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National Pharmacy and Therapeutics Committee
5-HT_{1b/1d} receptor agonists “triptans”
NPTC Formulary Brief
November 2016*



Background:

A class review of the Serotonin 5-HT_{1b/1d} 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 worldwide²⁹. Cluster headache is much less common, affecting approximately 0.1% of the population and mostly affects men^{27, 16, 17, 15}. Although rare, effective treatment of cluster headache is very important as it is considered one of the most severe pain syndromes in humans²⁷.

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 headaches⁸. 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^{1, 30}. 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

In this Issue...

76 NPTC Formulary Brief: 5-HT_{1b/1d} receptor agonists “triptans”

79 NPTC Formulary Brief: Biosimilars

81 Electronic Subscriptions Available

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 sumatriptan²². In the 2016 Cochrane review, the combination sumatriptan/naproxen was slightly more effective than the individual agents (*sumatriptan/naproxen=58%*, *sumatriptan=52%*, *naproxen=44%*)²⁴. 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 AEs²³. 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 severity²⁵.

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)¹⁹. In 2015, a systematic review published in *Headache* found that frovatriptan, naratriptan and zolmitriptan were all superior to placebo for menstrual migraine²⁰ (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® and Onzetra® and both are sumatriptan formulations that differ only in their delivery system. Zembrace®, a prefilled SC sumatriptan pen, is the only sumatriptan formulation that has a 3 milligram dose¹³. There is no new data to support improved efficacy; the label is consistent with data used for sumatriptan SC agents. Onzetra® is a nasal, breath-powered delivery device^{6,12}. Onzetra® 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 treatments⁴. 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 outcomes³. 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.

For questions about this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

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*Indian Health Service
National Pharmacy and Therapeutics Committee
Biosimilars
NPTC Formulary Brief
November 2016*



Background:

Biologic medications represent a vast array of clinically potent products.¹ The definition of a ‘biological product’ includes viruses, therapeutic serums, toxins, antitoxins, vaccines, blood, blood components or derivatives, allergenic products, or proteins applicable to the prevention, treatment, or cure of a disease or condition of human beings.¹ Products differ dramatically from traditional small molecule drugs in a variety of ways including: immunogenicity, methods of production, characterization, shelf life, and storage conditions.^{2,3} Many biologic medications formed the basis of continued treatment success in various autoimmune, carcinogenic, and other conditions.^{2,3} As a result of recent legislation, many of these biologic medications will soon see competition from biosimilar medications. The intent of this presentation was to inform the IHS National Pharmacy & Therapeutic Committee (NPTC) of the current emerging market of biosimilar medications. As a result of this clinical and pharmacoeconomic review, the NPTC made no modifications to the IHS National Core Formulary.

Discussion:

The Hatch-Waxman Act of 1984 provided the basis of the current ‘generic’ drug approval process.⁴ The intent of this legislation was, in part, to encourage access to medication through cost competition for medications of similar safety and efficacy.⁴ However, many biologic medications were not on the market at this time, which prevented them from being included in this legislation. In 2009, the Biologic Price Competition and Innovation (BPCI) Act was passed that enable an FDA approval pathway for biosimilar medications.^{2,3} Again, the intent of this legislation was to enhance competition through increasing access and lowering cost.^{2,3}

The current approval process is governed under section 351(k) of the Public Health Service Act and in general, companies must prove the biosimilar: is similar in safety and efficacy to the original reference product, has the same mechanism of action; conditions of use; route of administration; dosage form; and strength as the reference product, and the biosimilar will be manufactured under Good Manufacturing Practice.^{2,3} In general, these products could be considered ‘interchangeable’ with the reference product at any point in the patient’s treatment course without intervention of the prescriber by meeting specific requirements, however final guidance on ‘interchangeability’ is expected to be released in 2017.⁵⁻⁷ In general, these biosimilar medications can differ in inactive ingredients and the number of indications but are limited to the indications of the reference product (although biosimilar manufacturers do not have to seek approval for all indications).⁵⁻⁷

Due to the potential for many biosimilar medications to be released for one reference drug, the Food and Drug Administration (FDA) created an informational tool for determining which biosimilar may be appropriate in relation to the current reference product.⁸ The Purple Book is similar to the FDA Orange Book in that it helps define which products are biosimilar and/or interchangeable with the reference product.⁸ This resource can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>.

The FDA also commented that the naming of biosimilars should contain some special conventions.⁹ The reasoning for this decision is due in part to allow for enhanced pharmacovigilance.⁹ The original naming convention for the first biosimilar approved was the “Core Name + Four Letter suffix” (manufacturer code).⁹ The first biosimilar product was registered as Zarxio® (filgrastim-sndz). However, the FDA has since indicated that biosimilar products should be named as follows: “Core Name + Random Four Letter suffix”. For instance, the infliximab biosimilar is named Inflectra® (infliximab-dyyb).⁹

At this time, there are four biosimilar products that have received approval from the FDA including Zarxio® (filgrastim-sndz), Inflectra® (infliximab-dyyb), Erelzi® (etanercept-szsz) and Amjevita® (adalimumab-atto).⁸

Findings:

Biosimilar products represent a great opportunity to expand the availability of highly efficacious medications to more patients in the IHS through increased access and decreased cost. The biosimilar approval process within the U.S. is still new and further process changes are expected as additional products are approved and lingering issues are addressed (e.g., interchangeability guidance, product naming). Pharmacy Benefits Managers (PBMs) are expected to prefer biosimilar products as cost savings begins to become more transparent.¹⁰ Recently, two major PBMs plan to prefer Zarxio® (filgrastim-sndz) on their upcoming formularies.¹⁰ The Department of Veterans Affairs recently removed Neupogen® (filgrastim) from its National Formulary and replaced it with Zarxio® (filgrastim-sndz).¹¹ As more biosimilars enter the market, it is anticipated that price reductions of 20% or greater may be realized.

For questions about this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

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