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Advocating for Benzalkonium Chloride-Free Unit Dosing in Ophthalmic Preparations

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Abstract

Preservatives have long been considered essential in liquid dosage forms to prevent microbial contamination and maintain sterility, but their safety lacks sufficient study and is increasingly scrutinized due to documented adverse effects. Parabens, such as methylparaben and propylparaben, have been linked to hormonal disruptions and numerous skin reactions, prompting a shift to paraben-free products. Benzyl alcohol, associated with "gasping baby syndrome" in neonates, is used cautiously in pediatric formulations. Benzalkonium chloride (BAK), the most commonly used preservative in ophthalmic preparations, disrupts microbial membranes but has been linked to ocular surface toxicity, tear film disruption, and corneal damage in long-term use. This review advocates adopting BAK-free ophthalmic formulations, especially for long-term therapies and certain clinical scenarios, such as treatment following eye surgery. The trend towards BAK-free ophthalmic solutions aims to enhance patient safety, adherence, and satisfaction, improving overall treatment outcomes and quality of life.

Keywords: Benzalkonium Chloride; Ophthalmic Preparations; Pharmaceutical Formulations; Dosing

Abbreviations: BAK: Benzalkonium; COPD: Chronic Obstructive Pulmonary Disease; EDTA: Ethylenediaminetetraacetic Acid; QAC: Quaternary Ammonium Compounds; USP: US Pharmacopeia; EP: European Pharmacopoeia; IOP: Intraocular Pressure; OSD: Ocular Surface Disease; OTC: Over-The-Counter

Introduction

The Role of Preservatives in Pharmaceutical Formulations

Preservatives have been successfully used for over a century in various dosage forms to reduce the risk of microbial contamination. While they play a crucial role in ensuring the sterility and efficacy of pharmaceuticals, many preservatives have received increased scrutiny in recent years due to unforeseen side effects. For example, parabens such as methylparaben and propylparaben have raised concerns over potential long-term health risks [1]. For instance, studies on parabens have shown that they may exhibit estrogenic activity, leading to concerns about their potential to disrupt hormonal balance in both men and women [2]. Additionally, paraben use has been linked to skin irritation and contact dermatitis [3]. Consequently, there has been a noticeable trend towards paraben-free formulations, particularly in topical products such as sunscreens and cosmetics, where the absence of parabens is often prominently displayed on product packaging. Benzyl alcohol, another preservative that has stirred controversy, has been associated with adverse effects, particularly in neonates. It has been implicated in a condition known as "gasping baby syndrome," wherein neonates exposed to benzyl alcohol-containing medications exhibit symptoms such as respiratory distress, gasping, and even fatalities in severe

cases [4,5]. This association has led to heightened scrutiny and caution regarding its use, especially in pediatric formulations. Consequently, regulatory agencies, healthcare providers, and consumers are increasingly advocating for alternative preservative strategies to minimize the risk of such adverse events and improve patient outcomes.

A common preservative in both liquid and semisolid preparations is benzalkonium chloride (BAK) (Figure 1). Introduced in the 1930s and popularized by Gerhard Domagk under the commercial name Zephiran, BAK was initially marketed as a superior disinfectant. The first commercial product containing BAK became available in the United States in 1947. Since then, BAK has been widely used in prescription and over-the- counter medications as well as agricultural, cosmetic, and industrial products. It is widely considered the preservative of choice for ophthalmic eye drops. Approximately 75% of ophthalmic formulations include BAK as a preservative [6]. Despite its widespread use, significant research on the safety of BAK and its mechanism of action has been limited. As a quaternary ammonium compound and detergent, BAK is believed to exert its antimicrobial effects by disrupting the membranes of microorganisms. However, recent in vitro and in vivo studies have raised concerns about potential adverse effects, particularly long-term use in ophthalmic preparations [7]. This review will explore the use of BAK in ophthalmic formulations, and examine the safety concerns associated with BAK which is the most utilized preservative in ophthalmic topical preparations. This review advocates developing additional preservative-free single-vial formulations to enhance patient safety and treatment efficacy. In-depth reviews by Baudouin and Goldstein offered an excellent foundation and discussion on eliminating BAK from ophthalmic formulations [7-10].

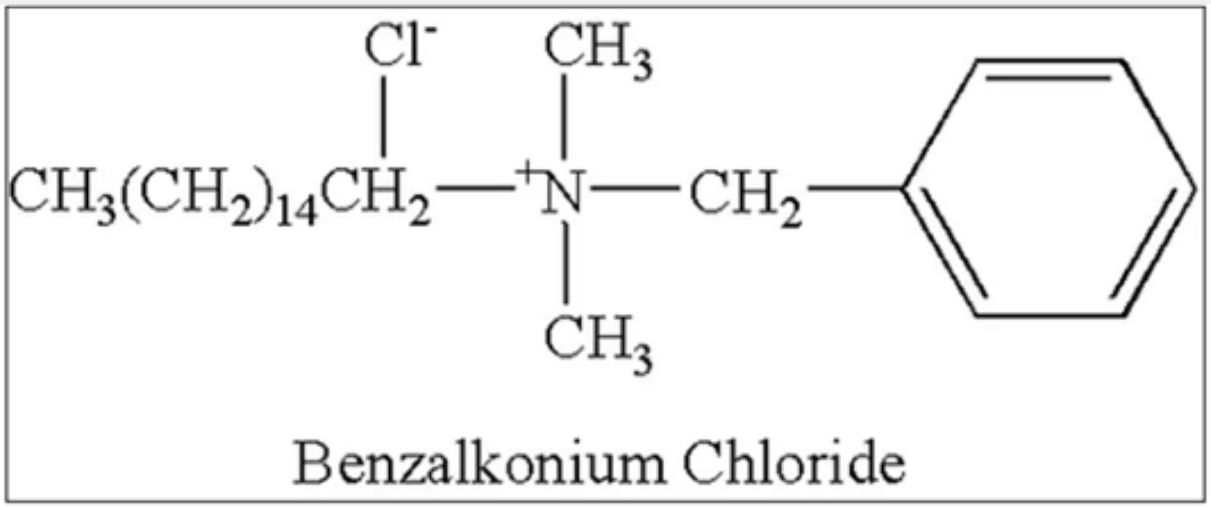

Figure 1: Chemical Structure of Benzalkonium Chloride.

Benzalkonium Chloride (BAK) in Nebulizer Solutions

Since the introduction of nebulizer solutions in the 1950s and 1960s, their use has increased significantly, driven by the rising prevalence of asthma and chronic obstructive pulmonary disease (COPD). Initially, these solutions were commonly available in multidose vials, which necessitated the inclusion of preservatives to prevent microbial contamination. Two common excipients used as preservatives and stabilizing agents in nebulizer solutions were benzalkonium chloride (BAK) and ethylenediaminetetraacetic acid (EDTA). Data accumulated over the years linked BAK to bronchospasm in asthma patients. By the mid to late 1990s, numerous reports, clinical observations, and case studies demonstrated a connection between BAK and EDTA and paradoxical bronchoconstriction [11,12]. These findings led to a concerted effort to remove preservatives like BAK from multi-dose nebulizer solutions. By the late 1990s, preservative-free single-use nebulizer solutions became available, reflecting a growing awareness of the potential adverse effects of preservatives. Today, millions of patients worldwide benefit from preservative-free nebulizer solutions, underscoring the importance of safety in unit-dose formulations. The removal of BAK has positively impacted patient outcomes, serving as a valuable case study in evaluating and regulating pharmaceutical preservatives.

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A 1989 Safety Report for Benzalkonium Chloride Use in the Cosmetic Industry

In cosmetic formulations, BAK is utilized as a surfactant, cleansing agent, conditioner, preservative, and bactericide. According to a safety report by Liebert, high doses of BAK can have significant effects on biological systems [13]. Below is a summary of findings from the Liebert report: In animal studies, BAK has been shown to disrupt various biological processes. Depending on the concentration, BAK can affect histamine levels which are crucial for proper immune function and influence multiple enzymatic reactions. In addition, a study using a 0.1% BAK concentration, sub chronic inhalation of BAK showed no harmful effects in animals. Also, studies on creams with different BAK concentrations found no toxic or damaging effects. Chronic oral administration of BAK via a stomach tube produced minimal effects, though some dogs displayed signs of hyperemia, irritation, and congestion in the stomach and intestines. A study on the effects of BAK on hair involved applying various amounts of BAK along the midline of the neck. Results showed that BAK could cause adverse effects such as unkempt hair, hyperemia, necrosis, and weight loss, primarily at 6.5% and 50% BAK concentrations. Another study examined prolonged BAK exposure in the ear canal. The bulla cavity was filled with either a BAK-DI solution or a BAK-alcohol solution, both with a 0.1% BAK concentration, and observed over 10, 30, and 60 minutes. This exposure led to tissue fibrosis, inner hair loss, and destruction of vestibular neuroepithelia.

BAK's impact on epithelial cells and fibroblasts in tissue was also studied. Cells isolated from the prostate gland and heart showed significant growth inhibition at all BAK dosages. Prolonged exposure resulted in 50% cell damage in the cell culture, and increasing BAK concentrations led to higher hemolysis rates in defibrinated blood. Animal studies on BAK's ocular effects revealed that aqueous solutions with 1.0% and 2.0% BAK caused irritation, necrosis, ulceration, corneal haziness, severe iritis, and cloudiness. Intraocular toxicity studies showed that BAK caused corneal epithelial desquamation and necrosis, corneal endothelium swelling, retinal elevation, and other issues. BAK's skin effects were also tested in various studies. Depending on the concentration, BAK could cause reactions ranging from erythema to necrosis, rawness, eschar formation, and total necrolysis of the epidermis.

Moisturizing cream with BAK did not produce positive reactions. Some studies investigated the teratogenic effects of BAK. Instillation through the vagina did not cause noticeable problems until day 6 when maternal body weight gain was significantly reduced, particularly at higher doses. The highest dose caused vaginal inflammation and reduced the mean number of implantations, a critical pregnancy stage, in treated animals. BAK did not show mutagenic effects in some Salmonella, E. coli, or Bacillus subtilis strains but did show genetic toxicity in E. coli strains W3110 and p3478. Ocular irritation and intraocular toxicity were also assessed in a clinical setting. BAK at 0.02% concentration did not cause significant reactions in fourteen patients, and a qualitative assessment showed no damage to the corneal endothelium with a BAK solution of 0.01 mg/ml. The safety report concludes that cosmetic agents containing BAK concentrations of 0.1% or lower are safe as currently used.

BAK found in Breast Milk

During the COVID-19 pandemic, there was a dramatic increase in the use of disinfectants containing Quaternary Ammonium Compounds (QACs) such as BAK. These compounds were widely employed in disinfection practices involving sprays and wipes to sanitize surfaces. In an experimental study conducted by Zheng et al., it was observed that QACs, specifically BAK, can enter the body, likely through respiratory pathways or skin-blood barriers, and appear in breast milk [14]. The study revealed that breast milk samples from mothers using QAC-containing disinfectants like sprays and wipes contained, on average, 1.3 times higher concentrations of QACs (including BAK, DDAC, and ATMAC) compared to mothers who did not use such products [14]. Moreover, mothers who frequently used sprays had breast milk with concentrations of QACs approximately two times higher than those who primarily used wipes. This underscores the prevalence of BAK use in many different products other than ophthalmic eye preparations and also calls for additional scientific and clinical studies regarding the toxicity of BAK.

Discussion

Since the 1970s, the FDA, US Pharmacopeia (USP), and European Pharmacopoeia (EP) have mandated that multidose eye drops contain a preservative to prevent microbial contamination. These preservatives are effective against bacterial and fungal growth in maintaining sterility, but they were not designed to be pleasant to the eye. Preservatives tend to be harsh compounds capable of damage as noted in the U.S. Environmental Protection Agency and the European Commission [15,16]. Additionally, the antimicrobial effect is concentration-dependent, so the concentration of the preservative in the ophthalmic formulation is crucial to its effectiveness [17]. It is essential for health practitioners providing eye care to comprehend the effects of preservatives on eye health. Benzalkonium chloride has long been the gold standard preservative for ophthalmic preparations. Its prevalence in these formulations is remarkably high, with the overwhelming majority of ophthalmic products containing BAK as a preservative. BAK is a quaternary ammonium compound that acts as a detergent, disrupting the cell membranes of microorganisms. Prolonged exposure to BAK has been associated with a range of adverse effects, including ocular surface toxicity, disruption of the tear film, and damage to corneal epithelial cells. These side effects have led to increased scrutiny and calls for the development of more preservative-free alternatives.

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In addition to its role in preventing bacterial contamination in eye drops, BAK has traditionally been utilized in glaucoma treatments to enhance the penetration of drugs. This enhancement has been leveraged to increase efficacy and enable certain eye medications to maintain their clinical effectiveness at lower concentrations, thereby reducing the potential for adverse effects. For example, by increasing BAK concentration fourfold, the concentration of bimatoprost could be reduced from 0.03% to 0.01%, which has been demonstrated to decrease the occurrence of conjunctival hyperemia [18]. It is suggested that this improved penetration of ocular drugs occurs through disruption of the hydrophobic barrier of the corneal epithelium. Differences in pharmacokinetics (such as hydrophilic versus lipophilic formulations) among eye drops may also influence their effectiveness. For instance, it is hypothesized that beta-blocker eye drops may exhibit reduced penetration of the active ingredient without BAK due to their hydrophobic nature. Numerous studies have explored this issue and found that concerns about reduced efficacy when switching to preservative-free formulations are generally unfounded [7].

In a study by Easty et al., they compared preserved versus non-preserved formulations of timolol gel 0.1%, the non-preserved formulation demonstrated a non-inferior reduction in intraocular pressure (IOP) compared to its preserved counterpart. Though the global tolerance assessments were found to be similar among the two treatment groups, the incidence of irritations, burning, or stinging upon installation was twice as high in the preserved timolol group after three months of therapy [19]. Similar results demonstrating intraocular pressure (IOP)-lowering efficacy equivalence are also seen with two comparative studies of travoprost 0.004% with and without BAK [20,21]. One study even showed both formulations maintained a prolonged duration of action 60 hours after the last administration [21]. Furthermore, this non-inferior intraocular pressure (IOP) reduction is also maintained using fixed combination products such as preservative-free latanoprost-timolol and preservative-free dorzolamide- timolol when compared to their BAK-containing comparators [22,23]. This review aims to explore the use of BAK in ophthalmic preparations, assess the associated safety concerns, and advocate for preservative- free single-vial dosing to improve patient outcomes and safety in ophthalmic treatments. The transition to preservative-free formulations, as seen in the case of nebulizer solutions, could significantly benefit patients with chronic conditions requiring long-term ophthalmic therapies.

Cytotoxic Effects of BAK on Ocular Tissue

BAK, a detergent, is used to penetrate the cell layers to promote drug permeation and disrupt microbial membranes. However, that penetrative ability can be a double-edged sword with the proliferation of adverse and cytotoxic effects. Systemic absorption of topical eye drops resulting in systemic adverse drug events remains a growing concern, especially for conditions, such as glaucoma, where chronic use of multiple eye drops is common. A single instilled drop has a significantly larger volume compared to the volume of the preocular tear film. Because of this difference in volume, the excess volume can be systemically absorbed through the nasopharyngeal mucosa, making systemic absorption and systemic, non-ocular adverse drug events such as bronchoconstriction possible. Therefore, this association of bronchoconstriction with BAK-containing products may be further compounded by the risk of respiratory complications also associated with topical beta-blocker therapy, a commonly used medication for the treatment of glaucoma and ocular hypertension. Further studies are needed to evaluate this possible and potentially serious interaction between BAK and antiglaucoma Tous drugs.

Results from animal studies and in vitro indicate that the cytotoxic effects of BAK are dose-dependent [24]. From concentrations starting at 0.0025% and ending at 0.01%, the adverse effects of BAK can range from microvilli removal to peeling of the cell layers. This is only a subset of the possible concentrations as ophthalmic preparations can have BAK concentrations from 0.004% to 0.02%. Therefore, using the data presented by the animal studies, some ophthalmic preparations containing BAK could have more adverse effects than previously documented. A study by Baudouin et al. demonstrates a link between BAK and damage to the trabecular meshwork. It appears that BAK can stimulate and influence the levels of TNF-α, a pro-inflammatory cytokine. Damage to the trabecular meshwork would be an expected response to BAK as the preservative would penetrate cellular layers and induce an immune response. Through other studies, TNF-α is also known to cause glaucomatous neuropathy. As a result, we can infer that people who use ophthalmic preparations with BAK for extended periods could be experiencing TNF-α accumulation which could lead to problems, especially for patients with glaucoma. One could infer that it may make the pathology worse. This article also expands on the potential for chronic inflammation and trabecular meshwork apoptosis [25].

Implications for Ocular Surface Disease (OSD) associated with BAK

Ocular Surface Disease (OSD) is a broad term encompassing various eye pathologies, including conjunctivitis, lid disease, allergic manifestations, keratitis, and dry eye disease. These conditions can significantly impact the quality of life by causing discomfort, visual disturbance, and a potential risk of more severe ocular complications. Patients with chronic conditions such as glaucoma often necessitate prolonged administration of topical medications, many of which employ BAK as a preservative, particularly in multidose formulations. However, the sustained use of BAK-containing treatments has been linked to various adverse effects, especially notable in individuals with pre-existing ocular surface disease. BAK's impact on surface ocular health is

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profound and multifaceted. It disrupts the tear film, diminishing lipid layer density and stability, exacerbating dry eye symptoms, and escalating tear evaporation and instability.

Additionally, BAK induces corneal epithelial toxicity, evidenced by delayed wound healing, epithelial cell loss, and increased permeability to other medications, further aggravating ocular surface irritation. Chronic exposure to BAK also triggers inflammatory responses within the conjunctiva and cornea, exacerbating conditions like allergic conjunctivitis and keratitis [7]. The incidence of OSD significantly rises among glaucoma patients using BAK-containing eye drops, adversely impacting both their quality of life and treatment efficacy. Moreover, the discomfort and pain caused by BAK often lead to poor adherence to prescribed glaucoma medications. Non-compliance jeopardizes effective intraocular pressure (IOP) management, potentially advancing disease progression and risking vision loss. Symptoms such as redness, burning sensations, and foreign body perception can impede daily activities, compounding compliance challenges in consistently using the eye drops as prescribed.

Ophthalmic Preparations and Sterility

In the fall of 2023, the FDA issued a guidance document titled "Quality Considerations for Topical Drug Products" aimed at the pharmaceutical industry [26]. This draft followed another document released just two months earlier in October 2023. During this period, the FDA initiated a nationwide voluntary recall of 27 eye drop products manufactured by Kilitch Healthcare India Limited between October and December. During 2023, several other major recalls affected numerous eye drop preparations, primarily artificial tears in multi-dose vials produced under unsanitary conditions. These recalls were prompted by severe consequences, including four deaths from sepsis, 14 cases of vision loss, and over 80 infections. Such incidents underscore the critical need for unit dosing, particularly in managing dry eyes and other ocular pathologies, assuming a sterile vial preparation environment. Antibiotic resistance poses an escalating challenge in healthcare. In their publication, Short et al. discuss how benzalkonium chloride (BAK) inhibits the action of gentamicin and other aminoglycosides [27]. They also highlight BAK's role in promoting drug resistance among colonies of A. baumannii. This is worrisome given that gentamicin, a commonly used ophthalmic antibiotic often contains BAK as a preservative.

Additionally, the risk of contamination of multi-dose preparations with regular use must also be considered, especially considering that poor eye drop instillation technique occurs in more than 50% of patients with glaucoma [28]. Contamination rates are expected to be higher when using non-preserved ophthalmic preparations, but contamination when using preserved multi-dose preparations is still possible. One study found bacterial contamination occurred in 28% of BAK-preserved topical antiglaucoma medications used in a community setting with the frequency of contamination increasing with longer duration of use and the most common location of contamination being the tip of the eye drop bottle [29]. Another study evaluating the incidence of microbial contamination of topical ophthalmic medications across multiple settings found that the contamination rates were the highest among eye drops being applied by patients at 24.4% compared to 19.5% of eye drops used in the ward, 17.1% used in the outpatient unit, and 5.3% used in the operating room with glaucoma medications being the most common offenders [30]. This frequent contamination of multi-dose eye drops calls into question whether preservative-free single-dose eye drops may be preferred in chronic ocular conditions such as glaucoma, dry eye disease, and allergic conjunctivitis. Considering these significant concerns, there is a compelling argument for developing and adopting preservative-free formulations for chronic ocular conditions. Preservative-free single-vial dosing can mitigate the adverse effects associated with BAK, ensuring sterile drug delivery that enhances patient comfort, treatment adherence, and overall ocular health.

Post-Surgical Treatment and Other Clinical Scenarios

Preservative-free ophthalmic preparations are highly valued in post-surgery care, particularly due to their ability to minimize irritation and allergic reactions commonly associated with preservatives like BAK. Intraoperative manipulations and exposure to ophthalmic preservatives may lead to postoperative inflammation, which may stem from alterations in the eye surface and tear film stability resulting in discomfort and delayed recovery [31]. After eye surgery, when the eyes are sensitive and vulnerable, BAK- free formulations will likely be advantageous due to avoiding potential delays or complications caused by preservative toxicity. Maca et al. conducted a study to compare the anti-inflammatory efficacy and subjective tolerability of preservative-free and preserved diclofenac 0.1% and preserved ketorolac 0.5% eye drops for prophylaxis and management of inflammation post-cataract surgery and found that the three 3 formulations exhibited equal anti-inflammatory efficacy as measured by decreased anterior chamber flare post-procedure and prevention of post-procedure macular edema. Subjects treated with preservative-free diclofenac ophthalmic drops described significantly better subjective tolerability scores, reported less ocular discomfort and experienced earlier reduction of post-surgical conjunctival hyperemia [32].

BAK has been noted to stimulate ocular lens epithelial cells to prompt mediators engaged in inflammation and apoptosis, which may lead to the formation of lens opacities [24]. Surgical cataract repair can address this issue of cataract development and may be performed concurrently with glaucoma procedures when necessary. However, prior long-term BAK exposure has been linked to higher surgical failure rates. Issues such as conjunctival fibrosis, cystoid macular edema, and induction of

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proinflammatory mediators affecting postoperative healing have been associated with preserved glaucoma therapies [24]. By eliminating preservatives, such preparations reduce the risk of infections and optimize comfort during the recovery period, crucially enhancing patient compliance with treatment regimens. Furthermore, their use supports long-term ocular health by preventing chronic dry eye and other surface disorders linked to prolonged exposure to preservatives. Overall, preservative-free options provide a safer and more effective approach to post-operative eye care, ensuring optimal conditions for healing and minimizing potential discomfort or complications.

Chronic topical therapies for glaucoma have been associated with the induction of subclinical conjunctival inflammation and may be considered a risk factor for trabeculectomy failure [33]. Previous studies indicate that prolonged antiglaucoma medication therapy is associated with an increased risk of failure for future procedures [33]. There is some debate as to culprit is the medication, the vehicle, or the preservative causing the deleterious effects. In vitro data and clinical evidence suggest the most likely candidate to be BAK [34-36]. Boimer and Brit's study yielded results that revealed a dose-response curve concerning the extent of BAK exposure preoperatively. Greater daily amounts of preservative-containing eye drops were associated with an increase in the surgical failure risk as noted by the early risk for failure increasing by a factor of 1.21 for each additional drop containing BAK [37]. Additionally, there is evidence that non-preserved eye drops and preserved eye drops do not differ in efficacy. Several studies have shown that switching from a preserved to a non-preserved formulation significantly improved the ocular surface and reduced symptoms [38,39]. Patients who have undergone surgical procedures to address cataracts often suffer from dry eye symptoms which may adversely impact quality of life and satisfaction. The incidence of postoperative dry eye events is significant, ranging from 9 to 100% and lasting up to 6 months in some patients. One of the many factors compromising the ocular surface is the use of BAK-preserved topical eye drops administered during the postoperative period. Preservative-free dexamethasone eye drops after cataract surgery caused milder dry eye symptoms as compared with preserved dexamethasone [40].

Preservative-Free Ophthalmic Formulations: A Growing Trend

Similar to the paradigm shift in the 1990s concerning nebulizer solutions, the contemporary landscape of ophthalmic solutions, both over-the-counter (OTC) and prescription, is experiencing a notable inclination towards preservative-free formulations. This trend is particularly pronounced in dry eye management, where a spectrum of non-prescription preparations are now available in preservative-free unit dose vials, marking a departure from traditional formulations. A comprehensive listing of these preservative-free non-prescription ophthalmic preparations is provided in Table 1. Furthermore, within the realm of prescription medications aimed at addressing dry eye disease, several preservative-free formulations exist, reflecting a concerted effort to mitigate potential ocular irritation and hypersensitivity associated with preservatives. Table 2 provides a comprehensive list of preservative-free prescription ophthalmic preparations tailored for dry eye management. Moreover, this shift in preservative-free formulations extends beyond dry eye therapeutics, encompassing a variety of ocular pathologies. Notably, a growing number of prescription ophthalmic preparations for various eye conditions are now available in preservative-free formulations, ensuring enhanced ocular tolerability and minimizing potential adverse effects. For a compilation of preservative-free ophthalmic preparations indicated for diverse ocular pathologies, refer to Table 3. While there are currently BAK-free ophthalmic topical preparations on the market, the number is insignificant compared to the total number of prescription and non-prescription eye drops containing BAK [41].

Table 1: List of Preservative-Free Non-Prescription Preparations That are Used to Treat Dry Eyes.

Brand Name	Manufacturer	Active Ingredients
Refresh Optive Advanced Preservative-Free	Abbvie Inc	Carboxymethylcellulose sodium, Glycerin, Polysorbate 80
Systane Ultra Preservative-Free	Alcon	Polyethylene glycol, Propylene glycol
Thera Tears Dry Eye Therapy Lubricant Eye Drops	Prestige Consumer Healthcare	Sodium carboxymethylcellulose
Blink Tears Preservative-Free	Johnson & Johnson	Polyethylene glycol
Oasis Tears Preservative-Free	Oasis Medical	Glycerin, Sodium hyaluronate
Hylo-Tear Preservative-Free	Candorvision	Sodium hyaluronate
Refresh Celluvisc Preservative-Free	Allergan	Carboxymethylcellulose sodium
Soothe Preservative-Free	Bausch + Lomb	Propylene glycol, Glycerin
Thera Tears Extra Dry Eye Therapy	Prestige Consumer Health Care	Carboxymethylcellulose sodium
Retaine MGD Preservative-Free	OCuSOFT	Light mineral oil, Mineral oil
Systane Hydration Preservative-Free	Alcon	Polyethylene glycol, Propylene glycol

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Table 2: List of Preservative-Free Prescription Ophthalmic Preparations Used to Treat Dry Eyes.

Brand Name	Manufacturer	Active Ingredient(s)	Indication
Restasis Multidose	Abbvie Inc.	Cyclosporine	Chronic dry eye disease
Xiidra	Bausch + Lomb	Lifitegrast	Dry eye disease
Cequa	Sun Pharma	Cyclosporine	Dry eye disease
Ikervis	Santen	Ciclosporin	Severe keratitis in dry eye disease
Eysuvis	Alcon	Loteprednol etabonate	Short-term treatment of dry eye disease
Verkazia	Harrow Eye	Cyclosporine	Severe vernal keratoconjunctivitis

Table 3: List of Preservative-Free Prescription Ophthalmic Preparations Used to Treat Various Eye Pathologies.

Brand Name	Manufacturer	Active Ingredient(s)	Indications
Vyzulta	Bausch + Lomb	Latanoprostene bunod	Glaucoma, Ocular hypertension
Zioptan	Thea Pharma Inc	Tafluprost	Glaucoma, Ocular hypertension
Timoptic in Ocudose	Bausch + Lomb	Timolol	Glaucoma, Ocular hypertension
Cosopt PF	Thea Pharma Inc	Dorzolamide, Timolol	Glaucoma, Ocular hypertension
Simbrinza	Alcon Laboratories	Brinzolamide, Brimonidine	Glaucoma, Ocular hypertension
Iluvien	Alimera Sciences	Fluocinolone acetonide	Diabetic macular edema
Ozurdex	Abbvie Inc	Dexamethasone	Macular edema, Uveitis
Dexycu	EyePoint Pharmaceuticals	Dexamethasone	Postoperative inflammation

Conclusion

The widespread use of BAK in ophthalmic preparations, particularly in patients requiring long-term treatment, underscores the need for a re-evaluation of its safety profile. The example of nebulizer solutions, where the removal of BAK has had a positive impact on patient outcomes, provides a compelling argument for similar changes in ophthalmic therapies. Transitioning to preservative-free single-vial dosing in ophthalmic preparations could significantly benefit patients with chronic conditions like glaucoma, reducing the incidence of ocular surface disease and enhancing their quality of life. There seems to be little clinical reasoning to utilize a preserved therapy over a preservative-free option. Beneficence and nonmaleficence would suggest the mitigation of an additional risk of potential harm to the eye surface produced by intentional exposure to the questionable preservatives utilized in ophthalmic therapies if it is possible to avoid. Previously, the costs related to the use of single-dose or preservative-free multidose containers were a substantial obstacle to the selection of preservative-free alternatives. However, preparations not containing preservatives such as BAK are more broadly obtainable and frequently with minimal to zero additional expense compared with preserved options. Health economic and outcome research studies comparing preserved vs. preservative-free options are needed to assess costs versus medical outcomes, quality of life outcomes, and compliance [42].

In summary, the ability to employ ophthalmic formulations without preservatives would extend clinically meaningful advantages to users, especially those sensitive to preservatives due to pre-existing conditions or multiple eye surface disorders, those utilizing combination therapies, those who may need ophthalmologic surgery, and those who may need long term or lifelong treatment. Preservative-free preparations should be considered for elevation as the standard of care sooner rather than later.

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