Dexmedetomidine (IGALMI)
National Drug Monograph
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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 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.

FDA Approval Information

Description/Mechanism of Action

- Dexmedetomidine is an alpha2-adrenergic receptor agonist

Indication(s) Under Review in This Document

- Dexmedetomidine is indicated in adults for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder
- NOTE: safety and effectiveness has not been established beyond 24 hours from the first dose

Dosage Form(s) Under Review

- Sublingual film: 120 mcg, 180 mcg

Clinical Evidence Summary

Efficacy Considerations [1,2]

- The efficacy of dexmedetomidine, supporting its FDA approval, was evaluated in two industry-sponsored, randomized, double-blind, placebo-controlled, phase 3, fixed-dose studies, in patients with schizophrenia, schizoaffective or schizophreniform (SERENITY I, Study 1, NCT04268303) and in patients with bipolar I or II disorder (SERENITY II, Study 2, NCT04276883, Preskorn et al).
- In Study 1 and Study 2, patients were randomly assigned to receive sublingual dexmedetomidine 180 mcg, sublingual dexmedetomidine 120 mcg, or placebo. The study medication was self-administered.
- The population for study 1 had a mean age of 46 years old (range 18-71); 37% female and 63% male; 78% Black, 20% White.
- The population for study 2 had a mean age of 47 years old (range 18-70); 45% female and 55% male; 56% Black, 41% White.
- The primary efficacy endpoint was the change from baseline in the Positive and Negative Syndrome Scale-Excited Component (PEC) total score 2 hours after taking the medication. The PEC comprises 5 items associated with agitation; poor impulse control, tension, hostility, uncooperativeness, and excitement, with each item rated from 1 (minimum) to 7 (maximum).

This provides a range of 5 (no agitation) to 35 (extremely severe agitation). Treatment response is defined as a >40% reduction in score within 2 h of treatment.

- For both Study 1 and Study 2, the mean baseline PEC scores (18; mild to moderate) were similar in all study groups. The mean change from baseline in the PEC total score at 2 hours after the first dose (primary endpoint) was significantly greater in the 120 mcg and 180 mcg groups compared to the patients who received placebo (Table 1).
- The secondary end point was the earliest time of a statistically significant change in PEC total score from baseline for the drug vs placebo. In Study 1, the decrease in agitation with dexmedetomidine, compared to placebo, was statistically significant beginning at 20 minutes following dosing with the 180 mcg dose and 30 minutes after the 120 mcg dose. In Study 2, the decrease in agitation with dexmedetomidine, compared to placebo, was statistically significant beginning at 20 minutes after treatment with the 120 mcg and 180 mcg doses.

Table 1. Primary Efficacy Endpoints.[1-3]

	Study 1			Study 2		
	Dex 180mcg (N=125)	**Dex 120mcg (N=129)**	**Placebo (N=126)**	**Dex 180 mcg (N=126)**	**Dex 120 mcg (N=126)**	**Placebo (N=126)**
Baseline PEC score Mean (SD)	17.6 (2.7)	17.5 (2.5)	17.6 (2.3)	18.0 (3.0)	18.0 (2.7)	17.9 (2.9)
PEC total score Mean (SD) Δ BL at 2 hours	-10.3 (4.5)	-8.5 (4.5)	-4.8 (4.5)	-10.4 (4.4)	-9.0 (5.3)	-4.9 (4.7)
Difference vs. Placebo (97.5% CI)	-5.5 (-6.5, -4.4)	- 3.7 (-4.8, -2.7)		-5.4 (-6.6, -4.2)	-4.1 (-5.3, -2.9)	
p-value (vs. Placebo)	P<0.001	P<0.001		P<0.001	P<0.001	

BL: baseline; SD: standard deviation; Dex, dexmedetomidine; PEC, Positive and Negative Syndrome Scale-Excited Component; CI, confidence interval

Safety Considerations

Table 2. Adverse Reactions, Study 1 and Study 2. [1]

Adverse reaction	Dex 180 mcg N=252 %	Dex 120 mcg N=255 %	Placebo N=252 %
Somnolence	23	22	6
Paresthesia	7	6	1
Dizziness	6	4	1
Hypotension	5	5	0
Orthostatic hypotension	5	3	<1
Dry mouth	4	7	1
Nausea	3	3	2
Bradycardia	2	2	0
Abdominal discomfort	2	0	1

Dex, dexmedetomidine

Other warnings / precautions:[1]

- Hypotension, orthostatic hypotension, and bradycardia
- QT interval prolongation
- Somnolence
- Risk of withdrawal reactions
- Tolerance and tachyphylaxis

Other Therapeutic Options

Table 3.

Drug	Formulary status	Agitation Severity	Other Considerations
Dexmedetomidine 120 mcg SL Dexmedetomidine 180 mcg SL	NF NF	Mild/moderate Severe	Avoid use in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope
Haloperidol 5 mg PO	F	Mild/moderate	Avoid in Parkinson's disease
Lorazepam 2 mg PO	F	Mild/moderate	Contraindicated in acute narrow-angle glaucoma.
Olanzapine 5 mg PO	F	Mild/moderate	May cause orthostatic hypotension
Haloperidol 5 mg IM	F	Severe	May cause QT prolongation
Lorazepam 2 mg IM	F	Severe	Contraindicated in severe respiratory insufficiency
Olanzapine 10 mg IM	F	Severe	Avoid concurrent use with IM benzodiazepines
Ziprasidone 20 mg IM	NF	Severe	Contraindicated in history of QT prolongation, recent acute MI, uncompensated heart failure, drugs that prolong QT interval

Projected Place in Therapy

- Increased psychomotor activity, motor restlessness, and irritability, characteristics of psychomotor agitation, can occur in people with psychiatric disorders (e.g., bipolar disorder, schizophrenia), among other conditions. Patients who are agitated but cooperative, may be managed by verbal de-escalation techniques. However, psychomotor agitation may progress to aggressive, violent and unpredictable behavior often requiring pharmacologic intervention.
- The results from Study 1 (SERENITY I) and Study 2 (SERENITY II) support the efficacy of dexmedetomidine 120 mcg and 180 mcg in reducing mild to moderate agitation in patients with schizophrenia or bipolar disorder. The efficacy of the two doses was comparable, with slightly greater PEC total score reduction (improvement) in the 180 mcg groups. However, the effectiveness has not be established beyond 24 hours from the first dose and efficacy compared to alternative treatments has not been established.
- For Study 1 and Study 2, the mean baseline PEC scores was 18, which may be interpreted as mild to moderate agitation severity. However, the prescribing information provides dosage recommendations for mild, moderate, or severely agitated adults. **Of note, patients in Study 1 and Study 2 were in sufficient behavioral control to be educated on the appropriate self-administration of the sublingual film and were able to provide informed consent**. These patients may not represent the population who receive prn medications for agitation on psychiatry units or in the emergency departments at VA.

- The most common adverse reactions are somnolence, paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension. In Study 1 and Study 2, the incidence of adverse events were comparable between the 120 mcg and the 180 mcg groups and more than twice the rate of placebo (39.5%, 37.3%, and 15.1% respectively, Study 1 and 34.9%, 35.7%, and 17.5% respectively, Study 2).
- The use of dexmedetomidine should be avoided in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. It also should be avoided in patients with risk factors for prolonged QT interval.
- The use of dexmedetomidine has not been discussed in current (dated) treatment guidelines. Comparative effectiveness studies with antipsychotics or benzodiazepines have not been conducted.
- The abuse potential of sublingual dexmedetomidine is not yet understood and therefore, may not be suitable for patients with comorbid SUD. Dexmedetomidine might be considered for patients with mild to moderate acute agitation associated with schizophrenia or bipolar disorder who cannot tolerate prn antipsychotics or benzodiazepines.

References

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Prepared August 2022. Contact person: Matthew A. Fuller, Pharm.D., BCPP, National PBM Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)