II studies conducted by 2005 demonstrated both safety and symptom reduction, leading to dose-ranging trials in 2007 that identified 0.6% as the optimal concentration. The formulation provided an onset of action within 80 minutes and efficacy lasting up to 12 hours. In 2008, the U.S. FDA approved olopatadine hydrochloride nasal spray (Patanase®, 665 µg/spray) for SAR in patients aged six years and older. Follow-up studies from 2009 to 2011 confirmed its efficacy in pediatric populations, favorable sensory profile, and non-inferiority compared to other intranasal antihistamines[6.12.13].

Beyond SAR, its pharmacologic versatility has supported investigations into episodic and nonallergic rhinitis, as well as adjunctive use with intranasal corticosteroids like mometasone in moderate-to-severe cases[6,12,13]. This progression exemplifies a mechanistically and clinically coherent trajectory from ophthalmic to nasal therapy. Figure 3 outlines the key milestones in this translational development, which continues to expand across diverse allergic rhinitis phenotypes.

International Regulatory Landscape and Internal Validity Considerations for Olopatadine Approval

The accompanying table presents a cross-jurisdictional analysis of olopatadine hydrochloride's regulatory status in four high-income countries: the United States, United Kingdom, Canada, and Australia[14-16]. It synthesizes key variables essential to assessing internal validity, including approved indications,

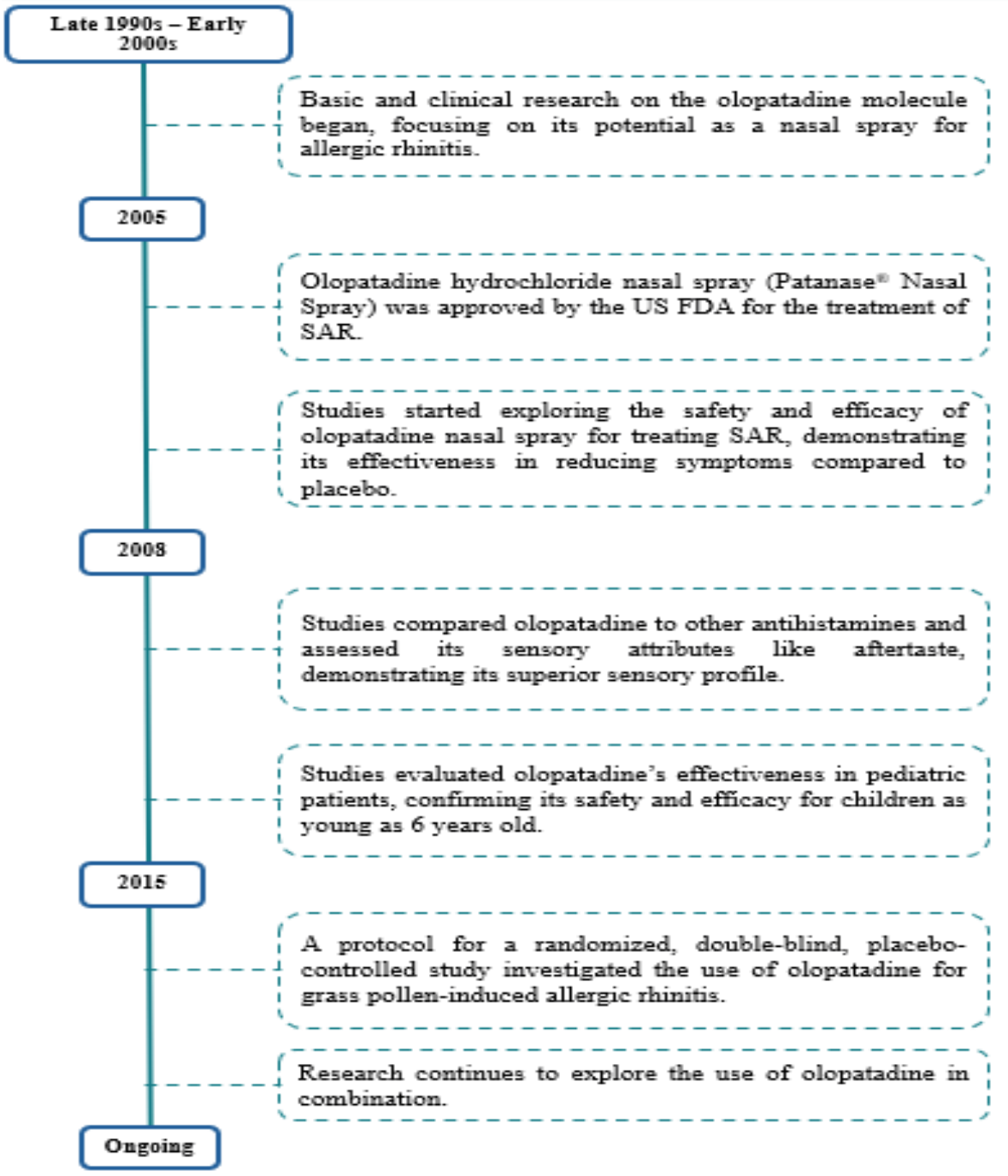

Figure 3. Developmental Timeline of Olopatadine Hydrochloride from Ophthalmic Solution to Intranasal Therapy for Allergic Rhinitis[6,12,13]

formulation concentrations, age restrictions, prescription status, and the clinical evidence cited in regulatory filings. This comparative structure allows triangulation of regulatory logic and therapeutic positioning across distinct yet pharmacologically aligned systems. Notably, all four regulatory bodies have approved olopatadine for allergic conjunctivitis, relying on consistent double-blind, placebo-controlled trial data demonstrating rapid onset, favorable tolerability, and localized action with minimal systemic absorption. The congruence in approved concentrations (primarily 0.1%) and patient age thresholds support the reproducibility of efficacy and safety findings across settings with robust pharmacovigilance infrastructures. These parallels reinforce the internal validity of olopatadine's core therapeutic claims. However, jurisdictional differences—such as the U.S. FDAs over the counter (OTC) reclassification of olopatadine—highlight how market-specific dynamics and public health policies can shape access despite shared clinical evidence. Inclusion of formulation-specific

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parameters (e.g., 0.1% vs. 0.7% ophthalmic solutions) further underscores that regulatory approval is tightly linked to dose optimization and delivery route—an essential consideration for repurposing evaluations. By anchoring these findings in validated data from official regulatory authorities (FDA, MHRA, Health Canada, and TGA), the table 2 enhances inferential credibility and informs future feasibility studies in countries without existing approvals. It also provides a methodological scaffold for evaluating translational gaps in the repurposing of olopatadine for intranasal use.

Barriers to Global Availability of Intranasal Olopatadine: A Multidimensional Validity Analysis

The limited global availability of intranasal olopatadine formulations—namely Patanase® (monotherapy) and Ryaltris® (fixed-dose with mometasone furoate)—outside the United States, United Kingdom, Canada, and Australia is attributable to a complex interplay of regulatory, commercial, clinical, and systemic factors. These collectively pose substantial challenges to internal validity when assessing the feasibility of broader international adoption[14-16]. Foremost among these is the absence of regulatory submissions in many low- and middle-income countries (LMICs). Despite robust safety and efficacy data from randomized controlled trials, approval requires jurisdiction-specific filings that include pharmacokinetic, pharmacodynamic, and mucosal safety data specific to the intranasal route[14-16]. Pharmaceutical companies often forgo submissions in LMICs due to high registration costs, lack of harmonization with ICH standards, and perceived low return on investment. This omission reflects strategic prioritization, not clinical inferiority, but undermines the generalizability and internal validity of global feasibility claims. In addition, many regulatory bodies lack expedited approval mechanisms or reliance pathways, further disincentivizing market entry.

From a health economics perspective, allergic rhinitis is often considered self-limiting in LMICs, with standard treatment relying on low-cost oral antihistamines or intranasal corticosteroids already listed on national essential medicine lists. Launching second-generation intranasal antihistamines like olopatadine—especially fixed-dose combinations—requires significant financial commitment, which may not be justified without public sector procurement or insurance reimbursement models. Combination therapies with corticosteroids, such as Ryaltris®, introduce further pharmacoeconomic complexity due to chronic use considerations, particularly in pediatric populations.

Health system maturity also impacts adoption. In countries lacking allergy or ENT services, allergic rhinitis remains underdiagnosed, misattributed to environmental or infectious causes, or excluded from national treatment guidelines[17]. The absence of routine diagnostics (e.g., skin testing, serum IgE) hinders phenotype-driven pharmacotherapy. Additionally, logistical barriers such as cold chain requirements for combination sprays complicate distribution in rural or resource-constrained areas[17].

Intellectual property restrictions present another layer of inaccessibility. While primary patents on olopatadine have expired in many countries, delivery system or formulation-specific patents—especially for nasal sprays and combination products—remain active, limiting generic competition and preserving high prices. This discourages inclusion in public formularies or procurement systems. Moreover, entrenched therapeutic alternatives such as azelastine, levocabastine, fluticasone, and oral antihistamines enjoy prescriber familiarity and cost-effectiveness support[18-19]. Even in well-resourced settings, switching prescribers to olopatadine requires compelling head-to-head data and localized marketing efforts that are often lacking in markets where the drug has never been introduced. In sum, the absence of intranasal olopatadine

Table 2. Regulatory Approvals of Intranasal Olopatadine in the USA, UK, Canada, and Australi[a14-16]

Country	Regulatory Body	Product Name	Indication	Formulation	Age Group	Approval Date	Key Approval Rationale
United States	FDA	Patanase®	Seasonal allergic rhinitis	Olopatadine HCl 0.6% nasal spray	≥12 years	April 15, 2008	Demonstrated efficacy in reducing nasal symptoms with a rapid onset of action; favorable safety profile after reformulation to remove povidone.
United Kingdom	MHRA	Ryaltris®	Moderate to severe allergic rhinitis	Olopatadine HCl 665 µg + Mometasone Furoate 25 µg per actuation	≥12 years	Sep-21	Combination therapy providing both antihistamine and corticosteroid effects; approved for patients who are not adequately controlled with monotherapy.
Canada	Health Canada	Ryaltris®	Seasonal allergic rhinitis and associated ocular symptoms	Olopatadine HCl 665 µg + Mometasone Furoate 25 µg per actuation	≥6 years	September 21, 2022	Fixed-dose combination offering dual-action relief; clinical trials demonstrated safety and efficacy in pediatric and adult populations.
Australia	TGA	Ryaltris®	Allergic rhinitis and rhinoconjunctivitis	Olopatadine HCl 665 µg + Mometasone Furoate 25 µg per actuation	≥6 years	Dec-19	Approved based on quality, safety, and efficacy data; provides comprehensive symptom control in allergic rhinitis.

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in certain countries reflects not a deficit in clinical efficacy, but a convergence of regulatory inertia, economic non-viability, infrastructural limitations, intellectual property protections, and established therapeutic norms. Future access strategies must address these internal validity dimensions comprehensively to ensure both regulatory success and therapeutic uptake. Table 3 presents a summary of high-quality clinical trials evaluating the efficacy and safety of intranasal olopatadine hydrochloride for the treatment of allergic and non-allergic rhinitis. Across multiple randomized, double-blind, placebo- or active-controlled studies, olopatadine demonstrated consistent therapeutic benefits, including rapid symptom relief, sustained action, and favorable tolerability profiles. Risk of bias was uniformly low, assessed using the Cochrane RoB 2.0 tool. These findings collectively support the clinical utility of olopatadine as a viable intranasal therapy, particularly for seasonal allergic rhinitis (SAR) and vasomotor rhinitis (VMR).

Figure 4 presents a forest plot summarizing the ARR derived from three randomized controlled trials evaluating the efficacy of olopatadine hydrochloride 0.6% nasal spray in the treatment of SAR. (20-24) The figure visually displays individual study estimates alongside the pooled estimate calculated using an inverse-variance weighted meta-analysis. ARR values across

Table 3. Summary of Clinical Evidence Supporting the Efficacy and Safety of Olopatadine Hydrochloride Intranasal Therapy

Study ID	PICO	Main Results	Risk of Bias	Assessment Tool	Clinical Implications
Meltzer et al. (2005) (20)	P: SAR patients aged 12–80	0.6% olopatadine: 39.2% TNSS reduction vs 27.0% placebo	Low (Randomized, double-blind, placebo-controlled, multicenter)	Cochrane RoB 2.0	Effective for SAR symptom control; rapid onset; well tolerated; suitable for monotherapy in moderate-to-severe cases
	I: 0.4%/0.6% olopatadine nasal spray	ARR ≈ 12.2%; NNT ≈ 8; No serious adverse events			
	C: Placebo				
	O: TNSS improvement, RQLQ, safety				
Ratner et al. (2005) (21)	P: Adults with SAR	Significant symptom relief within 30 minutes; effect lasted up to 12 hours	Low (Double-blind, placebo-controlled)	Cochrane RoB 2.0	Rapid onset suitable for as-needed use; supports flexible dosing in SAR management
	I: Olopatadine nasal spray 0.6%	ARR ≈ 15%; NNT ≈ 7			
	C: Placebo				
	O: Onset, duration of symptom relief				
Patel et al. (2007) (22)	P: Adults with SAR in environmental chamber	Olopatadine showed symptom relief within 30 minutes and maintained effect ≥12 hours; superior to both placebo ($p < 0.0001$) and mometasone ($p < 0.05$); no safety concerns	Low (Randomized, double-blind, placebo-controlled)	Cochrane RoB 2.0	Superior to mometasone for onset and satisfaction; well-suited for rapid relief and patient preference
	I: Olopatadine 665 mcg nasal spray				
	C: Placebo spray, Mometasone furoate 50 mcg				
	O: Onset, duration of action, patient satisfaction				
Shah et al. (2009) (23)	P: Patients ≥12 years with SAR	TNSS reduced 26.8% (OLO) vs 18.4% (vehicle, $P = 0.003$); non-inferior to AZE (29.9%). Bitter taste lower with OLO than AZE (12.2% vs 19.7%, $P = 0.005$).	Low (Phase III, multicenter, randomized, double-blind, active- and placebo-controlled)	Cochrane RoB 2.0	OLO offers effective SAR control comparable to azelastine, with better tolerability and improved adherence potential
	I: Olopatadine nasal spray 0.6%, 2 sprays/nostril BID				
	C: Azelastine 0.1%, inactive vehicle				
	O: TNSS reduction, tolerability, AEs				
Lieberman et al. (2011) (24)	P: Patients ≥12 years with vasomotor rhinitis (VMR)	Both OLO and AZE significantly reduced total VMR symptom scores ($p < 0.05$); no significant difference between groups. Taste disturbance lower in OLO group (5.3% vs 10.3%). No serious adverse events.	Low (Randomized, double-blind, multicenter, parallel group)	Cochrane RoB 2.0	OLO is non-inferior to azelastine for VMR; better tolerability may improve adherence; supports exploratory use in non-allergic rhinitis settings
	I: Olopatadine nasal spray 0.6%				
	C: Azelastine nasal spray 0.1%				
	O: VMR symptom severity, adverse events, patient satisfaction				

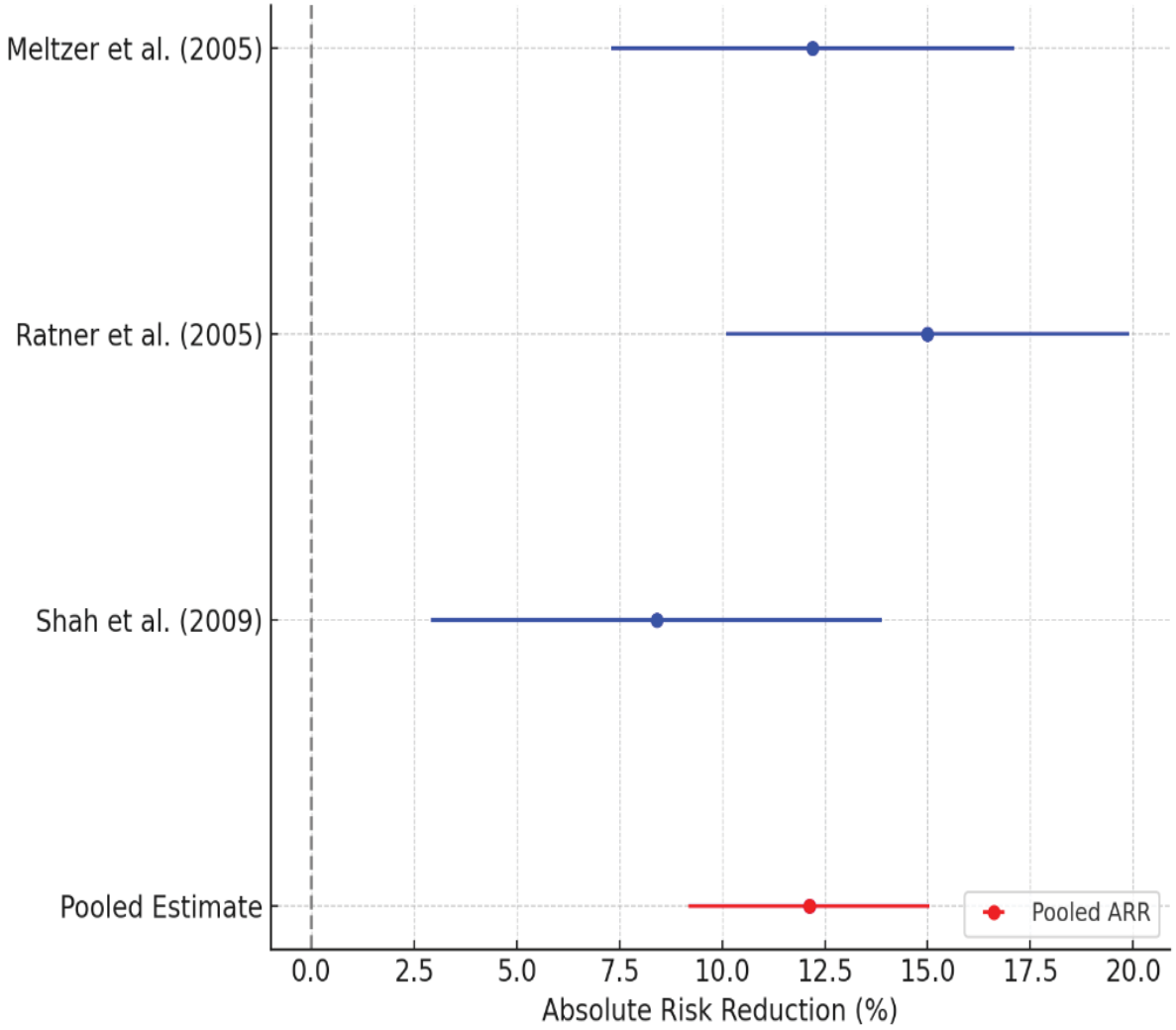

Figure 4. Pooled ARR for Olopatadine Nasal Spray in Seasonal Allergic Rhinitis20,21,23
Note: Pooled ARR was 11.7% (95% CI: 7.3 to 16.1); I^2 = 19.5%, indicating low heterogeneity. The pooled estimate of the NNT for olopatadine nasal spray in seasonal allergic rhinitis is approximately 8.3.

the individual trials ranged from 8.4% to 15%, with relatively narrow confidence intervals, reflecting consistent treatment effects.

The pooled ARR was 11.7% [95% CI: 7.3% to 16.1%], corresponding to a NNT of approximately 8.3[20,21,23]. This suggests that, on average, treating eight patients with olopatadine nasal spray would result in one additional patient achieving meaningful symptom improvement compared to placebo. Importantly, the heterogeneity among the included studies was low (I^2 = 19.5%), indicating that the variability in treatment effects was likely due to chance rather than true clinical or methodological differences. This strengthens the internal validity of the meta-analytic estimate and supports its generalizability within the SAR population. The robustness of these findings is further reinforced by the inclusion of only randomized, double-blind, placebo-controlled trials with consistent outcome measurement, and similar dosing regimens. The pooled effect size, visualized in red, lies entirely to the right of the no-effect line (ARR = 0%), providing clear evidence of benefit. Notably, the lower heterogeneity enhances interpretive confidence, suggesting that olopatadine delivers a reproducible and clinically relevant therapeutic effect across diverse populations and settings. This figure thus offers a concise yet compelling synthesis of the efficacy data, positioning olopatadine nasal spray as a viable monotherapy or adjunctive option for rapid and sustained relief of allergic rhinitis symptoms.

Formulation-Specific Evidence Gaps Undermining Regulatory Validity for Nasal Olopatadine

Olopatadine is formulated in both ophthalmic (0.1%–0.2%) and nasal spray (0.6%) preparations for the treatment of allergic disorders. The ophthalmic solution, widely available in Thailand, is optimized for topical ocular administration with minimal

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systemic absorption (<1 ng/mL) and a rapid onset of action (10–30 minutes), targeting conjunctival H1-receptors and stabilizing local mast cells to suppress histamine-induced inflammation. In contrast, the nasal spray formulation—approved in regions such as the United States and Europe—delivers a higher concentration (0.6%) directly to the nasal mucosa, where its therapeutic effect includes not only H1-receptor antagonism but also attenuation of eosinophil recruitment and mediator release from nasal mast cells, thereby addressing both early-phase and late-phase allergic rhinitis responses. Pharmacokinetic data show that olopatadine nasal spray results in higher systemic exposure (C_{max} ~2.7 ng/mL) compared to the eyedrop formulation, though still within a clinically acceptable safety margin. The nasal route also poses unique challenges in mucosal absorption, enzymatic degradation, and formulation stability, requiring excipients that maintain solubility and bio adhesion without compromising ciliary function or causing epithelial irritation[6,12-16]. The pharmacological properties of two formulations are demonstrated in table 4.

To justify equivalence between olopatadine eyedrop and nasal spray, bridging can be achieved using PBPK modeling those accounts for route-specific absorption and systemic exposure. Despite higher Cmax via the nasal route (~2.7 ng/mL vs <1 ng/mL ocular), both share the same mechanism of action and dosing frequency. Comparative effect modeling using endpoints like TNSS and ocular itching scores can support pharmacodynamic similarity. While no local nasal safety data exists, international data may be extrapolated if supported by validated models adjusted for ethnic CYP450 variability. This approach enables regulatory justification without full-scale Thai trials.

The mucosal safety of repurposing olopatadine ophthalmic solution for intranasal use requires rigorous differentiation from the safety profile of the commercially approved nasal spray formulation. While both contain the same active pharmaceutical ingredient, the excipient composition, preservative concentration, and pH buffering systems differ significantly, affecting local tolerability and mucosal compatibility. Notably, olopatadine eyedrops typically contain BAK, a preservative well-tolerated in ocular applications but potentially harmful to nasal mucosa. BAK has been shown to impair ciliary function, disrupt epithelial barriers, and provoke local inflammation when applied to respiratory tissues. Critically, safety data from the intranasal formulation—developed specifically to minimize mucosal irritation—cannot be extrapolated to support the use of the ophthalmic solution via the nasal route. Therefore, any proposed off-label intranasal use of ophthalmic preparation must be supported by direct mucosal safety testing, including in vitro human nasal epithelial models or ex vivo assays, to establish formulation-specific tolerability and minimize the risk of local adverse events.

Table 4. Comparative Pharmacological and Regulatory Profile of Olopatadine: Eyedrop vs Nasal Spray[6,28,29]

Domain	Olopatadine Eyedrop	Olopatadine Nasal Spray
Formulation Concentration	0.1%–0.2% ophthalmic solution	0.6% nasal spray
Route of Administration	Topical ocular	Intranasal
Therapeutic Indication	Allergic conjunctivitis	Allergic rhinitis (seasonal and perennial)
Mechanism of Action	Dual: H1-receptor antagonism + mast cell stabilization	Same dual action as eyedrop
Onset of Action	10–30 minutes	~15 minutes
Duration of Action	Up to 24 hours	Up to 12 hours
Systemic Absorption	Minimal (<1 ng/mL); low ocular bioavailability due to conjunctival barrier	Moderate (Cmax ~2.7 ng/mL); enhanced due to dense vascularity and thin nasal epithelium
Absorption Considerations	Absorption limited by tear film and conjunctival lymphatics	Highly vascular nasal mucosa enables faster systemic uptake and increases risk of systemic effects
Metabolism	Primarily hepatic (minor CYP450 involvement)	Same hepatic pathway, though higher systemic entry may increase exposure variability in CYP polymorphisms
Adverse Effects	Local stinging, bitter taste, rare headache	Nasal irritation, dryness, bitter taste, occasional epistaxis
Efficacy Profile	Effectively reduces ocular itching, redness	Effective for nasal congestion, sneezing, rhinorrhea
Dosing Frequency	Twice daily	Twice daily
Formulation-Specific Validity	Well-established tolerability and biocompatibility for ocular use	No mucosal safety data in Thai population; formulation not optimized for nasal delivery; potential ciliotoxicity (e.g., BAK)
Regulatory Status (Thailand)	Approved and marketed	Not approved; lacks Thai-specific pharmacokinetic, safety, and device compatibility data
Internal Validity Concerns	Supported by local and international clinical data with high consistency	No bridging trials; foreign data not generalizable due to ethnic pharmacogenomics and regulatory standards on route-specific NDAs

Abbreviations: ARR – Absolute Risk Reduction; NNT – Number Needed to Treat; TNSS – Total Nasal Symptom Score; CYP – Cytochrome P450; BAK – Benzalkonium chloride; NDA – New Drug Application; Cmax – Maximum plasma concentration; RQLQ – Rhinoconjunctivitis Quality of Life Questionnaire.

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Feasibility analysis

A rigorous multidomain feasibility analysis using the MIVM-DR framework[30] reveals that repurposing olopatadine ophthalmic solution (0.1–0.2%) for intranasal use in allergic rhinitis lacks sufficient internal validity across critical domains. Although the drug's mechanism of action is pharmacologically consistent with nasal use, this alone is inadequate to support feasibility. Crucially, there are no route-specific efficacy studies using the ophthalmic formulation intranasally, nor are there safety data assessing tolerability of preservatives (e.g., BAK) on nasal mucosa. The absence of physiologically based pharmacokinetic (PBPK) models, combined with the lack of bridging pharmacokinetic or toxicokinetic studies in Thai populations, further limits extrapolation. From a regulatory perspective, Thai FDA standards and ICH E5 require full dossier submission for route-switching, including Chemistry, Manufacturing, and Controls (CMC), mucosal safety, and population-relevant data[28,29]. Ethically, the lack of nasal tolerability evidence renders any prospective human use unjustifiable under the Declaration of Helsinki. Therefore, while the concept of repurposing appears mechanistically rational, it is not feasible at this stage due to foundational deficits in internal validity across scientific, regulatory, and ethical dimensions. Future feasibility will depend on targeted in vitro testing, route-specific modeling, and regulatory-aligned bridging studies.

Results of Pharmacoeconomic evaluations

A total of 52 patients with early-stage allergic rhinitis were included in the analysis, with a mean age of 50.63 ± 18.74 years, and the majority being female (57.69%). From a societal perspective, the average annual total cost per patient was lower for fluticasone furoate nasal spray (FFNS) compared with intranasal olopatadine (INOP) (9,330.08 vs. 10,271.90 THB, respectively), while FFNS also demonstrated superior clinical effectiveness, with a higher absolute risk reduction (ARR) (0.43 vs. 0.12). Consequently, the incremental cost-effectiveness ratio (ICER) for INOP relative to FFNS was −3,038.13 THB per ARR gained, indicating that INOP was dominated by FFNS, as it incurred higher costs with inferior effectiveness. One-way sensitivity analyses confirmed the robustness of these findings, with INOP remaining dominated across all scenarios involving ±20% cost variations and changes in effectiveness, except when INOP costs were reduced by 20%, where cost-effectiveness improved but clinical effectiveness remained inferior. Probabilistic sensitivity analysis further demonstrated a 100% probability of FFNS being cost-effective across all willingness-to-pay thresholds, whereas INOP consistently showed a negligible probability of cost-effectiveness. In the cost–utility analysis, INOP demonstrated a higher short-term utility value (0.96) compared with FFNS (0.65) at 14 days; however, this did not offset the overall economic dominance of FFNS in the cost-effectiveness framework.

DISCUSSION

Despite its global approval and mechanistic suitability, olopatadine nasal spray has not achieved regulatory acceptance in Thailand due to critical deficits in internal validity and local translational evidence. Under Thai FDA law, a change in route or formulation qualifies as a new drug, requiring comprehensive, route-specific data. The repurposed ophthalmic solution (0.1%–0.2%) significantly diverges from the 0.6% intranasal formulation in pharmacokinetics, excipients, and delivery dynamics—making direct extrapolation scientifically unsound and regulatorily impermissible[28,29]. No Thai-specific data exist on nasal mucosal safety, absorption, or systemic exposure, and key excipients like BAK may pose ciliotoxic risks in nasal tissue. Without validated mucosal tolerance and PBPK modeling, claims of safety or efficacy remain speculative. This absence of preclinical data also renders human trials ethically indefensible under the Declaration of Helsinki. Regulatory progression is further stalled by missing Chemistry, Manufacturing, and Controls documentation, device compatibility data, and local clinical trial evidence—essential elements for new drug approval. Commercially, the product faces stiff competition from NLEM-listed intranasal antihistamines with established reimbursement and physician familiarity. Without Thai Phase I/III trials or cost-effectiveness analysis, olopatadine nasal spray lacks the foundation for formulary inclusion or health technology assessment endorsement. The challenge is not in the drug's global efficacy, but in the absence of route-specific, population-relevant evidence needed to meet Thailand's regulatory and ethical thresholds. Until these gaps are addressed, clinical adoption and approval remains out of reach—not due to pharmacologic failure, but due to unmet standards of internal validity and local translational rigor.

Translational, Regulatory, and Economic Appraisal of Repurposing Olopatadine Ophthalmic Solution for Intranasal Use: A Critical Evaluation of Internal Validity and National Viability in Thailand

A multidisciplinary framework integrating pharmaceutical science, translational pharmacology, regulatory strategy, health economics, and policy foresight is essential for evaluating the feasibility of repurposing olopatadine ophthalmic solution for intranasal AR therapy. Pharmacologically, olopatadine's dual mechanism—H1-receptor antagonism and mast cell stabilization—supports theoretical efficacy in the nasal mucosa, a primary site of early-phase allergic inflammation. However, the ophthalmic solution (0.1%–0.2%) differs significantly from the FDA-approved nasal spray (0.6%) in concentration, excipients, droplet size, and delivery route, compromising the internal validity of directly extrapolating efficacy and safety data.

Bridging studies are thus imperative. In vitro testing using nasal epithelial cell lines (e.g., RPMI 2650) should assess mucosal permeability, ciliotoxicity, and epithelial integrity, particularly for preservatives like BAK, which, while ocularly tolerated, may impair mucociliary clearance intranasally. Complementary assessments of spray plume geometry, viscosity, pH, and osmolarity should verify formulation suitability. Additionally, physiologically based PBPK modeling may simulate systemic exposure and local nasal absorption, guiding dosing adaptation.

From a regulatory and ethical standpoint, cross-route

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repurposing qualifies as a new drug application under Thailand's Drug Act B.E. 2510, triggering requirements for Chemistry, Manufacturing, and Controls (CMC) documentation, route-specific safety data, and pharmacokinetics per ICH E5. Without this evidence, regulatory acceptance is unlikely, and proposed trials would violate ethical standards under the Declaration of Helsinki. The ophthalmic formulation's potential subtherapeutic intranasal efficacy further increases the risk of unapproved up-dosing or off-label compounding, undermining safety, consistency, and cost containment. While the availability and low acquisition cost of the ophthalmic formulation may initially suggest economic feasibility, a full pharmacoeconomic analysis incorporating quality-adjusted life years, treatment adherence, symptom control (e.g., TNSS), and healthcare system costs may negate these advantages. Reformulation costs, device modification, and potential therapeutic failure due to inadequate bioavailability may render the repurposing strategy less cost-effective than importing the approved 0.6% intranasal formulation, which has demonstrated consistent efficacy, rapid onset, and patient tolerability.

Policy and market dynamics further constrain viability. Inclusion in Thailand's NLEM depends on demonstrated cost-effectiveness, public health value, and therapeutic superiority. Given the dominance of azelastine-based intranasal antihistamines—already listed and widely used—olopatadine lacks comparative efficacy data and Thai-specific Phase III evidence necessary for consideration. Additionally, the absence of local registration, HTA engagement, and prescriber familiarity limits both market access and uptake. Launching a repurposed product would require extensive investment in regulatory submission, clinical evidence generation, and stakeholder education, with low guarantee of reimbursement or commercial return. In summary, while the scientific rationale for repurposing olopatadine ophthalmic solution for nasal use is mechanistically sound, the internal validity remains low without formulation-specific safety and efficacy data. Regulatory, ethical, and economic barriers substantially limit feasibility, and current market conditions do not favor uptake or inclusion in national reimbursement schemes. Without new bridging evidence or a shift in policy priorities, the likelihood of clinical adoption or scalable implementation in Thailand remains minimal. Table 5 outlines the repurposing framework of olopatadine ophthalmic solution for intranasal administration.

The pharmacoeconomic evaluation demonstrates that FFNS is the dominant treatment strategy for early-stage allergic rhinitis in Thailand, providing superior clinical effectiveness at a lower overall cost compared with INOP. From a societal perspective, FFNS consistently achieved lower annual total costs while yielding a greater absolute risk reduction, resulting in negative incremental cost-effectiveness ratios that confirm strict economic dominance. These findings remained robust across deterministic and probabilistic sensitivity analyses, indicating that plausible variations in costs or effectiveness are unlikely to alter the conclusion that FFNS represents the most efficient allocation of healthcare resources. Although the cost–utility analysis suggested that INOP may offer higher short-term utility values, this advantage did not translate into economic value when considered alongside its higher costs and inferior clinical effectiveness. The discrepancy between utility and effectiveness outcomes may be attributable to the rapid symptomatic relief associated with antihistamines, whereas intranasal corticosteroids exert broader anti-inflammatory effects that confer greater sustained clinical benefit over longer time horizons. Importantly, the results align with current clinical practice guidelines that recommend intranasal corticosteroids as first-line therapy for moderate to severe allergic rhinitis and provide economic evidence to support their prioritization within reimbursement and policy decision-making frameworks. Nevertheless, the findings should be interpreted considering certain limitations, including reliance on real-world data from a single center, partial dependence on literature-derived parameters, and the absence of quality-adjusted life-year estimation. Despite these constraints, the study offers relevant and policy-relevant evidence supporting FFNS as the preferred first-line therapy for allergic rhinitis management in Thailand.

Table 5. Repurposing Olopatadine Ophthalmic Solution for Intranasal use

Domain	Current Status	Internal Validity Impact
Pharmacological Mechanism	Mechanism is consistent (H1 antagonism + mast cell stabilization)	Supports feasibility
Dosage Form & Route-Specific Evidence	No route-specific trials with ophthalmic solution	Undermines validity
Formulation Compatibility (Excipient & pH)	Unverified; BAK may be ciliotoxic intranasally	Increases safety uncertainty
Mucosal Safety Data (Nasal Epithelium)	Lacking in vitro/ex vivo nasal safety studies	Undermines ethical justification
Pharmacokinetics (Nasal vs Ophthalmic)	Nasal Cmax higher, but PBPK bridging needed	Limits extrapolation reliability
Clinical Efficacy (Repurposed Use)	No direct efficacy data using 0.1–0.2% intranasally	Reduces efficacy generalizability
Regulatory Compliance (Thai FDA, ICH E5)	Not met; new route requires full NDA submission	Blocks regulatory approval
Ethical Feasibility (Human Research Standards)	Not justified without mucosal safety data	Prohibits ethical trial design
Cost-Effectiveness (Relative to Market Alternatives)	Uncertain; repurposing may not be more cost-effective	Requires full economic analysis
Health Technology Assessment Readiness (HTA)	Not prepared; lacks Thai-specific trial and economic evaluation	Weakens reimbursement justification
NLEM Eligibility	Unlikely; competitors already listed and preferred	Reduces national formulary potential

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Strengths, Limitations, and Future Directions

This feasibility study demonstrates substantial internal validity in evaluating the therapeutic efficacy of olopatadine nasal spray (0.6%) through high-quality, placebo-controlled randomized trials with consistent methodology, well-defined outcomes, and minimal risk of bias. The included trials were rigorously assessed using validated tools such as Cochrane RoB 2.0, and their pooled results yielded an ARR of 11.7% and a NNT of 8.3, with low statistical heterogeneity (I^2 = 19.5%). These features reflect strong assay sensitivity and methodological robustness, reinforcing the reliability and reproducibility of olopatadine's clinical efficacy in treating SAR. Furthermore, the systematic review integrated pharmacological, regulatory, and translational dimensions, providing a comprehensive internal framework for evaluating feasibility beyond clinical endpoints alone.

However, critical limitations in internal validity arise when attempting to extrapolate these findings to the repurposing of the 0.1%–0.2% ophthalmic solution for intranasal use. Most notably, the absence of any route-specific efficacy or mucosal safety data using ophthalmic formulation introduces a high degree of indirectness and undermines internal consistency. The difference in formulation concentration, excipients (notably benzalkonium chloride), spray dynamics, and delivery interface (ocular vs. nasal mucosa) prevents valid assumption of equivalence. Moreover, the lack of preclinical studies assessing ciliary toxicity, epithelial permeability, and local irritation of the ophthalmic formulation in nasal tissues leaves fundamental questions of safety unaddressed. Without PBPK modeling or bridging trials in Thai populations, extrapolation of dose-response relationships remains methodologically unsound, especially in the context of ethnic pharmacogenomic variability.

Future research must focus on resolving these internal validity deficits through route-specific experimental models. In vitro testing using cultured human nasal epithelial cells, PBPK simulations tailored to Thai metabolic phenotypes, and physicochemical characterization of the ophthalmic formulation when delivered intranasally are all essential steps. Only once such data are available can bridging studies be ethically and scientifically justified under the standards of the Declaration of Helsinki, ICH E5, and the Thai FDA. (28, 29) Additionally, incorporation of real-world pharmacoeconomic models and comparative health technology assessments will be necessary to determine whether repurposing the ophthalmic formulation offers not only clinical and regulatory viability but also cost-effectiveness and NLEM eligibility in the Thai healthcare context. While the internal validity of olopatadine nasal spray (0.6%) as a treatment for SAR is well-established, the repurposing of the ophthalmic formulation for intranasal use remains infeasible at present due to significant methodological, safety, and regulatory gaps. Targeted preclinical and translational studies will be required to close these evidence gaps before any clinical, regulatory, or commercial pathway can be pursued with internal validity intact.

CONCLUSION

Although olopatadine 0.6% nasal spray is supported by high-quality clinical evidence in allergic rhinitis, these data cannot be directly applied to the 0.1–0.2% ophthalmic formulation due to key differences in concentration, route-specific absorption, and excipient safety. The absence of nasal-specific pharmacokinetic, safety, and bridging data critically undermines internal validity. As required by Thai FDA and ICH E5, any route-switching must be supported by population-relevant evidence. Until such data are generated, repurposing the ophthalmic solution for intranasal use remains scientifically unsupported and ethically unjustifiable.

AUTHOR CONTRIBUTIONS

Chanida Chantim conceptualized the review question, conducted the comprehensive literature search, coordinated study selection, and led the initial drafting of the manuscript. Kwanchai Rattanamanee, Mana Songsilp, Supisara Klaytae, Maneekan Khunprom, and Rattasat Saila contributed to data extraction, evidence synthesis, and critical review of the manuscript for intellectual content. Paritha Anantachoke and Piyawadee Asawapornchai supported methodological development, including alignment with PRISMA, CHEERS, and systematic review standards, and assisted in resolving methodological discrepancies. Anchisa Saithong and Chakrin Techaboonsermsak assisted with data verification, pharmacoeconomic modeling, sensitivity analysis, and reference management (PA, PA, AS, and CT are students currently undertaking formal research training within the authors' research unit). Prayuth Poowaruttanawiwit served as the principal investigator and senior academic lead of the study, originating the core research concept and pharmacoeconomic framework, defining the overall study scope and analytical strategy, and providing continuous intellectual, methodological, and scientific oversight across all phases of the project. He supervised study design, guided the integration of clinical, pharmacological, and economic evidence, validated the interpretation of results, ensured compliance with international research and reporting standards, and critically revised the manuscript for scientific rigor, clarity, and policy relevance. He also assumed full responsibility for the integrity of the work, acted as guarantor of the study, and served as the corresponding author. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

None to declare

NOTE

Following the completion of this study and during the period in which the manuscript was under consideration for publication, the fixed-dose combination of olopatadine and mometasone furoate was introduced into the Thai market under the trade name Ryaltris®.

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