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Real-World Safety and Performance of Saline Nasal Spray Products for Nasal Cleansing and Reducing Obstruction of the Nasal Cavity

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Abstract

Background and Objectives: Three post-marketing clinical follow-up studies were performed in Europe to confirm the safety and performance of four nonprescription, nasal cleansing medical devices: Otrivin Sea Water (OSW) pressurized spray, OSW with aloe vera (OSWAV), Otrisal 0.74% NaCl Metered-Dose Spray (MDS), and Prorhinel spray. **Material and Methods:** Observational, single-arm, retrospective studies consisting of a single online questionnaire were performed between July 2021 and December 2021. Eligible participants were adults who used the device or supervised use of the device in a participant under 18 years of age within 6 months of completing the questionnaire. Demographics, safety, and device performance were assessed. **Results:** Based on questionnaires submitted on OSW (n = 556), OSWAV (n = 555), Otrisal MDS (n = 555), and Prorhinel (n = 555), proportions of users who reported safety events were 1.8% for OSW, 2.3% for OSWAV, 1.4% for Otrisal MDS, and 2.0% for Prorhinel. Proportions of users who indicated they were satisfied or very satisfied with device performance ranged from 72.0% - 89.0% across all devices. Device performance for all products was also supported for additional preventative and symptomatic uses through exploratory analyses. **Conclusions and Significance:** These data confirm device safety and performance of OSW, OSWAV, Otrisal MDS, and Prorhinel for their intended uses.

Keywords

Saline Solution, Sodium Chloride, Common Cold, Allergens, Postmarketing Product Surveillance

1. Introduction

Exposure to environmental pathogens, irritants, pollutants, or allergens can lead to increased nasal secretion, irritation, and other symptoms that can negatively affect overall function and quality of life [1] [2]. While nasal and sinus conditions can be effectively treated with medications such as decongestants and intranasal steroids [3], a range of isotonic or hypertonic saline solution formulations is commercially available without a prescription for nasal cleansing and washing of the nasal cavity [4] [5]. These products may function by helping remove trapped particulate matter and/or thick or dried mucus from the nose to improve mucociliary clearance while moisturizing the nasal cavity [5] [6] [7]. Clinical trials in children and adults have revealed that daily nasal cleansing with saline formulations is well tolerated and can alleviate symptoms of chronic or allergic rhinosinusitis, influenza, or the common cold while reducing the need for medications, improving well-being, and reducing days missed from work or school [7]-[12]. Studies have also shown that the benefits of saline formulations may be enhanced when administered via nasal aspirator [8] [13].

Otrivin Sea Water (OSW) pressurized spray, OSW with aloe vera (OSWAV), Otrisal 0.74% NaCl Metered-Dose Spray (MDS), and Prorhinel spray are non-prescription nasal saline administration medical devices that have been commercially available for adults and children in Europe for more than 10 years. To confirm the ongoing safety and performance of these devices for their intended uses in a real-world setting, each device was recently investigated in post-market clinical follow-up (PMCF) studies, the results of which are summarized here.

2. Methods

2.1. Study Design

Three observational, single-arm, retrospective, PMCF studies were conducted to assess the real-world safety and performance of OSW and OSWAV (both commercialized under the trademarks of *Narhinel*, *Rinazina*, *OtriCare*, *Otrimer*, and *Rhinomer*; and OSWAV as *OtriNatura*, *Otrinatural*, *Otrivine*, *Prorhinel* [*Hygiène du nez à l'Aloe Vera* | *Prorhinel Eau de mer à l'Aloe Vera*], and *Pirinatural*); Otrisal MDS (commercialized under the trademarks of *Otrivin* and *OtriNatura*), and Prorhinel spray (commercialized under the trademark of *Prorhinel*). All are products of GSK Consumer Healthcare SARL, a Haleon company, and trademarks are owned by or licensed to the Haleon group of companies. Each study consisted of a single online questionnaire that device users were invited to answer via awareness campaigns. No follow-up or clinical investigation–related procedures were performed after the questionnaire was completed and submitted by (or for) the participant.

Recruitment was conducted in countries where the devices are marketed. OSW and OSWAV were investigated in Norway, Spain, and Sweden (target was achieved without the need to open France and Italy for recruitment) between July and October 2021, Otrisal MDS in the Netherlands in December 2021, and

Prorhinel spray in France in December 2021.

Each study was conducted according to the applicable portions of European Union (EU) Medical Device Regulation 2017/745 and European Nation International Organization for Standardization (EN ISO) 14155:2020, International Council for Harmonisation and Good Clinical Practice, the Declaration of Helsinki and its amendments, and any applicable national guidelines in their respective countries. These studies were also conducted in accordance with Medical Device Coordination Group (MDCG) 2020-7, and EN ISO 14155:2011. Study protocols were submitted to national and local authorities for ethical review if/when required by participating countries.

2.2. Participants

Eligible study participants were adults (including pregnant or breastfeeding women) able to complete the electronic questionnaire who, within the 6 months prior to submitting the questionnaire, had used the device themselves or supervised use of the device for someone younger than 18 years of age. Participation in each study was voluntary, and no personal identifying information was collected; thus, informed consent (or assent for minors) was not required but was assumed based on the terms and conditions of data collection agreement required before initiating the online questionnaire. Data were strictly protected during capture, forwarding, processing, and storage.

2.3. Investigational Medical Devices

OSW is an isotonic sea water solution for use by infants, children, and adults (including pregnant and breastfeeding women) and, as such, is available in a baby nozzle variant suitable for infants 2 weeks of age and older, children, and adults; a regular nozzle suitable for adults and children older than 6 years of age; and a jet nozzle suitable for adults only. OSWAV is OSW with the addition of aloe vera powder, and it is suitable for use by adults and children older than 2 years of age. The intended uses for OSW and OSWAV are for relief of the symptoms of nasal secretion, nasal irritation, blocked nose, and dry nose, and for daily nasal cleansing.

Otrisal MDS is a 0.74% NaCl solution for use by infants 2 weeks of age and older, children, and adults (including pregnant and breastfeeding women). Intended uses are to gently cleanse the nasal cavities when the nose is blocked (e.g. during a cold or in allergic conditions) by washing away excess mucus or allergen particles such as dust or pollen, to moisturize the nasal mucosa when dry or irritated in case of minor nasal irritations or due to low humidity (e.g. due to heated/air-conditioned rooms, high altitude, air travelling), and to thin and loosen nasal secretions and help their removal.

Prorhinel is a nasal pressurized spray containing a solution with sodium chloride and surfactants (benzododecinium bromide and polysorbate 80) for use by infants 2 weeks of age and older, children, and adults. As such, Prorhinel is

available with three different nozzles: as a spray for infants and young children, a spray for children and adults, and a spray jet tonic for adults. Intended uses are to allow elimination of mucus and infective agents, reduce nasal obstruction, free the nose to make it easier to breathe, and humidify nasal passages.

2.4. Questionnaires

Each medical device was evaluated via an online questionnaire that collected user demographics and assessed safety and device performance. Questionnaires were designed to take approximately 15 minutes to complete, with single- or multiple-select answers for each question and dynamics that directed the user to follow-up questions related to the answer(s) provided. Questions about device performance were answered on a 5-point (single-select) Likert scale with the choices of very unsatisfied, unsatisfied, neutral, satisfied, or very satisfied. Additional multiple-choice questions relating to symptomatic improvement were based on a 4-point Likert scale rating the level of improvement as strong, moderate, mild, or none. Additional details about the questionnaires are provided in the **Supplement**.

2.5. Primary Endpoints

The primary endpoints of each study were safety and device performance. Safety was based on the proportions of users who reported an adverse event (AE), side effect (SE), and/or device malfunction (DM) in the previous 6 months; however, specific AEs/SEs were not collected. Device performance was based on the percentage of questionnaires with answers of "very satisfied" or "satisfied" on performance-related questions about intended uses of the device.

2.6. Exploratory Endpoints

Exploratory endpoints were also included for each product to assess performance during both preventative and symptomatic uses. Exploratory endpoints related to preventative use included performance for general nasal hygiene and prevention of common cold symptoms, and endpoints related to symptomatic use included amount of improvement across a range of symptoms related to allergies and the common cold, including when the device was used with a nasal aspirator.

2.7. Statistical Analyses

At least 555 completed questionnaires per device were expected, based on assumptions that ≤1% of participants would experience AEs/SEs and/or DMs (ensuring the 95% one-sided confidence interval [CI] would have an upper limit within 1% - 2% of the observed proportion) and ≥80% would report being either satisfied or very satisfied on the performance assessment for the previous 6 months (ensuring the 95% one-sided CI would have a lower limit within 3% of the observed proportion). Only completed questionnaires were included in this

analysis. Safety analyses were performed on all device users for whom questionnaires were completed, and performance analyses were performed based on questionnaires submitted without formatting errors, missing or erroneous data in a given field (e.g. an open-ended response to a yes/no question), or other inconsistencies.

For safety analyses, proportions of participants who reported AEs/SEs and/or DMs while using the device in the past 6 months were calculated with exact one-sided upper 95% CI using the Clopper-Pearson method. Observed proportions of infants (<2 weeks of age) and pregnant and breastfeeding women were calculated separately. Performance analyses were based on proportions of users with answers of "satisfied" or "very satisfied" on performance questions, calculated with exact one-sided lower 95% CI based on the Clopper-Pearson method.

For each device, subpopulation analyses on infants and pregnant and/or breastfeeding women were also computed separately and are summarized descriptively.

Participants were not allowed to submit multiple completed questionnaires for the same product; therefore, a 1:1 ratio of questionnaires and device users in the safety and full analysis set was assumed in each study. As this was an observational descriptive study, no statistical inference, modelling, or data imputation was performed.

3. Results

3.1. Participants and Device Usage

A total of 2606 device users completed questionnaires for OSW (n = 555), OSWAV (n = 555), Otrisal MDS (n = 555), and Prorhinel (n = 555), all of whom were included in the safety analyses. Questionnaires that met criteria to be included in the performance analyses were submitted by, or on behalf of, 546 (OSW), 543 (OSWAV), 551 (Otrisal MDS), and 540 (Prorhinel) device users (**Figure 1**). The majority of device users for whom questionnaires were submitted were older than 18 years of age, the proportions of which ranged between cohorts from 81.4% (OSW) to 94.4% (Prorhinel) (**Table 1**). Pregnant and/or breastfeeding women constituted up to 15.9% and 7.9% of the OSW and OSWAV cohorts, respectively, while these subpopulations represented less than 1% of the Otrisal MDS and Prorhinel cohorts, and infants comprised less than 1% of any cohort (**Table 1**). Nasal aspirator use was not assessed in the OSWAV cohort, while 117 (21.4%), 151 (27.4%), and 159 (29.4%) users in the OSW, Otrisal MDS, and Prorhinel cohorts, respectively, reported that they coupled utilization of the device with a nasal aspirator.

3.2. Safety

For the primary safety endpoint, the proportions (95% CI) of users who reported (or reported on behalf of users) an AE/SE or DM were 1.8% (0.0% - 3.0%) for OSW, 2.3% (0.0% - 3.7%) for OSWAV, 1.4% (0.0% - 2.6%) for Otrisal MDS, and

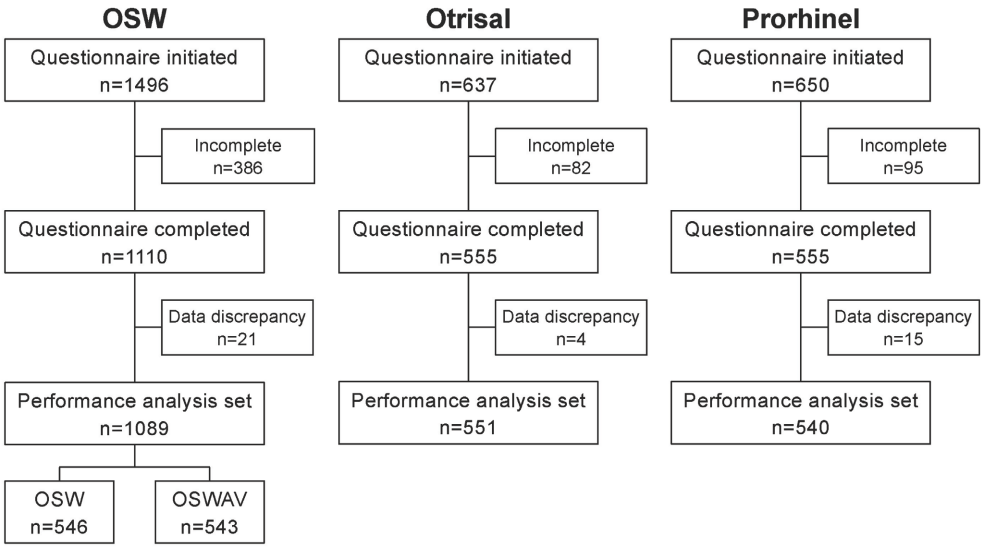

Figure 1. Disposition. Abbreviations: OSW, Otrivin Sea Water; OSWAV, Otrivin Sea Water with Aloe Vera.

Table 1. Demographics (safety analysis set).

	OSW (n = 555)	OSWAV (n = 555)	Otrisal (n = 555)	Prorhinel (n = 555)
Age category, n (%)				
<2 weeks	5 (0.9)	—	3 (0.5)	1 (0.2)
≥2 weeks - 18 years	98 (17.7)	39 (7.0)	34 (6.1)	30 (5.4)
>18 years	452 (81.4)	516 (93.0)	518 (93.3)	524 (94.4)
Pregnant, n (%)[a]	88 (15.9)	44 (7.9)	2 (0.4)	3 (0.5)
Breastfeeding, n (%)[a]	50 (9.0)	26 (4.7)	5 (0.9)	3 (0.5)
Pregnant and breastfeeding, n (%)[a]	31 (5.6)	16 (2.9)	—	2 (0.4)

Abbreviations: OSW, Otrivin Sea Water; OSWAV, Otrivin Sea Water with Aloe Vera. [a]Women who were both pregnant and breastfeeding are included in the counts for all three categories.

2.0% (0.0% - 3.3%) for Prorhinel (Table 2). In subpopulation analyses, safety events were reported by four (3.0%) pregnant women and three (3.9%) breastfeeding women who used OSW (with or without AV) and by one (33.3%) pregnant woman in the Prorhinel cohort. No events were indicated on questionnaires submitted on behalf of infants.

3.3. Device Performance

For the primary performance endpoint, proportions of users who indicated they were satisfied or very satisfied with each device ranged from 72.0% - 77.2% for OSW, 84.3% - 89.0% for OSWAV, 69.5% - 87.1% for Otrisal MDS, and 73.8% - 88.4% for Prorhinel across the intended uses of each device (Table 3). Device performance was highest with OSW and OSWAV for relief of symptoms of nasal

Table 2. Device safety.

	OSW (n = 555)	OSWAV (n = 555)	Otrisal (n = 555)	Prorhinel (n = 555)
Experienced AE/SE or DM				
n (%)	10 (1.8%)	13 (2.3%)	8 (1.4%)	11 (2.0%)
95% CI	0 - 3.0	0 - 3.7	0 - 2.6	0 - 3.3
By subpopulation, n (%)				
Pregnant women	4/132 (3.0%)		0/2	1/3 (33.3%)
Breastfeeding women	3/76 (3.9%)		0/5	0/3

Abbreviations: AE, adverse event; CI, confidence interval; DM, device malfunction; OSW, Otrivin Sea Water; OSWAV, Otrivin Sea Water with Aloe Vera; SE, side effect.

Table 3. Frequency of use and performance of device for intended uses.

	Use initiated for symptom/need, n (%)	Device performance,[a] % (95% CI)
OSW (N = 546)		
Relief of symptoms of nasal secretion	182 (33.3)	76.4 (70.6 - 100)
Relief of symptoms of nasal irritation	145 (26.6)	77.2 (70.8 - 100)
Relief of blocked nose	161 (29.5)	72.0 (65.6 - 100)
Relief of dry nose	129 (23.6)	73.6 (66.5 - 100)
Daily nasal cleansing	123 (22.5)	76.4 (69.3 - 100)
OSWAV (N = 543)		
Relief of symptoms of nasal secretion	268 (49.4)	87.3 (83.5 - 100)
Relief of symptoms of nasal irritation	163 (30.0)	89.0 (84.1 - 100)
Relief of blocked nose	178 (32.8)	84.3 (79.1 - 100)
Relief of dry nose	143 (26.3)	88.8 (83.5 - 100)
Daily nasal cleansing	124 (22.8)	87.1 (81.1 - 100)
Otrisal (N = 551)		
Relief of blocked nose	287 (52.1)	87.1 (83.4 - 100)
Relief of runny nose	329 (59.7)	78.4 (74.4 - 100)
Nasal moisturization	273 (49.5)	75.5 (70.8 - 100)
Loosening nasal secretions to aid removal	272 (49.4)	69.5 (64.6 - 100)
Prorhinel (N = 540)		
Elimination of mucus and infective agents	372 (68.9)	88.4 (85.3 - 100)
Reduction of nasal obstruction	387 (71.7)	85.5 (82.3 - 100)
Free the nose to ease breathing	370 (68.5)	73.8 (69.8 - 100)
Humidification of nasal passages	67 (12.4)	79.1 (69.3 - 100)

Abbreviations: CI, confidence interval; OSW, Otrivin Sea Water; OSWAV, Otrivin Sea Water with Aloe Vera. [a]Defined as the proportion of participants who reported being "Very satisfied" or "Satisfied" with the device for each symptom, with exact one-sided lower 95% CI based on the Clopper-Pearson method.

irritation (77.2% and 89.0%, respectively), and with Otrisal and Prorhinel for relief of blocked nose (87.1%) and elimination of mucus and infective agents (88.4%), respectively (Table 3). The distributions of satisfaction scores for each device are summarized by intended use in Figure 2. Subpopulation analyses of device performance with OSW exceeded 70% and 64% among pregnant and breastfeeding women, respectively; however, the numbers of pregnant and breastfeeding women for Otrisal MDS and Prorhinel, and of infants for all devices, precluded assessments in these subpopulations.

3.4. Exploratory Endpoints

Exploratory analyses provided additional evidence of device performance during a range of symptomatic and preventative uses. Based on questionnaires submitted for OSW and OSWAV, respectively, users reported being very satisfied or satisfied when using the devices for relief of symptoms of cold and flu (83.2% and 95.3%), airborne particle or pollutant exposure (88.3% and 90.4%), allergen exposure (79.8% and 89.3%), nasal congestion (77.2% and 92.2%), nasal itching (84.2% and 85.4%), and sneezing (73.4% and 85.7%) (Figure 3).

Among Otrisal MDS users, 76.6%, 69.5%, and 68.6% reported experiencing strong improvements in nasal congestion, sinus infection, and allergy symptoms, respectively, when using the device (Figure 4). Of 151 participants who used Otrisal MDS with a nasal aspirator, 136 (90.0%) reported strong improvement in

Figure 2. Device performance ratings by intended use. For OSW, 0.0% reported being very unsatisfied for "daily nasal cleansing." For OSWAV, 0.0% reported being very unsatisfied for "nasal secretion relief," "nasal irritation relief," "relief of a blocked nose," or "relief of dry nose." For Otrisal, 0.0% reported being very unsatisfied for "loosening nasal secretions to aid their removal." For Prorhinel, 0.0% reported being unsatisfied for "humidification of nasal passages." Abbreviations: OSW, Otrivin Sea Water; OSWAV, Otrivin Sea Water with Aloe Vera.

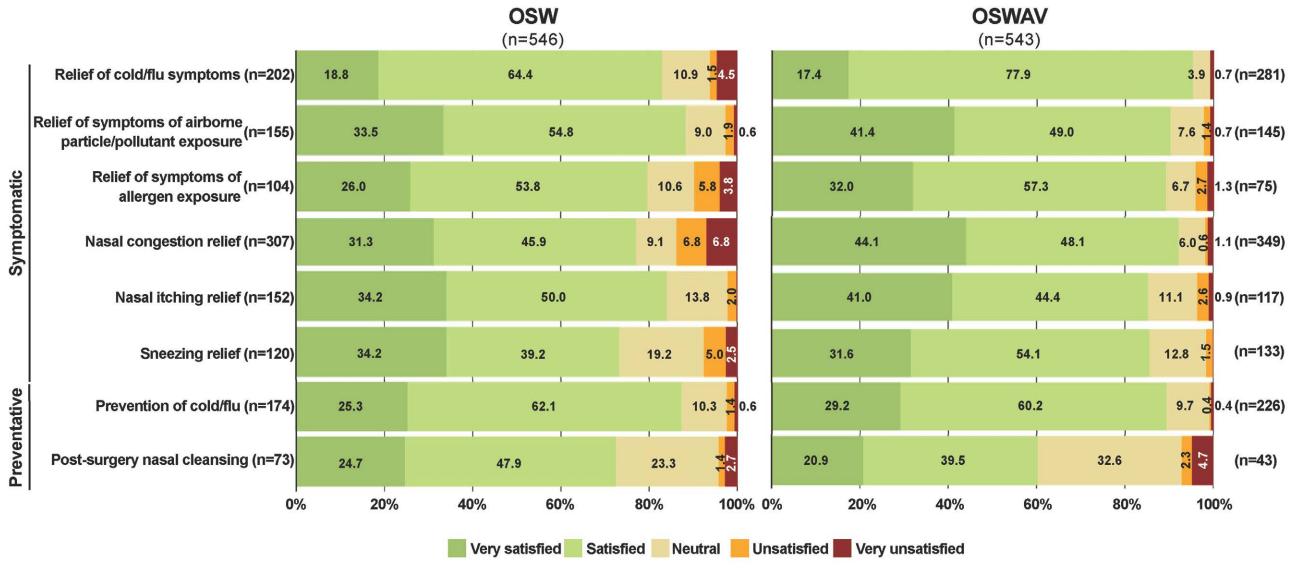

Figure 3. OSW/OSWAV exploratory performance analyses for symptomatic and preventative uses. For OSW, 0.0% reported being very unsatisfied for "nasal itching relief." For OSWAV, 0.0% reported being very unsatisfied for "sneezing relief." Abbreviations: OSW, Otrivin Sea Water; OSWAV, Otrivin Sea Water with Aloe Vera.

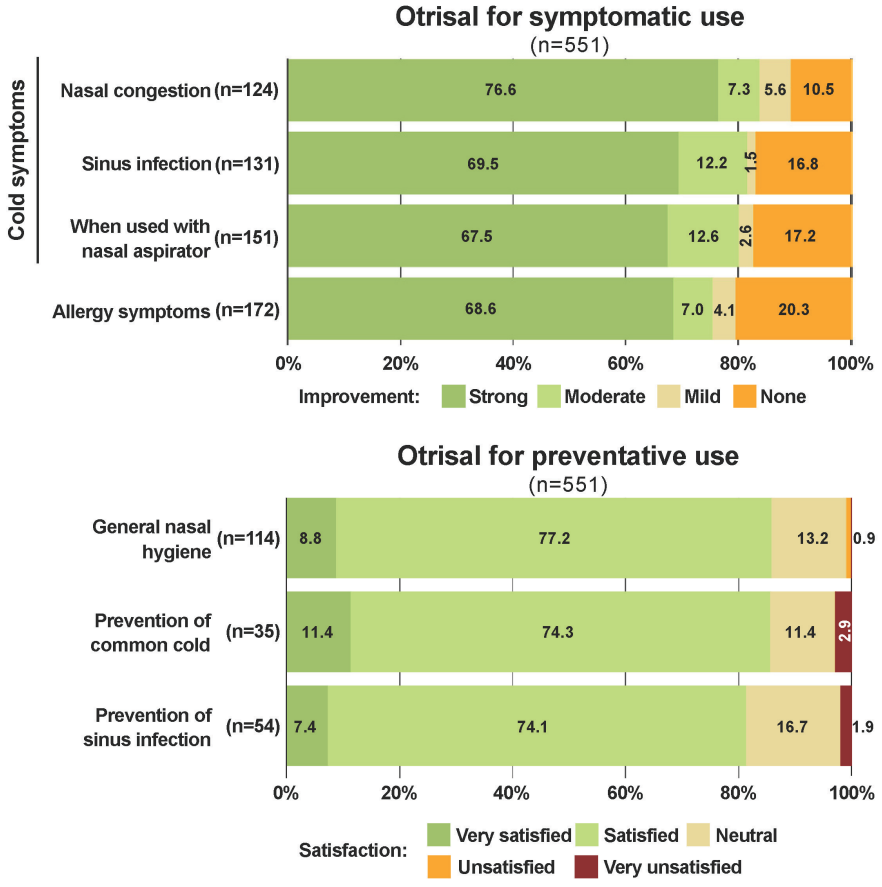

Figure 4. Otrisal exploratory performance analyses for symptomatic and preventative uses. For "satisfaction with device for general nasal hygiene," 0.0% reported being very unsatisfied. For "satisfaction with device for prevention of common cold," 0.0% reported being unsatisfied. For "prevention of sinus infection," 0.0% reported being unsatisfied.

the symptom(s) that prompted the device usage. This included all three breast-feeding women and the one infant who used Otrisal with a nasal aspirator (not shown).

Among Prorhinel users, 73.5%, 79.3%, and 79.2% reported experiencing strong improvements in nasal congestion, sinus infection, and allergy symptoms, respectively, when using the device (Figure 5). Additionally, of 159 participants who used Prorhinel with a nasal aspirator, 114 (71.7%) reported strong improvement in the symptom(s) that prompted device usage. Among those who used Prorhinel for sleep difficulties, between 71.8% and 77.8% indicated experiencing strong or moderate improvements in sleep-related symptoms.

Device performance was also supported for preventative use based on proportions of users who reported being very satisfied or satisfied with OSW for

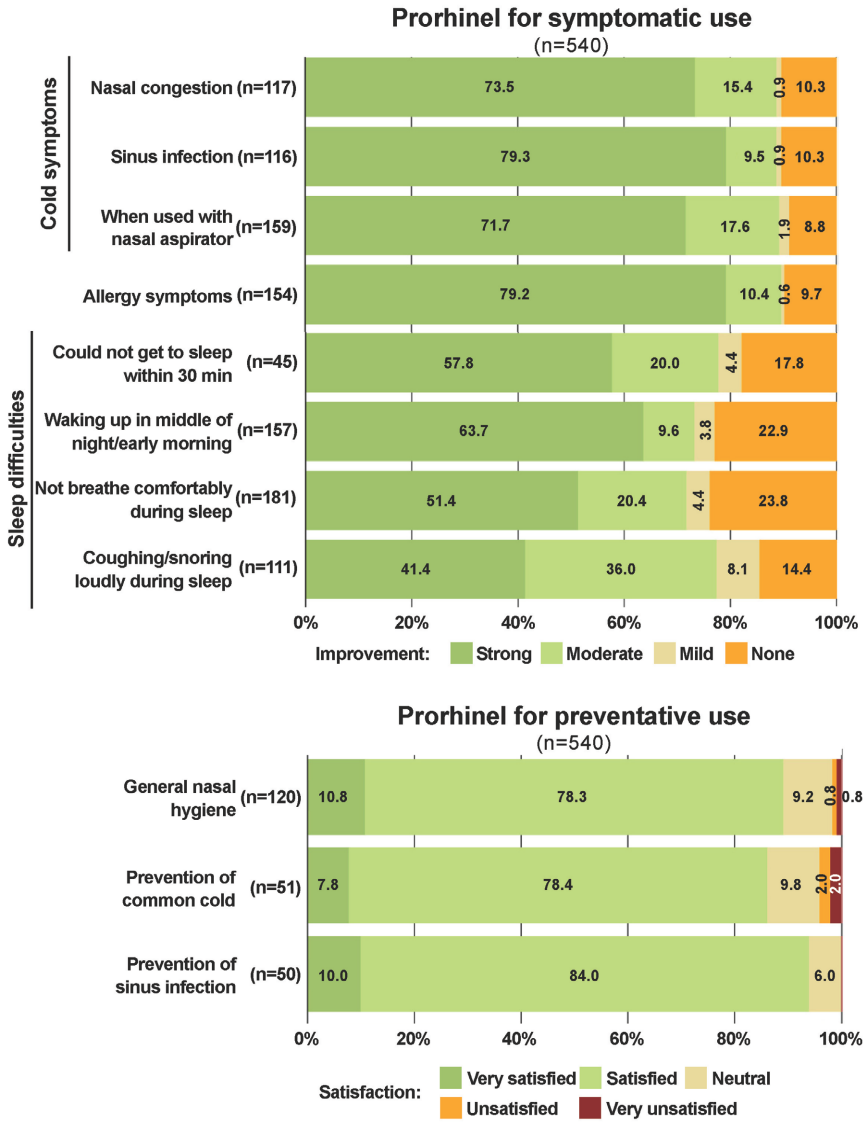

Figure 5. Prorhinel exploratory performance analyses for symptomatic and preventative uses. For "satisfaction with device for prevention of sinus infection," 0.0% reported being unsatisfied or very unsatisfied.

prevention of cold/flu (87.4%) and postsurgery nasal cleansing (72.6%), with corresponding rates for OSWAV of 89.4% and 60.4%, respectively (**Figure 3**). Additionally, 86.0%, 85.7%, and 81.5% of Otrisal MDS users (**Figure 4**) and 89.1%, 86.2%, and 94.0% of Prorhinel users (**Figure 5**) reported being very satisfied or satisfied with the device for preventative use for general nasal hygiene, prevention of the common cold, and prevention of sinus infection, respectively.

4. Discussion

The results of these studies provide evidence confirming the ongoing safety and performance of the nasal saline medical devices OSW, OSWAV, Otrisal MDS, and Prorhinel for their intended uses in the real-world setting. These findings also contribute to data on the general therapeutic approach of nasal saline lavage that dates back at least as far as the 1800s [14] and has been investigated in randomized controlled clinical trials dating almost 40 years [15] in patients with a variety of respiratory conditions. In a randomized clinical trial of 401 children (6 - 10 years of age) being treated for rhinitis associated with cold or flu, the addition of isotonic saline washing to standard therapy (including antipyretics, nasal decongestants, mucolytics, and/or systemic antibiotics as clinically appropriate) resulted in faster resolution of symptoms, reduction of medical treatment, and improved health status compared with standard treatment alone; furthermore, continued saline washing after the acute illness lowered the risk of recurrence of upper respiratory tract infections (URTI) [12]. In a prospective study of 108 patients with sinonasal disease (e.g. allergic rhinitis, atrophic rhinitis, and postnasal drip) treated with nasal irrigation, results showed that symptoms of nasal congestion, postnasal drip, seasonal/perennial allergies, and nasal discharge significantly improved over 6 weeks of nasal saline irrigation compared with sinonasal disease–free control patients (n = 20) [7]. Patients treated with nasal irrigation also reported having improved sleep, reduced stress, and improved health status compared with control patients [7]. Results from a multicenter, retrospective study of 144 adult patients with acute URTI showed that patients assigned to use of a sea-salt-derived saline nasal spray reported a ≥30% symptom score reduction from baseline in nasal congestion and runny nose, improved sleep quality, and improved appetite compared with those who did not use saline nasal spray [16]. This large body of clinical data on the effects of nasal saline administration has yielded consensus supporting the regular use of nasal saline sprays to help protect from airborne pathogens, pollutants, and allergens, and support respiratory health by reducing the impact of unpleasant stimuli in the nose [5] [17].

In our studies, less than 2.5% of users of any device reported experiencing safety events. SEs typically associated with nasal saline cleansing include nasal discomfort, burning sensation/nasal mucosal stinging, headaches, or discomfort or irritation in the nose and ears [4] [18]; however, overall rates of AEs reported have been consistently low [5] [17]. OSW was investigated in a double-blind, placebo-controlled clinical trial in 61 adults with nasal congestion associated

with common cold. In that study, no treatment-related AEs were reported after OSW administration three times per day for approximately 5 - 6 days [19].

Although our data are based on large cohorts of adults, device performance and safety within subpopulations of pregnant and/or breastfeeding women, children, and infants were also of interest, but affected by small sample sizes. For example, although safety analyses for OSW and OSWAV included robust numbers of pregnant and/or breastfeeding women and revealed event rates comparable to those for the overall cohorts, fewer than five pregnant or breastfeeding women responded to the Otrisal MDS and Prorhinel questionnaires, preventing subpopulation safety conclusions for those devices. Nonetheless, no specific safety concerns were revealed for Otrisal MDS and Prorhinel, which is consistent with prior evidence that suggests nasal saline irrigation is safe and well tolerated for pregnant and breastfeeding women, as well as in infants and children [5] [17] [20] [21].

Methodological Considerations/Limitations

These studies were limited by the observational, self-report design that includes variability in interpretation or understanding of the questions asked, as well as potential recall bias. Also, in response to demographic survey questions, caregivers may have entered their age but provided answers for their children, which would account for most of the population being listed as adults when the products are clearly designed for babies. Additionally, the generalizability of these results may be limited as the study populations self-selected for individuals willing to complete the online questionnaire.

5. Conclusion

The results of these three PMCF studies provide clinical evidence confirming safety and performance of OSW, OSWAV, Otrisal MDS, and Prorhinel medical devices for their intended uses that include daily nasal cleansing; relief of dry, runny, blocked, or irritated nose; and relief of nasal secretions, symptoms from cold/flu, allergens, or airborne particles/pollutants in their targeted populations. Device performance was additionally supported by assessment during a range of preventative and symptomatic uses, including general nasal hygiene and prevention and/or alleviation of symptoms of the common cold, flu, and/or sinus infection.

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Disclosure Statement

M.A., G.S., M.F., P.N. and M.H. are employees of Haleon. N.P. is an employee of GSK.

Data Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from https://haleon-study-register.idea-point.com.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplemental Materials

Additional Information about Questionnaires

A total of three questionnaires were developed: one for the Otrivin Sea Water (OSW) and Otrivin Sea Water with Aloe Vera (OSWAV) study, and one each for the Otrisal and Prorhinel studies. Study designs prompted users to submit multiple questionnaires for various members in their household who have also used the product and for every applicable product they used.

Each questionnaire consisted of one continuous screen, and the number of items ranged from 33 to 63, which was subject to activation of conditional logic that released more questions based on the answers to previous questions. All items released to a participant were marked as mandatory by the system. If conditional logic activated a question to be presented to the participant, it had to be answered for the questionnaire to be submitted; however, questions not activated by conditional logic were not required for submission. Respondents were able to scroll through the entire questionnaire for review prior to submitting.

Cookies were not used to assign a unique identifier; a general laravel cookie was used instead. Duplicate entries were avoided as each questionnaire was identified by the unique participant ID, and the most recent entry was used as the final answer. As study design allowed for and encouraged multiple entries, no other log file analysis techniques were employed for identification of multiple entries.