Research Article Volume 01, Issue No. 01. 2024

The International Medical Journal of Opthalmology

A Comparative Study of Olopatadine and Ketotifen in the Management of Allergic Conjunctivitis: A Systematic Review

[1] Rizky Cyntia Simamora , [1] Junia Rumenta R Hutabarat, [2] Daniel Setiawan Nathan, [3] Vania

[1] Faculty of Medicine, North Sumatera University, Medan City, North Sumatera, Indonesia
[2] Faculty of Medicine, Maranatha Christian University, Bandung City, West Java, Indonesia
[3] Faculty of Medicine, Pelita Harapan University, Tangerang Regency, Banten, Indonesia
Correspondence: rizkycsm3@gmail.com

Article History :
Received date : 2024/07/02
Revised date : 2024/08/11
Accepted date : 2024/09/12
Published date : 2024/10/07

Copyright: *© 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (https://creativecommons.org/licenses/by-nc/4.0/).*

ABSTRACT

Background: Allergic conjunctivitis is a prevalent non-traumatic inflammatory condition affecting millions globally, primarily caused by environmental allergens. Characterized by symptoms such as itching, redness, and tearing, it significantly impacts patients' quality of life. **Methods:** Following PRISMA guidelines, eligible studies were identified, focusing on peer-reviewed RCTs published between 2014 and 2024. Data on treatment efficacy, safety, and symptom relief were analyzed. **Results:** The analysis revealed that olopatadine often outperforms ketotifen in symptom relief and tolerability. **Conclusion:** Despite the promising findings, the review acknowledges limitations such as study heterogeneity and short follow-up durations. Further research is warranted to enhance understanding of long-term efficacy and safety profiles of these treatments, ultimately improving management strategies for allergic conjunctivitis.

Keywords: allergic conjunctivitis, olopatadine, ketotifen, efficacy, safety, systematic review, randomized controlled trials, treatment

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

INTRODUCTION

Allergic conjunctivitis is one of the most prevalent non-traumatic extraocular inflammatory conditions, impacting millions of individuals worldwide.[1-3] It accounts for approximately 90% of all cases of ocular allergy, with vernal conjunctivitis and spring catarrh being the predominant subtypes.[3,4] Characterized by a seasonal pattern, particularly during summer, allergic conjunctivitis often follows episodes of rhinoconjunctivitis in both adults and children, especially in those with a family history of atopic disorders. Environmental allergens such as grass, tree, and weed pollens, as well as outdoor molds, are well-recognized triggers of this condition.[6,7] Clinically, allergic conjunctivitis presents with a constellation of symptoms, including recurrent bilateral itching, redness, tearing, burning, stinging, photophobia, and watery or mucoid discharge. These symptoms are often accompanied by visible signs such as lid edema, conjunctival chemosis, hyperemia, and papillary reactions, significantly affecting the patient's quality of life.[8,9]

Traditional treatments for allergic conjunctivitis focus on symptom relief and involve strategies like allergen avoidance, cold compresses, and the use of artificial tears.[10] Pharmacological interventions typically target the modulation of the immune response, employing agents such as topical antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, and corticosteroids. However, these conventional treatments often have limited efficacy or come with adverse effects, including conjunctival hyperemia, corneal stinging, and burning.[11,12]

In recent years, newer-generation multiple-action topical anti-allergic agents, such as olopatadine and ketotifen, have been introduced as first-line therapies for allergic conjunctivitis.[13-15] Despite their widespread use, direct comparisons of their effectiveness and safety are scarce. To address this gap, we conducted a systematic review of randomized controlled trials (RCTs) to evaluate the comparative efficacy and safety of olopatadine versus ketotifen in the treatment of allergic conjunctivitis. The findings of this systematic review aim to provide

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

evidence-based guidance on optimizing therapeutic strategies for this common yet often challenging condition.

METHODS

Protocol

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensuring a transparent, replicable, and methodologically sound approach. The primary objective was to evaluate the comparative efficacy and safety of olopatadine versus ketotifen in the treatment of allergic conjunctivitis through a comprehensive analysis of randomized controlled trials (RCTs). This approach aimed to minimize bias and provide reliable conclusions.

Criteria for Eligibility

This review focused on comparing the treatment efficacy and safety of olopatadine and ketotifen in allergic conjunctivitis. The inclusion criteria for eligible studies were as follows:

1. Published between 2014 and 2024,
2. Peer-reviewed and written in English,
3. Randomized controlled trials (RCTs) evaluating either or both drugs (olopatadine and ketotifen) for allergic conjunctivitis,
4. Reported outcomes related to efficacy, safety, and symptom relief (e.g., itching, redness, tearing),
5. Included a DOI for authenticity verification. Studies such as reviews, editorials, case reports, or duplicate publications were excluded to ensure that only high-quality original research contributed to the findings.

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Search Strategy

The search strategy was designed to identify RCTs that compare olopatadine and ketotifen for allergic conjunctivitis. The databases used for this search included PubMed, ScienceDirect, and Cochrane Library. Keywords used in the search included "olopatadine," "ketotifen," "allergic conjunctivitis," "RCT," and "efficacy." Specific search strategies for each database are outlined below.

Data Retrieval

Articles were initially screened by title and abstract for relevance. Full-text articles were then thoroughly reviewed to ensure they met the inclusion criteria. Studies that did not align with the research objectives were excluded. This thorough screening process ensured that only the most relevant and high-quality studies were considered for final analysis. Variables assessed included study design, sample size, dosage, treatment duration, efficacy outcomes, and adverse events.

Quality Assessment and Data Synthesis

A detailed quality assessment of each included study was conducted to ensure robustness, focusing on methodological rigor, relevance to the research question, and risk of bias. Studies that met the quality standards underwent in-depth synthesis, with the results summarized and analyzed to compare the efficacy and safety profiles of olopatadine and ketotifen. This approach helped minimize bias and strengthened the conclusions drawn from the review.

Table 1. Search Strategy

Database	Search Strategy	Hits
PubMed	("olopatadine" AND "ketotifen" AND "allergic conjunctivitis")	143
ScienceDirect	("olopatadine" AND "ketotifen" AND "allergic conjunctivitis")	102
Cochrane Library	("olopatadine" AND "ketotifen" AND "allergic conjunctivitis")	19

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

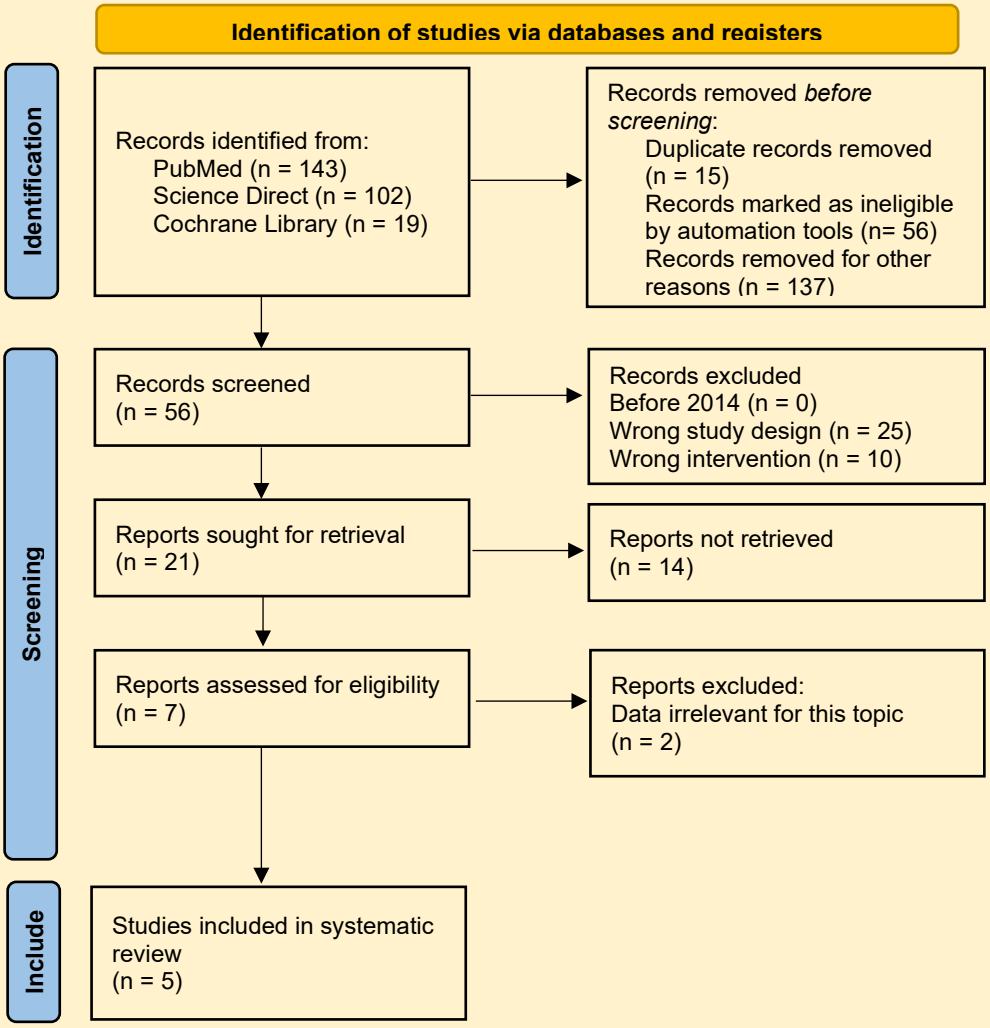

Figure 1. Article search flow chart

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Table 2. Critical appraisal of Study

Parameters	Logan et al., 2023.[16]	Ul Abidin et al., 2022.[17]	Mortemousque et al., 2014.[18]	Sah et al., 2019.[19]	Patel D et al., 2018.[20]
1. Bias related to temporal precedence					
Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation					
Was there a control group?	Yes	Yes	Yes	No	Yes
3. Bias related to confounding factors					
Were participants included in any comparisons similar?	Yes	Yes	Unclear	Yes	Yes
4. Bias related to administration of intervention/exposure					
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Yes	Yes	Yes	Yes	Yes
5. Bias related to assessment, detection, and measurement of the outcome					
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Yes	Yes	Unclear	Yes	Yes
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Unclear	Yes	Yes
6. Bias related to participant retention					
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Unclear	Unclear	Unclear	Unclear	Unclear
7. Statistical conclusion validity					

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Was appropriate statistical analysis used?	Yes	Yes	Unclear	Yes	Yes

RESULT

We initiated the investigation by systematically gathering a significant assortment of papers from reputable sources such as Science Direct, PubMed, and Cochrane Library. After a thorough three-stage screening process, we selected five papers that were considered very pertinent to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our study, we have included a concise summary of the evaluated information in Table 3.

Table 3. The literature included in this study

Logan et al., 2023.[16]	US	Randomized controlled trial.	159 participants	This study enrolled 159 participants who had a mean ± SD age of 26.3 ± 7.7 years, and 78.6% of the participants were female. The VAS found that the 0.7% olopatadine drop was more comfortable than the 0.035% ketotifen fumarate drop at all time-points. There were no between-eye differences in LogMAR visual acuities, yet bulbar redness was significantly less in 0.7% olopatadine treated eyes compared 0.035% ketotifen fumarate treated eyes.
Ul Abidin et al., 2022.[17]	Pakistan	Prospective comparative study.	A total of 200 patients were included in the study making 100 patients in each group	A total of 100 patients were included in each group. The mean age of the study participants was 30.944±3.349 years. 148 (74%) patients were maleswhile 52 (26%) were females. The difference in mean score ofsymptoms in group A was 5.76±1.39 while in group B was 3.33±2.51. Application of

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

			after block randomization.	t-test revealed that topical Olopatadine 0.1% was superior to Ketotifen Fumarate in reducing the symptoms of acute allergic conjunctivitis on the third day of treatment (p-value<0.001).Conclusion: Seasonal allergic conjunctivitis was the commonest type of allergic conjunctivitis seen in our study participants. Topical Olopatadine 0.1% emerged as a better treatment option when compared to Ketotifen Fumarate for immediate management of acute allergic conjunctivitis among patients managed at a tertiary care ophthalmology hospital.
Mortemousque et al., 2014.[18]	France	a comparative, randomised, investigator-masked, pilot clinical study in adult patients with documented history of SAC and presenting with moderate to severe itching and conjunctival hyperemia.	Seventy-five patients were randomised (ketotifen: 38 patients; olopatadine : 37 patients).	At day 28, the composite score for primary criteria (itching, tearing, and conjunctival hyperemia) improved from 6.8±1.2 to 0.9±1.0 in the Ketotifen group, without statistically significant difference between treatment groups (P=0.67). There was no relevant difference between treatment groups in other efficacy parameters, except a trend for a more rapid resolution of conjunctival hyperemia in the Ketotifen group. Both drugs were well tolerated, with a trend for a better tolerability reported by patients on ketotifen compared to those on olopatadine at day 7 (P=0.054).
Sah et al., 2019.[19]	India	A prospective, comparative study.	90 subjects with seasonal	All the study drugs showed comparable efficacy in reducing conjunctival

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

			allergic conjunctivity.	hyperemia, papillary reaction, and itching. Among them, olopatadine was distinctly more effective than other two drugs at all the visits. Ketotifen and epinastine were equally effective in relieving conjunctival hyperemia, and epinastine was more effective in relieving papillary reaction and ocular itching compared to ketotifen. The study medications showed good tolerability with less severe AEs.
Patel D et al., 2018.[20]	India	Randomized control trial.	a total of 120 patients (67 men and 53 women) with a mean age of 36.35 ± 11 years.	Compared to baseline, scores of itching, tearing, redness, eyelid swelling, chemosis and papillae addition of all the individual scores mentioned above and QOL scores reduced significantly (P = 0.001) by the 4th and 15th days of olopatadine and ketotifen application. Compared with ketotifen, olopatadine significantly reduced itching, tearing, hyperemia, and total AC scores by the 4th day (P = 0.001) and conjunctival papillae by the 15th day (P = 0.001). Adverse reactions were reported in 10% and 18% of patients treated with olopatadine and ketotifen, respectively.

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

DISCUSSION

Recent studies have explored the efficacy and tolerability of olopatadine and ketotifen fumarate in treating allergic conjunctivitis, offering valuable insights into their clinical applications. In a randomized controlled trial by Logan et al., the authors found that 0.7% olopatadine provided significantly better ocular comfort than 0.035% ketotifen fumarate at all assessed time points. The study involved 159 participants, predominantly female, and highlighted that eyes treated with olopatadine exhibited significantly less bulbar redness. These findings suggest that olopatadine may not only enhance patient comfort but could also contribute to better adherence to treatment due to its favorable side effect profile.[16]

Ul Abidin et al. conducted a prospective comparative study with 200 patients, demonstrating that olopatadine 0.1% was superior to ketotifen in reducing symptoms of acute allergic conjunctivitis by the third day of treatment, with a p-value of less than 0.001. This research confirmed that seasonal allergic conjunctivitis was the most common type observed among participants, underscoring the importance of effective management strategies in this prevalent condition. The consistency in olopatadine's efficacy across different studies strengthens the argument for its use as a first-line treatment option for allergic conjunctivitis. [17]

In contrast, Mortemousque et al. performed a pilot study comparing preservative-free ketotifen and preserved olopatadine in patients with moderate to severe seasonal allergic conjunctivitis. Although both treatments showed improvements in primary symptoms like itching and conjunctival hyperemia, there were no statistically significant differences between the two groups. However, a trend favoring quicker resolution of symptoms in the ketotifen group was noted, as well as a slight preference for ketotifen in terms of tolerability at day seven. This suggests that while both medications are effective, patient preferences and experiences may vary. [18]

Sah et al. further examined the efficacy of olopatadine in comparison to ketotifen and epinastine, finding that olopatadine was distinctly more effective at

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

all visits. While ketotifen and epinastine performed comparably in relieving conjunctival hyperemia, epinastine showed superior results for papillary reaction and ocular itching. This variability in efficacy among the drugs indicates that while olopatadine is often favored, the choice of treatment may depend on specific patient symptoms and preferences. [19]

Finally, Patel et al. conducted a randomized controlled trial involving 120 patients, which reinforced the findings of earlier studies. Their results indicated that olopatadine significantly reduced scores for itching, tearing, hyperemia, and overall allergic conjunctivitis scores by the fourth day of treatment. Notably, adverse reactions were reported in 10% of patients using olopatadine compared to 18% for those on ketotifen, suggesting a better safety profile for olopatadine. [20]

This systematic review is not without its limitations, which should be acknowledged when interpreting the findings. One significant concern is the heterogeneity of the included studies. The studies varied in design, sample sizes, and methodologies, which can complicate the generalizability of the results. Differences in participant demographics, such as age, sex, and baseline characteristics, may introduce biases that affect the comparability of outcomes, potentially skewing the overall conclusions about the efficacy and tolerability of olopatadine versus ketotifen.

Another limitation is the short follow-up duration of many studies. Most investigations focused on immediate or short-term efficacy, which restricts the assessment of long-term effects, including the durability of symptom relief and the potential for delayed adverse reactions. Without longer follow-up periods, it is difficult to determine how these treatments perform over time, which is crucial for managing chronic conditions like allergic conjunctivitis. The reliance on subjective outcome measures is also a noteworthy limitation. Many studies utilized patient-reported symptom scores and comfort assessments, which can introduce variability due to individual perceptions of symptoms. This variability may lead to inconsistencies in the reported outcomes and, consequently, the interpretation of the effectiveness of the treatments.

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Additionally, the reporting of adverse events was often limited in scope. Some studies did not provide comprehensive data on side effects, which could lead to an underestimation of the safety profile of each medication. Inadequate reporting of adverse events hampers the ability to fully understand the risks associated with olopatadine and ketotifen, making it difficult for clinicians to make informed treatment decisions. Moreover, the review may be susceptible to publication bias. Studies with positive results are more likely to be published than those with negative or inconclusive findings, which could skew the overall understanding of the efficacy and tolerability of the two treatments. This bias emphasizes the need for transparency and comprehensive reporting in clinical research. In light of these limitations, further research is warranted. Future studies should ideally involve large-scale, multicenter trials with standardized methodologies to enhance the reliability of the findings and provide clearer guidance for clinicians managing allergic conjunctivitis.

CONCLUSION

In summary, this systematic review highlights the comparative efficacy and tolerability of olopatadine and ketotifen fumarate in the treatment of allergic conjunctivitis. The majority of studies indicate that olopatadine often outperforms ketotifen in terms of both symptom relief and patient comfort, supporting its use as a preferred first-line treatment option. Despite the promising findings, the review also underscores several limitations, including study heterogeneity, short follow-up durations, reliance on subjective outcome measures, and limited reporting of adverse events. Given these limitations, further research is necessary to provide a more comprehensive understanding of the long-term efficacy and safety profiles of these medications. Future studies should focus on larger, well-designed, and multicenter trials with standardized methodologies to better inform clinical decision-making. Ultimately, the goal is to optimize treatment strategies for patients with allergic conjunctivitis, improving their quality of life and overall management of this prevalent condition.

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

REFERENCES

1.
2.
3. Bielory L, Delgado L, Katelaris CH, et al. ICON: diagnosis and management of allergic conjunctivitis. Ann Allergy Asthma Immunol 2020; 124: 118-34.
4. Villegas BV, Benitez-Del-Castillo JM. Current knowledge in allergic conjunctivitis. Turk J Ophthalmol 2021; 51: 45-54.
5. Miyazaki D, Fukagawa K, Okamoto S, et al. Epidemiological aspects of allergic conjunctivitis. Allergol Int 2020; 69: 487-95.
6. Wei CC, Kung YJ, Chen CS, et al. Allergic conjunctivitis-induced retinal inflammation promotes myopia progression. EBioMedicine 2018; 28: 274-86.
7. Singhal D, Sahay P, Maharana PK, et al. Vernal keratoconjunctivitis. Survey Ophthalmol 2019; 64: 289-311.
8. Fauquert JL. Diagnosing and managing allergic conjunctivitis in childhood: the allergist's perspective. Pediatr Allergy Immunol 2019; 30: 405-14.
9. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy 2018; 73: 765-98.
10. Kafashan HA, Khosravi AR, Alyasin S, et al. Airborne pollens and their association with meteorological parameters in the atmosphere of Shiraz, Southwest Iran. Iran J Allergy Asthma Immunol 2021; 20: 294-302.
11. Norris MR, Khaimov M, Bielory L. Use of allergen immunotherapy for treatment of allergic conjunctivitis. Curr Opin Allergy Clin Immunol 2020; 20: 609-15.
12. Ronconi CS, Issaho DC, Ejzenbaum F, et al. Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis. Arq Brasil Oftalmol 2021; 85: 415-25.
13. Vazirani J, Shukla S, Chhawchharia R, et al. Allergic conjunctivitis in children: current understanding and future perspectives. Curr Opin Allergy Clin Immunol 2020; 20: 507-15.
14. Erdinest N, London N, Solomon A. Chemokines in allergic conjunctivitis. Curr Opin Allergy Clin Immunol 2020; 20: 516-27.
15. Kang MS, Lee J, Park SH, et al. Development of allergic conjunctivitis induced by Acanthamoeba excretory-secretory protein and the effect of resolvin D1 on treatment. Curr Eye Res 2021; 46: 1792-9.
16. Logan A, Pucker AD, Franklin Q, et al. Determining initial ocular comfort differences between 0.7% olopatadine and 0.035% ketotifen fumarate. Contact Lens and Anterior Eye. 2023;46(2). doi:10.1016/j.clae.2022.101769
17. Ul Abidin F, Sarfraz MH, Javaid H, et al. Therapeutic efficacy of topical olopatadine 0.1% versus ketotifen fumarate in allergic conjunctivitis. Pak Armed Forces Med J 2022; 72: 16-9.

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved

18. Mortemousque B, Bourcier T, Khairallah M, et al. Comparison of preservative-free ketotifen fumarate and preserved olopatadine hydrochloride eye drops in the treatment of moderate to severe seasonal allergic conjunctivitis. J Fr Ophtalmol. 2014;37(1):1-8. doi:10.1016/j.jfo.2013.02.007
19. Sah D, Pathak SK, Singh SD. Efficacy and tolerability comparison of olopatadine, ketotifen, and epinastine in seasonal allergic conjunctivitis: a prospective open-label comparative study. Int J Pharm Clin Res 2019; 14: 110-6.
20. Patel D, Sarala N, Datti NP. Topical Olopatadine Hydrochloride versus Ketotifen Fumarate for Allergic Conjunctivitis. J Ophthalmic Vis Res. 2018;13(2):119-123. doi:10.4103/jovr.jovr_85_17

Downloaded from The International Medical Journal of Opthalmology
Copyright © International Medical Journal Corp. Ltd. All rights reserved