Important Safety Information (cont'd)

Vivitrol® (naltrexone for extended-release injectable suspension)

WARNINGS AND PRECAUTIONS (cont'd)

Hepatotoxicity:

- Cases of hepatitis and clinically significant liver dysfunction have been observed in association with VIVITROL. Warn patients of the risk of hepatic injury; advise them to seek help if experiencing symptoms of acute hepatitis. Discontinue use of VIVITROL in patients who exhibit acute hepatitis symptoms.

Depression and Suicidality:

- Alcohol- and opioid-dependent patients taking VIVITROL should be monitored for depression or suicidal thoughts. Alert families and caregivers to monitor and report the emergence of symptoms of depression or suicidality.

When Reversal of VIVITROL Blockade Is Required for Pain Management:

- For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

Please see additional Important Safety Information on next slide.
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Important Safety Information (cont'd)

Vivitrol® (naltrexone for extended-release injectable suspension)

WARNINGS AND PRECAUTIONS (cont'd)

Eosinophilic Pneumonia:

- Cases of eosinophilic pneumonia requiring hospitalization have been reported. Warn patients of the risk of eosinophilic pneumonia and to seek medical attention if they develop symptoms of pneumonia.

Hypersensitivity Reactions:

- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.

Intramuscular Injections:

- As with any IM injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder.

Alcohol Withdrawal:

- Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

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Important Safety Information (cont'd)

Vivitrol® (naltrexone for extended-release injectable suspension)

ADVERSE REACTIONS

- Serious adverse reactions that may be associated with VIVITROL therapy in clinical use include severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose, and depression and suicidality.
- The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules, and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.
- The adverse events seen most frequently in association with VIVITROL in opioid-dependent patients (ie, those occurring in ≥2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

You are encouraged to report side effects to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Prescribing Information and Medication Guide.

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VIVITROL was studied in a double-blind trial[1,2]

Vivitrol® (naltrexone for extended-release injectable suspension)

VIVITROL in opioid dependence

Six-month, **double-blind trial with monthly injections**

- Participants screened after completion of detoxification
- Required to abstain from opioids 7 days prior to treatment
- Randomized into 2 groups
- Both groups received psychosocial support*

*Psychosocial support consisted of biweekly counseling sessions of individual drug counseling, adapted for opioid dependence.

References: 1. VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc.; rev December 2015. **2.** Krupitsky E et al. *Lancet*. 2011;377(9776):1506-1513.

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VIVITROL in opioid dependence: primary study endpoint[1,2]

Vivitrol® (naltrexone for extended-release injectable suspension)

124 PLACEBO | 126 VIVITROL 380 mg

Patients treated with VIVITROL and counseling had higher rates of complete abstinence

- All weekly visits (weeks 5-24)

Completely abstinent placebo patients (with psychosocial support) (n=28)

Completely abstinent VIVITROL patients (with psychosocial support) (n=45)

P=0.0224 (adjusted)

Confirmed abstinence=negative urine drug test and no self-reported opioid use. Complete abstinence=opioid-free at all weekly visits, weeks 5-24.

References: 1. VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc.; rev December 2015. **2.** Krupitsky E et al. *Lancet*. 2011;377(9776):1506-1513.

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VIVITROL in opioid dependence: primary study endpoint[1,2]

Vivitrol® (naltrexone for extended-release injectable suspension)

124 PLACEBO | 126 VIVITROL 380 mg

Patients treated with VIVITROL and counseling had a significantly higher percentage of opioid-free weeks

- During weeks 5-24

Median placebo patients (with psychosocial support) had 35% cumulative opioid-free weeks.

Median VIVITROL patients (with psychosocial support) had 90% cumulative opioid-free weeks.

P=0.0002

Confirmed abstinence=negative urine drug test and no self-reported opioid use.

References: 1. VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc.; rev December 2015. **2.** Krupitsky E et al. *Lancet*. 2011;377(9776):1506-1513.

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VIVITROL in opioid dependence: secondary study endpoint

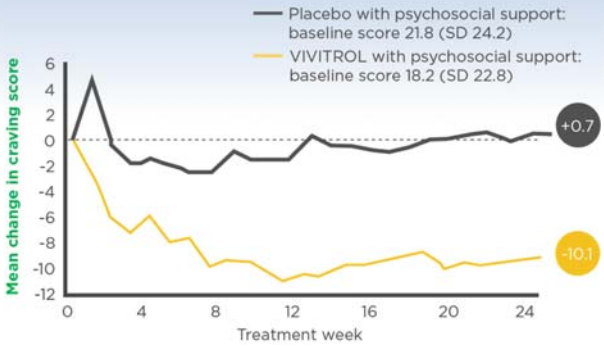
Vivitrol® (naltrexone for extended-release injectable suspension)

124 PLACEBO | 126 VIVITROL 380 mg

Patients treated with VIVITROL and counseling had a 55% decrease in self-reported opioid craving from baseline

- Weeks 1-24

Mean change in self-reported craving



Craving was reported according to a visual analogue scale of 0-100: 0=not at all; 100=very much so.

P<0.0001 (adjusted)

Reference: Krupitsky E et al. *Lancet*. 2011;377(9776):1506-1513.

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Adverse reactions

Vivitrol® (naltrexone for extended-release injectable suspension)

The adverse events seen most frequently in association with VIVITROL therapy in opioid-dependent patients (ie, those occurring in ≥2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

Please see complete list of adverse events in the VIVITROL Prescribing Information.

Body system	Adverse event/ preferred term	Placebo N=124		VIVITROL 380 mg N=126	
		n	%	n	%
Investigations	Alanine aminotransferase increased	7	6	16	13
	Aspartate aminotransferase increased	3	2	13	10
	Gamma-glutamyltransferase increased	4	3	9	7
Infections and infestations	Nasopharyngitis	3	2	9	7
Psychiatric disorders	Insomnia	1	1	8	6
General disorders and administration site conditions	Injection site pain	1	1	6	5
Gastrointestinal disorders	Toothache	2	2	5	4

In a controlled trial of 6 months, 2% of opioid-dependent patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 2% of the opioid-dependent patients treated with placebo.

Reference: VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc.; rev December 2015.

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X:BOT: Head-to-head study in the treatment of opioid dependence

Vivitrol® (naltrexone for extended-release injectable suspension)

A 24-week, US-based, multicenter, open-label randomized clinical trial

- Participants screened during voluntary, usual care, inpatient detoxification
- Randomized to extended-release naltrexone (XR-NTX, VIVITROL) or to buprenorphine-naloxone (BUP-NX)
  - XR-NTX treatment could be initiated after detoxification
  - BUP-NX treatment could be initiated when withdrawal symptoms emerged
- Intention-to-treat population
  - All participants who were randomly assigned to a study treatment
- Per-protocol population
  - All participants who were successfully inducted into a study treatment

Intention-to-Treat	Per-protocol
283 XR-NTX	204 XR-NTX 380 mg/4 wks
287 BUP-NX	270 BUP-NX 8-24 mg/d

Reference: Lee JD et al. *Lancet.* 2018;391(10118):309-318.

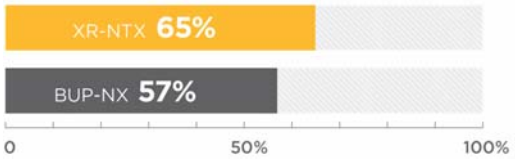
X:BOT primary outcome measure: time to a relapse

Vivitrol® (naltrexone for extended-release injectable suspension)

Both extended-release naltrexone (XR-NTX) and buprenorphine-naloxone (BUP-NX) were equally safe and effective for relapse prevention among participants once initiated.

The intention-to-treat (ITT) population included all randomized participants

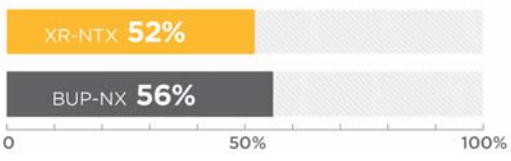
OPIOID-RELAPSE, WEEKS 3-24, ITT



OR 1.44, 95% CI 1.02-2.01; *P*=0.036

The per-protocol population included only the participants who successfully began study medication

OPIOID-RELAPSE, WEEKS 3-24, PER PROTOCOL



OR 0.87, 95% CI 0.60-1.25; *P*=0.44

In the per-protocol population, median time to relapse was similar, rates of study completion were similar

Reference: Lee JD et al. *Lancet.* 2018;391(10118):309-318.

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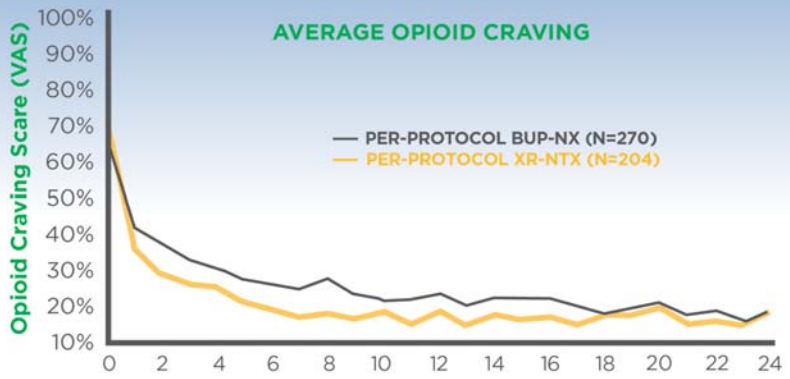
X:BOT secondary endpoint: opioid craving

Vivitrol® (naltrexone for extended-release injectable suspension)



Craving was self-reported with an opioid-craving VAS, range 0–100. VAS=visual analog scale

- Subjective opioid craving declined rapidly from baseline in both treatment groups
- Average opioid craving was initially less for the XR-NTX group (P=0.0012 at week 7) than for the BUP-NX group, then converged by week 24 (P=0.20)

Reference: Lee JD et al. *Lancet.* 2018;391(10118):309-318.

X:BOT adverse events

Vivitrol® (naltrexone for extended-release injectable suspension)

Adverse events*

- The proportion of participants reporting adverse events and serious adverse events did not differ between groups, with the exception of injection site reactions among XR-NTX group that were of minor to moderate severity
- Five fatal overdoses occurred, 2 participants treated with XR-NTX and 3 participants treated with BUP-NX

	Adverse Events and Serious Adverse Events			
	XR-NTX group (n=283)		BUP-NX group (n=287)	
Treatment-emergent adverse events	All	Serious	All	Serious
Participants with one or more treatment-emergent adverse event*	111 (54%)	29 (14%)	141 (52%)	29 (11%)
Number of treatment-emergent adverse events	247	39	334	35
Study medication discontinued due to adverse event	6		8	
Type of treatment-emergent adverse event				
Injection site reaction, mild or moderate	46		NA	
Gastrointestinal	34		59	
Psychiatric disorders	30	9	29	11
Injury, poisoning, and procedural complications	23		25	
Infections and Infestations	22	5	27	6
Nervous system disorders	22		28	
Pregnancy		3		4
Death		3		4
Overdose Events	All	Per-protocol	All	Per-protocol
Participants with one or more overdose event	15†	9‡	8†	7‡
Number of overdose events	18§	10	10§	9
Fatal overdose events	All	Per-protocol	All	Per-protocol
Number	2	2	3	3

*Treatment emergent is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.
†p=0.14 (Fisher's exact).
‡p=0.31 (Fisher's exact).
§Four participants reported more than one overdose event. Three of the four participants were randomly assigned to XR-NTX (two of these induction failures, one successfully inducted); each reported two overdose events. One of the four was randomly assigned to BUP-NX (successfully inducted) and reported three overdose events. None of these nine overdoses were fatal.

***Please see complete list of adverse events in the VIVITROL Prescribing Information.**

Reference: Lee JD et al. *Lancet.* 2018;391(10118):309-318.

X:BOT study limitations

Vivitrol® (naltrexone for extended-release injectable suspension)

Study limitations

- Study sites varied in detoxification protocols and length of inpatient stay
- Ease of induction is a well-known limitation of extended-release naltrexone compared to buprenorphine-naloxone
- A real-world effectiveness study such as this includes more sources of bias than a tightly-managed efficacy study, but has potentially higher generalizability

Reference: Lee JD et al. *Lancet.* 2018;391(10118):309-318.

A second head-to-head study showed noninferiority of XR-NTX to BUP-NX across 3 primary endpoints

Vivitrol® (naltrexone for extended-release injectable suspension)

- Norway-based, 12-week, multicenter, open-label, randomized clinical trial[1]
- Participants randomized to oral BUP-NX (n=79) or XR-NTX (n=80)[1]

MEAN DIFFERENCE IN DAYS OF USE

RETENTION TIME ON XR-NTX NONINFERIOR TO BUP-NX

P=0.33, log-rank test

TOTAL NUMBER OF OPIOID-NEGATIVE UDTs

UDT=urine drug test.

The authors of the X:BOT study reported that the findings of the two studies were consistent. Both studies found that for participants who were able to begin treatment, extended-release naltrexone and BUP-NX were equally safe and effective in preventing relapse.[1,2]

References: 1. Tanum L et al. *JAMA Psychiatry.* 2017;74(12):1197-1205. **2.** Lee JD et al. *Lancet.* 2018;391(10118):309-318.

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Study limitations

Vivitrol® (naltrexone for extended-release injectable suspension)

- The study was not blinded. Participants of each group knew which medication they were receiving
- For the study to have been blinded, it would have required placebo injections like the XR-NTX kits and placebo tablets for BUP-NX
- Patients would be able to determine their respective treatment quite quickly, given their long experience with opioid use
- Due to an increased risk of overdose in newly detoxified opioid users, the use of placebo and/or masking of medications was considered unethical

Reference: Tanum L et al. *JAMA Psychiatry*. 2017;74(12):1197-1205.

A retrospective claims-based study reviewed healthcare utilization and costs of VIVITROL compared with other opioid dependence therapies

Vivitrol® (naltrexone for extended-release injectable suspension)

- Adults (≥18 years) with a diagnosis of opioid dependence and treated with one of the following:
  - VIVITROL (n=1,041)
  - Buprenorphine (n=20,566)
  - Methadone (n=745)
  - Non-pharmacological therapy (NPT) (n=6,883)
- Claims were filed between January 1, 2011 and December 31, 2014
- Index date was date of the first MAT claim or psychosocial therapy visit
- Healthcare costs were evaluated for each cohort during the 12-month baseline and follow-up

Study limitations included:

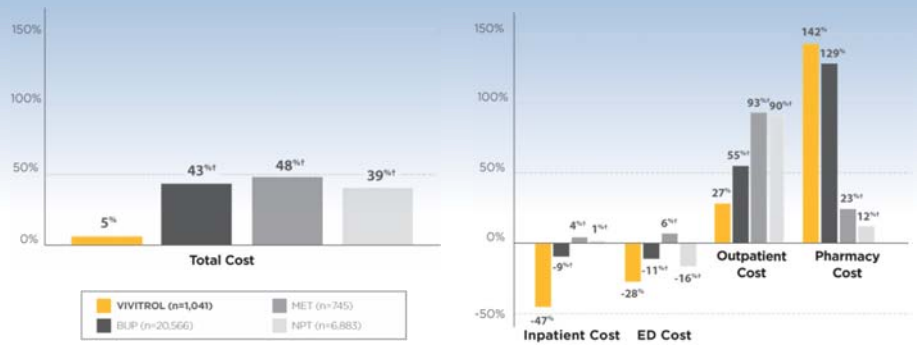
- Potential data entry errors in administrative claims
- Claims do not indicate whether the medication was taken as prescribed
- No capture of variables such as disease severity
- Findings may not be generalizable to those without commercial insurance
- Significant differences in baseline characteristics between groups
- Additional unobserved confounding variables

Reference: Shah A et al. *J Med Econ*. 2018;21(4):406-415.

VIVITROL was linked with significantly lower total cost increases and healthcare utilization vs other opioid dependence therapies*

Vivitrol® (naltrexone for extended-release injectable suspension)

DIFFERENCE IN MEAN HEALTHCARE COSTS DURING BASELINE AND FOLLOW-UP PERIODS: BETWEEN GROUPS COMPARISONS



*Total mean costs from baseline to follow-up were $30,817-$32,372 for VIVITROL, $13,797-$19,731 for BUP, $9,220-$13,621 for MET, and $19,331-$26,839 for NPT.
†*P*<0.05 compared with the VIVITROL group. *P* values were based on generalized linear models (GLM) with a log-link function and gamma distribution after controlling for baseline covariates.
Adapted from Shah A, et al. *J Med Econ*. 2018;21(4):406-415

Patients in the VIVITROL group had the greatest percentage decrease from baseline in emergency department and inpatient utilization and costs, despite having more comorbidities and higher baseline costs

Reference: Shah A et al. *J Med Econ*. 2018;21(4):406-415.

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Summary

Vivitrol® (naltrexone for extended-release injectable suspension)

- The opioid epidemic is a public health emergency contributing to high costs across the healthcare spectrum[1-3]
- MAT is recognized as an effective treatment approach, but most patients are not able to access MAT, often due to utilization management measures[4-8]
- VIVITROL, an opioid antagonist MAT option, is indicated for the prevention of relapse to opioid dependence, when used in conjunction with counseling and following detoxification[9]
- VIVITROL has been found to be as equally safe and efficacious as buprenorphine once initiated and there may be economic value in the use of VIVITROL[10-12]

References: 1. The President's Commission on Combating Drug Addiction and the Opioid Crisis. https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-15-2017.pdf. Accessed February 20, 2018. **2.** Florence CS et al. *Med Care*. 2016;54(10):901-906. **3**. Shei A et al. *J Manag Care Spec Pharm*. 2015;21(10):902-912. **4.** Substance Abuse and Mental Health Services Administration. https://store.samhsa.gov/shin/content//SMA18-5063FULLDOC/SMA18-5063FULLDOC.pdf Accessed March 13, 2018. **5.** Knudsen HK et al. *J Addict Med*. 2011;5(1):21-27. **6.** Liu X et al. *Med Care Res Rev*. 2000;57(2):182-195. **7.** Alanis-Hirsch K et al. *J Subst Abuse Treat*. 2016;62:68-73. **8.** The National Center on Addiction and Substance Abuse. https://www.centeronaddiction.org/download/file/fid/1678. Accessed March 14, 2018. **9.** VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc.; rev December 2015. **10.** Lee JD et al. *Lancet*. 2018;391(10118):309-318. **11.** Tanum L et al. *JAMA Psychiatry*. 2017;74(12):1197-1205. **12.** Shah A et al. *J Med Econ*. 2018;21(4):406-415.

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