IMPORTANT REMINDER
This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description
Triptans are a rescue treatment for immediate pain relief of an acute migraine headache attack, available in a variety of dosage forms: oral tablets, nasal spray, or injection.
This policy applies to the following triptan containing products, unless otherwise excluded below: naratriptan, rizatriptan, sumatriptan, and zolmitriptan.
This policy does not apply to the brand-only triptan products (Alsuma™, Axert®, Frova®, Relpax®, Sumavel®, Zecuity™, or Zomig® nasal), nor sumatriptan-naproxen combination (Treximet®).

The intended purpose of this policy is that it be used as a guide to determine medical necessity for generically available triptans and their branded equivalents (unless the branded equivalent is addressed specifically in a separate policy). To the extent that this policy conflicts with a
medication-specific policy for a branded triptan product, the medication-specific policy will control. If a branded product is generically available and the branded product is not specifically addressed in a separate policy, the criteria in this policy will be used to make medical necessity determinations.

Policy/Criteria

I. Naratriptan, rizatriptan, sumatriptan, and zolmitriptan containing tablets, nasal spray, or injection) in quantities up to 12 tablets, 6 nasal spray canisters or 6 injections per month may be considered medically necessary and may be covered without authorization

II. Naratriptan, rizatriptan, sumatriptan, and zolmitriptan containing oral tablets in quantities of 13 to 24 tablets per month may be considered medically necessary when either criteria A or B are met:
   A. Diagnosis of **cluster headache**.
   OR
   B. Diagnosis of **migraine headache** and the following criteria below are met.
      1. Prophylaxis with medications from three of the different therapy classes listed in Appendix 1 has been ineffective, not tolerated, or contraindicated.
      AND
      2. There is documentation of migraine prophylaxis continuously for the last four months.

III. Sumatriptan-containing nasal spray or injection in quantities of 7 to 12 nasal spray canisters or injections per month may be considered medically necessary when either criterion A or B is met:
   A. Diagnosis of **cluster headaches**.
   OR
   B. Diagnosis of **migraine headache** and the following criteria 1, 2 and 3 below are met.
      1. Prophylaxis with medications from three of the different therapy classes listed in Appendix 1 has been ineffective, not tolerated, or contraindicated.
      AND
      2. There is documentation of migraine prophylaxis continuously for the last four months.
      AND
      3. Headaches are associated with nausea/vomiting.
IV. Administration, Quantity Limitations and Authorization Period

A. RegenceRx considers sumatriptan to be a self-administered medication.

B. Quantities exceeding 24 tablets or 12 injections or 12 nasal sprays per month (in any combination of triptan products) are considered not medically necessary.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

Position Statement

Summary

- The intent of this policy is to encourage the use of generic triptan medications (sumatriptan, rizatriptan, naratriptan, and zolmitriptan) for the treatment of migraine headaches, as well as ensure appropriate use to minimize risk of medication overuse headache.

- All triptans are effective and relatively safe for the acute treatment of moderate to severe migraine headaches. [1-8, 22, 29, 33-34]

- All forms of sumatriptan are used for the acute treatment of migraine attacks with or without aura and sumatriptan injection is used for the acute treatment of cluster headache episodes.

- When an injectable triptan is required, generic sumatriptan is the best value. There is no clinically significant difference between the various injectable sumatriptan products.

- Frequent use of abortive therapies, including triptans, may lead to medication overuse headache. Use should be limited to twice per week.

- Generic triptans may be covered at the doses at which they have been shown to be safe and effective. Up to 12 triptan tablets, 6 nasal sprays or 6 injections per month may be covered per month. Coverage of quantities exceeding these limits is allowed only when specific criteria are met.

- There is moderate certainty in the evidence that preventive medications help gain control of migraine headaches by reducing how often they occur and the severity, as well as need for abortive therapies.

- Generic triptans are available as oral disintegrating tablets (ODTs), nasal sprays and injectable dosage forms, which provide additional clinical value for patients who cannot tolerate swallowing tablets or have nausea associated with migraines.

Clinical Efficacy

- There is moderate certainty in the evidence that several generic nasal and oral triptans are effective for the acute treatment of migraine attacks. [1-4,7]. There is low certainty in the evidence for the treatment of other types of headaches. [1-7]
- There is insufficient evidence that demonstrates that one triptan is more efficacious than another in the treatment of migraine headache.

* Among the available triptans, there is insufficient evidence that almotriptan, frovatriptan, or naratriptan offer additional clinical benefits over sumatriptan: [17-21, 26-28]

- In headache relief at two hours
- In headache recurrence rates

* There is some evidence that eletriptan has a lower migraine recurrence rate at two hours than oral sumatriptan. [31-32]* There are no trials to establish superiority of branded sumatriptan injection (Alsuma, Sumavel) over generically-available sumatriptan injection or any other triptan for the acute treatment of migraine.

- A triptan taken at the first sign of a migraine yields the best response (pain free, or significant decrease in pain).

- Sumatriptan injection has the best evidence for the treatment of cluster headaches. [1] There are no trials to establish superiority of branded sumatriptan injection (Alsuma, Sumavel) over generically-available sumatriptan injection for the treatment of cluster headache.

**Safety**

**PREVENTIVE (PROPHYLACTIC) THERAPY**

- Patients who suffer very severe or frequent migraine attacks may benefit from preventative therapy. [10]

- Current medical literature suggests that preventative therapy should be considered in patients experiencing greater than two migraine attacks per month. [10, 11]

- Preventative medication can help most people decrease the number of migraine headaches by half. Approximately one in ten patients becomes migraine-free with preventative medication. [11, 14]

- Consultation with a specialist experienced in the evaluation and treatment of refractory headache patients may be beneficial when three or more successive preventative drugs have not been effective. [14]

- The American Academy of Neurology (AAN) states that preventative medication may be indicated when a patient is experiencing one or more migraines per week. Severe may be defined as headache causing work loss.

- Frequent use of quick-relief (“abortive”) medication may cause medication overuse headache (MOH), including triptans, NSAIDs, acetaminophen and opioids.

- Many experts limit quick-relief therapy to two headaches per week on a regular basis. Patients with medication overuse headache should use preventive medication. [15]
- The American Academy of Neurology has suggests the best evidence for preventative drug efficacy is for amitriptyline, propranolol, timolol, and divalproex sodium. Evidence of efficacy also exists for other beta-blockers, tricyclic antidepressants (TCAs), and verapamil, a calcium channel blocker (CCB). [15]
- Triptans do not prevent migraines. [1-8, 22, 29, 33-34]
- All triptans carry warnings concerning the risk of serotonin syndrome when used with serotonergic medications, such as selective serotonin reuptake inhibitors (SSRIs) including fluoxetine.

MAXIMUM QUANTITIES
- Most people who have migraine headaches need fewer than 12 tablets per month.
- Approximately 85% of patients with migraine headaches suffer fewer than three to four attacks per month. [9] The median frequency of migraine attacks among migraine suffers is 1.5 per month. [11]
- Frequent use of quick-relief medications can lead to medication overuse headache and eventually chronic daily headache. Medication overuse headache is defined as headache frequency of more than 15 days per month after the frequent intake of quick relief medications for a minimum of three months. [10]
- Frequent use of triptans may lead to medication overuse headache. [12, 13]
- Medication overuse headache is the most common factor in patients referred to tertiary headache clinics. [14]
- The safety of treating more than four headaches with almotriptan, naratriptan, sumatriptan, frovatriptan, rizatriptan, or zolmitriptan (nasal spray) in a 30-day period has not been established. [1-7, 34-35]
- The safety of treating more than three headaches with zolmitriptan tablets or eletriptan in a 30-day period has not been established. [4, 33]
- The safety of treating an average of more than 5 migraine headaches in a 30-day period has not been established for sumatriptan/naproxen. [38]
- The manufacturer’s recommended dose for sumatriptan/naproxen is one tablet. The efficacy of taking a second dose has not been established. [38]
- The prescribing information states not to take more than two sumatriptan/naproxen tablets or use two sumatriptan transdermal patches (Zecuity) in 24 hours. [38, 40]
Appendix 1: Migraine Prophylaxis Drug Therapy Classes

The following are examples of medication classes used for migraine prophylaxis:

- Anticonvulsants (a.k.a. anti-epileptic drugs, AEDs) (e.g. divalproex sodium, topiramate).
- Beta Blockers (e.g. propranolol, atenolol, metoprolol).
- Antidepressants (TCAs or venlafaxine) (e.g. TCA amitriptyline, venlafaxine).
- Other antihypertensives (ACEIs, ARBs, alpha-agonists) (e.g. candesartan, clonidine (Catapres®), guanfacine, lisinopril)

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; TCAs: tricyclic antidepressants.

Appendix 2: Product Availability

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dosage Form</th>
<th>Doses per Headache</th>
<th>Doses per Month (4 headaches)</th>
<th>Strengths Available</th>
<th>Doses per package</th>
</tr>
</thead>
<tbody>
<tr>
<td>naratriptan</td>
<td>naratriptan</td>
<td>Tablet</td>
<td>1 to 2</td>
<td>4 to 8</td>
<td>1 mg, 2.5 mg</td>
<td>9 tablets</td>
</tr>
<tr>
<td>rizatriptan tabs and</td>
<td>rizatriptan</td>
<td>Tablet, ODT</td>
<td>1 to 3 [a]</td>
<td>4 to 12</td>
<td>5mg, 10mg</td>
<td>various</td>
</tr>
<tr>
<td>orally dissolving</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25mg, 50mg, 100mg</td>
<td></td>
</tr>
<tr>
<td>tablet (ODT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 tablets; multi-dose bottles</td>
<td></td>
</tr>
<tr>
<td>sumatriptan</td>
<td>sumatriptan</td>
<td>Tablet</td>
<td>1 to 2 [a]</td>
<td>4 to 8</td>
<td>5mg, 20mg</td>
<td>6 sprays</td>
</tr>
<tr>
<td>sumatriptan</td>
<td>sumatriptan Nasal</td>
<td>Nasal Spray</td>
<td>1 to 2 [a]</td>
<td>4 to 8</td>
<td>5mg, 20mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syrup</td>
<td></td>
<td></td>
<td></td>
<td>6 sprays</td>
<td>2 syringes,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vial, cartridges</td>
</tr>
<tr>
<td>sumatriptan</td>
<td>sumatriptan Injection</td>
<td>Injection</td>
<td>1</td>
<td>4</td>
<td>6mg/0.5ml</td>
<td></td>
</tr>
<tr>
<td>zolmitriptan tablets</td>
<td>zolmitriptan Injection</td>
<td></td>
<td>1</td>
<td>4</td>
<td>2.5mg, 5mg</td>
<td>1, 3 or 6</td>
</tr>
<tr>
<td>and ODT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tabs</td>
</tr>
<tr>
<td>Relpax®</td>
<td>eletriptan</td>
<td>Tablet</td>
<td>1 to 2 [a]</td>
<td>4 to 8</td>
<td>20mg, 40mg</td>
<td>6 tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 tablets</td>
</tr>
</tbody>
</table>

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dru340.1
### Appendix 2: Product Availability

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dosage Form</th>
<th>Doses per Headache</th>
<th>Doses per Month (4 headaches)</th>
<th>Strengths Available</th>
<th>Doses per package</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NON-FORMULARY/NON-PREFERRED TRIPTANS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alsuma™ sumatriptan Injection 1 to 2 [a] 4 6mg/0.5ml 2 syringes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amerge® naratriptan Tablet 1 to 2 [a] 4 to 8 1mg, 2.5mg 9 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axert® almotriptan Tablet 1 4 6.25mg, 12.5mg 6 tablets 12 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frova® frovatriptan Tablet 1 to 3 [a] 4 to 12 2.5mg 9 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imitrex® sumatriptan Tablet 1 to 2 [a] 4 to 8 25mg, 50mg, 100mg 9 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imitrex® sumatriptan Nasal Spray 1 to 2 [a] 4 to 8 5mg, 20mg 6 sprays</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imitrex® sumatriptan Injection 1 4 6mg/0.5ml 2 syringes, vial, cartridges</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxalt®, Maxalt MLT® rizatriptan Tablet 1 to 3 [a] 4 to 12 5mg, 10mg 3 tablets 6 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumavel®DosePro® sumatriptan Injection 1 4 6mg/0.5ml 6 syringes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treximet® sumatriptan/naproxen Tablet 1 to 2[b] 5 to 10 85mg/500mg 9 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zecuity sumatriptan transdermal patch 1 4 6.5 mg over 4 hours 6 patches</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zomig® zolmitriptan Nasal Spray 1 to 2 4 to 8 5mg 6 sprays</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zomig®, Zomig ZMT® zolmitriptan Tablet 1 4 2.5mg, 5mg 6 tablets 3 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Dose may be repeated if first dose was not completely effective.
b. Headache recurs in less than 46% of patients within 24 hours. [16]
## Appendix 3: Cluster Headache Diagnostic Criteria

1. Severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes untreated.

AND

2. Headache is associated with at least one of the following signs on the pain side:
   - a. Conjunctival injection
   - b. Lacrimation
   - c. Nasal congestion
   - d. Rhinorrhea
   - e. Forehead/facial sweating
   - f. Miosis
   - g. Ptosis
   - h. Eyelid edema

AND

3. Current frequency of attack is at least 1 every other day.

AND

4. At least five attacks have occurred fulfilling the criteria listed above.
# Appendix 4: Subpopulation Consideration for Use of Triptans

<table>
<thead>
<tr>
<th>Generically available</th>
<th>Age</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>naratriptan tablet</td>
<td>Not established</td>
<td>C</td>
</tr>
<tr>
<td>rizatriptan tabs and orally dissolving tablet (ODT)</td>
<td>≥ 6 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>sumatriptan tablet</td>
<td>≥ 12 years&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>sumatriptan nasal spray</td>
<td>≥ 12 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>sumatriptan injection (generic)</td>
<td>Not established</td>
<td>C</td>
</tr>
<tr>
<td>zolmitriptan tablets and ODT</td>
<td>≥ 12 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Branded products</th>
<th>Age</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>almotriptan tablet (Axert)</td>
<td>≥ 12 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>eletriptan tablet (Relpax)</td>
<td>Not established</td>
<td>C</td>
</tr>
<tr>
<td>frovatriptan tablet (Frova)</td>
<td>Not established</td>
<td>C</td>
</tr>
<tr>
<td>sumatriptan injection (Alsuma, Sumavel Dose Pro)</td>
<td>Not established</td>
<td>C</td>
</tr>
<tr>
<td>sumatriptan transdermal patch (Zecuity)</td>
<td>≥ 12 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>sumatriptan/naproxen (Treimixet)</td>
<td>Not established</td>
<td>C</td>
</tr>
<tr>
<td>zolmitriptan nasal spray (Zomig&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>≥ 12 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C</td>
</tr>
</tbody>
</table>

<sup>a</sup> FDA approved for use in the listed age groups  
<sup>b</sup> Supported by the AAN Practice Guidelines for treatment of migraines in children. [41]  
<sup>c</sup> Trials in patients as young as 8 years of age. [41]  

## Cross References

Branded triptan products; (Alsuma<sup>TM</sup>, Amerge<sup>®</sup>, Axert<sup>®</sup>, Frova<sup>®</sup>, Relpax<sup>®</sup>, Sumavel<sup>®</sup>, Zecuity<sup>TM</sup>, or Zomig<sup>®</sup> nasal), RegenceRx Medication Policy Manual, Policy No.dru339

## Codes

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
References

1. Imitrex® tablets (sumatriptan) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; October 2013.
2. Imitrex® nasal spray (sumatriptan) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; October 2013.
4. Zomig® tablets (zolmitriptan tablets) [prescribing information]. Hayward, CA: AstraZeneca/Impax Pharmaceuticals; September 2012.
5. Axert® (almotriptan tablets) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; August 2014.
6. Frova® (frovatriptan tablets) [prescribing information]. Malvern, PA: Endo Pharmaceuticals; October 2013.
8. Imitrex® injection (sumatriptan injection) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; October 2012.
16. Welch KMA. A 27 year-old woman with migraine headaches. *JAMA* 1997; 278:322-328
22. Zomig® Nasal (zolmitriptan nasal spray) [prescribing information]. Hayward, CA: AstraZeneca/Impax Pharmaceuticals; September 2013.


