Tapentadol Tablets, SA (Extended Release) C-II
Criteria for Use
January, 2018

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

Transitioning Veteran *Tapentadol SA is on the DoD VHA Transitional Continuity of Care Drug List; if this criterion is met, the remainder of the criteria for use is not applicable.*

☐ Veteran is transitioning care from the Department of Defense to VHA. The Veteran and a VHA health care prescriber have determined the Veteran is to continue tapentadol SA.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive tapentadol SA:*

☐ Intended use is for treatment of mild pain
☐ Intended use is for treatment of acute pain
☐ Intended use is for postoperative pain (may be appropriate if patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time)
☐ Intended use is as an as-needed (prn) analgesic
☐ Patient has significant respiratory depression, condition predisposing to significant respiratory depression such as acute or severe bronchial asthma, or known/suspected gastrointestinal obstruction including paralytic ileus
☐ Patient has severe renal or severe hepatic impairment
☐ Patient has hypersensitivity to tapentadol or other SA tablet contents
☐ Patient is unable to swallow whole tablets/requires tablets to be crushed before administration
☐ Patient is receiving a monoamine oxidase inhibitor (MAOI) or has taken an MAOI within the last 14 days
☐ Patient has intent to consume or likelihood of consuming alcoholic beverages or prescription or non-prescription products containing alcohol while on tapentadol SA therapy

Inclusion Criteria *The following criteria must be fulfilled for provision of tapentadol SA :*

☐ Indication is management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options (non-opioid and immediate-release opioid) are inadequate (see *Issues for Consideration*).

AND

☐ Patient has a documented contraindication, history of intolerable medication-related adverse effects (to IR or SA forms), or inadequate analgesia despite appropriate upwards titration of dosage, in separate trials of morphine SA and oxycodone SA.

Dosage and Administration *See Product Information[2] and Reference 3 for additional dosing information*

- Tapentadol SA tablets are available in the following strengths: 50, 100, 150, 200, and 250 mg.
- Tablets must be swallowed whole and not crushed, chewed, or dissolved.
- Tapentadol SA may be administered with or without food.
- ***In opioid-naïve or opioid non-tolerant patients:*** initiate therapy at 50mg every 12 hours
- ***To convert to tapentadol SA from another opioid:*** use available conversion factors to obtain the estimated dose (see Table below)
- Titrate patients with dose increases of 50mg no more than twice daily every 3 days
- The maximum daily dose of tapentadol SA is 500 mg per day. Patients taking more than a morphine equivalent daily dose of 200 mg should not be converted to tapentadol since this maximum dose of tapentadol is unlikely to provide sufficient analgesia.
- Steady state plasma concentrations of tapentadol are achieved after the third dose, 24 hours after the first twice daily multiple dose administration.
- ***Elderly patients:*** Recommended doses for elderly patients with normal renal and hepatic function are the same as those recommended for younger patients with normal renal or hepatic function; consider starting therapy at lower range of recommended doses due to possibility of reduced clearance.
- ***Renal impairment:*** No dosage adjustment is recommended in patients with mild or moderate renal impairment. Use of tapentadol SA in patients with severe renal impairment (CrCl < 30 ml/min) is not recommended.

- ***Hepatic impairment:*** No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Score 5 to 6). Patients with moderate hepatic impairment (Child-Pugh score 7 to 9) should initiate treatment at 50 mg daily and receive no more than 100mg once daily. Tapentadol SA is not recommended in patients with severe hepatic impairment (Child-Pugh score 10 to 15).
- Conversion from fentanyl TDS: There are no FDA-approved dosing instructions on how to convert patients from fentanyl to tapentadol. Treatment with tapentadol may be initiated 18 hours after removal of the fentanyl TDS (which will allow an approximate 50% fall in serum fentanyl concentration). A conservative tapentadol SA dose, 50 mg every 12 hours, can be initially substituted for each 25 mcg of fentanyl TDS; tapentadol SA may then be titrated according to the patient's level of pain relief and tolerability.
- Conversion from methadone: It is recommended that a clinician with expertise in methadone dosing be consulted in converting methadone to an alternate opioid [also see the VA PBM-MAP-VPE document *Oral Methadone Dosing Recommendations for the Treatment of Chronic Pain*].

Morphine Milligram Equivalent Doses (MME)[1]	
Opioid Agent	**Conversion Factor**
Codeine	0.15
Tapentadol	**0.4**
Morphine	1
Hydrocodone	1
Oxycodone	1.5
Fentanyl TD, µg/h	2.4
Oxymorphone	3
Hydromorphone	4
Methadone	Consult with provider with detailed knowledge of methadone pharmacology and expertise in dosing

All doses in mg/day except for fentanyl. Multiply the daily dosage for each opioid by the conversion factor to determine the equianalgesic dose in MME. Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.

Do not use the calculated dose in morphine milligram equivalents (MME) to determine the doses to use when converting one opioid to another. When converting opioids, the new opioid is typically dosed at substantially lower than the calculated MME dose (reduction to 50-67% of the calculated MME) to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics.

Use particular caution with fentanyl because it is dosed in µg/h instead of mg/d, and absorption is affected by heat and other factors.

- When titrating opioids or converting between drug formulations or opioid agents, dosing requirements should be monitored and individualized to patient response; lower initial doses may be indicated in special patient populations.
- When converting to tapentadol SA tablets, rescue doses of tapentadol IR or other short-acting analgesic, either alone or in combination with acetaminophen, aspirin, or NSAIDs, may be administered for breakthrough pain as needed or about 1 h before anticipated incident pain.
- Co-therapy using a long-duration opioid and a nonopioid analgesic (acetaminophen or nonsteroidal anti-inflammatory drug [NSAID]) should be considered for opioid-sparing effects or additive analgesia.

Issues for Consideration

- Nonopioid therapy is preferred in the management of chronic pain; opioids should be used only when benefits for pain and function are expected to outweigh risks. When utilized, opioid therapy should not be initiated with an LA/ER opioid and LA/ER opioids should not be prescribed for intermittent ('as needed') use.[1]
- Tapentadol SA has a labeled indication for neuropathic pain associated with diabetic peripheral neuropathy severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Some consensus guidelines[4,5,6] list strong opioids as a 2nd line option for treatment of diabetic painful neuropathy; however, more contemporary guidance[7,8] has assigned a weak 3rd line recommendation for strong opioids due to questionable efficacy and significant safety concerns (i.e. abuse, misuse, and increased risk for overdose mortality).
- Methadone oral tablet is a long acting opioid alternative to tapentadol SA for management of severe pain (including peripheral neuropathic pain); however, only clinicians who are familiar with methadone's unique pharmacological characteristics, appropriate titration, and risk profile, and who are prepared to educate and closely monitor their patients, should consider initiation or titration of methadone for pain.[1]
- Similarly, due to safety concerns, only clinicians who are familiar with the dosing and absorption properties of fentanyl TDS and are prepared to educate their patients about its use should initiate or titrate fentanyl TDS therapy.[1]
- General principles, defined by CDC and VA/DoD Clinical Practice Guidelines for prescribing of opioids for chronic pain, should be utilized to guide management of long-term opioid therapy.[1,9] Practitioners should obtain informed consent from each patient after explaining the risks, benefits, and obligatory terms of longterm treatment with opioids. All federal and state guidelines on prescribing and dispensing opioids should be strictly followed. There should be an initial and periodic checking of the respective State(s) Prescription Drug Monitoring System (if available), consideration of provision of naloxone rescue, and exercise of other strategies to mitigate risk of chronic opioid therapy.

Safety *See Product Information for additional safety information*[2]

- Tapentadol SA does not offer any consistent advantages over morphine SA in terms of safety or tolerability. Serious adverse reactions include respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock. Non-serious adverse events are typically seen on initiation of therapy and decrease over time; they include commonly encountered opioid side effects such as constipation, nausea, and somnolence.
- Exposure to tapentadol SA places patients at risk of addiction, abuse, and misuse, which can lead to overdose and death.
- The co-ingestion of alcohol with tapentadol SA may result in increased plasma levels and a potentially fatal overdose of tapentadol. Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on tapentadol SA therapy.
- The concomitant use of tapentadol SA with other CNS depressants including other opioids, sedative hypnotics, tranquilizers, general anesthetics, and phenothiazines can increase the risk of respiratory depression, profound sedation, coma and death. When combined therapy with any of these medications is considered, the dose of one or both agents should be reduced.
- Tapentadol SA potential to cause hypotensive effects warrants monitoring of blood pressure during dose initiation and titration.
- Life-threatening respiratory depression is more likely to occur when tapentadol is given to elderly, cachectic or debilitated patients (who may have reduced clearance) or patients with significant respiratory disease (who may have substantially reduced respiratory reserve).
- Avoid use of tapentadol in patients with impaired consciousness or coma, head injury or increased intracranial pressure, as the respiratory depressant effects of the drug may be magnified in these clinical scenarios.
- Potentially life-threatening serotonin syndrome may occur with recommended doses of tapentadol SA when combined with drugs that have serotonergic activity including SSRIs, SNRIs, tricyclic antidepressants, triptans, mirtazapine, trazodone, tramadol, and MAOIs.
- Seizure disorders may be aggravated or induced by tapentadol; monitoring is recommended and this agent should be used with caution in patients with a history of seizures.
- Tapentadol is Pregnancy Category C; it should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
- Tapentadol SA should not be used in women during or immediately prior to labor; use of opioids during pregnancy can prolong labor and result in respiratory depression, physical dependence and withdrawal syndrome in the neonate.
- There is insufficient information on the excretion of tapentadol in breast milk; infants who may be exposed to tapentadol through breast milk should be monitored for excess sedation and respiratory depression during therapy and withdrawal symptoms when tapentadol is stopped.
- Crushing, chewing or dissolving tapentadol SA tablets will cause an uncontrolled delivery of drug which can lead to overdose or death.
- The concomitant use of tapentadol with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation or potentially result in coma. The VA/DOD Clinical Practice Guideline on the Management of Opioid Therapy (OT) for Chronic Pain (2017) https://www.healthquality.va.gov/, recommends against the concurrent use of opioids and benzodiazepines. When such combined therapy is contemplated, consider tapering one or both when risks exceed benefits and obtaining specialty consultation.

Provider-Related Guidance

Implement Risk Mitigation Strategies. Ensure risk mitigation strategies are in place when starting tapentadol per the VA/DOD Clinical Practice Guideline on the Management of Opioid Therapy (OT) for Chronic Pain (2017) https://www.healthquality.va.gov/, These strategies include an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. Other strategies and their frequency should be commensurate with risk factors and include:

- Ongoing, random urine drug testing (including appropriate confirmatory testing)
- Checking state prescription drug monitoring programs
- Monitoring for overdose potential and suicidality
- Providing overdose education
- Prescribing of naloxone rescue and accompanying education

Opioid Initiation/continuation. The VA/DOD Clinical Practice Guideline on the Management of Opioid Therapy (OT) for Chronic Pain (2017) https://www.healthquality.va.gov/, recommends against initiating long-term opioid therapy for chronic pain. For patients already on long-term opioid therapy, the guidelines recommend ongoing risk mitigation strategies, assessment for opioid use disorder, and consideration for tapering when risks exceed benefits.

Opioid Tapering Guidance. If a decision is made to taper the patient off opioids, ensure screening and treatment is offered for conditions that can complicate pain management before initiating an opioid taper. These include mental health disorders (PTSD, anxiety, depression), opioid use disorder (OUD) and other substance use disorders (SUD), medical complications (e.g. lung

disease, hepatic disease, renal disease), and sleep disorders including sleep apnea. Most commonly, tapering will involve dose reductions of 5% to 20% every 4 weeks. More specific guidance on opioid tapers is provided in the PBM Academic Detailing Service publication *Opioid Taper Decision Tool*.

Identifying and Managing Opioid Use Disorder. Aberrant behaviors may become more apparent and reveal an opioid use disorder when opioids are tapered or discontinued or as tolerance develops. DSM-5 Diagnostic Criteria for OUD include the following: craving or strong desire or urge to use opioids, tolerance, withdrawal, using a larger amount of opioids or over a longer period than originally intended, spending a lot of time to obtain, use, or recover from opioids, and continued use despite physical or psychological problems related to opioids. If an OUD is suspected, patients should receive addiction focused medical management in PACT or referral to an Interdisciplinary Pain Management Team with Addiction Medicine expertise and access to Medication-Assisted Treatment, or to Primary Care Mental Health or specialty care for evaluation and treatment of OUD/SUD. If they decline, offer treatment that can meet their needs in the setting they feel most comfortable with. Specific guidance on OUD is provided in the PBM Academic Detailing Service publication A VA Clinician's Guide to Identification and Management of Opioid Use Disorder (2016) and the VA/DOD Clinical Practice Guideline for the Management of Substance Use Disorder.

Updated January, 2018. Original Version September, 2016. Contact: Mitchell Nazario, PharmD, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services

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