Comparison of FDA-approved intranasal acute migraine treatment adverse event profiles

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Introduction

- ATZUMI (STS101) is an FDA-approved dihydroergotamine (DHE) nasal powder, drug-device combination product designed for intranasal administration for the acute treatment of migraine (with or without aura).[1]
- Common side effects of DHE include nausea and vomiting (regardless of dosage form or route of administration), which have been attributed to high peak plasma concentrations after initial administration (especially with injected formulations); while liquid nasal sprays have lower reported occurrences of nausea and vomiting, irritative nasal symptoms are common.[2,3]
- The advanced nasal powder and device technology minimizes post-dose pharmacokinetic variability, which may lead to improvements in adverse events (AEs).

Objective

- To compare the FDA-approved prescribing information for the most commonly listed AEs across intranasal acute migraine treatments.

Methods

- U.S. prescribing information for 6 intranasal products approved for the acute treatment of migraine was reviewed to identify and compare the most commonly reported AEs.
- TEAE data were derived primarily from short-term, double-blind, placebo-controlled studies.
- For ATZUMI and TRUDHESA, whose 505(b)(2) NDA applications relied in part on Migranal as the reference listed drug, AE data were obtained from 2 sources:
  - Short-term, placebo-controlled clinical trials of Migranal
  - Open-label, long-term (12-month) studies of the respective products
- Prescribing information reviewed was dated April 2025 for ATZUMI, April 2022 for Migranal, September 2021 for TRUDHESA, August 2025 for ZAVZPRET, December 2025 for Imitrex nasal spray, and November 2022 for Zomig nasal spray.[1,4-8]

Results

- The most common AEs reported in the prescribing information for the 6 FDA-approved intranasal treatments for acute migraine are summarized in Table 1.

Adverse events

- Overall, intranasal treatments for acute migraine were generally well tolerated.
- ATZUMI nasal powder was associated with lower rates of local AEs than the 2 nasal spray DHE products.
- Rates of dysgeusia reported for the 3 DHE products were lower than those reported for the triptan- or CGRP-based products.
- Discontinuations due to AEs were infrequent in historical placebo-controlled DHE nasal spray trials for Migranal and TRUDHESA (1.4%), with rhinitis the most common reason for discontinuation.
- In the long-term ATZUMI safety study, nasal discomfort was the most common AE leading to discontinuation (1.5%).

Local Adverse events

- Local irritative symptoms (irritation in the nose, throat, and/or disturbances in taste) were reported in approximately 30% of adults treated with Migranal nasal spray, compared with 9% of placebo-treated adults; in open-label studies permitting repeated use, such symptoms were reported in 52.3% of adults treated with Trudhesa and 29% treated with ATZUMI (Table 2).
- Because product-specific AE data for ATZUMI and TRUDHESA were derived from long-term studies of up to 12 months, reported AE rates for these products may be higher because of cumulative use than those reported in the short-term studies used for the other products.

Table 1. Most common AEs listed in the U.S. prescribing information for intranasal treatments for acute migraine

AE Term Used in PI	ATZUMI 5.2 mg (DHE nasal powder)	Migranal 2.0 mg (DHE nasal spray)	TRUDHESA 1.45 mg (DHE nasal spray)	ZAVZPRET 10.0 mg (zavegepant nasal spray)	Imitrex 20.0 mg (sumatriptan nasal spray)	Zomig 5.0 mg (zolmitriptan nasal spray)
Rhinitis (%)		26	19[c]			
Nasopharyngitis (%)	5[a]	3	21[c]			
Dysgeusia[d] (%)	8[a]	8	6[c]	18	24.5	21
Nasal discomfort[e] (%)	11[a]		7[c]	3	3.8	3
Nausea and/or vomiting (%)	14[b]	14	14[b]	6	13.5	4
Application site reaction (%)	6[b]	6	6[b]			
Rhinorrhea (%)	4[a]		1[c]			
Nasal congestion (%)	5[a]					
Sinusitis (%)			5[c]			
Paresthesia (%)						10
Hyperesthesia (%)						5

AE, adverse event; DHE, dihydroergotamine; PI, prescribing information.
[a]Data from ATZUMI studies; [b]Data from Migranal studies; [c]Data from Trudhesa studies; [d]Taste-related adverse event terminology varies across prescribing information: Migranal, "altered sense of taste" (dysgeusia); Zavzpret, "taste disorders" (dysgeusia and ageusia); Imitrex, "bad/unusual taste"; Zomig, "unusual taste". [e]Nasal discomfort terminology varies across prescribing information: Imitrex, "ear, nose, and throat disorder/discomfort of nasal cavity/sinuses"; Zomig, "disorder/discomfort of nasal cavity."

Table 2. Local irritative symptoms reported in prescribing information for DHE intranasal products

	ATZUMI 5.2 mg (DHE nasal powder)	Migranal 2.0 mg (DHE nasal spray)	TRUDHESA 1.45 mg (DHE nasal spray)
Composite local irritative symptoms (%)	29	30	52.3
Rhinitis (%)		26	19[c]
Nasopharyngitis/pharyngitis (%)	5[a] nasopharyngitis	3 pharyngitis	21[c] nasopharyngitis 3[c] pharyngitis
Dysgeusia[d] (%)	8[a]	8	6[c]
Nasal discomfort (%)	11[a]		7[c]
Application site reaction (%)	6[b]	6	6[b]
Sinusitis (%)		1	5[c]
Epistaxis (%)	2[a]		3[c]
Rhinorrhea (%)	4[a]		1[c]
Nasal congestion (%)	5[a]		
Olfactory test abnormal/change in smell (%)			4[c] olfactory test abnormal 1[c] change in smell

AE, adverse event; DHE, dihydroergotamine.
[a]Data from ATZUMI studies; [b]Data from Migranal studies; [c]Data from Trudhesa studies; [d]Taste-related adverse event terminology varies across prescribing information: Migranal, "altered sense of taste" (dysgeusia).

Conclusions

- Intranasal products approved for the acute treatment of migraine are generally well-tolerated.
- In the approved prescribing information, ATZUMI demonstrated a favorable tolerability profile during long-term PRN use, with lower reported rates of local AEs than the 2 FDA-approved DHE nasal sprays for acute migraine treatment.
- Among FDA-approved intranasal acute migraine treatments, ATZUMI was associated with low reported rates of local AEs in its prescribing information.

References

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