

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212295Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212295
PDUFA Goal Date	July 1, 2020
OSE RCM #	2019-790
Reviewer Name(s)	Somya Dunn, MD
Associate Division Director	Doris Auth, PharmD
Review Completion Date	July 1, 2020
Subject	Evaluation of Need for a REMS
Established Name	Remimazolam
Trade Name	Byfavo
Name of Applicant	Cosmo Technologies, Limited
Therapeutic Class	Sedative
Formulation(s)	Parenteral
Dosing Regimen	Adult Patients: Initial dose intravenously as a 5 mg push injection over a 1-minute time period. Supplemental doses of 2.5 mg intravenously over a 15-second time period. Debilitated Patients: Administer 2.5 mg to 5 mg over 1-minute time period. Supplemental doses of 1.25 mg to 2.5 mg intravenously over a 15 second time period.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Byfavo (remimazolam) is necessary to ensure the benefits outweigh its risks. Cosmo Technologies, Limited submitted a New Drug Application (NDA 212295) for Byfavo with the proposed indication for the induction and maintenance of procedural sedation in adults. Byfavo is a novel product, a short-acting benzodiazepine under review by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP). The risks associated with Byfavo are consistent with other benzodiazepines and other CNS depressants. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM believes that a REMS is not needed to ensure the benefits of Byfavo outweigh its risks. If approved, Byfavo will be administered via parenteral route similar to that of other benzodiazepines and other drugs used for sedation in healthcare settings. Parenteral benzodiazepines are generally not prescribed or administered outpatient. Thus, they are not kept at outpatient pharmacies or available for direct patient use. Their risk profile is well known, and patients are monitored during administration. Since Byfavo is proposed to be used where parenteral sedation drugs for procedural use are indicated and has a similar risk/benefit profile, a REMS is not needed for this product.

Should DAAP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Byfavo (remimazolam) is necessary to ensure the benefits outweigh its risks. Cosmo Technologies, Limited submitted a New Drug Application (NDA 212295) for Byfavo with the proposed indication for the induction and maintenance of procedural sedation in adults. The risks associated with Byfavo include those similar to other benzodiazepines such as profound sedation, respiratory depression, coma, and death with concomitant use of opioid analgesics. The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Byfavo (remimazolam) is a novel short-acting benzodiazepine intended for intravenous (IV) repeat bolus administration indicated for induction and maintenance of procedural sedation in adults. The Applicant claims that the advantages of Byfavo compared to other benzodiazepines and/or propofol is the rapid onset, the very short half-life and inactive primary metabolite. These features enable titration to an appropriate level of sedation followed by recovery very quickly after procedure completion. The Applicant is seeking approval of an initial dose of Byfavo intravenously as a 5 mg push injection over a 1-minute time period followed, if necessary, by supplemental doses of 2.5 mg over a 15-second time

period in adults. At least two minutes must have elapsed between the supplemental doses. Lower doses are proposed in debilitated patients.

The clinical program for Byfavo consisted of two main pivotal Phase 3 studies to support efficacy. Study CNS7056-006 was a Phase III, double-blind, placebo and midazolam-controlled trial assessing efficacy and safety of initial bolus dose and subsequent doses for procedural sedation. There were 458 subjects in the study undergoing colonoscopy. Study CNS7056-008 was a randomized, double-blind, placebo and midazolam-controlled trial assessing efficacy and safety of initial bolus dose and subsequent doses for procedural sedation. This study was conducted in 431 subjects undergoing procedural bronchoscopy. Both studies demonstrated statistically significant efficacy. A dedicated study (CNS7056-015) in American Society of Anesthesiologists Physical Status (ASA-PS)^a class III and IV patients (ASA III-IV) patients undergoing colonoscopy included dosing to support the proposed debilitated patient dosing.

Most adverse event differences between treatment groups in the clinical program were not clinically relevant and the observed events are consistent with those expected in conscious sedation. The Division of Risk Management (DRM) has determined a REMS is not necessary to ensure the benefits outweigh the risks for Byfavo. The safety concerns associated with Byfavo are consistent with those seen in other benzodiazepines. Labeling of the safety concerns will provide healthcare providers with the necessary information to mitigate the risks. Should DAAP have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

2.2 REGULATORY HISTORY

- July 6, 2018: Pre NDA Meeting preliminary comments were sent to the Sponsor indicating that the need for a REMS may be discussed at the upcoming Pre NDA meeting.
- July 12, 2018: Pre NDA meeting was held; a discussion of the need for a REMS did not occur.
- April 5, 2019: NDA was submitted without a REMS.
- July 17, 2019: The Agency sent a Filing Communication to the Applicant indicating that submission was complete and could undergo a standard review. In addition, the Agency indicated that the procedures used in the clinical program were considered short in duration compared to those to other commonly performed procedures requiring sedation.
- Nov 22, 2019: Midcycle Communication Meeting was held and significant review issues were communicated to the Applicant. They were reminded that the Agency considered the procedures in the clinical program to be in short in duration. The Agency added that this would likely be addressed in labeling but was a review issue and still under discussion. In addition, they were told that Dextran 40 is considered a new excipient and has not been adequately qualified for safety given the proposed conditions of use.

^a American Society of Anesthesiologists (ASA) Physical Status Classification System: <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system>, last updated Oct 2019.

Mar 9, 2020: The Applicant was informed that two previous submissions constitute major amendments to this application and the goal date would be extended by three months to provide time for a full review of the submission. The extended user fee goal date is July 5, 2020. One of the submissions from January 31 contained safety justification and lactational exposure information. The other from February 24, 2020 was a final animal study report for Dextran 40.

April 9, 2020: The Applicant sent an email inquiring about the possibility of expediting the approval of NDA 212295 to help mitigate the shortage of sedatives during the current COVID-19 public health emergency.

April 17, 2020: The Division noted the requests from April 9, 2020 and responded that the review team is working on finalizing the review of the application. The Applicant was also informed that since there is a need to rely on literature in order to better understand the metabolism, distribution, and genotoxicity profile of Dextran-40, the NDA would need to be characterized as a 505(b)(2) application, rather than a 505(b)(1) application.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION AND TREATMENT OPTIONS

Diagnostic and therapeutic procedures require sedation; for example, common procedures include biopsy and colonoscopy. There are several approved products used for induction and maintenance of procedural sedation that can be administered either with bolus dosing or continuous IV infusion. Table 1 displays the armamentarium of medications approved for procedural sedation in adults.

Table 1. Summary of Medications Administered for Procedural Sedation

Product Name	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
Midazolam	Procedural sedation	IV, IM, PO	Rapid onset/offset of action	Well-tolerated; titrated to clinical effect
Dexmedetomidine	Procedural sedation	IV - continuous infusion	Rapid onset/offset of action; minimal respiratory depression	Bradycardia; cardiac Arrhythmias; hypotension
Propofol	Procedural sedation	IV – bolus dosing or continuous	Rapid onset/offset of action; reduced incidence of post-	Burning sensation with administration; respiratory depression

Product Name	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
		infusion	operative nausea and vomiting	and apnea common
Ketamine	Sole anesthetic for diagnostic and surgical procedures	IV - bolus dosing or continuous infusion	Analgesic properties; cardiovascular and respiratory stability; airway reflexes mostly maintained	Dysphoric adverse reactions; salivation; nystagmus

IV: intravenous; IM: intramuscular; PO: oral

Source: Renee Petit-Scott, MD. Table 1 *Summary of Medications Administered for Procedural Sedation Clinical Review for DAAP*, June 30, 2020.

4 Benefit Assessment

The Applicant conducted two phase 3 adequate and well-controlled efficacy studies to support this application. Study CNS7056-006 (006) was conducted in patients undergoing colonoscopy and the other, study CNS7056-008 (008) was conducted in patients undergoing bronchoscopy. There was an additional phase 3 study designed to evaluate the safety of Byfavo in higher risk American Society of Anesthesiologists Physical Status (ASA-PS) class III and IV patients (ASA III-IV) patients undergoing colonoscopy (Study 015). In all three studies, efficacy was assessed by comparing the proportion of patients who met the criteria of procedure completion, did not have a requirement for a rescue sedative medication (midazolam), and did not need more than five doses of study medication within any 15-minute window. Studies 006 and 008 displayed higher rates of treatment success for Byfavo than placebo, with 91% (272/298) and 81% (250/310) of patients meeting the treatment success definition for Byfavo, respectively compared to 2% (1/60) and 5% (3/63) meeting statistically significant efficacy ($p < 0.0001$). Study 015 was designed as a safety study and statistical efficacy was not evaluated but the procedure success rates supported that found in the other two phase 3 studies.

The dosing regimen evaluated in the clinical studies was an initial IV bolus of 2.5 mg to 5 mg over one minute, followed by additional bolus dose administrations of 1.25 mg to 2.5 mg over 15 seconds; these could be given no sooner than two minutes apart. Reduced dosing was used for elderly and/or debilitated patients.

The Phase 3 studies were designed with an open-label midazolam group; therefore, direct comparisons between Byfavo and midazolam were not assessed. However, Dr. Renee Petit-Scott, the primary clinical reviewer, noted that the placebo treatment group receiving midazolam rescue were fully alert later than the Byfavo group. This difference was clinically significant and suggests that there is a benefit of rapid

onset and recovery. In addition, as Byfavo is a benzodiazepine, flumazenil can reverse the drug activity if needed which is an additional benefit over other medication classes for sedation.

5 Risk Assessment & Safe-Use Conditions

The safety of Byfavo was evaluated in a total of 22 clinical studies which included a total of 1731 patients that were exposed to intravenous Byfavo. There were no deaths the clinical program and only one reported in a patient seven months after treatment not thought to be related to treatment. There were 17 Byfavo treated patients who experienced a serious adverse events (SAE) compared to one in the midazolam treatment group and four in the placebo treatment group. The SAEs of pneumothorax, bronchospasm, and hypoxia occurred in two or more patients and additionally there were two events of respiratory failure. However, although the number of SAEs reported in the Byfavo treatment group was higher than those in the placebo or midazolam treatment groups, the overall incidence was similar (2.7% vs. 3%). Furthermore, there were no noted clinically significant differences in rates of respiratory depression, hypoxia, or respiratory rate in patients treated with Byfavo compared to placebo or midazolam treated patients. In addition, vital sign-related adverse events were lower in patients treated with Byfavo compared to either the placebo or midazolam. There was increased systolic and diastolic blood pressure consistently reported in patients treated with Byfavo which is thought to be related to drug affect and will be included in product labeling. There were no clinically relevant observations in incidences of adverse events associated with abuse, dependence, or withdrawal. Overall, Dr. Petit-Scott determined most adverse event differences between treatment groups were not clinically relevant and that the observed events are expected in conscious sedation.

Of note, Dr. Petit-Scott and the review team determined Byfavo should be used for procedures expected to be completed in 30 minutes or less due to the length of the procedures in the clinical program and the increased adverse events in longer duration of use.

Byfavo will have a boxed warning consistent with other benzodiazepines for opioid interaction and possible profound sedation, respiratory depression, coma and death. There will also be other warnings in the box consistent with this class of drugs such as hypoxia, bradycardia, and hypotension. In addition, hypersensitivity reactions to Dextran 40 will be included in the Warnings and Precautions section of the label as other products with this excipient contain this warning.

The Applicant had proposed that labeling language [REDACTED] (b) (4)
[REDACTED] The review division agreed but wanted the label to emphasize that a provider trained in airway management and resuscitation would be administering the medication. As a result, these instructions are potentially planned to be included in the boxed warning. Neonatal sedation will be a Warning and Precaution as this is a risk with this class of medications.

6 Expected Postmarket Use

Byfavo does appear to have a rapid time to onset of action and recovery and the review division has considered that Byfavo would be used for sedation for procedures lasting 30 minutes or less; the indication will include this time limitation. Dr. Petit-Scott describes in her review that gastroenterology procedures such as colonoscopy and upper endoscopy would likely be appropriate for sedation with Byfavo. These are common procedures and thus this medication has the potential to impact a large patient population.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or risk management plan. No rationale was provided; however, Byfavo is proposed to be used in healthcare settings under supervision of healthcare providers similar to other products in this class and other medications used for sedation during procedures. Patients will be monitored during and after administration of Byfavo.

8 Discussion of Need for a REMS

Since Byfavo is proposed to be used where medications for procedural sedation are indicated and has a similar risk/benefit profile, a REMS is not needed for this product. Benzodiazepines are administered in healthcare settings when patients are being monitored and the risk profile is well known. These products, intended for use in monitored healthcare settings, are not subject to a REMS. If Byfavo is approved, the label will have boxed warning similar to that of other benzodiazepines with a warning for concomitant use with opioids and other CNS depressants. In addition, there will be other boxed warnings for risks consistent with benzodiazepines such as hypoxia, bradycardia, and hypotension. The label is currently under review by DAAP.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks for Byfavo. If approved, Byfavo will be administered in healthcare settings under supervision of a healthcare provider. The risks evaluated in the clinical program are similar to that seen with the well-known risk profile of benzodiazepines and other medications used for procedural sedation. The risk profile will be fully characterized in the Prescribing Information.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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