Naltrexone Extended-release Suspension for Injection (VIVITROL)

in Opioid Dependence

National Drug Monograph ADDENDUM

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

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

*The Product Information should be consulted for detailed prescribing information.*

*See the VA National PBM-MAP-VPE Monograph on this drug at* [*www.pbm.va.gov*](http://www.pbm.va.gov) *or* [*http://vaww.pbm.va.gov*](http://vaww.pbm.va.gov) *for further information on its use in Alcohol Dependence.*

# SUMMARY

* Naltrexone extended-release suspension for injection (ER-NTX) was approved by the Food and Drug Administration in 2006 for the treatment of alcohol dependence and in October 2010 for the prevention of relapse to opioid dependence, following opioid detoxification. This monograph addendum provides an evidence review of ER-NTX for the opioid dependence indication.
* There are no randomized clinical trials directly comparing intramuscular and oral naltrexone formulations.
* In Russian outpatients with a DSM-IV diagnosis of opioid dependence, ER-NTX was superior to placebo (PBO) in terms of
  + Median proportion of weeks of confirmed opioid abstinence during weeks 5-24 (primary endpoint): 90% vs. 35%; difference, 55% (15.9–76.1).
  + Proportion of patients who achieved total confirmed abstinence: 36% vs. 23%; RR 1.58 (1.06–2.36)
  + Reduction in opioid craving on VAS score from BL: –10.1 vs. 0.7.
  + Treatment retention duration: >168 d vs. 96 d; RR 0.61 (0.44–0.86)
  + Improvement in EQ-5D function
  + Risk for HIV behavior scores
* ER-NTX was shown to be relatively safe in a subgroup of patients with underlying mild to moderate chronic HCV and/or HIV infections over a 24-week period. Hepatic safety of ER-NTX in the longer term in these populations is uncertain.
* Insomnia was the only adverse event that occurred in significantly more patients on ER-NTX than placebo (6% vs. 1%).
* The FDA is requiring the manufacturer to conduct postmarketing studies to evaluate whether there is a gender-related risk of injection site reactions, and if there is, the factors that might predispose to increased risk.
* Overall Evidence Quality: There was one moderate-quality major efficacy study with long-term extension study. Overall risk of bias was fair. Quality of this RCT was downgraded because of potential unmasking of treatment, a bias-prone method, high dropout, and relatively large difference in completion rates between treatment groups. The study was sponsored by the manufacturer (Alkermes) and the authors have potential financial conflicts of interest.
  + Consistency of Results: There was consistency of results within the study. There is no other study to validate the results.
  + Directness of Evidence: Evidence linking treatment to important clinical outcomes was direct. There were no head-to-head studies comparing two or more active treatments.
  + Precision of Results: The 95% CI for the treatment difference for one of two primary outcome measures (percentage of weeks of confirmed abstinence) was wide but excluded the possibility that ER-NTX was not better than PBO. The 95% CI for the relative risk of benefit for the other primary outcome measure (patients with total confirmed abstinence) was narrow but the lower limit (1.06) approached 1.00, suggesting a possibility that ER-NTX was not superior.
  + External Validity to VA: The study results were applicable to a selected subgroup of Russian opioid addicts and there were many exclusions to study entry. Nonetheless, there is no reason to exclude the U.S. Veteran opioid addict population from a therapeutic trial of ER-NTX.

Table Summary of Naltrexone ER Injection Studies in Opioid Dependence

|  |  |  |  |
| --- | --- | --- | --- |
| **Reference** | **Design, Study Population** |  | **Findings** |
| Krupitsky (2011) | 24-wk PC RCT  Opioid-detoxified patients receiving ER-NTX 380 mg once every 4 weeks in combination with psychosocial support |  | ER-NTX was superior to PBO in terms of   * Median proportion of weeks of confirmed opioid abstinence during weeks 5-24 (primary endpoint): 90% vs. 35%; difference, 55% (15.9–76.1). * Proportion of patients who achieved total confirmed abstinence: 36% vs. 23%; RR 1.58 (1.06–2.36); NNT 8 (95% CI 5–55) * Reduction in opioid craving from baseline: –10.1 vs. 0.7 * Treatment retention duration: >168 d vs. 96 d; RR 0.61 (0.44–0.86)   ER-NTX was generally well tolerated. |
| Mitchell (2012) | Hepatic safety subgroup analysis by HIV status (substudy of Krupitsky (2011)) |  | There were no cases of continued or persistent increase in LETs; LETs improved and returned toward BL despite continued tx in all pts in both tx groups.  The incidence of Increased AST, ALT, and GGT greater than three times the ULN was numerically but not statistically higher in HIV-positive patients receiving ER-NTX than in those on placebo during weeks 4 and 8.  ER-NTX can be used safely in pts with opioid dependence, even those with underlying chronic HCV and/or HIV infections. |
| Krupitsky (2013) | 1-yr open-label long-term safety and effectiveness observational extension study  114 opioid-dependent patients from RCT who continued on or were switched from PBO to ER-NTX |  | Responses seen in the DB RCT were maintained during the 1-yr extension trial:   * 62.3% of patients completed the phase * 50.9% were abstinent from opioids   No new safety concerns. |

Table Study Methods: Naltrexone ER Injection in Opioid Dependence

| Methods | Participants | Interventions | Outcomes | Funding,  Quality, Notes |
| --- | --- | --- | --- | --- |
| Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011 Apr 30;377(9776):1506-13. | | | | |
| 24-wk, 13-site MC DB PC phase III RCT (ALK21-013) in Russia  ITT, LOCF. Multiplicity correction was used for craving and retention outcomes. | ≥ 18 yo; DSM-IV dx of opioid dependence; completing inpatient opioid detoxification (≤ 30 d); off opioids for at least 7 d; voluntarily seeking tx (not under justice system coercion); supervised by significant other to adhere to study procedures.  Primarily young (29 yo), male (88%), white (99%), addicted to heroin for about 10 years.  Excluded pregnancy, breastfeeding, significant medical conditions, positive naloxone challenge; hepatic failure; hx of AIDS-indicator disease; active hepatitis or AST or ALT >3x ULN; intolerance or hypersensitivity to naltrexone, carmellose, or polylactide-co-glycolide; psychosis; bipolar disorder; major depressive disorder with suicidal ideation; present dependence on substances other than opioids or heroin, including alcohol; positive urine test for cocaine or amphetamines; naltrexone use within past 6 mo.  Prohibited drugs: naltrexone, buprenorphine, levacetylmethadol, methadone, other prescription opioids, antipsychotics, anticonvulsants, antidepressants, and anxiolytics.  Permitted co-drugs: anticonvulsants if dosing was stable; and short-acting insomnia drugs, such as zopiclone, as required. | ER-NTX 380 mg i.m. within 1 wk of detox then q4wk thereafter  PBO  24 wk (6 injections)  Offered 12 biweekly session of individual drug counseling  UDS for morphine and methadone qwk | POM: *Confirmed abstinence* response profiles (i.e., the cumulative percent of opioid-free weeks) during wks 5–24; confirmed abstinence responders. Confirmed abstinence was defined as a negative urine drug test and no self-reported opioid use on the timeline follow-back (TLFB) survey.  SOMs: self-reported opioid-free days on TLFB; opioid craving scores (VAS 0–100); number of days of retention; relapse to physiologic opioid dependence (naloxone challenge test).  Other: HIV risk; SF-36; EuroQol-5 general health; CGI.  Safety: TEAEs; VS; labs including LFTs; injection site; EKGs | Sponsor: Alkermes  GRADE: Moderate  Pts may have challenged the study tx and been unblinded (pts on PBO could get high on opioids). Wks 1–4 were prospectively omitted from the POM. Results reflect the more stable period of abstinence (5–24 wk) and may be biased.  Only 45.6% of all patients completed the study, with a relatively large absolute diff of 15.3% in completion rates between tx groups favoring NTX IMI.  External Validity to VA: Possible in some pts, particularly in young age, male, HIV+, HCV+, without serious active medical or psychiatric illnesses, and not on the excluded co-drugs. Diffs in country and health care system. Study authors suggested that ER-NTX may be a tx to consider in those whose employment prohibits opioid use, those with a relatively recent addiction to opioids, and those who wish to secure their recovery after a successful course of agonist therapy. |
| Mitchell MC, Memisoglu A, Silverman BL.Hepatic safety of injectable extended-release naltrexone in patients with chronic hepatitis C and HIV infection. J Stud Alcohol Drugs. 2012 Nov;73(6):991-7. | | | | |
| Subgroup analysis of Krupitsky (2011) | See Krupitsky (2011) |  |  | Authors noted another study that showed oral naltrexone was associated with LETs > 3.5x BL values in 2 / 114 pts (1.8%) over a median of 49 d of tx in veterans with HIV infection, 57% of whom were co-infected with HCV (Tetrault and Fiellin, 2012).  Alcohol use was not tracked. No reported use of INH, statins, or other potentially toxic drugs except 8 pts reported taking APAP (NMT 4 g/d). |
| Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness.Addiction. 2013 Sep;108(9):1628-37. doi: 10.1111/add.12208. Epub 2013 May 24. | | | | |
| 52-wk follow-on OL OS  Missing UDS results were imputed as positive; LOCF  Kaplan-Meier survival analysis (retention) | 114 pts who completed RCT and entered the OL phase; continued on ER-NTX (n = 67) or switched from PBO to ER-NTX (n = 47).  Excluded pts on oral naltrexone, buprenorphine, levomethadyl acetate/LAAM, methadone, other prescription opioids, antipsychotics, anticonvulsants, antidepressants and anxiolytics.  Predominantly young (29.5 yo), male (89%), white (100%), addicted to heroin for about 10 years, and had high rates of HIV (40%) and HCV (88%) infection. | ER-NTX 380 mg i.m. q4wk for up to 13 add’l doses (including the DB doses, this totals to 19 injections over 18 mos)  Manualized individual drug counseling monthly  Permitted co-meds: AEDs if dosing was stable and short-acting PRN insomnia medications | UDT qmo  Self-reported drug use (Timeline Follow-back/TLFB method)  Addiction Severity Index (ASI) monthly  Durability of effects: retention, opioid craving (VAS 0–100), SF-36v2 and EQ-5D health function, CGII  Responders were defined *a priori* as CGII of 1 (very much) or 2 (much) improved  Safety: TEAEs, VS, urine/blood tests inc LFTs, injection sites, ECG | Funding: Alkermes  GRADE: LOW  Pts who entered the OL phase were similar to those who did not.  All doses were given free to pts.  Results reflect a select subpopulation of predominantly abstinent, probably more highly motivated pts.  Pts were not tracked after dropout from tx.  External validity to VA: Possible |

Table Results of Major Efficacy Trial, 24 Weeks (Krupitsky, 2011)

| Outcome Measures | ER-NTX  (N=126) | PBO  (N=124) | Relative Effect  (95% CI) |  | P-value |
| --- | --- | --- | --- | --- | --- |
| Primary Outcome Measures | | | | | |
| Proportion of weeks of confirmed abstinence, % (95% CI) | 90.0 (69.9–92.4) | 35.0 (11.4–63.8) | Diff 55.0 (15.9–76.1) |  | 0.0002 |
| Pts with total confirmed abstinence, % (95% CI) | 35.7 (27.4–44.1) | 22.6 (15.2–29.9) | RR 1.58 (1.06–2.36)  Diff 13.1 (1.8–23.9)  NNT 8 (5–55) |  | 0.0224 |
| Secondary Outcome Measures | | | | | |
| Proportion of self-reported opioid-free days, % | 99.2 (89.1–99.4) | 60.4 (46.2–94.0) | Diff 38.7 (3.3–52.5) |  | 0.0004 |
| Craving: mean change in VAS score from BL | –10.1 (–12.3 to –7.8) | 0.7 (–3.1 to 4.4) | Diff –10.7 (–15.0 to 6.4) |  | <0.0001 |
| Number of days of retention | >168 (CI not calculable) | 96 (63–165) | RR 0.61 (0.44–0.86) |  | 0.0042 |
| Pts with positive naloxone challenge test, % | 0.8 (0.0–2.3) | 13.7 (7.7–19.8) | RR 17.3 (2.3–127.8) |  | <0.0001 |
| Other Outcomes | | | | | |
| Pts who completed DB tx period, % | 53.2 (44.5–61.9) | 37.9 (29.4–46.4) | RR 1.40 (1.06–1.85) |  | 0.0171 |
| Risk for HIV: mean change in behavior scores from BL | –0.187 (–0.224 to –0.150) | –0.130 (–0.173 to –0.087) | Diff –0.057 (–0.113 to –0.001) |  | 0.0212 |
| EQ-5D: mean change in VAS self-ratings from BL | 14.1 (9.6–18.7) | 2.7 (–1.9–7.8) | Diff 11.4 (5.0–17.8) |  | 0.0005 |
| Rated much or very much improved on CGI, % | 85.9 (77.8–94.0) | 57.5 (45.7 –69.5) | 1.49 (1.19–1.87) |  | 0.0002 |
| Safety |  |  |  |  |  |
| SAEs, % of pts | 2 | 3 | Diff –1 |  | NSD |
| WDAEs, % of pts | 2 | 2 | Diff 0 |  | — |
| DRAEs, % of pts | 26 | 10 | Diff 16 |  | 0.001 |
| ≥1 AE, % of pts | 50 | 32 | Diff 18 |  | 0.005 |
| Adverse Events Reported in ≥5% of Patients in Either Treatment Group | | | | | |
| Nasopharyngitis | 7 | 2 | 5 |  | NSD |
| Insomnia | 6 | 1 | 5 |  | 0.036 |
| Hypertension | 5 | 3 | 2 |  | NSD |
| Influenza | 5 | 4 | 1 |  | NSD |
| Injection Site Pain | 5 | 1 | 4 |  | NSD |

Table Liver Enzymes in Hepatic Safety Substudy (Mitchell, 2012)

| Outcome Measures | ER-NTX  (N = 126) | PBO  (N = 124) | P-value |  | Comments |
| --- | --- | --- | --- | --- | --- |
| Alanine aminotransferase, mean ± SD, IU/ml (ULN 55 IU/ml) | | | | | |
| Baseline | 52.2 ± 28.9 | 51.2 ± 29.9 | NSD |  | No cases of ALT > 3x ULN. |
| 24 wk | 56.0 ± 55.1 | 57.4 ± 41.2 | NSD |  |
| Aspartate aminotransferase, mean ± SD, IU/ml (ULN NR) | | | | | |
| Baseline | 39.8 ± 18.2 | 37.9 ± 18.9 | — |  |  |
| 24 wk | 44.0 ± 30.3 | 44.4 ± 31.2 | — |  |
| Gamma-glutamyl transferase, mean ± SD, IU/ml (ULN NR) | | | | | |
| Baseline | 84.6 ± 72.5 | 106 ± 111.7 | NSD |  | “Declined slightly” in both groups |
| 24 wk | NR | NR | NSD |  |
| Total Bilirubin, mean ± SD, micromol/ml) (ULN NR) | | | | | |
| Baseline | 7.21 ± 3.83 | 7.55 ± 3.57 | NSD |  | No cases of TBili > 2x ULN |
| 24 wk | 11.49 ± 6.33 | 9.65 ± 5.00 | NSD |  |

Table Rates of Increased Liver Enzymes by HIV Status (Mitchell, 2012)

| Outcome Measures | HIV– | HIV+ | All |  | Comments |
| --- | --- | --- | --- | --- | --- |
| Alanine aminotransferase 3 x ULN, n/N (%) | | | | | |
| ER-NTX |  |  |  |  |  |
| Baseline | 0 / 74 (0.0) | 0 / 52 (0.0) | 0 / 126 (0.0) |  | Peak of 11/103 (10.7) at Wk 4.  NSDs for ER-NTX vs. PBO and for HIV– vs. HIV+ gps. |
| Postbaseline | 9 / 62 (14.5) | 12 / 45 (26.7) | 21 / 107 (19.6) |  |
| PBO |  |  |  |  |  |
| Baseline | 0 / 70 (0.0) | 0 / 54 (0.0) | 0 / 124 (0.0) |  | Peak of 5 / 81 (6.2) at Wk 4.  NSD for HIV– vs. HIV+ gps. |
| Postbaseline | 8 / 51 (15.7) | 3 / 34 (8.8) | 11 / 85 (12.9) |  |
| Aspartate aminotransferase 3 x ULN, n/N (%) | | | | | |
| ER-NTX |  |  |  |  |  |
| Baseline | 0 / 74 (0.0) | 0 / 52 (0.0) | 0 / 126 (0.0) |  | Peak of 9 / 103 (8.7) at Wk 4.  NSDs for ER-NTX vs. PBO and for HIV– vs. HIV+ gps |
| Postbaseline | 2 / 62 (3.2) | 13 / 45 (28.9) | 15 / 107 (14.0) |  |
| PBO |  |  |  |  |  |
| Baseline | 0 / 70 (0.0) | 0 / 54 (0.0) | 0 / 124 (0.0) |  | Peak of 5 / 81 (6.2) at Wk 4.  NSD between HIV- and HIV+ gps. |
| Postbaseline | 5 / 51 (9.8) | 4 / 34 (11.8) | 9 / 85 (10.6) |  |
| Gamma-glutamyl transferase 3 x ULN, n/N (%) | | | | | |
| ER-NTX |  |  |  |  |  |
| Baseline | 10 / 74 (13.5) | 13 / 52 (25) | 23 / 126 (18.3) |  | Highest % was at BL. Postbaseline peak of 18 / 103 (17.5) at Wk 4.  NSDs for ER-NTX vs. PBO and for HIV– vs. HIV+ gps |
| Postbaseline | 11 / 62 (17.7) | 14 / 45 (31.1) | 25 / 107 (23.4) |  |
| PBO |  |  |  |  |  |
| Baseline | 11 / 70 (15.7) | 14 / 54 (25.9) | 25 / 124 (20.2) |  | Highest % was at BL. Postbaseline peak of 12 / 81 (14.8) at Wk 4.  NSD between HIV- and HIV+ gps. |
| Postbaseline | 11 / 51 (21.6) | 7 / 34 (20.6) | 18 / 85 (21.2) |  |

Level of significance was adjusted for multiplicity to p < 0.003 using Bonferroni method.

Table Results from Long-term Open-label Safety and Effectiveness Study

| Outcome Measures | ER-NTX / ER-NTX  (n=67) | PBO / ER-NTX  (n=47) | Overall  (n=114) |  | Comments |
| --- | --- | --- | --- | --- | --- |
| Retention and Durability of Effects | | | | | |
| Completed 1-yr OL study, % (95% CI) | 58.2 (45.4–70.2) | 68.1 (52.9–80.9) | 62.3 (52.7–71.2) |  |  |
| Retention x 1.5 yr of tx, % (95% CI) | 31% (23.0–39.8) | — | — |  |  |
| Abstinent x 1-yr of OL tx, % (95% CI) | 49.3 | 53.2 | 50.9 (41.5–60.4) |  |  |
| Opioid-negative UDTs, % of UDTs ± SD | 73.7 ± 33.2 | 81.0 ± 28.6 | 76.7 |  |  |
| Percent of opioid-free days, % ± SD | 80.6 ± 29.7 | 87.4 ± 23.8 | 83.4 ± 27.5 |  | 3/47 pts on DB PBO had opioid-positive UDT at start of OL phase |
| Addiction Severity Index for Opioids, OL BL / EOT, score ± SD | 0.3 ± 1.5 / 0.1 ± 0.5 | 0.0 ± 0.2 / 0.8 ± 3.8 | — |  | Little change was seen in ADS for alcohol (remained around 5 days / mo during DB and OL phases) |
| CGII Responders, OL BL / EOT, % | 91.0 / 97.0 | — / 89.4 |  |  |  |
| EQ-5D, OL BL / EOT, scores ± SD | 81.6 ± 12.4 / 83.8 ± 12.7 | 77.9 ± 18.10 / 82.7 ± 15.1 |  |  |  |
| Safety | | | | | |
| SAEs, % of pts | 4.5 | 0.0 | 2.6 |  | 4 SAEs in 3 pts: acute pancreatitis (possibly related), cardiomyopathy (probably not related), and hepatitis A + pulmonary TB |
| WDAEs, % of pts | 0.0 | 2.1 | 0.88 |  | 1 pt WD b/o persistent increase in LFTs |
| DRAEs, % of pts | 20.9 | 21.3 | 21.1 |  |  |
| ≥1 AE, % of pts | 43.3 | 40.4 | 42.1 |  |  |
| Adverse Events Reported in ≥5% of Patients Overall | | | | | |
| Injection site reaction | 6.1 |  |  |  | Majority were mild. |
| Influenza | 6.0 | 4.3 | 5.3 |  |  |
| Toothache | 4.5 | 8.5 | 6.1 |  |  |
| Laboratory Abnormalities | | | | | |
| Total, % of pts | 14.9 | 22.4 |  |  | 17 were considered to be Related to ER-NTX. None were considered clinically meaningful. |
| Increased LETs, % of pts | 19.4 | 12.8 | 16.7 |  |  |