

This educational material was developed by Nora Pharma Inc., as part of the Canadian Specific Opioids targeted Risk Management Plan (CSO-tRMP) for NRA-TRAMADOL/ACET. It is not intended for promotional use.

Dear Healthcare Professional:

NRA-TRAMADOL/ACET Educational Material for Healthcare Professionals on Opioid-Related Harm

This educational material is intended for healthcare professionals who are prescribing, dispensing or administering NRA-TRAMADOL/ACET tablets for the relief or management of moderate to moderately severe pain. This material is designed to highlight the importance of balancing the use of NRA-TRAMADOL/ACET with the risks of fatal or non-fatal opioid-related harms. It can also assist you with counseling patients and/or caregivers on the safe use, serious risks and proper storage and disposal of NRA-TRAMADOL/ACET tablets, thus ensuring appropriate use.

KEY POINTS TO CONSIDER WHEN PRESCRIBING NRA-TRAMADOL/ACET

Patient selection

- Consider whether NRA-TRAMADOL/ACET tablets are an appropriate treatment option. NRA-TRAMADOL/ACET should not be used in patients with pain that can be managed with other pain medications. NRA-TRAMADOL/ACET should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).
- Safety in patients under the age of 18 years has not been studied and therefore NRA-TRAMADOL/ACET tablets are not recommended in this patient population. Because of the risk of life-threatening respiratory depression and death, avoid the use of NRA-TRAMADOL/ACET in adolescents (12 to 18 years old) who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.
- TRAMADOL/ACET tablets are contraindicated for use in pregnant or nursing women as infants exposed *in-utero* or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Prolonged maternal use of NRA-TRAMADOL/ACET during pregnancy can also result in neonatal opioid withdrawal syndrome, which may be life-threatening.
- Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Each patient should be assessed for their risk prior to being prescribed NRA-TRAMADOL/ACET tablets. The likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain, the patient's own level of tolerance as well as risk factors for opioid use disorder (OUD). The risk factors include age of the patient, patient or family

history of alcohol or drug abuse or psychiatric conditions and a history of preadolescent sexual abuse.

Prescribing

Canadian Health Authorities requested that physicians specify the indication on each opioid prescription given to patients.

Dosing

- Instruct patients to swallow NRA-TRAMADOL/ACET tablets whole. Cutting, breaking, crushing, chewing, or dissolving NRA-TRAMADOL/ACET tablets can lead to dangerous adverse events including death.
- As with other opioids, tolerance and physical dependence may develop upon repeated administration of NRA-TRAMADOL/ACET tablets and there is a potential for development of psychological dependence.
 - For acute pain, prescribe NRA-TRAMADOL/ACET tablets for a maximum of 7 days at the lowest dose that provides adequate pain relief.
 - For the management of chronic non-cancer, non-palliative pain, it is recommended that a maximum daily dosage of 300 mg (50 morphine milligram equivalent) of NRA-TRAMADOL/ACET not be exceeded.
- Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.
- To reduce the risk of respiratory depression, proper dosing and titration of NRA-TRAMADOL/ACET are essential. Overestimating the dose of NRA-TRAMADOL/ACET when converting patients from another opioid product can result in a fatal overdose with the first dose.
- Reserve concomitant prescribing of NRA-TRAMADOL/ACET and benzodiazepines or other CNS depressants to patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation.
- NRA-TRAMADOL/ACET is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain). NRA-TRAMADOL/ACET should only be used during post-operative period in patients that can take oral medications.

Monitoring

All patients receiving NRA-TRAMADOL/ACET should be monitored for signs of opioid misuse and abuse and their level of pain should be assessed routinely to determine the most appropriate dose and the need for further use of NRA-TRAMADOL/ACET tablets.

- Adjust/reduce dosage or discontinue NRA-TRAMADOL/ACET accordingly.
- Assess your patient's compliance with the prescribed dosage and identify any signs and symptoms of opioid misuse, abuse and OUD. Be familiar with the available screening tools for risk of abuse:

- Canadian Centre on Substance Use and Addiction:
<https://www.ccsa.ca/opioid-resources>
- The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain:
<https://www.cmaj.ca/content/cmaj/suppl/2017/05/03/189.18.E659.DC1/170363-guide-1-at-updated.pdf>
- E-Practice Toolkit contains Tools To Use Before You Prescribe Opioids, Tools To Select The Right Opioids And Titrate Effectively, Tools To Monitor For Safety And Effectiveness And Opioid Tapering:
<https://nperesource.casn.ca/wp-content/uploads/2017/01/practicetoolkit.pdf>

Access the resources that are available to you in your province of practice to understand the provincial clinical guidelines on the management of OUD. Additional resources on the treatment of OUD are available and include the Canadian Research Initiative on Substance Misuse National Guideline for the Clinical Management of the OUD (https://crismprairies.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf).

- Monitor patients for signs and symptoms of respiratory depression, especially during initiation of NRA-TRAMADOL/ACET or following a dose increase.
- Monitor for the potential occurrence of medication error(s) in your patients by asking detailed questions regarding dosage and administration of the product.

Patient/Caregiver Counselling

- Emphasize the potential risk of opioid-related harm to your patient/caregiver.
- Remind patient/caregiver to report any adverse events to you or to their other healthcare professional.
- Provide clear dosing instructions to your patient/caregiver including the daily maximum dose and the duration of treatment.
- Discuss the safe storage and disposal of NRA-TRAMADOL/ACET tablets with your patient/caregiver, to reduce risk of accidental exposure/ingestion by household contacts, especially children/teens and to reduce risk of theft. Accidental exposure, especially by children, can result in a fatal overdose of tramadol and acetaminophen.
- Inform patient/caregiver of the availability of “free take-home naloxone kits” in their respective provinces: Refer to: <https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/naloxone.html>

Adverse Events Reporting

To report any suspected adverse events associated with the use of NRA-TRAMADOL/ACET tablets:

- Visit the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffectcanada.html>) for information on how to report online, by mail or by fax; or call toll-free at 1-866-234-2345.
- Contact Nora Pharma by phone at 1-888-270-9874 or by visiting the “Contact Us” page on Nora Pharma’s website at <https://norapharma.ca/en/contact-us/>

CONTINUING OPIOID TRAINING

Maintain your knowledge concerning the risks of opioid-related harm, weighing these risks before prescribing an opioid, and properly managing patients who are prescribed opioids, both for short and long-term use. Always be aware of the current conditions of use for NRA-TRAMADOL/ACET, as detailed in the Canadian Product Monograph.

Please refer to the links below for examples of the available Opioid Online Training.

- College of Family Physicians of Canada: <https://www.cfpc.ca/chronic-non-cancer-pain-management-opioid-resources/>
- McMaster University: https://machealth.ca/programs/opioids_clinical_primer/
- British Columbia Centre on Substance Use: <http://www.bccsu.ca/provincial-opioid-addiction-treatment-support-program/>
- University of British Columbia: <https://ubccpd.ca/course/provincial-opioid-addiction-treatment-support-program>

This educational material is not an exhaustive description of the risks associated with the use of NRA-TRAMADOL/ACET tablets. Refer to the full Product Monograph of NRA-TRAMADOL/ACET tablets