Migraine Agents—Triptans Subclass

Executive Summary

- See the August 2016 DoD P&T Committee meeting minutes for the most recent formulary recommendations, available at http://www.health.mil/PandT.
- The Triptans Subclass was last reviewed in June 2008. There are currently 12 triptans available in the United States. (See Table 1.) Most are available as generics. Five branded agents remain in the subclass, including eletriptan (Relpax), sumatriptan nasal powder (Onzetra Xsail), sumatriptan needle-free injection (Sumavel DosePro), sumatriptan 3 mg autoinjector (Zembrace SymTouch), and sumatriptan/naproxen (Treximet).
- Since the last class review, several agents are now available in generic form. Relpax generics are expected in late 2016/early 2017.
- There have been few active comparator trials for the triptans; where head-to-head data is available, the numbers of patients studied are minimal, limiting any conclusions that can be made for the entirety of the class. 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 headache.
- Onzetra Xsail, Zembrace SymTouch, and sumatriptan transdermal system (TDS) (Zecuity) have not been previously reviewed. In June 2016, Zecuity was voluntarily removed from the market due to safety concerns.
- Onzetra Xsail provides a new nasal sumatriptan formulation while Zembrace SymTouch is a new 3 mg autoinjector sumatriptan formulation. Both are FDA-approved for acute treatment of migraine with or without aura in adults.
    - Onzetra Xsail: FDA approval was based on reference data from sumatriptan- and placebo-controlled trials that showed two-hour headache resolution similar to other triptans. Statistically significant differences were noted at the 30-minute pain resolution endpoint. Limitations of the study included lack of active comparators.
    - Zembrace SymTouch: No new clinical efficacy data was presented as part of its approval by the FDA. Limitations of the data include the lack of new studies and lack of head-to-head comparisons with other triptans.
    - Onzetra Xsail and Zembrace SymTouch have safety and tolerability concerns related to their mode of delivery.
    - The new formulations – Onzetra Xsail and Zembrace SymTouch – offer no clinically compelling advantages over existing Uniform Formulary agents.
- The safety profiles of individual triptans are consistent in terms of cardiovascular effects and are well known.
- Aside from Zecuity safety concerns, there are no significant efficacy or safety updates for the class since the June 2008 review. Overall, safety monitoring recommendations are similar for the class, with the delivery method contributing to safety and tolerability differences.
- The generic products are adequate to meet the needs of the majority of DoD patients with migraine.
- Choice of treatment should be based on efficacy, tolerability, individual patient characteristics, and cost.

Previous Uniform Formulary (UF) Review

In June 2008, rizatriptan (Maxalt) was designated with Basic Core Formulary (BCF) status, with sumatriptan tablets and one injectable chosen for the BCF when multisource generics became available. All oral triptans were designated with UF status, with almotriptan, frovatriptan, and naratriptan made nonformulary. In May 2010, sumatriptan needle-free injection (Sumavel) was designated nonformulary. See the August 2016 DoD P&T Committee meeting minutes for the most recent formulary recommendations, available at http://www.health.mil/PandT.

Table 1: Triptans Available in the U.S.[1,2]

Active Ingredient	Brand (Manufacturer)	Strengths	FDA Approval	Patent Exp Date
almotriptan	Axert (Janssen, generics)	6.25, 12.5 mg tabs	May 2001	Nov 2015
eletriptan	**Relpax** (Pfizer)	20, 40 mg tabs	Dec 2002	Dec 2016
frovatriptan	Frova (Endo, generics)	2.5 mg tab	Nov 2001	Mar 2016
naratriptan	Amerge (GSK, generics)	1, 2.5 mg tabs	Feb 1998	-
rizatriptan	Maxalt, Maxalt MLT (Merck, generics)	5, 10 mg tabs 5, 10 mg ODT	Jun 1998	-

sumatriptan	Imitrex (GSK, generics)	6 mg (pen & vial) inj, 4 mg (pen) inj 25, 50, 100 mg tabs 5, 20 mg/spray nasal spray	Aug 1992	-
	Onzetra Xsail (Avanir)	11 mg nasal powder	Jan 2016	Mar 2020-Dec 2030
	Sumavel DosePro (Zogenix)	4 or 6 mg / 0.5ml needle-free injection	Jul 2009 Nov 2013	Dec 2015- Dec 2024
	Zecuity* (TEVA)	6.5 mg / 4 hr iontophoretic patch	Jan 2013	Feb 2018-Apr 2026
	Zembrace SymTouch (Reddy's)	3 mg / 0.5 ml inj (autoinjector)	Jan 2016	None unexpired
sumatriptan/ naproxen	**Treximet** (GSK)	85 mg / 500 mg tab 10 mg / 60 mg tab	Apr 2008 May 2015	Feb 2018-Apr 2026
zolmitriptan	Zomig (Astra Zeneca, generics)	2.5, 5 mg tabs, ODT 2.5, 5 mg / spray nasal	Nov 1997	May 2013-May 2021

GSK: Glaxo Smith Klein; BMS: Bristol-Myers Squibb

ODT: orally dissolving tablets

Note: Products in **bold** font are branded

*Zecuity transdermal system removed from market in June 2016

Indications

All of the triptans are indicated to treat migraine. Imitrex STAT dose injectable and Sumavel DosePro are also indicated for cluster headaches. Triptans with pediatric migraine indications include almotriptan (ages 12-17), rizatriptan (ages 6-17), sumatriptan/naproxen (Treximet) (ages 12-17), and zolmitriptan (ages 12-17).

Efficacy Measures

The primary efficacy measure in migraine headache studies is the pain free and pain relief status at the 2-hour post treatment endpoint, and sustained pain relief at the 24-hour endpoint. Most commonly, studies use a 4-point pain scale ranging from 0 (pain free) to 3 (severe pain). Research protocols often require patients to wait until pain is moderate or severe, whereas clinical practice is to treat the migraine early in its course. The primary endpoints of many studies, particularly non oral treatments, will include additional time endpoints that are earlier than 2 hours and beyond 24 hours. The International Headache Society prefers the 2-hour pain free outcome and the 24-hour sustained pain free outcome as the preferred endpoints.

Efficacy

Available data suggests all triptans are significantly superior to placebo for treating acute migraine. The oral agents, particularly triptans that are available in generic formulations, are the most convenient and easy to use, and are often preferred by patients and providers as the first choice treatment. The available data is not sufficient to clearly establish relative superiority of one oral triptan over another.

Systematic Reviews

None of the systematic reviews completed since 2008 include the newer agents. Derry (2013) compared sumatriptan delivered via oral, subcutaneous, intranasal, and rectal routes. The review found that a single sumatriptan dose administered via any of the routes was effective in relieving migraine headache pain. The subcutaneous route provided the greatest pain relief, with pain reduced from moderate or severe to none by 2 hours in 59% of patients taking the 6 mg sumatriptan dose versus 15% in placebo. The subcutaneous route was typically the fastest acting of the agents.

Law (2016) examined the combination of sumatriptan and naproxen. Overall the combination was superior to placebo for pain free and headache relief at two hours and was effective in the acute treatment of migraine headaches. However, using any nonsteroidal anti-inflammatory drug concurrently with a triptan will likely increase efficacy. Bird (2014) looked at zolmitriptan and again found the agent to be effective for treatment of migraine headaches. Numbers needed to treat for two-hour pain relief for the triptans administered in the typical doses via all routes ranged from 2.4 to 5.0.

Clinical Considerations

- 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.
- For patients who are unable to manage their migraines with oral options, alternative delivery options are required on the UF if the initial choice is not successful.
- While subcutaneous sumatriptan formulations provide the quickest onset of action and highest response rate, they also have the highest incidence of adverse effects and intolerability issues, along with a higher risk of recurrent migraine.
- Frovatriptan (Frova, generics) (Level A evidence), naratriptan (Amerge, generics), and zolmitriptan (Zomig, generics) (Level B evidence) have a therapeutic niche for treatment of menstrual-associated migraines, but are not specifically FDA-approved for this indication.

New Agents

There have been several new formulations approved since the June 2008 class review. Sumavel DosePro was previously reviewed as a new drug in an already reviewed class and made nonformulary. Onzetra Xsail, Zembrace SymTouch, and Zecuity TDS all contain sumatriptan and provide additional non oral alternatives to the currently available injectable and nasal spray formulations.

Sumatriptan Nasal Powder (Onzetra Xsail)

- Onzetra Xsail was approved in January 2016 and is indicated for the acute treatment of migraine with or without aura in adults. Approval was based on phase II and phase III trials and reference data from sumatriptan. Onzetra is delivered via an Xsail breath-powered delivery nasal device. The dose is two 11 mg sumatriptan capsules that are part of nosepiece.

- FDA approval is based on the pivotal TARGET trial. The trial assessed the primary endpoint of headache relief versus placebo at 15, 30, 60, 90 minutes, and 2-, 24-, 48-hour endpoints in 212 patients. The 2-hour headache relief endpoint was found to favor Onzetra Xsail by 68% to 45% for placebo. Statistical significance was reached at 30 minutes. The 2-hour no-headache endpoint favored Onzetra Xsail by 34% to 17% for placebo.

- In the COMPASS trial, efficacy and safety of Onzetra Xsail versus oral sumatriptan was compared. Although not part of the FDA submission, it was notable for its approach and findings. Patients were required to begin treatment early at migraine onset. While there was benefit at the 30-minute endpoint for headache relief, Onzetra Xsail did not show a statistically significant difference over placebo nasal system plus sumatriptan oral at the 2-hour headache relief and 2-hour no-headache endpoint.

Sumatriptan 3 mg Autoinjector (Zembrace SymTouch)

- Zembrace SymTouch was approved in January 2016 and provides a 3 mg prefilled ready to use, single dose disposable autoinjector for acute treatment of migraine with or without aura. Zembrace SymTouch is the only sumatriptan that delivers a 3 mg dose. The agent was approved with a new drug application but had no new data to support efficacy. The label is consistent with data used for sumatriptan subcutaneous agents.

- In prior dose finding studies of sumatriptan, 3 mg doses were comparable to currently approved 4 and 6 mg doses of sumatriptan for two hour pain relief end points. The 3 mg may also provide slightly reduced overall adverse events compared to currently approved 4 and 6 mg doses. The clinical significance of these findings are unclear.

Sumatriptan Transdermal System (Zecuity)

- Zecuity was approved in January 2013 and is indicated for acute treatment of migraine with or without aura in adults. It provided the first iontophoretic transdermal system to deliver sumatriptan at a rate of 6.5 mg over 4 hours. Efficacy was studied in a trial of 454 patients against placebo. The 2-hour headache relief endpoint was found to favor Zecuity by 53% to 29% for placebo. The 2-hour no-headache endpoint favored Zecuity by 18% to 9% for placebo.

- At the time of FDA approval, there was not a safety signal beyond application site reactions that would be expected given the mode of delivery. Zecuity was removed from the market by TEVA after an FDA Safety Alert published in June 2016 warned of the risk of burns and severe application site reactions.

Safety Concerns

- Since 2008, package insert safety sections have been updated for the class as a whole. All the triptans are contraindicated in patients with a history of coronary artery disease or coronary artery vasospasm, Wolff-Parkinson-White or other cardiac accessory pathway, history of stroke, transient ischemic attack, or basilar migraine, peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, recent use of another 5HT1 agonist or ergotamine-containing medication, use of MAO-A inhibitor, and known agent hypersensitivities.

- While adverse effects are fairly frequent, most reactions are mild and transient. Overall, the most commonly reported adverse effects include malaise/fatigue, dizziness/vertigo, asthenia, and nausea.
- Many of the triptans, particularly the subcutaneous formulations, can cause "triptan sensations," which include a sense of warmth, numbness, tingling, chest heaviness, or throat pain. However, these sensations are typically self-limiting and not harbingers of serious illness. This reaction occurs less frequently with the oral formulations.
- Overall, the class has mild to moderate adverse effects, which are usually transient. Some of the adverse effects are often unique to the delivery route. Nasal administration typically causes more pronounced nasal-related adverse effects, transdermal routes have been associated with application site reactions, and subcutaneous routes have injection-related concerns.

Overall Clinical Conclusion

The triptans have a moderate to high degree of therapeutic interchangeability. Some patients will prefer one formulation over another due to their personal headache characteristics and, based on available clinical data, 40% to 50% of patients will not respond to the initial agent chosen. Overall, the majority of patients in the Military Health System are well served by the available formulary options.

References

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