



Indian Health Service  
National Pharmacy and Therapeutics Committee  
**Formulary Brief: 5-HT<sub>1b/1d</sub> receptor agonists “triptans”**  
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**Background:**

A class review of the Serotonin 5-HT<sub>1b/1d</sub> receptor agonists (triptans) was last reviewed by the IHS National Pharmacy & Therapeutics Committee (NPTC) in 2010. Presently, the IHS National Core Formulary (NCF) for triptans is an “Open Class” formulary requirement, meaning any triptan can be selected on the local formulary, as long as at least one is listed and readily available. Following clinical and pharmacoeconomic evaluations, the NPTC voted to **ADD any 2 triptan agents to the NCF, one which must be sumatriptan.**

**Discussion:**

Migraine headache is a very common disorder, affecting an estimated 36 million Americans. The World Health Organization’s *Global Burden of Disease Study 2010* showed that migraine was the fourth most disabling medical disorder among women and the seventh most disabling medical disorder overall worldwide<sup>29</sup>. Cluster headache is much less common, affecting approximately 0.1% of the population and mostly affects men<sup>27, 16, 17, 15</sup>. Although rare, effective treatment of cluster headache is very important as it is considered one of the most severe pain syndromes in humans<sup>27</sup>.

The pathophysiology of migraine headache involves the activation of the trigemino-vascular system, which causes blood vessels to dilate, release irritants and stimulate the surrounding nerves. Triptans are very effective in the management of acute migraine headaches and are also used for the acute management of cluster headaches<sup>8</sup>. The overuse of acute medication (>10 times per month for 3 months) is a major risk in migraine patients and can lead to a chronic headache disorder called medication overuse headache<sup>1, 30</sup>. Proper education concerning the use of triptans as acute therapy is therefore of utmost importance.

Triptans are generally safe and well-tolerated. Contraindications for all triptans include ischemic heart disease, hemiplegic/basilar migraine, peripheral vascular disease, history of stroke/TIA, ischemic bowel disease, uncontrolled HTN, and recent use (within 24 hours) of another triptan or ergotamine/ergot medication. Triptans are available in tablet form, oral dissolvable tablets (ODT), nasal, and subcutaneous (SC) routes. Oral forms include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, and sumatriptan/naproxen. The ODT forms are available for rizatriptan and zolmitriptan. Nasal forms include sumatriptan and zolmitriptan. Sumatriptan is also available subcutaneously.

**Findings:**

There have been four relevant Cochrane Reviews since the NPTC review in 2010. In the 2014 evaluation of sumatriptan (all routes of administration), conclusions were as follows: sumatriptan, any route, is effective; adverse events (AE) are more common with SC route of administration and in higher doses of oral/nasal; SC had the greatest pain relief and is the fastest-acting but has the most AE’s; eletriptan outperformed sumatriptan (especially the 80mg dose); rizatriptan outperformed sumatriptan<sup>22</sup>. In the 2016 Cochrane review, the combination sumatriptan/naproxen was slightly more effective than the individual agents (*sumatriptan/naproxen=58%*, *sumatriptan=52%*, *naproxen=44%*)<sup>24</sup>. In the 2014 zolmitriptan review, both the 2.5 and 5mg doses were found to be effective as abortive treatment in acute migraine. Zolmitriptan benefited as many people, but not necessarily the same people, as sumatriptan 50mg for headache relief. Adverse events were more common than with placebo. The 10mg dose had slightly better results but more AEs<sup>23</sup>. A 2016 Cochrane Review of triptans for cluster migraines concluded that SC sumatriptan was superior to nasal zolmitriptan with a greater onset of efficacy. Adverse events were more common than with placebo but generally mild-to-moderate in severity<sup>25</sup>.

In the U.S., there are no specific “guidelines” for the use of triptans, as all triptans are FDA-approved for migraine. For cluster headaches, the American Headache Society found “level A” evidence for both sumatriptan SC and zolmitriptan nasal (only SC sumatriptan is FDA-approved for cluster)<sup>19</sup>. In 2015, a systematic review published in *Headache* found that frovatriptan, naratriptan and zolmitriptan were all superior to placebo for menstrual migraine<sup>20</sup> (all are off-label for menstrual migraine; there is no FDA-approved triptan for menstrual migraine).

There are two new triptan agents as of 2016, Zembrace<sup>®</sup> and Onzetra<sup>®</sup> and both are sumatriptan formulations that differ only in their delivery system. Zembrace<sup>®</sup>, a prefilled SC sumatriptan pen, is the only sumatriptan formulation that has a 3 milligram dose<sup>43</sup>. There is no new data to support improved efficacy; the label is consistent with data used for sumatriptan SC agents. Onzetra<sup>®</sup> is a nasal, breath-powered delivery device<sup>6,42</sup>. Onzetra<sup>®</sup> significantly reduced pain from 30 minutes to 2 hours post-dose compared with placebo; benefits are sustained at 24 and 48 hours (*phase 3 TARGET trial*).

Regarding tolerability, a network meta-analysis in August 2016 published in *Cephalalgia* evaluated the comparative tolerability of migraine treatments. The analysis had 141 trials covering 16 distinct treatments<sup>4</sup>. Of the triptans, sumatriptan, eletriptan, rizatriptan, zolmitriptan, and sumatriptan/naproxen all had a statistically significant increase in the odds of any AE or treatment-related AE compared with placebo. For secondary adverse outcomes (fatigue, chest discomfort, somnolence, nausea, vomiting, dizziness), with the exception of vomiting, all triptans except for almotriptan and frovatriptan were significantly associated with increased risk for all adverse outcomes. Almotriptan had a significantly increased risk of vomiting.

In 2014, *Cephalalgia* used a multiple treatment comparison meta-analysis, combining placebo and head-to-head trials, to establish which triptan had the highest odds of producing favorable relief outcomes<sup>3</sup>. This included data from 74 RCT's. Authors concluded that all triptans were significantly superior to placebo for all outcomes (with the exception of naratriptan) for 24 hour sustained, pain-free response. Eletriptan consistently had the highest odds of producing 2 hour pain relief, 2 hour headache response, 24 hour sustained pain relief, and 24 hour sustained headache response. Rizatriptan, zolmitriptan, and high-dose 100mg sumatriptan also appeared effective at 2 hours; whereas only zolmitriptan and high-dose sumatriptan appear to maintain their efficacy at 24 hours.

### Conclusion:

In summary, triptans are significantly superior to placebo for acute migraine, and appear to be more effective if taken early in the attack. Subcutaneous forms of triptans have the highest risk for AEs. For reasons that are not clear, clinicians can expect approximately half of all patients to not respond favorably to the first choice triptan, with limited ability to predict individual response. Other triptan agents should be tried if the first choice does not provide relief. There are a variety of dosage forms and routes of administration with potential clinical benefit for individual patients.

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