MTF Formulary Management for Triptan Migraine Drugs

Defense Health Agency Pharmacy Operations Division

Bottom Line

- Zolmitriptan tabs and ODT were added to the Basic Core Formulary (BCF); sumatriptan tabs and rizatriptan tabs and ODT remain on the BCF.
- Step therapy is now required, based on dosage form (oral, nasal, injectable). In general, generic formulations are step-preferred and branded products are non step-preferred, with the exception of Relpax tabs. (See page 3)
- Eletriptan (Relpax) was designated as a step-preferred brand on the UF. Generic formulations for eletriptan (Relpax) are expected as early as December 2016.
- The new drugs, Onzetra Xsail, Zembrace SymTouch, and Zecuity, offer no compelling advantages over existing agents and were made nonformulary and non step-preferred.
- While oral agents are by far the preferred option, alternative routes of delivery still have a role among migraneurs based on patient headache characteristics, prior response, and associated symptoms.

Uniform Formulary (UF) Decision: The Director, DHA, approved the recommendations from the August 2016 DoD P&T Committee meeting on November 8, 2016, with an implementation date of February 8, 2017.

Uniform Formulary (UF)		Nonformulary (NF) Agents
MTFs must have on formulary	**MTFs may have on formulary**	**MTFs must not have on formulary**
Step-preferred • sumatriptan tabs* • rizaptriptan tab and ODT • zolmitriptan tab and ODT	**Step-preferred** • eletriptan tabs(Relpax) †† • sumatriptan nasal spray (Imitrex, generics) • sumatriptan 4 mg and 6 mg injection (Imitrex STATdose, generics) **Non step-preferred** • naratriptan tabs (Amerge, generics) • zolmitriptan nasal spray (Zomig)	**Non step-preferred** • almotriptan tabs (Axert, generics) • frovatriptan tabs (Frova, generics) • sumatriptan/naproxen tabs (Treximet) • sumatriptan 4 mg and 6 mg needle-free (Sumavel DosePro) • sumatriptan 3 mg autoinjector (Zembrace SymTouch) • sumatriptan nasal powder (Onzetra Xsail) • sumatriptan TDS (Zecuity) †
*Sumatriptan 4 mg and 6 mg injection will be added to the BCF when multi-source cost-effective generic formulations are available. †Sumatriptan TDS currently not on the market; if re-introduced, will be designated nonformulary †† Relpax generics expected in December 2016; other step-preferred triptans are more cost-effective		

ODT – orally dissolving tablets TDS-transdermal delivery system

Background and Efficacy

- The Triptans Drug Class was previously reviewed for formulary placement in June 2008. There are currently eight oral triptan drugs available in the United States. Since the last review, several agents have become available in generic form, including naratriptan. Eletriptan (Relpax) and sumatriptan/naproxen (Treximet) remain the only oral branded agents in the class. Generic availability of eletriptan is expected in late 2016 to early 2017.
- This review addressed the oral, subcutaneous, nasal, and transdermal (TDS) delivery routes of triptan agents, with a focus on the remaining branded agents and new entrants, namely sumatriptan nasal powder (Onzetra Xsail), sumatriptan 3 mg autoinjector (Zembrace SymTouch), and sumatriptan TDS (Zecuity).
- In the Military Health System, the oral triptans comprise 93% of the market basket, followed by the injectable products (4%), and nasal formulations (3%), with the now discontinued Zecuity TDS accounting for less than 1% of the triptan market basket.
- The available evidence is insufficient to conclude that there is a clinically superior triptan for migraine headache when all efficacy endpoints are considered, including speed of relief, degree of relief at various time points, headache recurrence, and 24-hour headache-free response rates.
- Clinical practice guidelines and systematic reviews found that the triptans as a class have quality evidence to support use in the treatment of moderate to severe migraine. It is likely that some patients will respond to alternative oral options if the initial choice is not successful. Guidelines recommend considering non oral options if oral products are ineffective.

- While studies typically require patients to achieve moderate to severe levels of pain before instituting treatment, standard clinical practice typically encourages use of the triptans early on in the attack, which can result in improved outcomes.
- Naratriptan and zolmitriptan, while not FDA-approved for menstrual-associated migraines, have Level B supporting evidence for this use. Naratriptan also has a long half-life and the lowest headache recurrence potential at 24 hours. Naratriptan was added to the UF as a non step-preferred option.
- Sumatriptan/naproxen (Treximet) is a fixed-dose combination of a triptan with a nonsteroidal anti-inflammatory drug (NSAID). It is likely that combining any NSAID with a triptan increases efficacy. Treximet was made nonformulary and non step-preferred.

Newer Agents

Sumatriptan nasal powder (Onzetra Xsail)

Onzetra Xsail is a new nasal formulation of sumatriptan. It improved 2-hour pain relief and pain-free endpoints over placebo in a statistically significant manner in the trial that led to FDA approval. When compared to oral sumatriptan in one trial, its effect on efficacy endpoints was similar. Limitations include the short duration of the studies and lack of head-to-head comparisons with other triptans.

Sumatriptan 3 mg autoinjector (Zembrace SymTouch)

Zembrace provides a new dosage of sumatriptan (3 mg) in an autoinjector. No new clinical efficacy data for treating migraine was provided to the FDA for approval. In prior sumatriptan dose-finding studies, 3 mg was comparable to 4 mg and 6 mg sumatriptan injection doses (Imitrex STATdose) for two-hour pain relief endpoints. The 3 mg dose may also provide slightly reduced overall adverse events compared to the currently approved 4 mg and 6 mg doses. The clinical significance of these findings is unclear.

Sumatriptan transdermal system (Zecuity)

Efficacy data with Zecuity supported its use over placebo. However, Zecuity was voluntarily withdrawn from the market in June 2016, following the FDA Safety Alert regarding concerns over reports of increased risk of burns and severe application site reactions.

Safety and Tolerability

- While the triptans have contraindications and limitations for use in individuals with cardiovascular risks and adverse events are common, overall the class is well-tolerated with few serious adverse events reported.
- Tolerability and adverse events are often predicated on the route of delivery. Patients often describe “triptan sensations,” most commonly noted with the subcutaneous routes of delivery, but these are not harbingers of serious issues. While the subcutaneous route provides the fastest onset of action, it is associated with the highest incidence of adverse events and highest headache recurrence rates. Onzetra Xsail reports nasal issues as a predominant concern.

Clinical Summary

- The triptans are significantly superior to placebo in treating moderate to severe migraine headache.
- The oral triptans, in particular generic products, are the most convenient and easy to use, and are often preferred by patients and providers as the first choice treatment. Half of patients may not respond to the first choice, and there is limited ability to predict individual response. It is reasonable to try multiple oral triptans if the first choice fails.
- Alternative formulations may allow for potential clinical benefit in individual patients.
- While subcutaneous formulations offer the highest headache response rate, they also have the most discomfort, side effects, and headache recurrence potential.
- The triptans currently on the UF are adequate to meet the needs of the majority of DoD patients.
- Choice of treatment should be based on prior response to treatment, tolerability of formulations, individual patient headache characteristics, and cost.

Prior Authorization for Triptans

- All new users of nonformulary non-preferred oral, subcutaneous, nasal, and transdermal triptans are required to undergo automated (step therapy) prior authorization (PA) to ensure the preferred agents are utilized first.

- "Grandfathering" applies, in that only new patients are subject to the step therapy.
- The goal is to promote use of generically available, clinically, and cost-effective oral, nasal, subcutaneous, and non-transdermal options prior to use of the newer branded formulations. Step therapy accounts for the majority of cost avoidance within the class.
- For the oral and ODT triptans, patients must have tried and failed at least two different step-preferred products of two different chemical entities (e.g., generic rizatriptan, sumatriptan, zolmitriptan, or Relpax) before using the non step-preferred products (Amerge, Axert, Frova, and Treximet).
- For the nasal triptans, patients must have tried sumatriptan nasal spray prior to use of Zomig nasal or Onzetra Xsail.
- For the injectable triptans, patients must have tried and failed sumatriptan 4 mg/6 mg (Imitrex STATdose) prior to use of Sumavel DosePro or Zembrace SymTouch.
- Any future transdermal formulation will also be subject to step therapy, requiring at least two UF triptans, regardless of formulation, first.
- Manual Prior Authorization can be used for patients where use of the non step-preferred product is clinically required (e.g., for those patients with an adverse reaction, inadequate therapeutic response, or medical contraindication to the step-preferred products).
- Note that quantity limits also apply for the class.

References

- DoD P&T Committee minutes: http://www.health.mil/PandT
- Current/future drug classes under review by the DoD P&T Committee http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-PT-Committee
- TRICARE Formulary Search Tool: http://www.health.mil/formulary
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents and Executive Summaries available at: http://www.health.mil/DoDPTResources
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

Triptans – MTF Dose/Price Comparison	
Drug	**MTF Avg Cost/Day (Aug 2016)**
Basic Core Formulary	
sumatriptan tabs	**$ = Most Cost-Effective**
rizatriptan tabs and ODT	
zolmitriptan tabs and ODT	
Uniform Formulary	
naratriptan tabs	**$$ = Less Cost-Effective**
eletriptan tabs (Relpax)	
sumatriptan nasal (Imitrex)	
zolmitriptan nasal (Zomig)	**$$$ = Less Cost Effective**
sumatriptan 4 mg and 6 mg injectable (Imitrex STATdose)	
Nonformulary	
sumatriptan/naproxen (Treximet)	**$$$$ = Least Cost-Effective**
almotriptan tabs (Axert)	
frovatriptan tabs (Frova)	
sumatriptan nasal (Onzetra Xsail)	
sumatriptan 4 mg, 6 mg needle-free (Sumavel DosePro)	
sumatriptan 3 mg autoinjector (Zembrace SymTouch)	
sumatriptan TDS (Zecuity)	

Legend:
$ = "Most Cost-Effective" represents Rxs with the lowest cost and best clinical efficacy
$$ = "Less Cost-Effective" represents higher cost Rxs with similar clinical efficacy
$$$ = "Less Cost-Effective" represents next higher cost Rxs with similar clinical efficacy
$$$$ = "Least Cost-Effective" represents Rxs with the highest cost with similar clinical efficacy