BYFAVO™: A Benzodiazepine Intentionally Designed for Rapid Onset/Offset to Offer Clinicians a Predictable Level of Sedation and Procedural Efficiency

byfavo™ (remimazolam) IV for injection 2.5 mg/mL

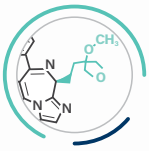
Rapid Onset/Rapid Offset Benzodiazepine[1]

- 3.0-3.5 minutes: median time to peak sedation following initial 5 mg (2 mL) bolus IV dose
- 11.0-14.0 minutes: median time to fully alert following last dose
- Rapidly metabolized via CYP450-independent pathways with no active metabolite

Procedural Efficiency

- BYFAVO met the composite primary endpoint for procedural sedation success in a broad and complex range of patients, including ASA III-IV, in various clinical settings[1-5,*,†]

Characteristic Benzodiazepine Safety Profile



- Most common adverse reactions (>10%) in patients receiving BYFAVO for procedural sedation were hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension[1]
- No increase in incidence of clinically significant vital sign abnormalities were observed in the BYFAVO arms compared to the placebo with midazolam rescue arms[2]
- Less fentanyl was utilized as an analgesic in the BYFAVO arms than in the placebo with midazolam rescue arms[1,3-5]

Offers a Predictable Level of Sedation

- In the BYFAVO arm, analysis of sedation level by time point assessments demonstrated a steep response curve immediately after administration to an adequate level of sedation to begin the procedure with a quick recovery[2]

- The target level of sedation (MOAA/S=2-4, moderate sedation) was maintained for a median 94.4% of the total procedure time in the BYFAVO arms in the pooled Bronchoscopy and Colonoscopy, ASA I-III, studies[2]

  Concomitant use of benzodiazepines, including BYFAVO, and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. See Boxed Warning.

- No clinically relevant effect on BYFAVO pharmacokinetics were observed based on: age, sex, race, BMI, or renal impairment[1]

  Half-life is prolonged with increasing severity of hepatic impairment, leading to a need for careful dose titration in those patients.[1]

Indication

BYFAVO is a benzodiazepine indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

Important Safety Information

WARNING: PERSONNEL AND EQUIPMENT FOR MONITORING AND RESUSCITATION AND RISKS FROM CONCOMITANT USE WITH OPIOID ANALGESICS

Contraindication

BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

For additional information regarding BYFAVO, please contact your Hospital Territory Manager, visit BYFAVO.com, or call 1-800-281-3470.

*BYFAVO was evaluated as a procedural sedative in 3 prospective, randomized, placebo- and active-controlled, multicenter, parallel-group studies comparing BYFAVO to placebo in a double-blind manner, with an open-label midazolam arm. The pivotal studies consisted of a Bronchoscopy Study in ASA I-III patients (N=446), a Colonoscopy Study in ASA I-III patients (N=461), and a Colonoscopy Study in ASA III-IV patients (N=79). Please see full Prescribing Information for dosing requirements.

†The primary endpoint in the ASA I-III studies was defined as a composite of the following components: completion of procedure, AND no need for rescue sedative medication (midazolam only in these trials), AND no requirement for additional bolus(es) (>5 total doses of BYFAVO in any 15-minute interval or >3 total doses of midazolam in any 12-minute interval in the open-label midazolam arm, according to midazolam prescribing information). The primary objective of the Colonoscopy, ASA III-IV, study was to assess the safety of multiple doses of BYFAVO; procedure success was a secondary objective.

ASA=American Society of Anesthesiologists Physical Status. BMI=body mass index. CYP450=cytochrome P450. IV=intravenous. MOAA/S=Modified Observer's Assessment of Alertness/Sedation.

Please see full Important Safety Information, including Boxed Warning, on next page and click to access full Prescribing Information.

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Personnel and Equipment for Monitoring and Resuscitation

- **Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO.**
- **Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.**
- **BYFAVO has been associated with hypoxia, bradycardia, and hypotension. Continuously monitor vital signs during sedation and during the recovery period.**
- **Resuscitative drugs, and age- and size-appropriate equipment for bag-valve-mask–assisted ventilation must be immediately available during administration of BYFAVO.**

Risks From Concomitant Use With Opioid Analgesics and Other Sedative-Hypnotics

Concomitant use of benzodiazepines, including BYFAVO, and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of intravenous BYFAVO can be accentuated by concomitantly administered CNS depressant medications, including other benzodiazepines and propofol. Continuously monitor patients for respiratory depression and depth of sedation.

Contraindication

BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

Personnel and Equipment for Monitoring and Resuscitation

Clinically notable hypoxia, bradycardia, and hypotension were observed in Phase 3 studies of BYFAVO. Continuously monitor vital signs during sedation and through the recovery period. Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO. Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation. Resuscitative drugs, and age- and size-appropriate equipment for bag-valve-mask–assisted ventilation must be immediately available during administration of BYFAVO. Consider the potential for worsened cardiorespiratory depression prior to using BYFAVO concomitantly with other drugs that have the same potential (eg, opioid analgesics or other sedative-hypnotics). Administer supplemental oxygen to sedated patients through the recovery period. A benzodiazepine reversal agent (flumazenil) should be immediately available during administration of BYFAVO.

Risks From Concomitant Use With Opioid Analgesics and Other Sedative-Hypnotics

Concomitant use of BYFAVO and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of IV BYFAVO can be accentuated when administered with other CNS depressant medications (eg, other benzodiazepines and propofol). Titrate the dose of BYFAVO when administered with opioid analgesics and sedative-hypnotics to the desired clinical response. Continuously monitor sedated patients for hypotension, airway obstruction, hypoventilation, apnea, and oxygen desaturation. These cardiorespiratory effects may be more likely to occur in patients with obstructive sleep apnea, the elderly, and ASA III or IV patients.

Hypersensitivity Reactions

BYFAVO contains dextran 40, which can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis. BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

Neonatal Sedation

Use of benzodiazepines during the later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) in the neonate. Observe newborns for signs of sedation and manage accordingly.

Pediatric Neurotoxicity

Published animal studies demonstrate that anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of this is not clear. However, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life but may extend out to approximately 3 years of age in humans.

Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Adverse Reactions

The most common adverse reactions reported in >10% of patients (N=630) receiving BYFAVO 5-30 mg (total dose) and undergoing colonoscopy (two studies) or bronchoscopy (one study) were: hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension.

Use in Specific Populations

Pregnancy

There are no data on the specific effects of BYFAVO on pregnancy. Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation and respiratory depression.

Lactation

Monitor infants exposed to BYFAVO through breast milk for sedation, respiratory depression, and feeding problems. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 5 hours after BYFAVO administration.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. BYFAVO should not be used in patients less than 18 years of age.

Geriatric Use

No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, there is a potential for greater sensitivity (eg, faster onset, oversedation, confusion) in some older individuals. Administer supplemental doses of BYFAVO slowly to achieve the level of sedation required and monitor all patients closely for cardiorespiratory complications.

Hepatic Impairment

In patients with severe hepatic impairment, the dose of BYFAVO should be carefully titrated to effect. Depending on the overall status of the patient, lower frequency of supplemental doses may be needed to achieve the level of sedation required for the procedure. All patients should be monitored for sedation-related cardiorespiratory complications.

Abuse and Dependence

BYFAVO is a federally controlled substance (CIV) because it contains remimazolam which has the potential for abuse and physical dependence.

Please see full Prescribing Information.

BYF HCP ISI 10/2020

1. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma Inc; 2020. **2.** Acacia Pharma. Data on File. **3.** Pastis NJ, et al. *Chest*. 2019;155(1);137-147. **4.** Rex DK, et al. *Gastrointest Endosc*. 2018;88(3):427-437. **5.** Rex DK, et al. *Dig Liver Dis*. 2021;53(1):94-101.

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