Texas Vendor Drug Program

Drug Use Criteria: Serotonin 5-HT1B/1D Receptor Agonists

Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Serotonin 5-$HT_{1B/1D}$ receptor agonists (SRAs) are FDA-approved to manage acute migraine headache attacks with or without aura. Injectable sumatriptan is also FDA-approved to manage cluster headache episodes. The maximum recommended adult doses for available SRAs are summarized in Tables 1 and 2. Dosages exceeding these recommendations will be reviewed.

Table 1. Maximum Recommended Daily Adult Dosages for SRAs - Monotherapy[1-17]

Drug Name	Treatment Indication	Dosage Form/Strength	Maximum Recommended Dosage
almotriptan (Axert®, generic)	migraine with or without aura	tablets (6.25 mg, 12.5 mg)	25 mg/day
eletriptan (Relpax®, generic)	migraine with or without aura	tablets (20 mg, 40 mg)	80 mg/day
frovatriptan (Frova®, generic)	migraine with or without aura	tablets (2.5 mg)	7.5 mg/day
naratriptan (Amerge®, generic)	migraine with or without aura	tablets (1 mg, 2.5 mg)	5 mg/day
rizatriptan (Maxalt®, generic)	migraine with or without aura	tablets (5 mg, 10 mg)	30 mg/day
rizatriptan (Maxalt -MLT®, generic)	migraine with or without aura	orally-disintegrating tablets (5 mg, 10 mg)	30 mg/day
rizatriptan propranolol patients	migraine with or without aura		15 mg/day
sumatriptan (Imitrex®, generic)	migraine with or without aura	intranasal spray (5mg/spray, 20 mg/spray - 6 per package)	40 mg/day
sumatriptan (Onzetra Xsail®)	migraine with or without aura	intranasal powder (11 mg/actuation)	44 mg/day*
sumatriptan (Imitrex®, generic)	migraine with or without aura	oral tablets (25 mg, 50 mg, 100 mg)	200 mg/day

Drug Name	Treatment Indication	Dosage Form/Strength	Maximum Recommended Dosage
sumatriptan (Imitrex®, generic)	migraine with or without aura	subcutaneous injection (4 mg and 6 mg STATdose system, 6 mg/0.5 mL single dose vial)	12 mg/day
	cluster headache		12 mg/day
sumatriptan (Sumavel® DosePro®)	migraine with or without aura	4 mg and 6 mg needle-free delivery system	12 mg/day
	cluster headache		12 mg/day
sumatriptan (Zembrace® SymTouch®)	migraine with or without aura	3 mg/0.5 mL autoinjector	12 mg/day
zolmitriptan (Zomig®, generic)	migraine with or without aura	tablets (2.5 mg, 5 mg)	10 mg/day
zolmitriptan (Zomig-ZMT®, generic)	migraine with or without aura	orally disintegrating tablets (2.5 mg, 5 mg)	10 mg/day
zolmitriptan (Zomig®)	migraine with or without aura	intranasal (2.5 mg/ actuation, 5 mg/ actuation)	10 mg/day

- * Alternatively, patients may receive a maximum Onzetra Xsail® dose of 22 mg plus one dose of another sumatriptan product at least 2 hours later

Table 2. Maximum Recommended Daily Adult Dosages for SRAs – Combination Therapy[1-17]

Drug Name	Treatment Indication	Dosage Form/Strength	Maximum Recommended Dosage
sumatriptan/ naproxen (Treximet®)	migraine with or without aura	tablets (10 mg/60 mg, 85 mg/500 mg)	170 mg/1000 mg per day

1.2 Pediatrics

Almotriptan, rizatriptan, sumatriptan/naproxen, and zolmitriptan nasal spray are the only SRAs FDA approved in children 6 to 17 years of age to treat acute migraine attacks in patients with a history of migraine with or without aura.[4, 8, 16-22] Children/ adolescents 6 to 17 years of age prescribed propranolol weighing less than 40 kg should not receive rizatriptan concurrently. Maximum recommended pediatric

doses for SRAs are summarized in Tables 3 and 4. Dosages exceeding these recommendations will be reviewed.

Table 3. Maximum Recommended Daily Pediatric Dosages for FDA-Approved SRAs to manage Acute Migraine With or Without Aura - Monotherapy[1-4, 8, 16, 17]

Drug	Patient Characteristics	Maximum Daily Dosage
almotriptan	12 to 17 years of age	25 mg
rizatriptan	6 to 17 years of age: 20 to 39 kg 40 kg or greater	 5 mg 10 mg
rizatriptan propranolol patients	6 to 17 years of age: 40 kg or greater	 5 mg
zolmitriptan nasal spray	12 to 17 years of age	10 mg

Table 4. Maximum Recommended Daily Pediatric Dosages for FDA-Approved SRAs to manage Acute Migraine With or Without Aura – Combination Therapy[1-4, 8, 16, 17]

Drug	Patient Characteristics	Maximum Daily Dosage
sumatriptan/naproxen	12 to 17 years of age	85 mg/500 mg

The remaining SRAs are not FDA-approved for use in patients less than 18 years of age as safety and efficacy have not been established in this patient population. Additionally, patients less than 18 years of age have demonstrated a significant placebo response following SRA use as well as an adverse event profile, including serious adverse events, comparable to that seen in adults.[5, 10, 11, 23]

No significant data are available evaluating SRA use in pediatric patients younger than 6 years of age. In limited randomized, controlled trials, sumatriptan nasal spray has demonstrated some efficacy in mitigating migraine attacks in adolescents; children as young as 6 years of age have achieved favorable responses with intranasal sumatriptan in a few small randomized and open-label studies.[24-27] However, oral sumatriptan tablets used in children 8 to 16 years of age to treat acute migraine attacks were not significantly better than placebo.[28] A few small studies with oral zolmitriptan have shown mixed outcomes.[29,30] Although not FDA-approved, Table 5 summarizes SRA doses that have been utilized in the pediatric population. Due to lack of definitive efficacy, prescriptions for SRAs not FDA-approved for pediatric patients will be reviewed in patients 6 to 18 years of age.

Table 5. Non FDA-Approved Pediatric Dosages for Select SRAs[24-27, 29, 30]

Drug	Patient Characteristics	Dose Utilized Per Headache
sumatriptan intranasal spray	6 to 17 years of age	20 mg
sumatriptan subcutaneous	6 to 18 years of age	0.06 mg/kg
sumatriptan subcutaneous	6 to 16 years of age Less than 30 kg Greater than 30 kg	 3 mg 6 mg
zolmitriptan tablets	6 to 18 years of age	2.5 mg

2 Duration of Therapy

Migraine headache is a chronic, recurrent condition usually requiring long-term, intermittent therapy for pain relief. Serotonin 5-$HT_{1B/1D}$ receptor agonists are approved for acute treatment of migraine attacks and may be utilized indefinitely to manage migraine headaches provided that the maximum dosage recommendation is not exceeded in a 24-hour period.[22, 31, 32] Additionally, the safety of treating more than 3 or 4 headaches during a 30-day time period has not been established. Children/ adolescents 6 to 17 years of age are allowed only one rizatriptan dose per 24 hours, as safety and efficacy have not been determined for multiple rizatriptan doses in pediatric patients.[8] Maximum quantities of serotonin 5-$HT_{1B/1D}$ receptor agonists to be dispensed in a 30-day time period, based on number of headaches to be treated, are summarized in Tables 6 and 7 for adults and Tables 8 and 9 for adolescents. Patient profiles documenting quantities of serotonin 5-$HT_{1B/1D}$ receptor agonists that exceed these recommendations will be reviewed.

Table 6. Maximum Recommended SRA Adult Dosage Frequency - Monotherapy[1-17]

Drug	Maximum Number of Headaches Treated per 30 Days	Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days
almotriptan tablets	4 headaches	8 x 12.5 mg tablets or 100 mg
eletriptan tablets	3 headaches	6 x 40 mg tablets or 240 mg
frovatriptan tablets	4 headaches	12 x 2.5 mg tablets or 30 mg
naratriptan tablets	4 headaches	8 x 2.5 mg tablets or 20 mg
rizatriptan tablets	4 headaches	12 x 10 mg tablets or 120 mg
rizatriptan orally disintegrating tablets (ODTs)	4 headaches	12 x 10 mg ODT or 120 mg

Drug	Maximum Number of Headaches Treated per 30 Days	Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days
rizatriptan propranolol patients (regular or ODT)	4 headaches	12 x 5 mg tablets/ODT or 60 mg
sumatriptan intranasal spray	4 headaches	8 x 20 mg spray or 160 mg
sumatriptan intranasal powder	4 headaches	8 x 22 mg powder or 176 mg
sumatriptan oral tablets	4 headaches	8 x 100 mg tablets or 800 mg*
sumatriptan subcutaneous injection	----+	----
zolmitriptan intranasal	4 headaches	8 sprays or 40 mg
zolmitriptan tablets	3 headaches	6 x 5 mg tablets or 30 mg*
zolmitriptan orally-disintegrating tablets	3 headaches	6 x 5 mg tablets or 30 mg*

- * After May 1st, 2002, the Texas Medicaid Vendor Drug Program extended dosage limits for oral sumatriptan to not exceed 900 mg/month (9 x 100 mg tablets) and oral zolmitriptan to not exceed 40 mg/month (8 x 5 mg tablets).
- + Patients taking Imitrex® or Sumavel® DosePro® should not receive more than 2 subcutaneous injections in a 24-hour time period; patients taking Zembrace® should not receive more than 4 subcutaneous injections per day

Table 7. Maximum Recommended SRA Adult Dosage Frequency – Combination Therapy[1-17]

Drug	Maximum Number of Headaches Treated per 30 Days	Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days
sumatriptan/naproxen tablets	5 headaches	10 tablets or 850 mg/5000 mg

Table 8. Maximum Recommended SRA Pediatric Dosage Frequency – Monotherapy[4, 8, 16, 17]

Drug	Maximum Number of Headaches Treated per 30 Days	Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days
almotriptan tablets	4 headaches	8 x 12.5 mg tablets or 100 mg
rizatriptan tablets	20 to 39 kg: 4 headaches Greater than or equal to 40 kg: 4 headaches	4 x 5 mg tablets or 20 mg 4 x 10 mg tablets or 40 mg
rizatriptan orally disintegrating tablets (ODTs)	20 to 39 kg: 4 headaches Greater than or equal to 40 kg: 4 headaches	4 x 5 mg tablets or 20 mg 4 x 10 mg tablets or 40 mg

Drug	Maximum Number of Headaches Treated per 30 Days	Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days
rizatriptan propranolol patients (regular or ODT)	4 headaches	4 x 5 mg tablets or 20 mg
zolmitriptan nasal spray	4 headaches	8 x 5 mg/actuation or 40 mg

Table 9. Maximum Recommended SRA Pediatric Dosage Frequency – Combination Therapy[4, 8, 16, 17]

Drug	Maximum Number of Headaches Treated per 30 Days	Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days
sumatriptan/naproxen tablets	2 headaches	2 tablets or 170 mg/1000 mg

3 Duplicative Therapy

Using two or more serotonin 5-$HT_{1B/1D}$ receptor agonists concurrently is not justified due to lack of additional therapeutic benefit and the potential for additive vasospastic effects. Patient profiles documenting receipt of multiple serotonin 5-$HT_{1B/1D}$ receptor agonists will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be reviewed to identify those drug regimens which may result in clinically significant drug-drug interactions. Clinically relevant drug-drug interactions for serotonin 5-$HT_{1B/1D}$ receptor agonists are summarized in Tables 10 and 11. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 10. Summary of Significant SRA Drug Interactions[2, 4-17, 34]

Triptan	Interacting Drugs						
	Amphetamines	CYP3A4 inhibitors	Ergots	Linezolid	MAOIs +	Propranolol	SNRIs#/SSRIs *
almotriptan	√	√	√	√	√	----	√

Triptan	Interacting Drugs						
eletriptan	√	√	√	√	√	----	√
frovatriptan	√	----	√	√	√	ns	√
naratriptan	√	----	√	√	√	----	√
rizatriptan	√	----	√	√	√	√	√
sumatriptan	√	----	√	√	√	----	√
zolmitriptan	√	----	√	√	√	ns	√

- ns = not significant
- + MAOIs = monoamine oxidase inhibitors
- # SNRIs = serotonin-norepinephrine reuptake inhibitors
- * SSRIs = selective serotonin reuptake inhibitors

Table 11. SRA Drug-Drug Interactions[2, 4-17, 34]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
SRAs	amphetamines	concurrent administration may stimulate serotonin neurotransmission and increase risk of serotonin syndrome (e.g., mental status changes, diaphoresis, tremor, fever), as amphetamines increase serotonin release	avoid combination, if possible; if adjunctive therapy necessary, observe for signs/symptoms of serotonin syndrome and adjust therapy as indicated	1-severe (CP)
almotriptan, eletriptan	CYP3A4 inhibitors (e.g., azole antifungals, macrolides)	adjunctive administration of CYP3A4 inhibitors with almotriptan or eletriptan (CYP3A4 substrates) may result in increased almotriptan/eletriptan serum levels and enhanced pharmacologic/toxic effects, including potential for vasospastic and/or cardiac events	eletriptan contraindicated for use within 72 hours of strong CYP3A4 inhibitor; lower almotriptan dosages required when used concurrently with CYP3A4 inhibitors (maximum dose, 12.5 mg); an alternative antifungal that does not inhibit CYP3A4 (e.g., terbinafine) may be an alternative for azoles	contraindicated, moderate (DrugReax) 1-severe, 2-major (CP)
SRAs	ergot derivatives/ ergot-type medications (e.g., bromocriptine)	combined administration may result in additive vasospastic effects	SRAs should not be used within 24 hours of ergot derivatives/ergot-type medications	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
SRAs	linezolid	concurrent administration with SRAs metabolized by monoamine oxidase (MAO) may increase serotonin levels and the potential for serotonin syndrome, as linezolid is nonselective monoamine oxidase inhibitor (MAOI)	adjunctive administration or administration within 14 days of MAOI discontinuation is contraindicated by SRA manufacturers; if combination necessary, observe patient closely for signs/symptoms of serotonin syndrome; eletriptan is not metabolized by MAO, and frovatriptan, naratriptan do not inhibit MAO - may be safe alternatives; almotriptan is metabolized by MAO but does not require dosage adjustments when used with MAOIs - may also be alternative	contraindicated (DrugReax) 2-major (CP)
SRAs	MAOIs+, including selegiline (high doses)	adjunctive administration of SRAs with other medications having serotonergic properties like MAOIs, which decrease serotonin metabolism, may increase serotonin levels and the potential for serotonin syndrome; selegiline in doses greater than 10 mg daily may behave like an MAOI	adjunctive administration or administration within 14 days of MAOI discontinuation is contraindicated by SRA manufacturers; if combination necessary, observe patient closely for signs/symptoms of serotonin syndrome; eletriptan is not metabolized by MAO, and frovatriptan, naratriptan do not inhibit MAO - may be safe alternatives; almotriptan is metabolized by MAO but does not require dosage adjustments when used with MAOIs and may also be alternative	contraindicated (DrugReax) 1-severe, 2-major (CP)
rizatriptan	propranolol	adjunctive rizatriptan-propranolol administration increases the rizatriptan AUC by as much as 70% as propranolol inhibits rizatriptan metabolism	reduce rizatriptan doses (maximum daily dose, 15 mg); observe patients for enhanced rizatriptan pharmacologic/adverse effects when co-administered	moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
SRAs	SNRIs*/ SSRIs#	adjunctive administration of SRAs with other medications having serotonergic properties like SNRIs/SSRIs may increase serotonin levels and the potential for serotonin syndrome	avoid combination, if possible; if combined therapy necessary, monitor patient closely for signs/symptoms of serotonin syndrome and modify drug therapy as necessary	major (DrugReax) 2-major (CP)

- #CP = Clinical Pharmacology
- +MAOIs = monoamine oxidase inhibitors
- #SNRIs = serotonin-norepinephrine reuptake inhibitors
- *SSRIs = selective serotonin reuptake inhibitors
- ^SRAs = serotonin 5-HT1B/1D receptor agonists

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