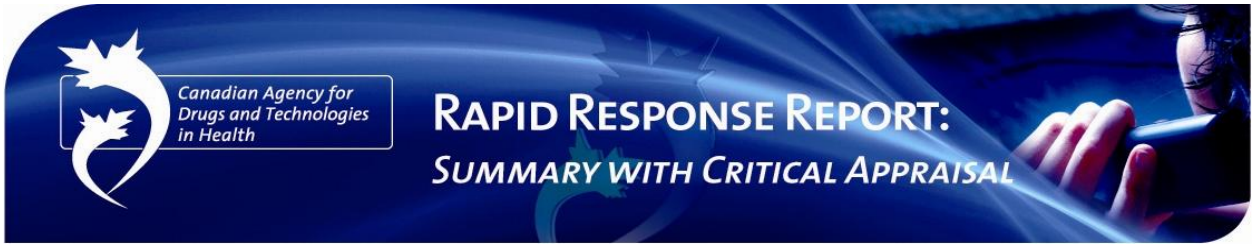

TITLE: Olopatadine for the Treatment of Allergic Conjunctivitis: A Review of the Clinical Efficacy, Safety, and Cost-Effectiveness

DATE: 23 March 2012

CONTEXT AND POLICY ISSUES

Allergic conjunctivitis is an inflammatory eye condition induced by allergens such as grass and tree pollen, mites, mold and animal dander.[1] Mast cells play an important role in ocular allergies. The first step in developing allergic conjunctivitis is exposure of the conjunctiva to environmental allergens followed by binding with specific IgE on conjunctival mast cells.[2] This results in conjunctival mast cell degranulation causing enhanced tear levels of histamine, tryptase, prostaglandins and leukotrienes.[2] It is estimated that allergic eye disease affects more than 20% of the population in industrialized countries and its prevalence is increasing worldwide.[2] Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most prevalent forms of ocular allergy.[3] The signs and symptoms of allergic conjunctivitis include itching, redness, tearing, eyelid swelling and chemosis.[4] Usually, allergic conjunctivitis does not pose a risk for the individual's vision but is an important health problem because it impacts the individual's quality of life, ability to function, and productivity.[1,5]

A number of anti-allergic agents are available for alleviating the signs and symptoms of allergic conjunctivitis. The mechanisms of action of the anti-allergic agents vary. Included among the anti-allergic agents for treatment of allergic conjunctivitis are olopatadine, ketotifen and cromolyn. Olopatadine and ketotifen both have a dual mechanism of action. They have histamine H_1- receptor antagonizing activity and mast-cell stabilizing ability.[2] Cromolyn is a mast cell stabilizer.[6]

The purpose of this review is to provide evidence on the efficacy, safety and cost-effectiveness of olopatadine, in comparison with ketotifen, cromolyn, or placebo to assist in the decision making with respect to these agents for the treatment of allergic conjunctivitis.

RESEARCH QUESTIONS

1. What is the clinical efficacy of olopatadine for the treatment of allergic conjunctivitis?

2. What is the clinical evidence on the safety of olopatadine for the treatment of allergic conjunctivitis?

3. What is the cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis?

KEY MESSAGE

Treatment of allergic conjunctivitis with olopatadine, ketotifen or cromolyn showed reductions in signs and symptom scores compared to baseline. Both olopatadine and ketotifen were well tolerated. The efficacy results of olopatadine compared to ketotifen were inconsistent. One study of limited quality showed that olopatadine and ketotifen have greater efficacy than cromolyn. There is limited amount of evidence on the cost-effectiveness of olopatadine compared with ketotifen or cromolyn.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, MEDLINE, EMBASE, The Cochrane Library (2012, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 1997 and February 23, 2012.

Selection Criteria and Methods

One reviewer screened articles retrieved from the literature search, based on titles and abstracts, selected potentially relevant articles for full-text review, and finally selected relevant articles according to the selection criteria in Table1.

Table 1: Selection Criteria

Population	Individuals with allergic conjunctivitis
Intervention	Olopatadine ophthalmic solution (Patanol and Pataday)
Comparator	Placebo, cromolyn (cromoglicic acid, cromoglycate), or ketotifen fumarate (ketotifen, zatidor)
Outcomes	Clinical benefits, clinical harms, cost-effectiveness
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials (RCT) and economic evaluations

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1; if they were published prior to 1997, duplicate publications of the same study, or included in a selected health technology assessment or systematic review; or if they were randomized controlled trials (RCTs) based on the Conjunctival Allergen Challenge (CAC) model. In the CAC model the participants are given the treatment agent and then challenged with an allergen.[7]

Critical Appraisal of Individual Studies

The quality assessment of the included RCTs and economic evaluations was based on the Down's and Black[8] and Drummond's[9] checklists respectively. The detailed results of the assessments are not provided. Instead, the strengths and limitations are summarized and presented. No systematic reviews were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 132 citations. Upon screening titles and abstracts, 105 articles were excluded and 27 potentially relevant articles were selected for full-text review. One potentially relevant article was identified from the grey literature. Of these 28 articles, 16 did not satisfy the inclusion criteria and were excluded. Of the 12 relevant articles, nine were RCTs[4,6,10-16] and three were economic evaluations.[5,17,18] No relevant health technology assessments or systematic reviews were identified. Details of the study selection process are outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included RCTs are summarized below and details are provided in Appendix 2.

Country of origin

Of the nine RCTs, three were conducted in Turkey[12,13,16], three in USA[4,14,15], one each in Italy[11] and Bangladesh[10] and one in multi-countries (Australia and six European countries).[6]

Population

Seven RCTs included patients with allergic conjunctivitis[6,10-13,15,16] and two included a mixed population with allergic conjunctivitis and rhinoconjunctivities[4,14]. Five RCTs included both adults and children,[10,12-14,16] two included only adults,[4,13], one did not state the age range of the included patients but the inclusion criteria mentioned ≥12 years,[15] and one did not state the age range.[11]

Intervention and comparators

Two RCTs compared olopatadine, ketotifen and placebo,[12,13] one compared olopatadine, ketotifen and cromolyn,[11] two compared olopatadine and ketotifen,[10,15] three compared olopatadine and placebo,[4,14,16] and one compared olopatadine and cromolyn.[6] Treatment

duration was two weeks in three studies,[10,12,16] three weeks in one study[15], four weeks in two studies,[11,13] 6 weeks in one study[6] and 10 weeks in two studies.[4,14]

Outcomes

All nine RCTs reported on changes in signs and symptoms of allergic conjunctivitis[4,6,10-16] and seven also reported on adverse events.[4,6,10,11,13-15]

Characteristics of the included economic evaluations are summarized below and described in Appendix 3.

Three economic evaluations were identified.[5,17,18] One was a cost-effectiveness analysis of five different agents used for the treatment of allergic conjunctivitis; included among these were olopatadine and ketotifen.[18] The study was conducted in Turkey. One was a cost minimization analysis and budget impact analysis of olopatadine compared with cromolyn from the perspective of the National Health Services (NHS) in the United Kingdom (UK).[17] One was a cost effectiveness comparison of three agents used for the treatment of allergic conjunctivitis; included among these were olopatadine and cromolyn.[5] The data used in this study was from seven European countries.

Summary of Critical Appraisal

All nine RCTs[4,6,10-16] clearly stated the objective and described the patient characteristics and interventions. Of the nine studies seven were double-blinded,[4,6,10,12-15] one was single-blinded[11] and blinding was not mentioned in one.[16] Two studies did not mention power calculations.[14,15] For all the studies the degree of compliance with drug use was unclear. External validity was limited for all studies; it was unclear if the study participants were representative of the majority of patients.

Two economic studies[17,18] clearly stated the objective, the patient population and interventions. For both studies, the analyses was based on the findings from a single RCT and quality of life, patient preferences or productivity loss were not considered in the analyses. One study[5] reported few methodological details, hence a critical appraisal was not possible.

Strengths and limitations of individual studies are provided in Appendix 4.

Summary of Findings

The overall findings are summarized below and findings from the individual clinical studies and economic studies are provided in Appendix 5 and 6 respectively.

<u>What is the clinical efficacy of olopatadine for the treatment of allergic conjunctivitis?</u>

One study[12] found no statistically significant differences between treatments with olopatadine and ketotifen for reduction in signs and symptoms of allergic conjunctivitis. One study[13] found no significant differences between olopatadine and ketotifen with respect to mean scores for tearing, itching, redness, eyelid swelling or chemosis at any time point. Two studies[10,15] showed that compared to ketotifen, olopatadine had a significantly greater effect in controlling itching and hyperemia. Compared to ketotifen, olopatadine demonstrated a greater effect in controlling tearing in one study[10] and no significant difference in effect in another study.[15]

One study[11] showed that olopatadine, ketotifen and cromolyn produced statistically significant reduction in mean scores for signs and symptoms compared to baseline ($P < 0.0001$). In this study[11] the percentages of patients showing 75% or more improvement of signs and symptoms at week 4 was highest for ketotifen, followed by olopatadine and cromolyn (signs: 84%, 50% and 43%; symptoms: 87%, 79% and 61% respectively). The percentages of patients showing at least 50% improvement of signs at week 4 was similar for ketotifen, olopatadine and cromolyn (97%, 92% and 100% respectively).[11] The percentages of patients showing at least 50% improvement of symptoms at week 4 was highest for ketotifen, followed by olopatadine and cromolyn (100%, 88% and 87% respectively).[11]

One study[6] showed that on day 42, the decreases in itching, redness, chemosis and eye swelling from baseline values were greater with olopatadine (range: 67.5% to 76.7%) than with cromolyn (range: 53.0% to 74.8%). At day 42, olopatadine demonstrated statistically significant reductions in itching and redness, when compared with cromolyn ($P < 0.05$).

Five studies[4,12-14,16] showed a statistically significant reduction in itching with olopatadine compared to placebo. Two studies[12,14] showed statistically significant reductions in redness with olopatadine compared to placebo. Two studies[12,13] showed statistically significant reductions in tearing with olopatadine compared to placebo, and one study[4] showed statistically significant reduction at one time point (day 14), but at other time points the change was not statistically significant. Reduction in eyelid swelling with olopatadine, in comparison to placebo, was statistically significant in one study[12] but not so in another study.[4]

For studies[4,6,11,14,16] that reported data at multiple time points, some representative time points are included in Appendix 5.

What is the clinical evidence on the safety of olopatadine for the treatment of allergic conjunctivitis?

Two studies[4,14] comparing olopatadine with placebo, reported that olopatadine was well tolerated. Three studies[10,12,15] mentioned that both olopatadine and ketotifen were well tolerated. One study[13] comparing olopatadine, ketotifen and placebo found no occurrences of adverse events in any group. One study[11] reported that olopatadine and ketotifen produced negligible discomfort at instillation. One study[16] did not report on adverse events.

In one study[6] the number of treatment related ocular adverse events was four in the olopatadine group and six in the cromolyn group. No patients discontinued the study in the olopatadine group. Two patients in the cromolyn group had to be withdrawn due to symptoms that coincided with the instillation of the drug.

Details of individual study findings can be found in Appendix 5.

What is the cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis?

A cost-effectiveness analysis[18] performed using clinical effectiveness and cost data from Turkey showed that the lowest cost per one point reduction in estimated symptom score (ESS) was obtained for olopatadine (US$ 34.14) followed by ketotifen (US$ 34.72).

A cost-minimization analysis[17] showed that for the NHS in UK the healthcare cost for treatment of SAC over a period of 4 months was estimated to be £92 (95% confidence interval [CI]: £46 to

£150) with olopatadine compared with £109 (95% CI: £65 to £166) with branded cromoglycate and £95 (95% CI: £51 to £152) with generic cromoglycate. The cost difference was mainly due to fewer repeat GP visits among olopatadine treated patients. There is some uncertainty in the findings as the model used was very sensitive to changes in success rate and number of repeat general practitioner (GP) visits. The authors reported that in the UK, olopatadine and cromoglycate accounted for 47% (46.4% for cromoglycate and 0.4% for olopatadine) of all prescriptions for SAC in primary care. The budget impact analysis[17] showed that with this distribution the estimated cost for managing 47% of SAC patients was £386 to £526 million, over four months. If, however, all 47% of the SAC patients were prescribed olopatadine, the corresponding estimated cost would be £396 to £525 million and switching patients to olopatadine would be expected to free up health care resources.

One study,[5] comparing cost-effectiveness of olopatadine with cromolyn showed that with olopatadine the cost savings ranged from €7.37 in Norway to €10.97 in Sweden. This study report contained very little detail about the analysis.

Details of individual study findings can be found in Appendix 6.

Limitations

None of the studies were conducted in Canada. Hence the applicability of the findings to the Canadian setting is uncertain. The studies were conducted in various countries, so there could be some confounding as the environmental conditions, in particular the amount and type of specific allergens, could be different. The extent of compliance with the medication was uncertain. Most of the clinical studies were of relatively small sample size. In six of the nine clinical studies there were less than 50 patients in each treatment arm. Two studies included a mixed population (allergic conjunctivitis and rhinoconjunctivitis); the percentage for each category was not specified. Only one study compared all three drugs olopatadine, ketotifen and cromolyn and it was single-blinded. There was limited amount of evidence available on the cost-effectiveness of these three agents. None of the economic evaluations included all the three agents of interest.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In conclusion all the active agents (olopatadine, ketotifen and cromolyn) investigated in this review were found to be more efficacious than placebo. There were inconsistencies in the efficacy results of olopatadine compared to ketotifen. Both olopatadine and ketotifen were better than placebo in relieving signs and symptoms of allergic conjunctivitis and were well tolerated. A single study of limited quality showed that olopatadine and ketotifen have greater efficacy than cromolyn. There was a suggestion of some cost savings with olopatadine compared with ketotifen. There appeared to be some cost savings with olopatadine compared to cromolyn; the main driver being reduction in repeat GP visits with olopatadine treatment. However these results should be viewed with caution as the evidence on the cost-effectiveness of olopatadine compared with ketotifen or cromolyn is limited, and economic evaluations in other countries may not be generalizable to the Canadian healthcare system.

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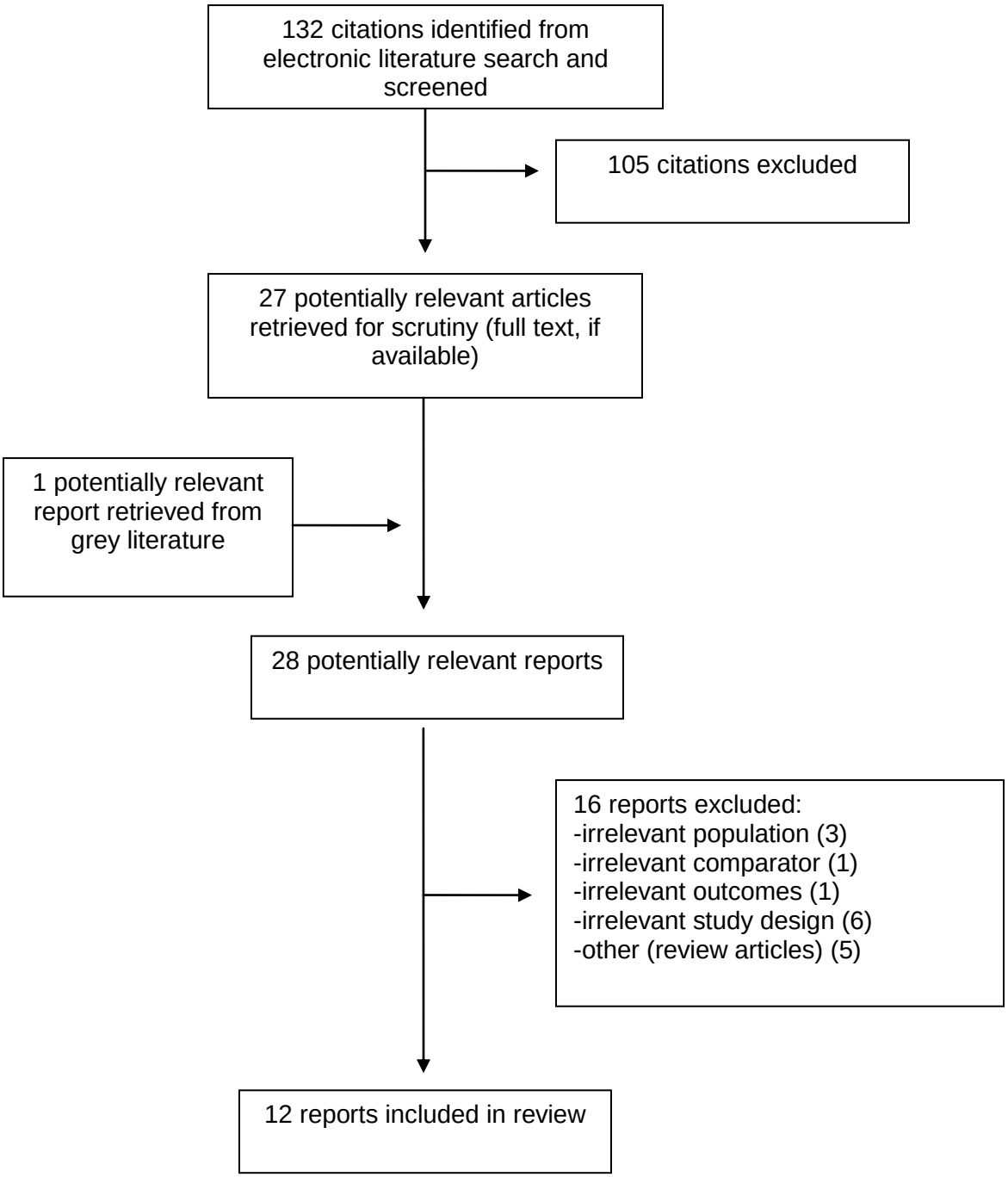
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study design, Length of Follow-up	Patient Characteristics, Sample size (N)	Intervention	Comparator	Clinical Outcomes
Sarker,[10] 2011, Bangladesh	Randomized, (stratified randomization based on age and sex), double blind; 2 weeks	Patients with diagnosis of allergic conjunctivitis, N=92 (83 completed the study), Age range=12-50 y Olopatadine: N=40, Age= 28±11 y M =18 (45%), Ketotifen: N=43, Age= 28±12 y M=18 (42%)	Olopatadine hydrochloride (0.1%); every twelve hour	Ketotifen fumarate (0.025%); every twelve hours	Hyperemia, tearing, itching and photophobia
Figus,[11] 2010, Italy	Randomized, single-blinded; 4 weeks	Patients with active allergic conjunctivitis, N=240 Olopatadine: N=30, Age= 37±20 y M/F=15/15 Cromolyn: N=30, Age= 37±15 y M/F=15/15 Ketotifen: N=30, Age= 39±15 y M/F=12/18 Other agents (not of interest for this review): N=150	Olopatadine hydrochloride (0.1%); twice daily	Cromolyn sodium (4%) /chloropheniramine maleate(0.2%), Ketotifen fumarate (0.05%), Other drugs (not of interest for this review), twice daily	Improvement in signs and symptoms, Discomfort
Borazan,[12] 2009, Turkey	Randomized, (randomly assigned to receive one of five treatments in one eye and	Patients with seasonal allergic conjunctivitis, N= 100, Age range= 10-55 y	Olopatadine (0.1%); BID	Placebo (vehicle ophthalmic solution), ketotifen, other agents (not of interest for this review); BID	Itching, redness, tearing, eyelid swelling and chemosis

First Author, Publication Year, Country	Study design, Length of Follow-up	Patient Characteristics, Sample size (N)	Intervention	Comparator	Clinical Outcomes
	placebo in other eye), double-blinded; 2 weeks	Olopatadine: N= 20 Age= 26.9±10.6 y M/F=10/10 Ketotifen: N=20, Age= 26.1±7.9 y M/F=10/10 Other agents (not of interest for this review): N=60			
Avunduk,[13] 2005, Turkey	RCT, double-blinded; 30 day	Patients with seasonal allergic conjunctivitis, N= 49, (39 completed the study), Age= 18-61 y, M/F= 20/19 Olopatadine: N= 16 (13 completed the study), Ketotifen: N= 16 (12 completed the study), Placebo (ATS): N= 17 (14 completed the study)	Olopatadine, (0.1%); BID	Placebo (ATS), ketotifen fumarate (0.025%); BID	Itching, redness, tearing, eyelid swelling, chemosis and adverse events
Abelson,[14] 2004, USA	RCT, double-blinded; 10 weeks	Patients with seasonal allergic conjunctivitis and rhinoconjunctivitis, N= 260, Age range= 11-75 y Olopatadine: N= 129, Age (mean±SD)= 36.8±14.8 y, M/F= 61/68; Placebo: N= 131,	Olopatadine (0.2%); once daily	Placebo (olopatadine vehicle); once daily	Itching, redness, and adverse events

First Author, Publication Year, Country	Study design, Length of Follow-up	Patient Characteristics, Sample size (N)	Intervention	Comparator	Clinical Outcomes
		Age (mean±SD)= 36.0±13.2 y, M/F= 62/69			
Abelson,[4] 2003, USA	RCT, double-blinded; 10 weeks	Patients with seasonal allergic conjunctivitis and rhinoconjunctivitis, N= 131, Age ≥18 y Olopatadine: N= 64, Age (mean±SD)= 38.53±11.61 y, M/F= 26/38; Placebo: N= 67, Age (mean±SD)= 38.16±11.31 y, M/F= 29/38	Olopatadine (0.1%); twice daily	Placebo (over-the-counter artificial tear product); twice daily	Itching, hyperemia, tearing, eyelid swelling, chemosis, and adverse events
Ganz, [15] 2003, USA	Randomized, double-blinded; 3 weeks	Patients with seasonal allergic conjunctivitis N= 66, Age ≥ 12 y (inclusion criteria) Olopatadine: N= 34, Age (mean±SD)= 35.2±14.4 y, M/F= 9/25; Ketotifen: N= 32, Age (mean±SD)= 37.47±16.8 y, M/F= 8/24	Olopatadine hydrochloride (0.1%); twice daily	Ketotifen fumarate (0.025%); twice daily	Itching, hyperemia, tearing, and adverse events
Yaylali,[16] 2003, Turkey	Randomized, (one eye with study drug and other eye with placebo); 2 weeks	Patients with seasonal allergic conjunctivitis N= 40, Age [mean (range)]= 19(15-25), M/F= 21/19	Olopatadine hydrochloride (0.1%), ketorolac (not of interest for this review); twice daily	Placebo; twice daily	Itching, hyperemia,
Katelaris,[6] 2002, Australia and six European countries	Randomized, double-blinded; 6 weeks	Patients with seasonal allergic conjunctivitis N= 185, Age range= 4-77	Olopatadine hydrochloride (0.1%);BID and placebo (olopatadine	Cromolyn sodium (2%); QID	Itching, redness, eyelid swelling, chemosis,

First Author, Publication Year, Country	Study design, Length of Follow-up	Patient Characteristics, Sample size (N)	Intervention	Comparator	Clinical Outcomes
		y Olopatadine: N=91, Age (mean±SD)= 33.0±19.38 y, M/F=51/40; Cromolyn: N=94, Age (mean±SD)= 36.8±20.91y, M/F=52/42;	vehicle); BID		and adverse events

ATS= artificial tear substitute, BID= two times a day, QID= four times a day, F= female, M= male, N= number of patients, SD=standard deviation, y = year

APPENDIX 3: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient population	Intervention(s)	Comments
Kockaya,[18] 2011, Turkey	Cost-effectiveness analysis	Patient sample in Turkey	Olopatadine, ketotifen, (other agents: fluorometholon, epinastine, emedastine; not of interest for this review)	Price list published by General Directorate of Pharmaceuticals and Pharmacy (04/09/2009) was used. Cost of physician visit was obtained from the Health Application Statement published in 2010 by the Social Security Institution. Exchange rate used: 1.5 Turkish Lira = 1 US$. Clinical effectiveness data was taken from one double-blinded randomized study conducted at a single center in Turkey.[12] For the pharmacoeconomic analysis, the mean of effectiveness data (including scores for signs and symptoms) was calculated to have one effectiveness data point termed as estimated symptom score (ESS) Sensitivity analysis was mentioned but details not provided.
Guest,[17] 2006, UK	Cost-minimization analysis from perspective of UK's National Health Service. (There was no evidence of any significant differences between	Patients with seasonal allergic conjunctivitis	Olopatadine; twice daily, branded or generic cromoglycate; four times a day	Time horizon = 4 weeks. Assumptions were made with respect to relevant resource use (such as numbers of repeat GP visits, monthly repeat prescriptions) Clinical effectiveness data was taken from one double-blinded randomized study conducted at multiple centers (Australia and 6 European countries) over 6 weeks.[6] For the economic analysis, the clinical efficacy data was extrapolated to 120 days A decision tree was constructed to simulate treatment with the three agents in a hypothetical cohort of patients with SAC.

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient population	Intervention(s)	Comments
	treatments with olopatadine and cromolyn with respect to duration of treatment and success rate after 42 days and 120 days of treatment. Hence a cost-minimization analysis was undertaken)			Probabilistic sensitivity analysis was conducted to examine the impact of varying probabilities, resource use values and unit costs.
Lafuma,[5] 2002, European countries	Cost-effectiveness comparison using European data	Patients with seasonal allergic conjunctivitis	Olopatadine, cromolyn, (others agent: levocobastine; not of interest for this review)	Limited study information reported

GP = general practitioner, SAC= seasonal allergic conjunctivitis

APPENDIX 4: Summary of Critical Appraisal

First Author, Publication Year, Country	Strengths	Limitations
Clinical studies		
Sarker,[10] 2011, Bangladesh	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. Description of double blinding provided • Power calculations performed • Withdrawals described • Adverse events reported	• Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Figus,[11] 2010, Italy	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, but single-blind study (patients were aware of their treatment). • Power calculations performed	• Single-blind study • Adverse events not reported • Withdrawals not described • Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Borazan,[12] 2009, Turkey	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. Description of double blinding provided • All patients completed the study	• Power calculation not reported • Adverse events not reported • Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Avunduk,[13] 2005, Turkey	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. Description of double blinding provided • Power calculations performed • Withdrawals described • Adverse events were reported	• Demographics of each group not reported separately. • Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Abelson,[14] 2004, USA	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. Description of double blinding	• A mixed population (allergic conjunctivitis or rhinoconjunctivitis % of each category not known) • Power calculation not mentioned. • Extent of compliance with drug use was unclear

First Author, Publication Year, Country	Strengths	Limitations
	provided • No patient discontinued the study due to adverse events • Adverse events were reported	• External validity limited,; uncertain as to whether study patients were representative of all patients
Abelson,[4] 2003, USA	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. Description of double blinding provided • Withdrawals described • Power calculations mentioned • Adverse events were reported	• A mixed population (allergic conjunctivitis or rhinoconjunctivitis % of each group not known. • Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Ganz,[15] 2003, USA	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. • All patients completed the study • Adverse events reported	• Description of double blinding not provided • Power calculation not mentioned • Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Yaylali,[16] 2003, Turkey	• Objectives were clearly stated • Interventions and outcomes were clearly described • Randomized study • All patients completed the study	• Demographics of each group not reported separately. • Blinding not mentioned • Power calculation not mentioned • Adverse events not reported • Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Katelaris,[6] 2002, Australia and six European countries	• Objectives were clearly stated • Patient characteristics, interventions and outcomes were clearly described • Randomized, double-blind study. Description of double blinding provided • Withdrawals described • Power calculations mentioned • Adverse events were reported	• Extent of compliance with drug use was unclear • External validity limited; uncertain as to whether study patients were representative of all patients
Economic studies		
Kockaya,[18] 2011, Turkey	• Objective, patient population and treatment options were clearly stated	• Analysis based on one clinical study • Details of analysis lacking

First Author, Publication Year, Country	Strengths	Limitations
	• The form of economic analysis undertaken was appropriate • Source of clinical efficacy data stated • Sensitivity analysis was conducted but details not provided	• No time horizon specified • Quality of life, improvements in general well-being and patient preferences were not included in the analysis
Guest,[17] 2006, UK	• Objective, patient population and treatment options were clearly stated • The form of economic analysis undertaken was appropriate • Source of clinical efficacy data stated • Time horizon was specified. • Sensitivity analysis was performed and details were provided	• Analysis based on one clinical study. • Assumptions made with respect to probability of success, resource use • Quality of life, improvements in general well-being and patient preferences were not included in the analysis
Lafuma,[5] 2002, European countries		Limited study information reported

APPENDIX 5: Summary of Individual Study Findings - Clinical

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td>Sarker,[10] 2011, Bangladesh</td><td>Difference in mean scores (mean ± SD) between baseline and week 2:

<table><tr><th></th><th>OHCL (0.1%)</th><th>KF (0.025%)</th><th>P-value</th></tr><tr><td>Itching</td><td>2.15 ± 0.80</td><td>1.30 ±0.56</td><td><0.001</td></tr><tr><td>Hyperemia</td><td>1.83 ± 0.71</td><td>1.23 ± 0.87</td><td>0.001</td></tr><tr><td>Tearing</td><td>1.10 ±0.50</td><td>0.67 ± 0.47</td><td><0.001</td></tr><tr><td>Photophobia</td><td>1.23 ± 0.58</td><td>1.09 ± 0.61</td><td>0.315</td></tr></table>
Both OHCL and KF were well tolerated; no marked adverse events were observed. Drug related adverse events were reported in 30% of patients treated with KF but they were minor and transient.</td><td>"0.1%OHCL is more effective and safer (in the short term) than 0.025% KF in the management of AC" (p.550)</td></tr>
<tr><td>Figus,[11] 2010, Italy</td><td>Mean scores (mean± SD) for signs at the beginning and end of the study (p-value for comparison of start and end of study)

<table><tr><th></th><th>Start</th><th>End</th><th>P-value</th></tr><tr><td>OHCL</td><td>14.6± 4.0</td><td>0.5± 1.6</td><td><0.0001</td></tr><tr><td>KF</td><td>20.4± 7.6</td><td>0.4± 1.1</td><td><0.0001</td></tr><tr><td>CR</td><td>19.2± 5.4</td><td>0.8± 1.6</td><td><0.0001</td></tr></table>
Mean scores (mean± SD) for symptoms at the beginning and end of the study (P-value for comparison of start and end of study)

<table><tr><th></th><th>Start</th><th>End</th><th>P-value</th></tr><tr><td>OHCL</td><td>29.2± 5.6</td><td>1.8± 1.3</td><td><0.0001</td></tr><tr><td>KF</td><td>33.9± 9.8</td><td>1.7± 2.1</td><td><0.0001</td></tr><tr><td>CR</td><td>33.0± 6.8</td><td>2.2± 2.0</td><td><0.0001</td></tr></table>
Percentage* of patients showing at least 50% improvement of symptoms at 1 week and 4 weeks respectively were:
Olopatadine: 0.79, 0.88
Cromolyn: 0.61, 0.87</td><td>"The topical ophthalmic solutions provided effective management of allergic ocular signs and symptoms" (p. 817)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>Ketotifen: 0.84, 1.00

Percentage* of patients showing at least 50% improvement of signs at 1 week and 4 weeks respectively were:
Olopatadine: 0.92, 0.92,
Cromolyn: 0.91, 1.00,
Ketotifen: 0.84, 0.97

Percentage* of patients showing 75% or more improvement of symptoms at 1 week and 4 weeks respectively were:
Olopatadine: 0.33, 0.79,
Cromolyn: 0.04, 0.61,
Ketotifen: 0.26, 0.87

Percentage* of patients showing 75% or more improvement of signs at 1 week and 4 weeks respectively were:
Olopatadine: 0.17, 0.50,
Cromolyn: 0.00, 0.43,
Ketotifen: 0.06, 0.84

Mean score (mean±SD) of discomfort after instillation:
Olopatadine: 1.9± 1.9,
Cromolyn: 2.2± 1.6,
Ketotifen: 1.6± 1.5

Olopatadine and ketotifen produced negligible discomfort at instillation</td><td></td></tr>
<tr><td>Borazan,[12] 2009, Turkey</td><td>Score [median (range)] for ocular signs and symptoms at different time points:

Itching
<table>
<tr><th></th><th>OHCL</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Baseline</td><td>2.60 (2-3)</td><td>2.50 (2-3)</td><td>0.376</td></tr>
<tr><td>Week 1</td><td>0.84 (0-2)</td><td>2.32 (1-3)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.60 (0-1)</td><td>2.21 (1-3)</td><td><0.001</td></tr>
<tr><th></th><th>KF</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Baseline</td><td>2.70 (2-3)</td><td>2.65 (2-3)</td><td>0.50</td></tr>
<tr><td>Week 1</td><td>0.94 (0-2)</td><td>2.45 (2-3)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.80 (0-1)</td><td>2.39 (1-3)</td><td><0.001</td></tr>
</table></td><td>"In patients with SAC, olopatadine, ketotifen … are more efficacious than fluorometholone acetate in preventing itching and redness. All the antiallergic agents gave similar results in terms of reducing tearing, chemosis and eyelid swelling" (p. 549)
(In addition to the agents of interest for this review, the authors had investigated other agents as well and concluded)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
Redness
<table>
<tr><td></td><td>OHCL</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>2.60 (2-3)</td><td>2.60 (2-3)</td><td>0.626</td></tr>
<tr><td>Week 1</td><td>0.95 (0-1)</td><td>2.55 (2-3)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.80 (0-1)</td><td>2.47 (1-3)</td><td><0.001</td></tr>
<tr><td></td><td>KF</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>2.75 (2-3)</td><td>2.70 (2-3)</td><td>0.50</td></tr>
<tr><td>Week 1</td><td>1.10 (1-2)</td><td>2.65 (2-3)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.95 (0-2)</td><td>2.60 (2-3)</td><td><0.001</td></tr>
</table>
Tearing
<table>
<tr><td></td><td>OHCL</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>1.55 (1-2)</td><td>1.55 (1-2)</td><td>0.624</td></tr>
<tr><td>Week 1</td><td>0.60 (0-1)</td><td>1.35 (1-2)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.45 (0-1)</td><td>1.35 (1-2)</td><td><0.001</td></tr>
<tr><td></td><td>KF</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>1.45 (1-2)</td><td>1.45 (1-2)</td><td>0.624</td></tr>
<tr><td>Week 1</td><td>0.50 (0-1)</td><td>1.25 (1-2)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.45 (0-1)</td><td>1.15 (1-2)</td><td><0.001</td></tr>
</table>
Eyelid swelling
<table>
<tr><td></td><td>OHCL</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>1.00 (0-2)</td><td>1.00 (0-2)</td><td>1.000</td></tr>
<tr><td>Week 1</td><td>0.30 (0-1)</td><td>0.95 (0-2)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.25 (0-1)</td><td>0.89 (0-2)</td><td><0.001</td></tr>
<tr><td></td><td>KF</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>1.05 (1-2)</td><td>1.10 (1-2)</td><td>0.50</td></tr>
<tr><td>Week 1</td><td>0.35 (0-1)</td><td>1.00 (0-2)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.30 (0-2)</td><td>0.95 (0-1)</td><td><0.001</td></tr>
</table>
Chemosis
<table>
<tr><td></td><td>OHCL</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>1.15 (1-2)</td><td>1.10 (1-2)</td><td>0.50</td></tr>
<tr><td>Week 1</td><td>0.30 (0-1)</td><td>0.95 (0-1)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.20</td><td>0.90</td><td><0.001</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>(0-1)</td><td>(0-2)</td><td></td></tr>
<tr><td></td><td>KF</td><td>Plb</td><td>P-value</td></tr>
<tr><td>Baseline</td><td>1.20 (1-2)</td><td>1.10 (1-2)</td><td>0.331</td></tr>
<tr><td>Week 1</td><td>0.40 (0-1)</td><td>1.00 (1-1)</td><td><0.001</td></tr>
<tr><td>Week 2</td><td>0.25 (0-1)</td><td>0.95 (0-1)</td><td><0.001</td></tr>
</table>

The authors mentioned that the olopatadine, ketotifen and the other agents investigated were more efficacious than placebo in providing relief of signs and symptoms of SAC.

Both olopatadine and ketotifen were well tolerated</td><td></td></tr>
<tr><td>Avunduk,[13] 2005, Turkey</td><td>Score (mean) for ocular signs and symptoms at different time points (P-values are for active agent compared to placebo):

Itching
<table>
<tr><td></td><td>OHCL</td><td>KF</td><td>Plb (ATS)</td></tr>
<tr><td>Day 0</td><td>1.84</td><td>2.08</td><td>2.00</td></tr>
<tr><td>Day 15</td><td>0.76 (P= 0.032)</td><td>1.08 (P= 0.042)</td><td>1.85</td></tr>
<tr><td>Day 30</td><td>0.76 (P= 0.026)</td><td>0.75 (P= 0.028)</td><td>1.71</td></tr>
</table>
Tearing
<table>
<tr><td></td><td>OHCL</td><td>KF</td><td>Plb (ATS)</td></tr>
<tr><td>Day 0</td><td>1.07</td><td>1.25</td><td>1.85</td></tr>
<tr><td>Day 15</td><td>0.17 (P= 0.038)</td><td>0.30 (P= 0.017)</td><td>1.07</td></tr>
<tr><td>Day 30</td><td>0.17 (P=NR)</td><td>0.38 (P= 0.02)</td><td>1.00</td></tr>
</table>
For redness, eyelid swelling or chemosis there were no significant within-group or between-group differences at any time point.

No adverse events were observed.</td><td>"Both active treatments were more efficacious compared with ATS and were well tolerated" (p.1392)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td>Abelson,[14] 2004, USA</td><td>Frequency of itching score >2:
Olopatadine (0.2%): 21%,
Placebo: 47%
(P < 0.001)

Frequency of redness score > 2:
Olopatadine (0.2%): 14%,
Placebo: 31%
(P < 0.003)

Severity of itching score >2:
Olopatadine (0.2%): 9%,
Placebo: 18%
(P < 0.049)

Severity of redness score >2:
Olopatadine (0.2%): 7%,
Placebo: 15%
(P < 0.048)

There were no treatment-related serious adverse events.

Overall adverse events (related or unrelated to treatment):
Olopatadine (0.2%): 32%,
Placebo: 26%</td><td>"In the patients enrolled in this trial, olopatadine 0.2% appeared to be effective and well tolerated when administered once daily for the treatment of the ocular signs and symptoms of allergic conjunctivitis or rhinoconjuntivitis" (p.1247)</td></tr>
<tr><td>Abelson,[4] 2003, USA</td><td>Mean scores:
Itching
<table>
<tr><th></th><th>Olopa-tadine (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>1.59</td><td>1.70</td><td>NR</td></tr>
<tr><td>Day 7</td><td>1.06</td><td>1.58</td><td><0.010</td></tr>
<tr><td>Day 14</td><td>1.19</td><td>1.60</td><td><0.041</td></tr>
<tr><td>Day 28</td><td>1.02</td><td>1.16</td><td>NS</td></tr>
<tr><td>Day 70</td><td>0.55</td><td>1.00</td><td><0.024</td></tr>
</table>
Total hyperemia
<table>
<tr><th></th><th>Olopa-tadine (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>0.39</td><td>0.39</td><td>NR</td></tr>
<tr><td>Day 7</td><td>0.62</td><td>0.69</td><td>NS</td></tr>
<tr><td>Day 14</td><td>0.63</td><td>0.69</td><td>NS</td></tr>
<tr><td>Day 28</td><td>0.53</td><td>0.80</td><td><0.013</td></tr>
<tr><td>Day 70</td><td>0.48</td><td>0.64</td><td>NS</td></tr>
</table></td><td>"In the population studied, 0.1% ophthalmic solution controlled ocular and nasal symptoms of allergic conjunctivitis and rhinoconjunctivitis and was well tolerated when administered twice daily for 10 weeks." (p. 945)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
Tearing
<table>
<tr><th></th><th>Olopa-tadine (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>1.28</td><td>1.18</td><td>NR</td></tr>
<tr><td>Day 7</td><td>0.73</td><td>1.00</td><td>NS</td></tr>
<tr><td>Day 14</td><td>0.61</td><td>1.01</td><td><0.020</td></tr>
<tr><td>Day 28</td><td>0.64</td><td>0.82</td><td>NS</td></tr>
<tr><td>Day 70</td><td>0.50</td><td>0.63</td><td>NS</td></tr>
</table>
Eyelid swelling
<table>
<tr><th></th><th>Olopa-tadine (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>0.01</td><td>0.01</td><td>NR</td></tr>
<tr><td>Day 7</td><td>0.03</td><td>0.04</td><td>NS</td></tr>
<tr><td>Day 14</td><td>0.05</td><td>0.07</td><td>NS</td></tr>
<tr><td>Day 28</td><td>0.01</td><td>0.03</td><td>NS</td></tr>
<tr><td>Day 70</td><td>0.02</td><td>0.05</td><td>NS</td></tr>
</table>
Chemosis
<table>
<tr><th></th><th>Olopa-tadine (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>0.08</td><td>0.05</td><td>NR</td></tr>
<tr><td>Day 7</td><td>0.13</td><td>0.19</td><td>NS</td></tr>
<tr><td>Day 14</td><td>0.24</td><td>0.16</td><td>NS</td></tr>
<tr><td>Day 28</td><td>0.04</td><td>0.15</td><td><0.031</td></tr>
<tr><td>Day 70</td><td>0.09</td><td>0.12</td><td>NS</td></tr>
</table>
On day 7, compared to placebo, olopatadine showed significantly greater reductions in rhinorrhea, sneezing, and post-nasal drip (P <0.043, P < 0.021, P < 0.015, respectively).

Adverse events were non-serious, mild and infrequent
</td><td></td></tr>
<tr><td>Ganz, [15] 2003, USA</td><td>
Mean scores (mean± SD); (score for the right eye is reported first followed by that of the left eye):
Itching
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>KF (0.025%)</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>2.353± 0.399</td><td>2.334± 0.410</td><td>0.951</td></tr>
<tr><td></td><td>2.353± 0.399</td><td>2.359± 0.406</td><td>0.966</td></tr>
<tr><td>Day 5</td><td>0.652± 0.897</td><td>0.234± 0.458</td><td>0.007</td></tr>
<tr><td></td><td>0.621± 0.884</td><td>0.219± 0.457</td><td>0.008</td></tr>
</table>
</td><td>"In a 3-week study under actual-use conditions during fall allergy season, ketotifen fumarate 0.025% ophthalmic solution was superior to olopatadine hydrochloride 0.1% ophthalmic solution in relieving the signs and symptoms of allergic conjunctivitis. No differences in comfort, tolerability, or safety were noted between groups over the course of the study" (p. 90)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
<table>
<tr><td>Day 21</td><td>0.823± 0.909</td><td>0.156± 0.296</td><td><0.0001</td></tr>
<tr><td></td><td>0.839± 0.916</td><td>0.156± 0.296</td><td><0.0001</td></tr>
</table>

Conjunctival hyperemia
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>KF (0.025%)</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>0.177± 0.424</td><td>0.322± 0.564</td><td>0.196</td></tr>
<tr><td></td><td>0.206± 0.566</td><td>0.328± 0.562</td><td>0.296</td></tr>
<tr><td>Day 5</td><td>0.227± 0.397</td><td>0.016± 0.088</td><td>0.048</td></tr>
<tr><td></td><td>0.273± 0.435</td><td>0.016± 0.088</td><td>0.032</td></tr>
<tr><td>Day 21</td><td>0.339± 0.651</td><td>0.016± 0.088</td><td>0.003</td></tr>
<tr><td></td><td>0.387± 0.715</td><td>0.016± 0.088</td><td>0.003</td></tr>
</table>

Tearing
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>KF (0.025%)</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>0.676± 0.967</td><td>0.594± 0.827</td><td>0.595</td></tr>
<tr><td></td><td>0.662± 0.983</td><td>0.547± 0.846</td><td>0.463</td></tr>
<tr><td>Day 5</td><td>0.227± 0.588</td><td>0.156± 0.390</td><td>0.652</td></tr>
<tr><td></td><td>0.212± 0.587</td><td>0.125± 0.381</td><td>0.583</td></tr>
<tr><td>Day 21</td><td>0.177± 0.439</td><td>0.047± 0.148</td><td>0.409</td></tr>
<tr><td></td><td>0.177± 0.439</td><td>0.032± 0.148</td><td>0.356</td></tr>
</table>

With respect to comfort level there was no significant difference between the two treatments.

One patient in the OHLC group had severe discomfort in the eye and was withdrawn from the trial. Burning and stinging were reported by 3 patients in the OHCL group and 2 patients in the KF group. Headache was reported by 2 patients in the OHCL group and 1 patient in the KF group.</td><td></td></tr>
<tr><td>Yaylali,[16] 2003, Turkey</td><td>Mean scores (mean ± SD):
Itching</td><td>Compared to placebo, olopatadine demonstrated greater improvement of signs and symptoms of SAC.</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>2.3 ± 1.1</td><td>2.2 ± 1.1</td><td>0.76</td></tr>
<tr><td>Day 2</td><td>0.5 ± 0.2</td><td>1.1 ± 1.2</td><td>0.0001</td></tr>
<tr><td>Day 7</td><td>0</td><td>1 ± 1.1</td><td>0.0001</td></tr>
<tr><td>Day 15</td><td>0</td><td>1 ± 1.1</td><td>0.0001</td></tr>
</table>
Hyperemia
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>Plb</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>2.0 ± 0.7</td><td>2.1 ± 0.7</td><td>0.664</td></tr>
<tr><td>Day 2</td><td>0.7 ± 0.5</td><td>1.6 ± 0.5</td><td>0.0001</td></tr>
<tr><td>Day 7</td><td>0.4 ± 0.5</td><td>1.4 ± 0.6</td><td>0.0001</td></tr>
<tr><td>Day 15</td><td>0.3 ± 0.4</td><td>1.3 ± 0.7</td><td>0.0001</td></tr>
</table>
</td><td></td></tr>
<tr><td>Katelaris,[6] 2002, Australia and six European countries</td><td>
Mean score:
Itching
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>CR</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>4.00</td><td>4.00</td><td>NR</td></tr>
<tr><td>Day 3</td><td>2.75</td><td>3.04</td><td>NR</td></tr>
<tr><td>Day 14</td><td>1.93</td><td>2.42</td><td><0.05</td></tr>
<tr><td>Day 42</td><td>1.30</td><td>1.88</td><td><0.05</td></tr>
</table>
Redness
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>CR</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>2.51</td><td>2.51</td><td>NR</td></tr>
<tr><td>Day 3</td><td>1.63</td><td>1.75</td><td>NR</td></tr>
<tr><td>Day 14</td><td>0.98</td><td>1.15</td><td>NR</td></tr>
<tr><td>Day 42</td><td>0.69</td><td>0.94</td><td><0.05</td></tr>
</table>
Eyelid swelling
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>CR</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>1.03</td><td>1.03</td><td>NR</td></tr>
<tr><td>Day 3</td><td>0.61</td><td>0.66</td><td>NR</td></tr>
<tr><td>Day 14</td><td>0.34</td><td>0.37</td><td>NR</td></tr>
<tr><td>Day 42</td><td>0.24</td><td>0.26</td><td>NR</td></tr>
</table>
Chemosis
<table>
<tr><th></th><th>OHCL (0.1%)</th><th>CR</th><th>P-value</th></tr>
<tr><td>Day 0</td><td>1.08</td><td>0.95</td><td>NR</td></tr>
<tr><td>Day 3</td><td>0.68</td><td>0.69</td><td>NR</td></tr>
<tr><td>Day 14</td><td>0.36</td><td>0.45</td><td>NR</td></tr>
<tr><td>Day 42</td><td>0.28</td><td>0.28</td><td>NR</td></tr>
</table>
</td><td>"Six weeks' instillation of olopatadine 0.1% ophthalmic solution BID had a significantly greater effect on the ocular signs and symptoms of allergic conjunctivitis compared with six weeks' instillation of cromolyn 2% ophthalmic solution QID. Both treatments were well tolerated by patients in all age groups; however, olopatadine appeared to have better local tolerability in children aged <11 years." (p. 1562)</td></tr>
</table>

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	In the olopatadine group, 4 patients had 4 treatment-related ocular adverse events (discharge, stinging and blurred vision). No serious adverse events occurred and no patients discontinued from the study. In the cromolyn group, 5 patients had 6 treatment-related ocular adverse events (dry eye, stinging, pruritus, and lacrimation). Two patients had to be withdrawn from the study due to symptoms that coincided with instillation of cromolyn.	

AC= allergic conjunctivitis, BID= two times a day, CR= cromolyn, KF= ketotifen fumarate, OHCL= olopatadine hydrochloride, NR= not reported, NS= not significant, Plb= placebo, QID= four times a day, SD= standard deviation, SE= standard error, SAC= seasonal allergic conjunctivitis, vs= versus

*Values are as reported by the authors

APPENDIX 6: Summary of Individual Study Findings - Economic

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td>Kockaya,[18] 2011, Turkey</td><td>The study included five drugs; only results of the two drugs of interest for this review are presented here.
Olopatadine (Patanol [0.1%]): US$ 9.2
Ketotifen (Zaditen [0.025%]): US$ 8.56

<table><tr><th>Drug</th><th>Cost of treatment (US$)</th><th>Absolute decrease in ESS</th><th>Cost per one point decrease in ESS (US$)</th></tr><tr><td>Olopatadine</td><td>44.05</td><td>1.29</td><td>34.14</td></tr><tr><td>Ketotifen</td><td>43.41</td><td>1.25</td><td>34.72</td></tr></table>
Lowest cost for 1% reduction in ESS was demonstrated by olopatadine (US$ 0.64) followed by ketotifen (US$ 0.66)</td><td>"It was concluded that olopatadine has the highest mean absolute and percentage decrease in estimated symptom score. Because of these olopatadine has the lowest cost for one point or 1% decrease estimated symptom score. Olopatadine was followed by ketotifen" (p. 75)</td></tr>
<tr><td>Guest,[17] 2006, UK</td><td>Cost minimization analysis:
Healthcare cost for treatment of SAC over a period of 4 months in UK is estimated to be £92 (95% CI: £46, £150) with olopatadine compared with £109 (95% CI: £65, £166) with branded cromoglycate and £95 (£51, £152) with generic cromoglycate. The cost difference was mainly due to fewer GP visits among olopatadine treated patients.

There is some uncertainty in the results as the model was very sensitive to the probabilities of success at different time points, numbers of repeat GP visits among successfully-treated patients and among patients who switched treatment after 14 days.

Budget impact analysis:
Considering the percentages of SAC patients receiving branded cromoglycate, generic cromoglycate and olopatadine were 38%, 9% and <1% respectively, the estimated cost to NHS for managing these patients was £386 to £526 million, over 4 months. If however all these patients received olopatadine, the cost to NHS was estimated as £396 to £525. If all 47% SAC patients were treated with olopatadine the number of repeat GP visits was expected to be 6.8 to 8.7 million and if all were treated with cromoglycate the number of repeat GP visits was expected to be 7.9 to 10.5 million over a 4 month period. .</td><td>"Use of olopatadine instead of branded or generic cromoglycate affords an economic benefit to NHS. Hence, within the limitations of the model, olopatadine is the preferred first-line treatment for use in SAC sufferers, since it is expected to lead to lower GP visits, thereby releasing healthcare resources for alternative use." (p. 1777)</td></tr>
</table>

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	Hence switching patients to olopatadine would be expected to free up health care resources.	
Lafuma,[5] 2002, European countries	Cost-effectiveness comparison of olopatadine with cromolyn showed that with olopatadine the cost savings were €7.37 in Norway, €7.49 in the Netherlands, €8.56 in Belgium, € 10.31 in Portugal, 10.60 in Germany, €10.62 in France, and €10.97 in Sweden.	"Further research is required in order to estimate precisely the cost effectiveness of this compound, particularly including indirect costs and in other countries" (p. 549) (Note "this compound" refers to olopatadine)

ESS= estimated symptom score, GP= general practitioner, SAC= seasonal allergic conjunctivitis