

# Serotonin 5HT-1 Receptor Agonists (“Triptans”) Clinical Pearls for the Washington Rx Therapeutic Interchange Program (TIP)

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## I. Background

In 2003, the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services-Medical Assistance Administration (DSHS-MAA), Labor and Industries (L&I), and the Health Care Authority-Uniform Medical Plan (UMP) declared rizatriptan to be the “preferred” triptan for patients covered by their prescription insurance. Patients currently using “non-preferred agents” must be evaluated for conversion to rizatriptan. Furthermore, MAA-DSHS patients presenting with prescriptions for non-preferred agents from endorsing practitioners (i.e., providers that have signed the TIP agreement) may be automatically converted to rizatriptan by pharmacists once the program is operational.

## II. Purpose

The purpose of this document is to inform pharmacists of the clinical, safety and cost rationale for these policy changes and to optimize their ability to assure safe and effective conversion of patients to the appropriate agent.

Triptans Available in US	
Almotriptan	(Axert <sup>®</sup> )
Eletriptan	(Relpax <sup>®</sup> )
Frovatriptan	(Frova <sup>®</sup> )
Naratriptan	(Amerge <sup>®</sup> )
<b>Rizatriptan</b>	<b>(Maxalt<sup>®</sup>)*</b>
Sumatriptan	(Imitrex <sup>®</sup> )
Zolmitriptan	(Zomig <sup>®</sup> )

\*Washington State Preferred Drug List Agent

## III. Overview of Migraines

- ◇ The International Headache Society defines a migraine as unilateral and pulsating pain usually accompanied by nausea/vomiting, photophobia, and phonophobia lasting 4-72 hours, 5 or more times a month. Headache prohibits normal daily activities and is aggravated by physical activity.
- ◇ Migraines are three times more common in women than men and tend to run in families. Typically, migraine sufferers are young, healthy women.
- ◇ Migraine without aura is the most prevalent type occurring about 80% of the time.
- ◇ Migraine attacks are theorized to be caused by primary neuronal dysfunction, which leads to intracranial and extracranial changes in the brain. Vasodilation occurs with migraines, but is not considered a causal factor.

## IV. Overview of Triptans

### A. Indications

Triptans are indicated for the treatment of moderate to severe migraine attacks. They are not indicated for prophylaxis. The subcutaneous form of sumatriptan also carries an indication for cluster headaches and has the most dosage forms with oral, subcutaneous and intranasal formulations on the market. Several triptans also have a sublingual formulation that is theorized to have a faster onset of action. None of the triptans have pediatric indications, although there have been trials conducted with sumatriptan, zolmitriptan and rizatriptan that showed some efficacy. These agents have generally not been studied in the geriatric population and should be used cautiously due to the increased incidence of cardiovascular disease and the potential for triptan-induced ischemic events.

### B. Mechanism of Action

Inhibition of serotonin 5-HT<sub>1B</sub> receptors causes vasoconstriction of cranial vessels and serotonin 5-HT<sub>1D</sub> receptors causes inhibition of trigeminal nerve afferents that innervate cranial vessels and the dura mater as well as neuronal “traffic”. This in turn inhibits release of vasoactive neuropeptides primarily calcitonin gene-related peptide (CGRP) that can cause to pain and inflammation. Although still preliminary, research is starting to focus on the serotonin

5-HT<sub>7</sub> receptor, which is known to play an excitatory role in neuronal systems and may also cause vasodilation of intracranial and extracranial vessels that cause pain and inflammation.

### C. Clinical Efficacy Comparison of Triptans

#### ◇ Outcome Measures in Trials

Usual outcome measures in migraine trials include pain relief, time to response, consistency of response, duration of single response, time to relapse, need for rescue medication (non-triptan medication), functional status (i.e., ability to resume normal activities after treatment), relief of associated symptoms and general satisfaction with treatment.

Patients differ in the value they place on each of these measures of efficacy, which are therefore, heavily influenced by patient perception and personal preference.

#### ◇ Results

The following results are based on 11 comparisons of oral agents from 8 fair to good quality head-to-head trials. These do not include frovatriptan, which currently has no published head-to-head trials. They also do not include comparisons of intranasal or subcutaneous sumatriptan to oral triptans.

Clinical Endpoint	Results
Pain relief at 1 hr	<b>Rizatriptan</b> >Naratriptan Zolmitriptan Sumatriptan Eletriptan Almotriptan
Return to normal function at 2 hr	Naratriptan > Zolmitriptan <b>Rizatriptan</b> Sumatriptan Eletriptan Almotriptan
Pain relief at 24 hr	<b>Rizatriptan</b> >Naratriptan Zolmitriptan Sumatriptan Almotriptan Eletriptan
Relief of migraine-related symptoms	<b>Rizatriptan</b> >Naratriptan Eletriptan Zolmitriptan Almotriptan Sumatriptan

Trials showed that patients received the same consistent pain relief over time with the same medication, regardless which one they were given. Rizatriptan consistently showed a trend toward equivalent or superior efficacy to other triptans in all categories. It also showed superiority to eletriptan for pain relief at 1 hour despite theories that eletriptan's higher lipophilicity would increase absorption across the blood-brain barrier. No long-term head-to-head trials analyzing consistency of triptans over multiple attacks or extended time were conducted.

#### ◇ Frovatriptan

In vitro and animal studies suggest that frovatriptan has more selectivity toward cerebral circulation than coronary blood vessels. There are no current head-to-head trials, but placebo-controlled studies suggest that it is not superior other triptans.

#### ◇ Patient Sub-Groups

Trials generally had few to no elderly or ethnically diverse patients with concomitant illnesses. None of the trials specifically looked at sex, age or other patient demographics. Therefore, no conclusion could be drawn from the reviewed literature.

### D. Safety and Adverse Effects with Triptans

#### ◇ Adverse Effects

None of the reviewed trials looked at adverse effects as a primary endpoint but most reported them. The main adverse effects were: dizziness, flushing, drowsiness, weakness and fatigue. Analyses of the nature and incidence of these adverse effects were inconclusive; they were not serious or life-threatening, usually mild to moderate in nature and transient. Eletriptan 80mg had the most adverse effects reported of any triptan.

◇ **Drug Interactions**

- **Antidepressants:** There have been rare documented cases of sumatriptan and antidepressants such as fluoxetine, venlafaxine and MAOIs causing serotonin syndrome marked by weakness, hyperreflexia and incoordination. This side effect can theoretically occur with all triptans, therefore, concomitant use of triptans with MAOIs is contraindicated and caution is warranted with SSRIs.
- **Ergotamine Derivatives:** All triptans are contraindicated within 24 hours of any ergot-type medication such as methysergide and dihydroergotamine.
- **Propranolol:** Propranolol can increase rizatriptan levels by as much as 70%. Halving the dose of rizatriptan to 5mg is recommended if both are taken concurrently.
- **Eletriptan:** Eletriptan is metabolized by the CYP450 3A4 enzyme and interacts with drugs that inhibit this pathway. This includes drugs such as ketoconazole and itraconazole, HIV antivirals (ritonavir and nelfinavir), amiodarone and verapamil. Administration of these medications is not recommended within 72 hours of eletriptan use. Grapefruit juice can also increase eletriptan levels.

◇ **Co-Morbid Conditions**

- **CV Ischemic Disease:** All triptans narrow coronary arteries by 10-20% at conventional doses causing potential cardiovascular ischemia. Sumatriptan especially has been found in post hoc analyses to cause chest discomfort and potentially fatal arrhythmias, stroke, angina and MI, although the incidence is low. **Therefore, triptans are contraindicated in patients with known cardiovascular disease** including angina, uncontrolled hypertension and peripheral vascular disease as well as history of MI or stroke. This contraindication also extends to ischemic bowel disease for the same reason.
- **Renal/Hepatic Impairment:** Triptans should be used with caution in patients with renal or hepatic impairment.

**E. Cost Comparisons of Triptans**

No generic agents are available and prices do not typically differ dramatically between agents. There is no literature on whether tablets can be split. Manufacturers recommend swallowing some of the tablets whole and not crushing or chewing them.

Drug	Cost per Tablet (\$)*
Almotriptan 12.5 mg	9.70
Eletriptan 40 mg	13.54
Frovatriptan 2.5 mg	13.30
Naratriptan 2.5 mg	17.20
Rizatriptan 10 mg	14.80
Sumatriptan 100 mg	17.70
Zolmitriptan 2.5 mg	13.80

\*Cost per DSHS reimbursement formula

**V. Information on Converting Patients to Preferred Triptans**

**Triptan Agent and Dosing Conversion Guide\***

	Rizatriptan	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Sumatriptan <sup>∞</sup>	Zolmitriptan
<b>Low Single Dose</b>	5mg	6.25mg	20mg	2.5mg	1mg	25-50mg	1.25-2.5mg
<b>Max Single Dose</b>	10mg	12.5mg	40mg	5mg	2.5mg	100mg	5mg
<b>Max Daily Dose</b>	30mg	25mg	80mg	7.5mg	5mg	200mg	10mg

\*This table does not represent exact or equivalent dosing conversions. It is based on FDA approved dosing ranges and comparative doses from clinical trials. Practitioners should exercise common sense in the practical application of this guide, including consideration for the patient's history of response to specific triptan agents and current clinical status.

<sup>∞</sup> Oral dosage forms only

◇ **Considerations in Converting Patients**

- **Triptan Use History:** Clinical response and tolerance of triptans are both subject to intra-patient variability. Therefore, patients should be questioned regarding their previous triptan use. Patients that have experienced therapeutic failure or intolerance to rizatriptan may require DSHS prior authorization approval for use of a non-preferred agent.
- **Dosage Formulation:** Patients currently using non-oral dosage formulations (ie, sumatriptan nasal spray or SQ injections) will need to be evaluated for conversion to oral rizatriptan or DSHS prior authorization approval for use of these non-preferred products.

◇ **Patient Education and Counseling**

- Patients should be counseled on appropriate use of their new agent and the rationale for conversion (ie, no data to demonstrate superiority of any one agent).
- Patients should be to follow the label instructions for the new triptan and to not combine use with the old triptan product. Instruct the patients that there is no advantage to combining two triptan products, however, there are greater risks of adverse effects.
- Patients should be advised to contact the prescriber if they are experiencing therapeutic failure with or are intolerant to rizatriptan to assure a complete review of the patient's condition and medication response.

**VI. References and Resources**

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