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Research Article

Post-marketing Surveillance of Long-term Use of Stérimar™ Seawater-based Nasal Irrigation Solutions

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Abstract

Saline nasal irrigation (SNI) is a simple, easy-to-use and efficient method to keep a healthy nasal mucosa and to be used as an adjuvant treatment in different sinonasal conditions. Although its efficacy has been clinically demonstrated, the long-term safety profile of SNI has only been empirically addressed. The aim of this article is to present the post-marketing surveillance (PMS) data of Stérimar, a pioneer brand of nasal hygiene offering a wide range of seawater-based solutions. The PMS data presented in this article was collected from January 2018 to April 2021 in four countries (France, United Kingdom, Mexico and Australia) and from different sources (social media, email, health authorities, distributors, among others). In that period, more than 23 million units of these seawater-based products were sold in these markets with only 37 reported complaints. The most frequent complaints were considered not serious adverse events, mostly related to getting the product into the eyes, epistaxis and pain/burning sensation. This data, along with the high-quality manufacturing process of these products confirms the long-term safety profile of this range of SNI products in babies, children and adults.

Keywords: Seawater; Nasal; Hygiene; Safety; Adverse Events

Abbreviations

HCPs: Health Care Professionals; PMS: Post-marketing Surveillance; SNI: Saline Nasal Irrigation; URTIs: Upper Respiratory Tract Conditions

Introduction

During the last years, the levels of airborne aggressors, such as pollen, pollutants and infectious agents, have been increasing. A healthy nasal mucosa represents a physical barrier to the ambient air that plays a fundamental role in controlling and maintaining healthy airways by entrapping inhaled airborne aggressors [1]. Nevertheless, some pathogenic microorganisms or pollutants can impair the function of the nose, leading to the irritation and subsequent inflammation of the nasal mucosa [1]. This inflammation results in nasal symptoms such as rhinorrhea, nasal congestion and sneezing [2,3].

Nasal irrigation with lavage is an old procedure for upper respiratory tract care that leads to the cleaning of nasal mucosa [4]. It plays a pivotal role in the prevention and treatment of numerous sinonasal disorders and during postsurgical care and recovery [5]. In fact, several studies recommend nasal irrigation with saline or seawater solutions (known as saline nasal irrigation or SNI) as an adjuvant treatment in different sinonasal pathologies [5]. The use of nasal sprays containing saline or seawater solutions represents a simple, easy-to-use and efficient way to remove entrapped airborne

aggressors such as pollen, pollutants, allergens and pathogenic microorganisms [5-8].

Although the efficacy of saline nasal irrigation has been confirmed in several studies and literature reviews, their long-term safety has only been empirically addressed [5-8]. Stérimar is a pioneer brand of nasal hygiene offering a wide range of seawater-based solutions. The aim of this publication is to present the analysis of post-marketing surveillance (PMS) data collected from direct consumer complaints (reported by social media, email, phone, letters, etc…) or indirect consumer complaints (reported to health authorities, HCPs, retailers and distributors) to evaluate the long-term safety of these range of SNI products in babies, children and adults. The PMS data presented in this article was collected from January 2018 to April 2021 in four countries (France, United Kingdom, Mexico, and Australia), where more than 23 million units of these seawater solutions were sold.

Materials and Methods

Subjects

Post-marketing surveillance data from these seawater solutions users were collected from January 2018 to April 2021 by Church and Dwight in four countries where this company have offices: France, United Kingdom, Mexico, and Australia.

PMS data collection

The adverse events presented and discussed in the current article were collected from different sources: Direct consumer complaints: Comments in social media platforms, emails, phone, letters…Indirect consumer complaints: Reported to health authorities, health professionals, retailers, and distributors.

Data were collected by Church and Dwight is a spreadsheet including the date of the received complaint and the product, the quote, source of the collected complaint and severity.

Results and Discussion

High-quality seawater and manufacturing process

The present brand of seawater solutions offers a range of isotonic and hypertonic seawater-based nasal solutions, targeting a variety of nasal conditions for babies, children, and adults.

All products are formulated with 100% natural seawater drawn in the Bay of Mont Saint-Michel (Cancale-France). This area is known to have very low pollution levels and is also famous for the highest tides in Europe (up to 13 meters in amplitude) which ensure constant renewal and high oxygenation of the water contributing to its high quality [9].

Atlantic Ocean seawater has been found to contain an average of 35 grams per liter of mineral salts, most abundant of which is sodium chloride (NaCl). NaCl plays a vital role in the hydro-electrolyte balance of the body [9].

In addition to sodium and chloride, seawater contains the full spectrum of minerals and trace elements found in the human plasma, such as Potassium, Calcium, Copper, Manganese, Sulphur, Zinc, and Magnesium [5,10]. The benefits of seawater over classic saline solutions for nasal hygiene has been reported in the literature [5].

Although present in very small quantities in the body, minerals and trace elements activate many metabolic processes and are essential for the growth of the cells of the nasal mucosa, especially in babies and children [9].

Seawater used for these products is taken from a specific location, chosen according to meteorological elements, tides and the study of currents to ensure its purity. The area is regularly monitored by the official French body IFREMER (French Research Institute for the Exploitation of the Sea), to guarantee the high and constant quality of the seawater [9].

As soon as it is received from the manufacturer, the seawater is chemically and bacteriologically checked to monitor the possible presence of heavy metals or accidental pollution; and heat-treated and filtered to ensure its sterilization. The high-quality seawater used in this range of products is classified as Class A seawater due to its low microbial levels [11]. Apart from microbial presence, the halide content is also tested during the manufacturing process to ensure a high quality and safe product.

The technology behind the can

Besides the high-quality control during the manufacturing process, these seawater-based nasal sprays rely on a high technology can. A sterile bag-on-valve system protects the solution from the contact with the aluminum of the bottle, while specific tips/nozzles for adults and babies allow a gentle microdiffusion for the administration of the solution in the nasal cavity [12].

In addition, the nasal spray pumps range uses a preservative-free "anti-reflux system" technology, which preserves 100% of the formula and thus avoids any contamination of the solution.

Preclinical and clinical efficacy of seawater solutions

Several preclinical and clinical studies have been performed to demonstrate the efficacy and safety of these seawater solutions. The most relevant features of these studies are presented in table 1 (preclinical studies) and table 2 (clinical studies).

Intervention	*in vitro* model	Results	Ref.
Isotonic seawater solution (Stérimar Nasal Hygiene; SNH) vs. electrodialyzed seawater (EDS)	3D reconstituted human nasal epithelium tissue model (MucilAir™)	The ionic balance of SNH was more similar to human plasma and pure seawater compared to EDS. Both solutions were safe to use on nasal epithelium as neither of them caused cytotoxicity or inflammation.	[10]
Hypertonic seawater solution enriched with hyaluronic acid, eucalyptus oil, copper and manganese salts (Stérimar Stop and Protect Cold and Flu; SSPCF) vs. no treatment	3D reconstituted human nasal epithelium tissue model (MucilAir™)	SSPCF treatment respected nasal epithelium tissue integrity and enhanced barrier function without inducing a cytotoxic response. It also improved decongestion activity and helped recover cellular organization. Therefore, SSPCF demonstrated to be a safe and effective NI formula.	[13]
Isotonic seawater solution (Stérimar Nasal Hygiene; SNH) vs. no treatment	3D reconstituted human nasal epithelium tissue model (MucilAir™)	SNH treatment did not compromise the integrity of the nasal epithelium *in vitro*. It also significantly increased mucociliary clearance and mucin secretion, enhancing wound repair and removal of foreign particles on nasal mucosa.	[14]
Hypertonic seawater solution enriched with hyaluronic acid, eucalyptus oil, copper and manganese salts (Stérimar Stop and Protect Cold and Flu; SSPCF) vs. saline control	3D reconstituted human nasal epithelium tissue model (MucilAir™)	SSPCF was effective against some rhinovirus infections and *S. aureus in vitro*. It also increases the phagocytosis rate in the treated tissue.	[15]
Hypertonic seawater solution enriched with manganese and copper salts (Stérimar Blocked Nose; SBN) vs. non-enriched seawater	3D reconstituted human nasal epithelium tissue model (MucilAir™)	SBN is a safe formula for use on human nasal epithelium. SBN treatment significantly increased mucociliary clearance and exerted a bactericidal effect on *S. aureus* and *P. aeruginosa* cultures, compared to non-enriched seawater.	[16]

Table 1: Preclinical studies performed in the last years to demonstrate the efficacy and safety of these seawater solutions.

Using a 3D reconstituted human nasal epithelium tissue model (MucilAir™), preclinical studies have demonstrated that seawater solutions are safe for their use without affecting Trans Epithelial Electrical Resistance (TEER), an indicator of epithelium integrity [13,14,16]. Moreover, these *in vitro* studies have demonstrated the antibacterial properties [15,16] and the effectiveness of these solutions to increase mucociliary clearance [14,16] and remove foreign aggressors.

Study design	Intervention	Participants	Results	AE	Ref.
Prospective, single-blind, randomized, crossover study	Comparison of 3 isotonic nasal hygiene systems: Stérimar Original vs. Emcur vs. Sinus Rinse	18 adult volunteers recruited to rate their experience over 3 days using 3 well-established nasal hygiene systems	No statistically significant differences found in terms of effectiveness and comfort. Stérimar Original was found to have the easiest instructions to understand. No significant differences between Stérimar Original and Sinus Rinse with regards to ease of use, but both were easier to use than Emcur.	N/A	[17]

Prospective, controlled clinical trial	Isotonic seawater nasal spray enriched with manganese (Stérimar Mn) vs. allergic rhinitis (AR) standard care	60 patients with chronic AR. 30 were treated daily during 5 months with Stérimar Mn, 30 patients received only the standard care (control group)	The treatment with Stérimar Mn was able to significantly decrease the number of episodes of acute AR and increase the quality of life of those patients.	N/A	[18]
Randomized, double-blind, controlled parallel-group, clinical study	Microfiltered hypertonic seawater solution enriched with hyaluronic acids, eucalyptus oil and copper salts (Stérimar Stop and Protect Cold for Adults;SSPCA) vs. hypertonic seawater solution enriched with copper salts (Stérimar Blocked Nose; SBN)	102 common cold patients were randomized to use SSPCA (n = 51) or SBN (n = 51) until the common cold episode was resolved (maximum 14 days).	Both SSPCA and SBN are safe and effective solutions that enable symptomatic relief and decrease the presence of nasal viruses in common cold patients. SSPCA had a faster onset of action compared to SBN in nasal decongestion and breathing relief.	N/A	[19]
Randomized, controlled clinical trial	Isotonic seawater solution (Stérimar) vs.hypertonic seawater solution (Stérimar Hypertonic)	60 patients with history of chronic rhinosinusitis (30 received isotonic solution; 30 received hypertonic solution) completed a questionnaire (patient logbook) regarding the use of the solutions, symptoms…during the 15-day study period.	Hypertonic seawater solution proved to be better than isotonic seawater solution in eliminating the symptoms of nasal congestion, rhinorrhea, cough, headache and waking up during the night.	N/A	[20]

Table 2: Clinical studies performed in the last years to demonstrate the efficacy and safety of these seawater solutions. AE: Adverse Events; N/A: Not Applicable.

Clinical studies have confirmed the efficacy and safety of these Medical Devices in reducing the symptoms of the most common upper respiratory tract conditions (URTIs) such as the common cold, allergic rhinitis or chronic rhinosinusitis. This effect can be associated with the NaCl concentration of these solutions. Hypertonic seawater-based solutions (>0,9% NaCl) have demonstrated to be more effective than isotonic solutions (0,9% NaCl) in improving symptoms of URTIs [20], probably to the reduction of excess water from nasal mucosa contributing to the unblocking of the upper respiratory tract [21,22].

Long-term safety evaluation: PMS data analysis

Unit sales 2018-2021

Although these seawater solutions have been sold for more than 45 years, their long-term safety in babies, children and adults has not been previously documented in a dedicated publication. With this purpose, post-marketing surveillance (PMS) data of four markets (France, United Kingdom, Mexico, and Australia) corresponding to a 40-month period (from January 2018 to April 2021) were collected and analyzed. These data were collected from direct consumer complaints (raised from social media, email, phone, letters, etc…) or indirect consumer complaints through health authorities, health professionals, retailers, and distributors.

Unit sales of these products during that period in the different markets are presented in table 3.

	France	United Kingdom	Mexico	Australia	Other markets
Unit sales	7,559,423	7,678,579	8,069,669	46,925	32,987,985
Total unit sales	23,354,596				32,987,985
Total unit sales worldwide	56,342,581				

Table 3: Unit sales of the analyzed seawater solutions in four selected markets (France, United Kingdom, Mexico, and Australia) and other markets within a 40-month period (from January 2018 to April 2021).

In that period, more than 56 million units of the seawater solutions were sold worldwide, from which more than 40% (more than 23 million units) were sold in four markets (France, UK, Mexico, and Australia).

Reported adverse events 2018-2021

In the 40-month period (January 2018-April 2021), only 37 complaints were registered in France, United Kingdom, Mexico, and Australia. The number of reported adverse events per country are represented in table 4. United Kingdom was the country with more reported complaints (27), while in Australia no adverse events were reported in 40 months. Consequently, United Kingdom was the country where the unit sales/complaint ratio was lower: for each 284,392 units sold, one complaint was registered. Total unit sales/complaint ratio is higher: 631,205 units were needed in the four markets to register a complaint. Therefore, although these seawater solutions are widely sold in different markets, few complaints were reported, confirming the safety of these products.

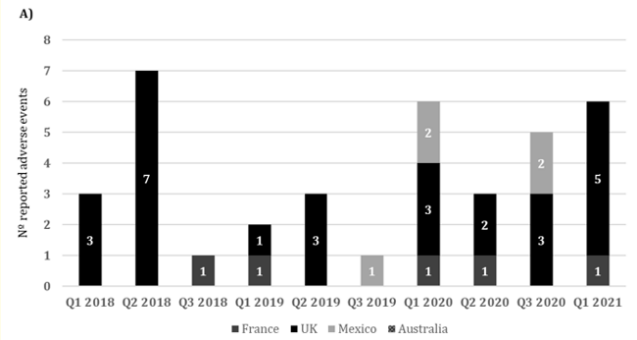
The high-quality seawater and manufacturing process and the technology behind the cans [9,12] contribute to the long-term safety profile of these nasal hygiene products. Nevertheless, the low number of complaints could also be since some users may not be aware of the option of reporting an adverse event. The analyzed products are manufactured via the same process and at the same location independently in which market they will be sold. Although United Kingdom is the country with the most reported complaints (27), the physical product characteristics and manufacturing process is the same than for other markets. The only assumption for complaints to be higher in the UK would be linked to the recent launch of the brand in this country, where people were less used to use nasal sprays and, therefore they would be less informed of how correctly use these devices compared to other countries such as France.

	France	United Kingdom	Mexico	Australia
Nº complaints/ country	5	27	5	0
Unit sales/ complaint ratio	1,511,885	284,392	1,613,934	0
Total complaints	37			
Total unit sales/ complaint ratio	631,205			

Table 4: Number of reported complaints per country (January 2018 - April 2021). Unit sales/complaint means the amount of unit sales registered to report a complaint.

The distribution of the reported complaints per date and location is represented in Figure 1. During the collection of PMS data, there were four peaks of reported adverse events: Q2 2018 (May-August), Q1 2020 (January-April), Q3 2020 (September-December) and Q1 2021 (January-April). Overall, the highest number of reported complaints (14) was registered in 2020.

A)



B)

	France	United Kingdom	Mexico	Australia	Total
2018	1	10	0	0	**11**
2019	1	4	1	0	**6**
2020	2	8	4	0	**14**
2021	1	5	0	0	**6**

Figure 1: A) Reported adverse events per quarter and location during 2018-2021 period (Q1: January-April; Q2: May-August; Q3: September-December). B) Reported adverse events per year and country. * Only the first quarter of 2021 was analyzed.

Figure 2 shows the different kinds of complaints reported during 2018-2021. The data indicates that the most frequent complaints were related to getting the product into the eyes, epistaxis (i.e., nose bleeding) and pain/burning sensation, among others. Some of these complaints coincide with the most frequent adverse events of saline nasal irrigation, such as epistaxis, nasal irritation and burning [23,24]. Epistaxis is, in general a benign symptom which has been estimated to occur in up to 60% of the population at least once during their lifetime [25]. The nose is one of the most vascularized organs. This high quantity of blood vessels plays an important role in thermal regulation and humidification of the inhaled air [26]. The high vascularization of the nose makes it an easy target for bleeding. According to the literature, the most common cause of epistaxis is trauma [27]. It has also been shown that hot and dry environments or the excessive use of hypertonic solutions, due to the withdrawal of liquid from the nasal mucosa [28], could dry out the nasal membrane [29], leading to nose bleeding.

Hypertonic solutions have demonstrated to be more effective than isotonic solutions in treating the symptoms of numerous sinonasal disorders, such as allergic rhinitis [30] or chronic rhinosinusitis [20]. Nevertheless, high concentrations of NaCl in these solutions have been associated with irritation and burning sensation when used on healthy mucosa [31]. Therefore, it is important to educate the users when to use hypertonic solutions (symptomatic treatment of sinonasal disorders) vs. isotonic solutions (daily nasal hygiene) and to improve product usage instructions to avoid undesired spatter of the product into the eyes.

The reported complaints are not considered serious adverse events, suggesting a very positive safety profile of these seawater nasal products for long-term use in babies, children, and adults.

Figure 2: Most frequent complaints reported during 40 months (January 2018-April 2021).

Conclusion

A regular hygiene of the nose is essential to cleanse, eliminate impurities, restore the natural moisture of the nasal mucosa, and prevent upper respiratory tract conditions such as rhinosinusitis, allergic rhinitis, or viral/bacterial infections. In cases of nasal congestion, saline nasal irrigation can also help to unblock the nose [4,32]. In this article, the PMS data of a range of seawater-based medical devices for nasal hygiene, sold worldwide during more than 45 years, has been discussed.

The lack of serious adverse events as per the PMS data analyzed in the present article, in addition to the high purity of the water, the strictly controlled manufacturing process and the technology of the can, together with all the safety data gathered from *in vitro* and human studies makes nasal irrigation with these seawater solutions a safe, simple solution to improve, restore and maintain the normal function of the nasal epithelium in babies, children and adults.

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Conflict of Interest

The author reports no conflicts of interest in this work.

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