Nalmefene Nasal Spray (OPVEE)
Mini-Monograph
Sept 2023

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

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: MOA=mechanism of action; TBD=to be determined; VANF=VA National Formulary; NF = non-formulary

FDA Approval	**Description/MOA**	Opioid receptor antagonist
	Indication(s) Under Review	Emergency treatment of known or suspected overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older. [1]
	Dosage Form(s)	Single-use, nasal administration device containing 2.7mg of nalmefene (3mg nalmefene HCl) in 0.1mL total volume. [1] Two dose units supplied per package[2] **NOTE: OPVEE also is formulated with dodecylmaltoside (DDM), an absorption enhancer, which resulted in 12-fold increase blood levels in phase 1 studies vs. nalmefene in absence of the DDM excipient.*[1,4]

Clinical Evidence	**Study/Design**	Nalmefene nasal was approved on basis of 2 pharmacokinetic (PK) [3] and 1 pharmacodynamic (PD) [2] study which were all open-label and randomized. PK studies were plasma levels at various time-points after administration of intranasal (IN) nalmefene and active comparators of either intramuscular (IM) nalmefene or IN naloxone. PD studies evaluated the reversal effect of nalmefene IN vs. naloxone IN in an experimental model of remifentanil induced respiratory depression. Pharmacodynamic studies were not available in peer reviewed journal at time of draft and only available for review within the FDA application documents.[2] One pre-submission PK study assessed the impact of a proprietary absorption enhancer (e.g., DDM) in intranasal nalmefene vs. intramuscular (IM) nalmefene.[4]
	Population	Total of 151 healthy study subjects from the PK and PD studies which represent the safety population
	Demographics	OPNT003-PK-1 study – 68 healthy volunteers; OPNT003-PK-2 study – 24 healthy volunteers; OPNT003-OOD-001 study – 69 healthy volunteers described as opioid experienced but not dependent. No greater detail or specifics to what "opioid experienced" meant was found in FDA submission materials.
	Intervention	Single 2.7mg dose of IN nalmefene vs. single 1mg dose of IM nalmefene (PK study 1); single dose of 2.7mg IN nalmefene vs. 2 doses (5.4mg nalmefene total) sequentially administered in either same or alternate nares (PK study 2); Nalmefene 2.7mg IN vs. naloxone 4mg IN administered as rescue to an experimental remifentanil induced respiratory depression (PD study OPNT003-OOD-001).
	Results	Nalmefene IN formulated with DDM absorption enhancer resulted in detectible levels of nalmefene within 2.5 minutes, exhibited dose proportionality at all doses studied, and yielded higher plasma levels than 1mg nalmefene administered intramuscularly at all time points assessed. Plasma half-life of nalmefene was approximately 11 hours. In the pharmacodynamic study of experimental, remifentanil-induced respiratory depression, nalmefene was non-inferior to naloxone in reversal of respiratory depression. Adverse effects (AEs) in PK studies were primarily nasal irritation. In PD studies, AEs were common and as would be expected with abrupt reversal of opioid agonism (e.g., nausea, vomiting, HA, etc. see details in safety section below).
	Limitations	Phase I studies only.
	Summary	Single dose of nalmefene IN resulted in rapid achievement of plasma levels greater than usual dose of IM nalmefene. Nalmefene IN, as marketed in Opvee nasal spray, is intended for bystander administration. Nalmefene IN was non-inferior to naloxone IN in an experimental model of overdose with a high-potency fentanyl analogue.

SAFETY:	**Boxed Warnings**	None	
	Contraindications	OPVEE is contraindicated in patients known to be hypersensitive to nalmefene or excipients	
	Warnings/ Precautions	*Risk of recurrent respiratory or central nervous system depression especially in setting of poly-drug overdose *Risk of limited efficacy with partial agonists or mixed agonists/antagonists (e.g., buprenorphine, pentazocine) *Risk of severe, precipitated opioid withdrawal *Risk of overdose from attempts in an OPVEE rescued patient to overcome the blockade	
	Adverse reactions (AE)	**Reported AEs in PK-1 study (n=66)** Nasal discomfort (56%) Dizziness (6%) Fatigue (4.5%) Headache (4.5%) Nausea (3%)	**Reported AEs in remifentanil+nalmefene PD study (n=151)** Headache (59%) Nausea (39%), Hot flush (23%) Dizziness (18%) Anxiety (16%) Vomiting (11%)

Conclusions/Projected Place in Therapy

- Nalmefene nasal spray rapidly achieves plasma levels several-fold greater than the originator product (e.g., nalmefene inj.) and can be reasonably expected to provide opioid antagonism of at least similar effect to the competitor product (e.g naloxone IN) in real world settings.
- Nalmefene has a half-life at least twice that of naloxone.
- Claims of nalmefene having a higher potency which thus confers an advantage over naloxone in reversal of overdose with illicit fentanyl and fentanyl analogues[3,5], at this point in time in the absence of real-world experience, are overstated. In fact, only post-marketing, published study of the originator products (e.g., nalmefene inj vs. naloxone inj) found no difference in recovery rates of suspected opioid overdose in an emergency department setting.[6]

References

1. OPVEE full prescribing information Combined-USPI_Patient-Info_IFU_Clean_05July2023.pdf (opvee.com) Accessed August 2023
2. OPNT003 FDA filing documents 217470Orig1s000MedR.pdf (fda.gov) Accessed August 2023
3. Crystal R, Ellison M, Purdon C, Skolnick P. Pharmacokinetic Properties of an FDA-approved Intranasal Nalmefene Formulation for the Treatment of Opioid Overdose. Clin Pharmacol Drug Dev. 2023 Jul 27
4. Krieter P, Gyaw S, Crystal R, Skolnick P. Fighting Fire with Fire: Development of Intranasal Nalmefene to Treat Synthetic Opioid Overdose. J Pharmacol Exp Ther. 2019 Nov;371(2):409-415
5. Skolnick P. On the front lines of the opioid epidemic: Rescue by naloxone. Eur J Pharmacol. 2018 Sep 15;835:147-153.
6. Kaplan JL, Marx JA, Calabro JJ, Gin-Shaw SL, Spiller JD, Spivey WL, Gaddis GM, Zhao N, Harchelroad FP., Jr (1999) Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. *Ann Emerg Med* 34:42–50