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Collegium Pharmaceutical, Inc.

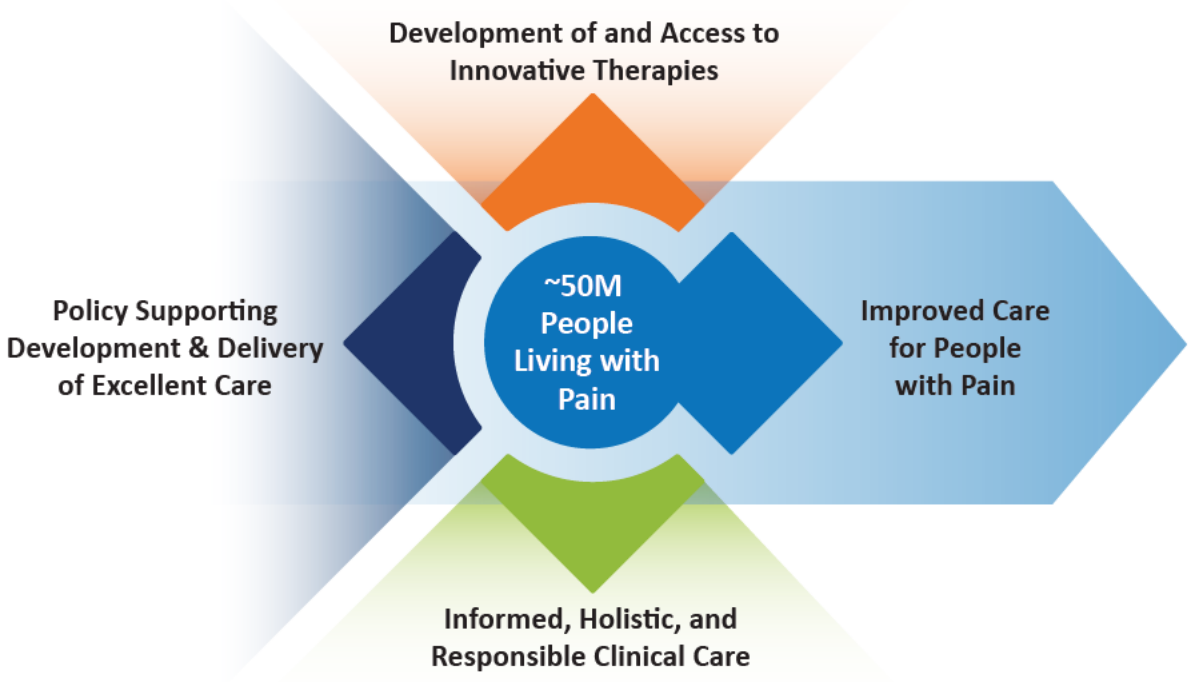
Collegium is Committed to Being the Leader in Responsible Pain Management

We are a company focused on helping people living with pain. We lead by bringing innovative and differentiated products to market and promoting those products ethically.

Our portfolio includes:

- **Xtampza ER**, an abuse-deterrent extended release formulation of oxycodone;
- **Nucynta ER**, an extended release formulation of tapentadol; and
- **Nucynta**, an immediate release formulation of tapentadol

An integrated multi-modal and multidisciplinary public health approach to both the crisis of chronic pain and the opioid crisis is vital.



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MME Challenges Are Amplified When Applied to Atypical Opioids

Traditional opioids

- Benefits and risks are primarily mediated by μ-receptor activation[1]
- MMEs have the potential to provide an adequate measure of dose equivalency between traditional opioids[2]
- There are no FDA-labeled dose limits specific to active ingredients and as defined by safety findings[3]

"Atypical" opioids

- Benefits and risks are not solely dependent on μ-receptor activation[2]
- MMEs may not provide an adequate measure of dose equivalency between opioids[4]
- Atypical opioids have dose limits in FDA-approved labeling specific to active ingredients and informed by safety findings[3]
- CDC guidelines do not include MME conversion factors for buprenorphine or tramadol[5]

MME = morphine milligram equivalents

1. Trescot AM, et al., *Pain Physician* 2008;11(2 Suppl):S133–S153 **2**. Nielsen S, et al., *Pharmacoepidemiol Drug Saf*. 2016;25(6):733-737. **3**. FDA Joint Meeting of the DSaRM Advisory Committee and AADPAC 2019, https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-11-12-2019-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and, accessed April 2020. **4**. Pergolizzi JV, et al., *Adv Ther* 2019;36:1235-1240. **5**. Dowell D, et al., *MMWR Recomm Rep*. 2016;65(1):1-49.

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Impact of Applying the 90 mg MME Limit to Tapentadol

Opioid	CDC-Provided Conversion Factor[1]	CDC MME Dosage Limit[1]	Tapentadol Dose at 90 MME	Average Therapeutic Dose[2-5]	FDA-Approved Maximum Daily Dose[6,7]
Tapentadol	0.4	90 mg MME/day	225 mg/day	300-400 mg/day	500-600 mg/day

- The CDC-proposed dosage limit is:
  - Less than the average therapeutic dose of approximately 300-400 mg/day identified by phase 3 studies in both chronic low back pain and painful diabetic neuropathy[2-5]*
  - Less than 50% of the FDA-approved maximum daily dose[6,7]
- Physicians have reported reluctance to prescribe tapentadol:
  - Fear of the optics of having their doses exceed MME limits
  - Concern that an efficacious dose will not be reached given the difference between the MME limit and the average therapeutic dose range identified in phase 3 studies

**Therapeutic dose based on patients is Phase 3 trials and analysis of real-world data*
MME = morphine milligram equivalents

1. Dowell D, et al., *MMWR Recomm Rep*. 2016;65(1):1-49. **2**. Buynak R, et al., *Expert Opinion on Pharmacotherapy*, 11(11):1787-1804. 3. Afilalo M, et al., *Clin Drug Investig.* 2010;30(8):489-505; **4**. Kress HG, et al., *Pain Physician* 2014;17(4):329-43. **5**. Lawal O, et al., Presented at AAPM 34th Annual Meeting; April 26-29, 2018; Vancouver, BC. Poster 2108. **6**. NUCYNTA® (tapentadol) tablets [package insert]. Stoughton, MA: Collegium Pharmaceutical, Inc.; 2021. **7**. NUCYNTA® ER (tapentadol) extended-release tablets [package insert]. Stoughton, MA: Collegium Pharmaceutical, Inc.; 2021.

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Why Is This Problematic?

Tapentadol had lowest rate of serious adverse events (including death, major medical effect, or hospitalization) and no reported deaths[1]

Tapentadol ER had lower rates of past 30-day abuse than abuse deterrent formulation (ADF) ER and non-ADF ER opioid comparators[2]

Abuse of tapentadol was infrequent relative to other opioids among individuals entering treatment for opioid use disorders[3]

Tapentadol had lower rates of abuse than the buprenorphine products indicated for the management of pain on a population basis and was similar on a prescription basis[4]

- Artificial barriers to tapentadol prescribing may lead opioid prescribing clinicians to drugs that have not performed as well with regard to misuse, abuse, diversion, or overdose over the past decade

1. Murphy DL, et al. *Drug Saf.* 2018;41(8):787-795. 2. Vosburg SK, et al. *Pain Med.* 2020;21(9);1891-1901. 3. Severtson, SG, Olsen, H, Iwanicki, JL, Dart, RC. Abuse of Tapentadol Among Individuals Entering Treatment for Opioid Use Disorder. Poster presented at PAINWeek, September 11-13, 2020. 4. Data on File, Collegium Pharmaceutical

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Conclusions

- We applaud FDA efforts to examine the science behind MME and its application to clinical practice
- Problems with MME are amplified when applied to atypical opioids
- Real-world evidence related to tapentadol has found relatively lower rates of abuse, misuse, diversion and death
  - Utilization may in part be reduced by an artificially low MME limit, which has the potential to negatively impact public health
- Tapentadol, like other atypical opioids, should not have a specific MME conversion and instead prescribers should be allowed to dose the medication as per the FDA approved label

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