[4] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid.

Abbreviations: APAP: acetaminophen; ASA: acetylsalicylic acid; CNS: central nervous system; CrCl: creatinine clearance; d: day(s); ER: extended-release; hr: hour(s); IBU: ibuprofen; LOT: long-term opioid therapy; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mg: milligram(s); min: minute(s); mL: milliliter(s); SSRIs: selective serotonin reuptake inhibitors

B. Long-acting/Extended-release Opioids

Table D-2. Use of Long-acting/Extended-release Opioids in Adults [198]

- Long-acting/ER opioids expose patients and other users to the risks of opioid misuse and OUD, which can lead to overdose and death, even when used at recommended dosages. Long-acting/ER opioids should be reserved for patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or provide inadequate control of pain. Assess each patient's risk prior to prescribing long-acting/ER opioids and institute risk mitigation strategies.
- The FDA has mandated that long-acting/ER opioids be subject to a structured Risk Evaluation and Mitigation Strategy (REMS) program to manage known or potential serious risks associated with their use (see http://www.er-la-opioidrems.com/IwgUI/rems/home.action).
- Most abuse deterrent technologies have been designed to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. In spite of these efforts, no opioid formulation prevents consumption of a large number of intact capsules or tablets, which continues to be the most common method of abuse.
- Long-acting/ER opioids should not be used for management of acute pain (with exception of oxycodone/acetaminophen ER tablets), as an as-needed medication, or on initiation of LOT (see Recommendation 13).

Source: https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine buccal film ▪ Available in strengths of 75, 150, 300, 450, 600, 750 and 900 mcg/film for twice daily administration	▪ 75 mcg once or twice daily for at least 4 days, then increase dose to 150 mcg every 12 hr ▪ There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine	▪ After initial dosing, dosing changes as necessary can proceed in increments of 150 mcg every 12 hr, no more frequently than every 4 days ▪ Patients on prior dose of opioid 30 to 89 mg MEDD may initiate buprenorphine film at 150 mcg every 12 hr, 90 to 160 mg MEDD may initiate at 300 mcg every 12 hr; if prior opioid is >160 mg MEDD – consider an alternative analgesic ▪ Time to steady state ~3 days with every 12 hr dosing	▪ *Elderly:* Initiation at the low end of the dosing range is recommended ▪ *Renal dysfunction:* No dose adjustment recommended ▪ *Hepatic dysfunction:* Patients with severe hepatic impairment should have starting and titration doses reduced by half that of patients with normal liver function	▪ QTc prolongation reported with recommended doses of buprenorphine; maximum dose of 900 mcg every 12 hr established due to the potential for this adverse effect; avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic drugs ▪ Buprenorphine buccal film is a potential treatment option for patients with significant renal impairment and those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered medications
Buprenorphine TDS ▪ Available in every 7 day patch formulation that delivers transdermal buprenorphine at the following rates: 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr	▪ In opioid-naïve or in patients on <30 mg MEDD of alternate agent: Initiate treatment with 5 mcg/hr patch ▪ There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine; the 10 mcg/hr patch may then be initiated at the next dosing interval	▪ The maximum dose of buprenorphine TDS 20 mcg/hr may not provide adequate analgesia for patients requiring greater than 80 mg MEDD; an alternate analgesic should be considered ▪ Steady state achieved in ~3 days	▪ Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment, renal impairment, or in the elderly ▪ Potential treatment option for patients with significant renal impairment or those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of oral medications	▪ Buprenorphine patch 10 mcg/hr is approximately equivalent to an oral MEDD of 18-28 mg; the 20 mcg/hr patch is approximately equivalent to a MEDD of 36-55 mg ▪ Dose of one 20 mcg/hr patch per week should not be exceeded due to risk of QTc prolongation ▪ Avoid use in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications ▪ Advise patients that application of external heat (e.g., hot baths, sunbathing, saunas, heating pads) increases maximum plasma concentration of buprenorphine and risk of fatal overdose

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Fentanyl TDS ▪ Available in every 3 day patch formulation that delivers transdermal fentanyl at the following rates: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr	▪ Fentanyl TDS is contraindicated in non-opioid-tolerant patients ▪ Fentanyl TDS is contraindicated in the management of mild or post-operative pain, and as an "as-needed" analgesic ▪ The initial dose of fentanyl TDS in opioid-tolerant patients [2] is 25 mcg/hr, applied every 72 hr; the 12 mcg/hr dose has not been evaluated as an initial dose	▪ Fentanyl TDS must be used only on intact skin ▪ Dose change increments should be based on supplemental opioid doses, using a ratio of fentanyl TDS 12 mcg/hr for every 45 mg/24 hr of supplemental oral MEDD ▪ Dosing changes, as necessary, should occur at least 3 days after the initial dose; thereafter, not more often than every 6 days	▪ *Elderly:* Twice as sensitive to fentanyl as younger patients; avoid initiation at doses >25 mcg/hr unless patient is already taking >135 mg oral morphine or equivalent ▪ *Hepatic / Renal dysfunction:* Reduce dose by 50% in mild-moderate impairment and avoid use if impairment is severe ▪ *Patients with fever*: Increased body temperature may increase release of fentanyl from the TDS; monitor patients for opioid adverse effects and modify dosage as necessary	▪ Consider fentanyl TDS in patients with persistent, moderate-to-severe pain who cannot take oral ER morphine or oral ER oxycodone ▪ Avoid application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, hot baths, sunbathing, heated water beds) to the application site while the patch is worn as heat may increase release and speed absorption of fentanyl ▪ Using damaged or cut fentanyl TDS patches can lead to rapid release of the contents of the patch and fatal overdose ▪ Use of fentanyl TDS with CYP3A4 inhibitors[3] can result in increased fentanyl plasma concentrations, increased or prolonged opioid effects, including fatal respiratory depression; use extreme caution and frequent monitoring in patients receiving these combinations ▪ CYP 3A4 inducers may increase fentanyl clearance

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydrocodone ER ■ **ER tablets** contain 20, 30, 40, 60, 80, 100 or 120 mg hydrocodone for once daily administration ■ **ER capsules** contain 10, 15, 20, 30, 40 or 50 mg hydrocodone for every 12 hr administration	■ *Opioid-naïve patients:* 20 mg ER tablet once daily ■ *Opioid-naïve patients:* 10 mg ER capsule every 12 hr ■ *Opioid tolerant [2] patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ *For opioid-experienced, both ER tablets and capsules:* Convert current opioid to equianalgesic hydrocodone dose then reduce that dose by 25%; initiate at nearest whole-tablet or capsule strength, rounding down as necessary ■ *For both tablets and capsules:* Dose change increments of 20 mg per day may be made every 3 to 7 days ■ Steady state achieved in ~3 days of dosing	■ *Elderly:* No significant pharmacokinetic differences ■ *Patients with renal impairment:* Hydrocodone plasma concentrations are increased in moderate or severe impairment; use low initial dose and monitor closely for adverse events such as excessive sedation and respiratory depression ■ *Patients with hepatic impairment:* no dosage adjustment is required in mild or moderate hepatic impairment; start with the lowest dose, 10 mg, in patients with severe hepatic impairment, and monitor closely	■ CYP3A4 inhibitors[3] may decrease clearance of hydrocodone, increase plasma concentrations, and increase risk of overdose; CYP3A4 inducers[4] may increase clearance and reduce opioid effect ■ Both ER tablets and ER capsules are formulated with polyethylene oxide which imparts ER properties ■ Hydrocodone ER tablets or capsules must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose ■ ER tablet has abuse deterrent labeling related to resistance to crushing and high viscosity when dissolved in aqueous solution ■ ER capsule has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydromorphone ER Tablets ▪ Available as 8, 12, 16, and 32 mg tablets for once daily administration	▪ Not indicated in opioid-naïve patients due to the risk of respiratory depression ▪ *Opioid tolerant*[2] *patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	▪ Dosage adjustments may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia ▪ Steady state reached after 3 to 4 days of once-daily dosing	▪ *Elderly:* No specific guidance; monitor closely, particularly when initiating or titrating dosage ▪ *Patients with renal impairment:* Start patients with moderate impairment at 50% of usual dose, and patients with severe impairment at 25% of usual dose ▪ *Patients with hepatic impairment:* Start patients with moderate impairment at 25% of usual dose in non-impaired patients	▪ Hydromorphone ER tablets must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose ▪ Hydromorphone ER contains sulfites ▪ Hydromorphone ER has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Methadone ▪ Available as 5 and 10 mg tablets and oral solution, 5 or 10 mg/5 ml, for every 8 to 12 hr administration	▪ Should not be used for as-needed supplemental OT ▪ *Initial dose:* 2.5 to 5 mg orally every 8 to 12 hr; more frequent administration (every 6 hr) may be necessary during initiation to maintain analgesia ▪ START LOW AND GO SLOW ▪ See Appendix D for detailed dosing information including dosing recommendations in patients previously exposed to opioids ▪ Monitor patients carefully during initiation, conversions to and from other opioids, and dose titration	▪ Dose change increments of ▪ 2.5 mg every 8 hr may be made every 5 to 7 days ▪ Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses, e.g., on days 2 to 5; if patient has excessive sedation during this timeframe, consider temporarily holding dose(s), lowering the dose, and/or slowing the titration rate ▪ Once a stable analgesic dose is reached, the dosing interval may be extended to every 8 to 12 hr or longer	▪ *Elderly or debilitated*: Consider reduced dosing in elderly or debilitated patients who may be more sensitive to opioid adverse effects ▪ *Hepatic dysfunction*: No dosage adjustments required in patients with stable chronic liver disease or mild-to-moderate hepatic dysfunction; avoid in severe liver disease ▪ *Renal dysfunction*: Methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50-75% is recommended in patients with CrCl <10 mL/min	▪ Prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone ▪ Plasma half-life (22 to 128 hr short-term; 24 to 48 hr at steady-state) may be longer than the analgesic duration ▪ Methadone has little cross-tolerance with other opioids; therefore, even patients with a high degree of opioid tolerance may be at risk for overdose when switched to methadone ▪ Methadone is the only long-acting opioid available as an oral solution ▪ Methadone may be subject to drug interactions with agents that can influence CYP2B6 (e.g., ticlopidine) ▪ May prolong QTc intervals on ECG; risk of torsade de pointes; see Appendix D for detailed QTc monitoring information

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Morphine CR or SR ■ Available in 15, 30, 60, 100, and 200 mg strengths for every 8 to 12 hr administration ■ Morphine ER capsules available in 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, and 200 mg capsule strengths for once daily administration **Morphine and Naltrexone ER Capsule** ■ Available as 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 capsule strengths (mg morphine/mg naltrexone) for once or twice-daily administration	■ *Opioid-naïve patients:* Morphine CR or SR 15 mg every 8 to 12 hr ■ Total daily increments of <30 to 40 mg/d may be made every 2 days ■ *Opioid-naïve patients:* Morphine ER capsules are not indicated in opioid-naïve patients ■ *Patients who are not opioid tolerant:* Start morphine ER at 30 mg daily, may adjust every 1 to 2 days ■ *Opioid-naïve patients:* Initiate at the lowest dose, 20 mg/0.8 mg once daily ■ *Opioid tolerant*[2] *patients:* Convert current opioid to equianalgesic daily dose of morphine; reduce the calculated amount by 33-50% for initial start dose (see Table D-3) ■ Dose may be up titrated no more frequent than every other day	■ Morphine CR or SR tablets should be swallowed whole, not broken, chewed, or crushed ■ For patients who have difficulty swallowing, SR and ER capsules may be opened and the pellets may be sprinkled onto a small amount of soft food (for administration without chewing) or administered via 16F gastrostomy tube ■ Steady state achieved with morphine ER within 24 to 36 hr ■ Morphine/naltrexone must be swallowed whole or the contents of the capsules sprinkled on apple sauce; crushing, dissolving, or chewing pellets may cause a fatal overdose (particularly in the opioid-naïve patient) and the absorption of naltrexone could increase the risk of precipitating withdrawal in opioid tolerant patients ■ Morphine/naltrexone: If once daily administration results in inadequate analgesia, may switch to twice daily dosing	*Information applies to all formulations of morphine listed* ■ *Elderly:* Use with caution and at lower dose ■ *Patients with renal dysfunction:* Bioavailability is increased and clearance is decreased; metabolites M3G and M6G accumulate significantly ■ Reduce dose or, if severe renal impairment exists, avoid use ■ *Patients with hepatic dysfunction:* Clearance decreases and half-life increases; M3G and M6G to morphine ratios are reduced; use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times	■ Morphine SR is preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with use, and lower cost ■ M6G, an active metabolite, may accumulate in renal impairment and contribute to excessive opioid effects ■ M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia ■ Morphine/naltrexone ER capsule has abuse deterrent labeling related to potential to precipitate withdrawal if drug is taken by other than oral route

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone ER ■ **Tablets** available in 10, 15, 20, 30, 40, 60, and 80 mg strengths for every 12 hr administration ■ **Capsules** available in 9, 13.5, 18, 27 and 36 mg strengths for every 12 hr administration	■ *Opioid-naïve patients:* 10 mg (tablets) or 9 mg (capsules) orally every 12 hr ■ *Opioid tolerant*[2] *patients:* Convert current opioid to equianalgesic daily dose of oxycodone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ *Dose change increments:* May increase to 20 mg (tablets) or 18 mg (capsules) every 12 hr after 1 or 2 days; thereafter, the total daily dose may be increased by 25-50% of the current dose every 1 or 2 days ■ ER tablets are not bioequivalent to ER capsules; 10 mg oxycodone HCl (ER tablet) = 9 mg oxycodone base (ER capsule) ■ Steady state achieved with tablets or capsules in 24 to 36 hr with repeat dosing	■ *Elderly*: Plasma concentrations of oxycodone are increased ~15% in the elderly; however, usual dosing and dosing intervals may be appropriate ■ *Patients with renal dysfunction*: Plasma concentrations of oxycodone are increased ~50% in patients with CrCl <60 ml/min; dose conservatively and adjust according to clinical situation ■ *Patients with hepatic dysfunction*: Reduce initial dose to 1/3 to 1/2 of the usual dose and monitor closely	■ Recommended for patients who experience intolerable, unmanageable adverse effects to long- acting morphine ■ Both ER tablets and ER capsules have abuse deterrent labeling related to resistance to abuse by intranasal and intravenous means ■ ER tablets should be swallowed whole, not broken, chewed, or crushed ■ ER capsules may be opened and sprinkled on soft food or administered via feeding tube

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone/APAP ER ■ Available as tablets containing oxycodone 7.5 mg and APAP 325 mg for every 12 hr administration	■ *Opioid-naïve patients:* May initiate therapy with the standard dose of 2 tablets every 12 hr ■ A standard, single dose consists of 2 tablets totaling 15 mg oxycodone/650 mg APAP ■ This is the only long-acting/ER opioid to have an acute pain indication	■ The polyethylene oxide content causes the tablet to swell and become sticky when wet. This has the potential to cause obstruction of the airway or GI obstruction ■ Steady state concentration of both components are reached within 24 hr of product initiation	■ *Elderly:* Take precautions when determining the dosing amount and frequency in geriatric patients since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients ■ *Patients with renal or hepatic dysfunction:* Patients with renal dysfunction (CrCl <60 ml/min) or hepatic dysfunction should initiate therapy with 1 tablet every 12 hr and adjust as needed	■ This long-acting/ER opioid is an exception to the REMS requirements due to the relatively low amount of oxycodone contained in each tablet ■ Oxycodone/APAP ER tablets are formulated with PEO which is responsible for its ER in addition to labeled abuse deterrent properties ■ Patients should be instructed not to pre-soak, lick, or otherwise wet tablets prior to swallowing and to take one tablet at a time with adequate water to insure complete and immediate swallowing

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone/APAP ER ■ Available as tablets containing oxycodone 7.5 mg and APAP 325 mg for every 12 hr administration	■ *Opioid-naïve patients:* May initiate therapy with the standard dose of 2 tablets every 12 hr ■ A standard, single dose consists of 2 tablets totaling 15 mg oxycodone/650 mg APAP ■ This is the only long-acting/ER opioid to have an acute pain indication	■ The polyethylene oxide content causes the tablet to swell and become sticky when wet. This has the potential to cause obstruction of the airway or GI obstruction ■ Steady state concentration of both components are reached within 24 hr of product initiation	■ *Elderly:* Take precautions when determining the dosing amount and frequency in geriatric patients since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients ■ *Patients with renal or hepatic dysfunction:* Patients with renal dysfunction (CrCl <60 ml/min) or hepatic dysfunction should initiate therapy with 1 tablet every 12 hr and adjust as needed	■ This long-acting/ER opioid is an exception to the REMS requirements due to the relatively low amount of oxycodone contained in each tablet ■ Oxycodone/APAP ER tablets are formulated with PEO which is responsible for its ER in addition to labeled abuse deterrent properties ■ Patients should be instructed not to pre-soak, lick, or otherwise wet tablets prior to swallowing and to take one tablet at a time with adequate water to insure complete and immediate swallowing

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxymorphone ER Tablets ▪ Available as 5, 7.5, 10, 15, 20, 30 and 40 mg tablets for every 12 hr administration	▪ *Opioid-naïve patients:* Initiate at 5 mg every 12 hr ▪ *Opioid tolerant[2] patients:* Convert current opioid to equianalgesic daily dose of oxycodone; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	▪ *Dose change increments:* May increase by 5 to 10 mg every 12 hr every 3 to 7 days ▪ Oxymorphone ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth ▪ Steady-state plasma levels are achieved after 3 days of multiple dose administration	▪ *Elderly:* Plasma drug levels are about 40% higher in elderly versus younger subjects; use caution, starting at the low end of dosing range and titrating slowly ▪ *Patients with renal dysfunction:* Bioavailability is increased by 57% in moderate impairment and by 65% in severe impairment; in patients with CrCl <50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly ▪ *Patients with hepatic dysfunction:* Use with caution in patients with mild hepatic impairment, starting with lowest dose and titrating slowly ▪ Contraindicated in patients with moderate or severe hepatic impairment	▪ Must be taken on an empty stomach at least 1 hr before or 2 hr after a meal; food has been shown to increase peak levels of oxymorphone ER by 50% ▪ Must NOT be taken concomitantly with alcohol, which can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270%

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Tapentadol ER ▪ Available as tablets containing 50, 100, 150, 200, or 250 mg tapentadol for twice daily dosing	▪ *In opioid-naïve and non-tolerant patients:* Initiate therapy with 50 mg twice daily; use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression ▪ There are no established conversion ratios for conversion from other opioid to tapentadol ER; convert current opioid to an estimated equianalgesic daily dose of tapentadol; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	▪ *Dose change increments:* May increase dose by no more than 50 mg twice daily every 3 days ▪ *Maximum daily dose*: 500 mg daily ▪ Tapentadol ER tablets must be taken whole; crushing, chewing, or dissolving tablets will result in uncontrolled delivery of tapentadol and can lead to overdose or death ▪ Steady state is attained after the third dose (24 hr after the first twice daily multiple dose administration)	▪ *Elderly:* No dosing adjustment needed, consider starting at lowest recommended dosage ▪ *Patients with renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment ▪ *Patients with hepatic dysfunction:* Use not recommended in severe hepatic impairment	▪ Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration and cause fatal overdose ▪ Use with or within 14 days of MAOIs is contraindicated
Tramadol ER ▪ Available as 100, 200 and 300 mg tablets for once daily administration	▪ *Patients not currently on tramadol:* 100 mg once daily ▪ Converting from tramadol IR: Start at 24 hr dosage equivalent rounded down to closest 100 mg increment	▪ *Dose change increments:* May increase by 100 mg every 5 days based on analgesia and tolerability ▪ Maximum dose: 300 mg/day	▪ *Elderly:* Start at low end of dosing range; use particular caution, especially in patients >75 years ▪ *Renal dysfunction:* Avoid use if CrCl <30 ml/min ▪ *Hepatic dysfunction:* Avoid use in severe hepatic impairment (Child- Pugh Class C)	▪ Must be swallowed whole and must not be chewed, crushed, or split ▪ See warnings and precautions under Other Considerations for tramadol IR (Table D-1)

[1]Check local formulary for available formulations.

[2] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid.