and should not be used for self-injection or any filler procedures. The statement also emphasizes that filler products that are not FDA-approved should not be used for dermal fillers. Furthermore, the American Society for Dermatologic Surgery Association issued a patient safety alert on the use of hyaluron pens and particularly how this trend poses a great safety risk to children who are influenced to perform self-injections. On September 13, 2019, Health Canada (the national health policy department) issued a recall stating that it is illegal to advertise, import, or sell these “handheld medical devices” without proper licensing. In the United States, the administration of medication is defined under each state’s “practice of medicine” regardless of the route of administration. Thus, because “needle-free injectors” including hyaluron pens can be classified as handheld medical devices, there should be restrictions in obtaining and purchasing such devices.

The injection of filler product by nonmedical professionals increases the risk of serious adverse effects. The lack of expertise can lead to infection, vascular occlusion, skin necrosis, and blindness. Dermatologists and medical professionals should be aware of this trend because patients who experience adverse effects may present to the office. Although many videos demonstrating DIY filler self-injection have been flagged by some social media platforms, content is readily available for viewers of all ages. The accessibility to these videos poses a great public safety risk, and more restrictions should be implemented to decrease their availability online.

Ten-Year Global Postmarket Safety Surveillance of Delayed Complications With a Flexible Cheek Filler

Hyaluronic Acid (HA)-based dermal fillers have been used extensively in the recent years because of their immediate predictable results, safety, and minimal downtime postprocedure. Even though HA fillers have a great safety profile and patient satisfaction, rare adverse events (AEs) still occur. These AEs are immediate, early (<14 days post-treatment), or delayed-onset (≥14 days post-treatment). Although rare, physicians focus on delayed-onset nodules, granulomas, and hypersensitivity, because they can be difficult to treat.

Restylane Contour (HACON) Galderma, Uppsala, Sweden is an HA filler that has been available outside of the US (known as Restylane Volyme) since 2010 and was recently FDA-approved in the US for cheek augmentation (June 2021). It is manufactured using XpresHAn technology (Optimal Balance Technology, ex-US), which provides flexibility to support dynamic movement and a larger calibration size—ideal for tissue expansion and smooth contouring of the cheeks and midface. No delayed-onset events related to HACON were reported in clinical studies conducted throughout Europe and the US, which involved 319 subjects followed-up for up to 18 months.

This article discusses manufacturer-reported global postmarketing safety surveillance (PMS) data for HACON from 2011 to July 2021 (10 years postapproval ex-US) with a focus on delayed-onset nodules (noninflammatory and inflammatory) and inflammatory reactions (hypersensitivity and granulomas).

Methods

This safety review was conducted by gathering PMS reports from an internal manufacturer global database between 2011 and July 2021 for HACON (10 years). PMS reports from physicians, health care providers, consumers, or various literature were recorded, analyzed, and compiled for appropriate health authorities. All AEs were coded using MedDRA and presented using preferred terms (MedDRA PT). Internal medical experts assessed the relationship to products based on the compiled case information.

All PMS reports with early-onset (<14 days) events, such as bruising and swelling, or unclear time to onset were excluded in the current analysis. Delayed-onset AEs (≥14 days) were grouped based on MedDRA PT coding: nodules (“mass,” “nodule,” “papule,” “induration”), granulomas (“granuloma,” “foreign body”), and hypersensitivity (“hy-
persensitivity,” “inflammation,” “swelling”). Nodules were further divided into “noninflammatory” and “inflammatory” based on the nodule characteristics. Inflammatory nodules (“hot nodules”) were accompanied by pain, swelling/inflammation, tenderness, redness, or irritation, whereas noninflammatory (“cold nodules”) were just palpable lumps. Hypersensitivity reactions were confirmed if there was delayed swelling in injected areas of the face, diffuse (widespread), or persistent facial swelling. Positive histologic analyses confirmed true granulomas, otherwise, they were recategorized based on the description. The total number of single-use syringes sold worldwide during the search period was used for calculating the incidence.

**Results**

From 339 events coded as potential events of interest (EOI) for HACON, only 52 (15.3%) were identified as delayed-onset, giving a reporting frequency of 0.003% during the period of 2011—July 2021. Cases were reported from 2013 to 2021, with most between 2016—2019 (66%).

The most frequent EOI for HACON was nodule formation (30; 0.002%), with a total of 17 inflammatory nodules (0.001%) and 13 noninflammatory nodules (0.0008%). The remaining EOIs were hypersensitivity reactions (22; 0.001%). There were no delayed-onset histologically confirmed granulomas.

Fourteen of these EOIs reported degree of severity: 14.3% (2/14) were mild, 64.3% (9/14) moderate, and 21.4% (3/14) severe (1 inflammatory nodule, 1 noninflammatory nodule, and 1 hypersensitivity). Of the total 52 events, 35 had reported outcomes, and 60.0% (21/35) were resolved or resolving at the time of reporting. Time to onset ranged from 2 weeks to 2 years, with a mean of 4.2 months.

Treatments of the AEs were recorded in most cases (81.1%; 43/53). Most of the noninflammatory nodules were treated with hyaluronidase, and inflammatory nodules and hypersensitivity reactions were treated with one or a combination of hyaluronidase, corticosteroids, antihistamines, or antibiotics.

**Discussion**

This postmarketing safety review focuses on delayed-onset events, including nodules, granulomas, and hypersensitivity reactions after treatment with HACON. There were 52 delayed EOIs (0.003%) with a mean onset of 4.2 months. Nodules were the most common delayed-onset events (0.002%) followed by hypersensitivity reactions (0.001%), with no histologically confirmed granulomas.

The relative incidence presented in this review for delayed complications (0.003%) is comparable to previous reports for XpresHAn technology fillers between 2011 and 2015 (0.003%) using the same database. Furthermore, these data align with retrospective studies, which suggest the estimated percentage of delayed complications is <1% across various HA fillers. Because of significant under-reporting of events, the incidences captured in PMS are likely lower than what can be expected in clinical practice. Despite this, these data suggest a long-term safety profile (10 years) for HACON with low incidences of delayed-onset events (nodules, hypersensitivity, and granulomas) reported since 2011. Furthermore, given the mean time to onset (4.2 months), it is reasonable to postulate that although no delayed EOIs were reported in clinical studies, they could have been captured during that timeframe.

**Conclusion**

HACON has a low reporting frequency of delayed nodules and inflammatory events during a 10-year postmarket surveillance since approval in 2010 outside of the US. These data align with previous safety reports and demonstrate a long-term safety profile for HACON, which supports its FDA-approval in the US for cheek augmentation and treatment of midface contour deficiencies.

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