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DISTRICT COURT

CLARK COUNTY, NEVADA

ALVOGEN, INC.,

Plaintiff,

v.

STATE OF NEVADA;

NEVADA DEPARTMENT OF CORRECTION;

JAMES DZURENDA, Director of the Nevada Department of Correction, in his official capacity;

IHSAN AZZAM, Ph.D, M.D., Chief Medical Officer of the State of Nevada, in his official capacity;

And JOHN DOE, Attending Physician at Planned Execution of Scott Raymond Dozier, in his official capacity;

Defendants.

Case No.: A-18-777312-B

Dept. No.: Department 27

COMPLAINT FOR EMERGENCY INJUNCTIVE RELIEF AND RETURN OF ILLEGALLY-OBTAINED PROPERTY

(Business Court Requested)

COMES NOW Alvogen, Inc. ("Alvogen"), and for its Complaint for Emergency Injunctive Relief states as follows:

PARTIES, JURISDICTION AND VENUE

1. Plaintiff Alvogen is a Delaware corporation with its principal place of business located at 10 Bloomfield Avenue, Pine Brook, New Jersey.

2. Defendant State of Nevada ("Nevada") is the sovereign government of Nevada.

3. Defendant Nevada Department of Corrections ("NDOC"), led by its Director James Dzurenda ("Dzurenda"), is a Nevada state governmental entity, with offices in Nevada, including at 3955 West Russell Road, Las Vegas, Nevada, 89118.

4. Defendant Dr. Ihsan Azzam, Ph.D, M.D., serves as the Nevada State Chief Medical Officer at the Nevada Department of Health and Human Services, Division of Public and Behavioral Health, with offices in Nevada, including in Las Vegas.

5. Defendant John Doe I is an individual who will serve as the attending physician at the planned execution of inmate Scott Raymond Dozier. To the extent that there are multiple individuals who will serve attending physicians at the planned execution, they are named herein as John Doe II, John Doe III, et seq.

6. Jurisdiction over Defendants is appropriate in this Court as each of them is an entity or agent of the State of Nevada, conducting business in Nevada. Venue in this Court is appropriate, including pursuant to NRS 13.020, as material events giving rise to this action – including the Defendants' illegitimate acquisition of the drug midazolam – occurred in Clark County, Nevada.

INTRODUCTION

7. Defendants have announced plans to utilize an Alvogen drug they illegitimately acquired called midazolam in the upcoming planned execution of Scott Raymond Dozier, scheduled to take place on Wednesday, July 11, 2018 at 8:00 pm in Nevada's Ely State Prison. Defendants acquired that drug despite a clear and unambiguous prior warning from Alvogen that they could not acquire it directly from Alvogen and could likewise not legitimately acquire it through a third-party distributor. Midazolam is not approved for use in such an application. Past

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attempts by other states to use the medicine in lethal injections have been extremely controversial, and have led to widespread concern that prisoners have been exposed to cruel and unusual treatment. Several attempts have been characterized by media as "botched" executions.

8. Not only did Alvogen warn Defendants that they could not legitimately acquire midazolam from Alvogen or an intermediary, it also demanded that Defendants immediately return any such product in exchange for a full refund. Nonetheless, after Defendants received that notification, Defendants purchased a quantity of Plaintiff's medicine by subterfuge with the undisclosed and improper intent to use it for the upcoming execution in complete disregard of Plaintiff's rights. Plaintiff's executives learned of this plan for the first time on Saturday, July 7, 2018, by way of an inquiry from the press.

9. Notably, one or more of Defendants have acknowledged that they have taken efforts to maintain the secrecy of and/or conceal the fact of their acquisition of Alvogen midazolam because of a concern that information as to "where a state obtains execution drugs" may be used "to persuade the manufacturer and others to cease selling that drug for execution purposes." *Order, ACLU Nevada Foundation v. State of Nevada*, No. 18-OC-00163, July 6, 2018 at 4.

10. Plaintiff has already been the subject of unfavorable press coverage regarding Defendants' proposed use of its medicine in the upcoming execution. If Defendants are allowed to proceed with the misuse of the illegitimately-acquired midazolam, Plaintiff will suffer immediate and irreparable harm.

ALVOGEN AND APPROVED AND UNAPPROVED USES OF MIDAZOLAM

11. Alvogen is a leading pharmaceutical company focused on developing, manufacturing and selling life-saving and life-enhancing products around the world.

12. Alvogen distributes Midazolam Hydrochloride Injection, Solution (Abbreviated New Drug Application number 090850) (the "Alvogen Midazolam Product"). The Alvogen Midazolam Product is an injectable medication approved by the U.S. Food and Drug Administration ("FDA") for use in inducing general anesthesia and preoperative sedation/anxiolysis/amnesia. Midazolam is on the World Health Organization's List of Essential

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Medicines, the most safe and effective medicines for use in any health system for priority conditions. Midazolam is also a Schedule IV controlled substance.

13. In addition to its uses by physicians, midazolam has been used by some state correctional facilities as a component of those states' and facilities' capital punishment regimens. Midazolam acts as a sedative to render the condemned prisoner unconscious, at which time other drugs are administered to stop the prisoner's breathing and heart, but it is not approved by FDA for this purpose.

14. Midazolam was introduced in executions by lethal injection to replace pentobarbital in some states' capital punishment regimen when the manufacturer of pentobarbital disallowed that drug's use for executions.

15. The use of midazolam in executions is extremely controversial, in part because of the role it played in Oklahoma's high-profile "botched" execution of Clayton Lockett in April, 2014. Lockett apparently regained consciousness and started speaking midway through his execution, after Oklahoma prison officials began administering an untested three-drug cocktail using 100 mg of midazolam. Prison officials reportedly cancelled the execution and discussed taking him to the hospital before he was pronounced dead of a heart attack 40 minutes after the execution began.

16. In July, 2014, Arizona attempted to execute Joseph R. Wood III with a combination of drugs that included midazolam. Observers reported that Wood gasped, snorted and convulsed for well over an hour after the drugs were injected. The entire procedure, which should have taken approximately ten minutes, took almost two hours.

17. On December 8, 2016, Alabama attempted to execute Ronald Bert Smith by lethal injection using midazolam. According to reports, the execution went awry soon after midazolam was administered. His execution took 34 minutes. During the 13 minutes after being administered midazolam, Smith appeared to be struggling for breath and heaved, coughed, and clenched his left fist, while his lips moved and one eye appeared to be slightly open.

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18. As a result of these and other instances of prolonged and botched executions, manufacturers of pharmaceuticals used in lethal injection have prohibited the sale of these medicines for use in lethal injections.

DEFENDANTS OBTAIN THE ALVOGEN MIDAZOLAM PRODUCT FOR UNAPPROVED EXECUTIONS BY SUBTERFUGE

19. Upon information and belief, the Nevada Department of Corrections, along with corrections departments around the country in states with the death penalty, was well aware of manufacturers' restrictions on the distribution of drugs for lethal injection. As reported by the Las Vegas Review-Journal on October 7, 2016, after its stockpile of at least one drug used in executions expired, the Nevada Department of Corrections on September 2, 2016 sent out 247 requests for proposals to manufacturers for the purchase of those drugs. Not one supplier offered to fulfill the request. Nevada prison officials were quoted as saying that the state, in light of its inability to obtain such drugs through this process, would have to "explore its options" to carry out executions. A true and correct copy of that article is attached hereto as Exhibit 1.

20. In an article published May 13, 2016, the New York Times listed some of the ways in which state departments of corrections have attempted to obtain drugs for lethal injections. Some have resorted to obtaining supplies that are not FDA approved, such as from compounding pharmacies. Others have obtained supplies surreptitiously from unsuspecting manufacturers by purchasing under assumed names or by misrepresenting to the seller the intended use of the drug, since drugs like midazolam have FDA.-approved therapeutic uses potentially applicable to clinics associated with corrections facilities.

21. Alvogen began distributing its Midazolam Product in or around August, 2017. A true and correct copy of the approved labeling for the Alvogen Midazolam Product is attached hereto as Exhibit 2.

22. As a result of the controversy over the use of midazolam in lethal injections, Alvogen has maintained a policy of not allowing midazolam to be diverted for use in execution protocols.

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23. On April 20, 2018, Alvogen sent letters to the Governors, Attorneys General, and Department of Corrections Directors in every state that has a death penalty. In that letter, Alvogen stated "in the clearest possible terms that Alvogen strongly objects to the use of its products in capital punishment." Alvogen specifically identified its Midazolam Product as one that should not be used in executions, and noted that use of midazolam or other products in executions "clearly runs counter to the FDA-approved indication for these products." The letter went on to explain:

> To ensure our products are not purchased for use in lethal injection executions, Alvogen does not accept orders from any state departments of corrections. Further, Alvogen has controls in place and directs its customers not to sell its medicines to correctional facilities or otherwise for use in connection with lethal injection executions. These controls reflect our company's policy of ensuring the appropriate use of our medicines.

24. In its April 20, 2018 letter, Alvogen specifically requested that any state that obtained products for execution return them immediately for a full refund:

> If your state has purchased products manufactured by Alvogen for use in capital punishment procedures – either directly or indirectly – we ask that you immediately return our products in exchange for a full refund.

25. In addition, Alvogen warned Defendants against attempting to obtain its Midalozam Product for executions surreptitiously, illicitly, and/or by subterfuge:

> I have been informed that some states have implemented "secrecy policies/laws" which they hope will enable them to bypass company control systems and purchase manufactured medicines for use in executions. Alvogen closely tracks the distribution of its medicines as required by law and will take action in case of such diversions. Transparency across the supply chain is important to protect public health and the commercial interests of healthcare companies.

26. One of Alvogen's April 20, 2018 letters was sent directly to the Nevada Department of Corrections' facility at Ely State Prison, where Nevada's newly-constructed death penalty chamber is located. A true and correct copy of the letter, along with the envelope in which it was contained (addressed to "Warden Timothy Filson, Ely State Prison, P.O. Box 1989, 4569 North State Rt., Ely, NV 89301") is attached hereto as Exhibit 3.

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27. Alvogen also sent a letter to Defendant Dzurenda. A true and correct copy of that letter is attached hereto as Exhibit 4.

28. Alvogen has also sought to reinforce this message by including the following notice on its website's description of its Midazolam Product:

> Alvogen endorses the use of its products in accordance with FDA-approved indications. To this end, Alvogen has undertaken controls to avoid diversion of this product for use in execution protocols. In furtherance of this effort, Alvogen does not accept direct orders from prison systems or departments of correction. In addition, Alvogen is working to ensure that its distributors and wholesalers do not resell, either directly or indirectly this product, to prison systems or departments of correction.

29. A true and correct copy of the webpage (accessible at http://alvogenus.com/products/product/midazolam) is attached hereto as Exhibit 5.

30. One of Alvogen's wholesale distributors is Cardinal Health. When Alvogen began distributing its Midazolam Product in the United States, Alvogen understood from communications with Cardinal Health that it would not distribute the Alvogen Midazolam Product to corrections facilities for use in lethal injection protocols. Alvogen and Cardinal Health also entered into negotiations regarding a formal amendment to their Generic Wholesale Service Agreement to memorialize the terms on which Cardinal Health would restrict such sales. The final agreement was executed in May, 2018. During the course of those negotiations, Alvogen understood that Cardinal Health would not sell the Alvogen Midazolam Product to prisons for use in lethal injections.

31. On or about July 7, 2018, Alvogen was contacted by members of the press and told that Nevada had announced its intent to conduct the execution of Scott Raymond Dozier on Wednesday, July 11, 2018 by use of a three-drug cocktail that included the Alvogen Midazolam Product. Alvogen subsequently learned that the NDOC had adopted a new execution protocol on July 3, 2018 that included the use of midazolam. In addition, Alvogen learned from disclosures made in response to litigation by the Nevada branch of the American Civil Liberties Union that NDOC had acquired the midazolam it intends to use in the execution from Cardinal Health by way of purchase orders from May 2018 that were to be completed in June 2018.

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32. Upon information and belief, when NDOC officials, under the direction of the Nevada Chief Medical Officer, acquired the Alvogen Midazolam Product from Cardinal Health, they knew that all manufacturers of FDA-approved products, including Alvogen, had prohibited the distribution, sale, and transfer of such drugs for purposes of use in execution protocols. Upon information and belief, NDOC nonetheless acquired the Alvogen Midazolam Product by use of subterfuge through a source that was not authorized to sell to the NDOC for the non-approved use in an execution.

33. On information and belief, following their receipt of the letters attached as Exhibits 3 and 4 (The "April Alvogen Letters"), Defendants thereafter sought to circumvent Alvogen's policy by purchasing the Alvogen Midazolam Product through an unsuspecting intermediary and without disclosing to said intermediary the contents of the April Alvogen Letters and/or the fact that they planned to use the Alvogen Midazolam Product for a non-therapeutic use. Defendants were thus able to illicitly and through subterfuge obtain the Alvogen Midazolam Product in a manner that they would not have been able to accomplish had they disclosed the contents of said letter to the intermediary and/or the fact that they planned to use the Alvogen Midazolam Product for a non-therapeutic use.

34. In the April Alvogen Letters, Alvogen specifically demanded that should Defendants somehow circumvent Alvogen's controls, intentions, and property rights to illicitly obtain any of Alvogen's Midazolam Product, Defendants should immediately return said Midazolam products in exchange for a full refund. In spite of said demand, Defendants have refused to return the Midazolam products that they illicitly and improperly obtained.

35. Defendants have announced plans to use Alvogen's Midazolam Product for a purpose for which it is neither indicated nor intended to be used – to wit, to intentionally cause death. Defendants' proposed use for the Alvogen's Midazolam Product clearly runs counter to the FDA-approved indication for this product. While Alvogen takes no position on the death penalty itself, Alvogen's products were developed to save and improve patients' lives and their use in executions is fundamentally contrary to this purpose.

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36. To make its purchases, NDOC had to provide Cardinal Health proof of a medical license issued to NDOC's medical director.

37. Under the Nevada controlled substances statute, "a physician ... may prescribe or administer controlled substances *only for a legitimate medical purpose* and in the usual course of his or her professional practice." NRS § 453.381(1) (emphasis added). A physician may not use a non-physician to evade that prohibition.

38. On information and belief, NDOC's May 2018 purchase orders to Cardinal Health leveraged the Nevada Chief Medical Officer's license to surreptitiously, evasively, illicitly, and by subterfuge obtain the Alvogen Midazolam Product. In so doing, NDOC intended Cardinal Health to believe that the order was placed at the request of or for the benefit of the physician and would be used for a legitimate medical purpose, consistent with the Nevada controlled substances statute and Nevada State Board of Medical Examiners regulations.

39. On information and belief, Defendants failed to disclose to the unsuspecting intermediary that they intended to use the Alvogen Midazolam Product for executions.

40. On information and belief, Defendants sought to circumvent Alvogen's controls by issuing purchase orders for the Alvogen Midazolam Product for completion in June 2018 with an unsuspecting distributor.

41. To further the implication that the midazolam was for a legitimate medical purpose, NDOC had the midazolam shipped to NDOC's Central Pharmacy at the NDOC's administrative building in Las Vegas, rather than directly to the Ely State Prison, where Nevada's newly-constructed execution chamber is located.

42. Defendants undertook these actions with full knowledge that Alvogen does not permit sales of midazolam to state correctional facilities nor to any entity for purposes of capital punishment.

IF DEFENDANTS ARE NOT ENJOINED FROM USING THE ALVOGEN MIDAZOLAM PRODUCT IN THE UPCOMING EXECUTION OF SCOTT RAYMOND DOZIER, ALVOGEN WILL SUFFER IMMEDIATE AND IRREPARABLE INJURY

43. There has been significant public discussion of NDOC's intent to execute Scott Raymond Dozier within days after adopting an entirely new and untested protocol using the

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Alvogen Midazolam Product, including several critical reports linking midazolam to multiple botched executions. A true and correct copy of the July 5, 2018 Fox News article, "Drug company threatens legal action to prevent drug from being used in Dozier's execution" is attached as Exhibit 6. A true and correct copy of the July 7, 2018 Associated Press article, "Nevada releases records on sedative to be used in execution" is attached as Exhibit 7.

44. As a result of the intense public backlash against Defendants' plans, Alvogen has been publicly identified as the manufacturer of the drug to be used in this controversial execution. As more fully set forth herein, Defendants' actions have caused, and will continue to cause unless enjoined, substantial and irreparable injury to Alvogen, its reputation, and its goodwill.

COUNT I: ACQUISITION OF A CONTROLLED SUBSTANCE BY MISREPRESENTATION, FRAUD, DECEPTION OR SUBTERFUGE

45. Paragraphs 1 through 44 are incorporated by reference as if fully set forth herein.

46. On information and belief, Defendants sought to circumvent Alvogen's controls by issuing purchase orders for the Alvogen Midazolam Product for completion in June 2018 with an unsuspecting distributor. Thus, on or about May 9, May 11, and May 29, 2018, the NDOC Pharmacy submitted a purchase order for the Alvogen Midazolam Product Midazolam to Cardinal Health, a wholesaler for the Alvogen Midazolam Product, for use in the execution of Raymond Scott Dozier scheduled for July 11, 2018. Midazolam is a Schedule IV controlled substance. The purchase orders were scheduled to be completed in June 2018.

47. Nevada law makes it unlawful for "a person to knowingly and intentionally ... [a]cquire or obtain or attempt to acquire or obtain possession of a controlled substance ... by misrepresentation, fraud, forgery, deception, subterfuge or alteration." Nevada Revised Statute (NRS) § 453.331(1)(d). Defendants each qualify as a "person" for the foregoing.

48. As described above in Paragraphs 19 through 29, Defendants knew that Alvogen is strongly opposed to the use of its products, including the Alvogen Midazolam Product, in execution protocols. Indeed, on April 20, 2018, Alvogen sent a letter to Defendants informing them "in the clearest possible terms that Alvogen strongly objects to the use of its products in capital punishment" and that Alvogen was actively taking steps "to ensure that [its] products are

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not purchased for use in lethal injection executions." As described above in Paragraph 9, the NDOC's own statements in other litigation related to this execution further show that the NDOC was aware of and actively fought disclosure of certain execution-related information because such information had been used to persuade manufacturers to cease selling their products for executions.

49. On information and belief, following their receipt of the April Alvogen Letters, Defendants thereafter sought to circumvent Alvogen's policy by purchasing the Alvogen Midazolam Product through an unsuspecting intermediary and without disclosing to said intermediary the contents of the April Alvogen Letters and/or the fact that they sought to obtain the Alvogen Midazolam Product for non-therapeutic purposes (*i.e.*, an execution). Defendants were thus able to illicitly and through subterfuge obtain the Alvogen Midazolam Product in a manner that they would not have been able to accomplish had they disclosed the contents of said letter and/or their intended non-therapeutic use of the Alvogen Midazolam Product to the intermediary.

50. On information and belief, Defendants sought to circumvent Alvogen's controls by issuing purchase orders for the Alvogen Midazolam Product for completion in June 2018 with an unsuspecting distributor. Upon information and belief, Defendants acted in concert with one another to acquire the Alvogen Midazolam Product from Cardinal Health. At the time of their actions, Defendants knew and had been placed on notice that Alvogen, along with all other sources of FDA-approved products, had prohibited the distribution, sale, and transfer of such drugs for use in execution protocols. Upon information and belief, Defendants acted in concert with one another – and with at least one physician in violation of Nevada law – to acquire the Alvogen Midazolam Product by use of subterfuge through a source that was not authorized to sell to the NDOC for the non-approved use in an execution.

51. To further the implication that the midazolam was for a legitimate medical purpose, Defendants specified that the Alvogen Midazolam Product should be shipped to NDOC's Central Pharmacy at the NDOC's administrative building in Las Vegas, rather than directly to the Ely State Prison, where Nevada's newly-constructed execution chamber is located.

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By way of the foregoing, Defendants thus tacitly and erroneously misrepresented that the Midazolam would be used for legitimate medical purposes.

52. Defendants undertook these actions with full knowledge that Alvogen does not permit sales of midazolam to state correctional facilities nor to any entity for purposes of capital punishment.

53. Based on the foregoing, and on information and belief, NDOC's purchases from Cardinal Health leveraged the NDOC Chief Medical Officer's license to surreptitiously, evasively, illicitly, and by subterfuge obtain the Alvogen Midazolam Product. In so doing, NDOC intended Cardinal Health to believe that the order was placed at the request of or for the benefit of the physician and would be used for a legitimate medical purpose, consistent with the Nevada controlled substances statute and Nevada State Board of Medical Examiners regulations.

54. Because of Defendants' wrongdoing, Alvogen has suffered and continues to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor and prospective investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT II: ACQUISITION BY A PHYSICIAN OF A CONTROLLED SUBSTANCE BY MISREPRESENTATION, FRAUD, DECEPTION OR SUBTERFUGE

55. Paragraphs 1 through 54 are incorporated by reference as if fully set forth herein.

56. On information and belief, Defendants sought to circumvent Alvogen's controls by issuing purchase orders for the Alvogen Midazolam Product for completion in June 2018 with an unsuspecting distributor. Thus, on or about May 9, May 11, and May 29, 2018, the NDOC Pharmacy submitted a purchase order for the Alvogen Midazolam Product Midazolam to Cardinal Health, a wholesaler for the Alvogen Midazolam Product, for use in the execution of Raymond Scott Dozier scheduled for July 11, 2018. Midazolam is a Schedule IV controlled substance. The purchase orders were scheduled to be completed in June 2018.

57. Upon information and belief, including the procedures outlined in the NDOC Execution Manual, Defendant Azzam, the Nevada Chief Medical Officer, a licensed physician,

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acquired and/or directed the acquisition of the Alvogen Midazolam Product by or for Defendants and in active concert with the other Defendants.

58. Nevada law prohibits a physician from "[a]cquir[ing] any controlled substances from any pharmacy or other source by misrepresentation, fraud, deception or subterfuge." Nevada Administrative Code (NAC) § 630.230(d).

59. As described above in Paragraphs 19-29, Defendants knew that Alvogen is strongly opposed to the use of its product, including the Alvogen Midazolam Product, in execution protocols. Indeed, on April 20, 2018, Alvogen sent a letter to Defendants informing them "in the clearest possible terms that Alvogen strongly objects to the use of its products in capital punishment" and that Alvogen was actively taking steps "to ensure that [its] products are not purchased for use in lethal injection executions." As described above in Paragraph 9, the NDOC's own statements in other litigation related to this execution further show that the NDOC was aware of and actively fought disclosure of certain execution-related information because such information had been used to persuade manufacturers to cease selling their products for executions.

60. On information and belief, following their receipt of the April Alvogen Letters, Defendants, at the direction of and/or with the approval of Defendant Azzam, thereafter sought to circumvent Alvogen's policy by purchasing the Alvogen Midazolam Product through an unsuspecting intermediary and without disclosing to said intermediary the contents of the April Alvogen Letters and/or the fact that they sought to obtain the Alvogen Midazolam Product for non-therapeutic purposes (*i.e.*, an execution). Defendants were thus able to illicitly and through subterfuge obtain the Alvogen Midazolam Product in a manner that they would not have been able to accomplish had they disclosed the contents of said letter and/or their intended non-therapeutic use of the Alvogen Midazolam Product to the intermediary.

61. On information and belief, Defendants sought to circumvent Alvogen's controls by issuing purchase orders for the Alvogen Midazolam Product for completion in June 2018 with an unsuspecting distributor. Upon information and belief, Defendants, including Defendant Azzam, acted in concert with one another to acquire the Alvogen Midazolam Product from Cardinal

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Health. At the time of their actions, Defendants knew and had been placed on notice that Alvogen, along with all other FDA-approved sources, had prohibited the distribution, sale, and transfer of such drugs for use in execution protocols. Upon information and belief, Defendants acted in concert with one another – and with at least one physician in violation of Nevada law – to acquire the Alvogen Midazolam Product by use of subterfuge through a source that was not authorized to sell to the NDOC for the non-approved use in an execution.

62. To further the implication that the midazolam was for a legitimate medical purpose, Defendants specified that the Alvogen Midazolam Product should be shipped to NDOC's Central Pharmacy at the NDOC's administrative building in Las Vegas, rather than directly to the Ely State Prison, where Nevada's newly-constructed execution chamber is located. By way of the foregoing, Defendants thus tacitly and erroneously misrepresented that the Midazolam would be used for legitimate medical purposes.

63. Defendants undertook these actions with full knowledge that Alvogen does not permit sales of midazolam to state correctional facilities nor to any entity for purposes of capital punishment.

64. Based on the foregoing, and on information and belief, NDOC's purchases from Cardinal Health leveraged the NDOC Chief Medical Officer's license to surreptitiously, evasively, illicitly, and by subterfuge obtain the Alvogen Midazolam Product. In so doing, NDOC intended Cardinal Health to believe that the order was placed at the request of or for the benefit of the physician and would be used for a legitimate medical purpose, consistent with the Nevada controlled substances statute and Nevada State Board of Medical Examiners regulations.

65. Because of Defendants' wrongdoing, Alvogen has suffered and continues to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor and prospective investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT III: UNLAWFUL OBTAINMENT OF A CONTROLLED SUBSTANCE

66. Paragraphs 1 through 65 are incorporated by reference as if fully set forth herein.

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67. Under Nevada law, "a person shall not ... unlawfully take, obtain or attempt to take or obtain a controlled substance from a manufacture, wholesaler, pharmacist, physician, ... or any other person authorized to administer, dispense or possess controlled substances." Nevada Revised Statute (NRS) § 453.391(1). Defendants each qualify as a "person" for purposes of the foregoing.

68. Defendants obtained the Alvogen Midazolam Product in an unlawful manner because, *inter alia*, it was obtained from Alvogen and/or Cardinal Health – both of whom are "authorized to . . . dispense or possess controlled substances" – by way of misrepresentation, deception, evasion, and/or subterfuge, in violation of NRS § 453.331(1)(d); NAC § 630.230(d).

69. Further, Defendants obtained the Alvogen Midazolam Product in an unlawful manner for the reasons explained in Counts VI through VIII, as Defendants' acquisition of the Alvogen Midazolam Product is in derogation of, and violates, Alvogen's property rights.

70. Further, Defendants obtained the Alvogen Midazolam Product in an unlawful manner for the reasons explained in Counts IV and V, as Defendants' acquisition of the Alvogen Midazolam Product was undertaken for purposes of unlawfully administering it for a non-therapeutic use (an execution) as well as for unlawfully furnishing it to non-physician administrators.

71. Because of Defendants' wrongdoing, Alvogen has suffered and continues to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT IV: ADMINISTRATION OF A CONTROLLED SUBSTANCE FOR AN ILLEGITIMATE PURPOSE

72. Alvogen incorporates paragraphs 1 through 71 above as if fully set forth herein

73. Under Nevada law, "a physician ... may prescribe or administer controlled substances only for a legitimate medical purpose and in the usual course of his or her professional practice." NRS § 453.381(1). A physician may not use a non-physician to evade that prohibition.

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74. Under the NDOC's Execution Manual, "an attending physician or other properly trained and qualified medical professional" will be present at the execution to assess the inmate's need for pre-execution sedatives, observe the preparation of the lethal drugs, advise on the venipuncture for the delivery of the lethal drugs, monitor the inmate's consciousness during the execution, and respond in the event the execution is ordered to be stopped. *See* Nevada Department of Corrections, *Execution Manual Sec. 110.02 – Execution of Condemned Inmate* (Effective Date: June 11, 2018).

75. As the "Attending Physician," the doctor who attends the execution is ultimately responsible for the care and treatment of the patient, including the administration of any drugs to that patient. *See, e.g.*, Center for Medicare and Medicaid Services, *Glossary* (accessed on July 8, 2018), *available* at https://www.cms.gov/apps/glossary/default.asp?Letter=ALL (defining the attending physician as the licensed physician "who has primary responsibility for the patient's medical care and treatment"); Educational Commission for Foreign Medical Students, Health Care Team (accessed on July 8, 2018), *available* at https://www.ecfmg.org/echo/team-doctors-attending-physician.html (stating that the attending physician is "ultimately responsible for all patient care" and "has legal and ethical responsibility for directing care of the patient").

76. Execution by lethal injection is not a "legitimate medical purpose." *See, e.g.*, American Medical Association, Code of Medical Ethics Opinion 9.7.3 (stating "as a member of a profession dedicated to preserving life when there is hope in doing so, a physician must not participate in a legally authorized execution").

77. Defendants threaten to imminently – by July 11, 2018 at 8 p.m. Nevada time – have a physician administer and/or direct and supervise the administration of the Alvogen Midazolam Product for a purpose that is neither therapeutic nor in furtherance of the "healing arts" (as they are called under Nevada law), but rather to facilitate a patient's death. The administration of the Alvogen Midazolam Product for a lethal injection constitutes the administration of a controlled substance for a purpose (ending a life) that does not qualify as a legitimate medical purpose.

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78. Accordingly, to the extent permitted to implement Defendants' proposed execution protocol, John Doe I will violate Nevada law by directing the administration of the Alvogen Midazolam Product, a controlled substance, for a purpose that is outside of the therapeutic purposes set forth in the Alvogen labeling and for a use (ending a life) that does not qualify as a legitimate medical purpose.

79. To the extent that Defendants intend to employ non-physicians to administer the Alvogen Midazolam Product, John Doe I would again be acting in violation of Nevada law, the attending physician is ultimately responsible for the administration of anesthetic agents like the Alvogen Midazolam Product. *See* NAC § 630.830 (prohibiting a delegating practitioner from delegating or allowing a medical assistant "to administer an anesthetic agent which renders a patient unconscious or semiconscious").

80. Unless enjoined, Defendants' threatened and imminent wrongdoing will cause Alvogen to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor and prospective investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT V: UNLAWFUL FURNISHING OF A CONTROLLED SUBSTANCE

81. Alvogen incorporates paragraphs 1 through 80 above as if fully set forth herein.

82. Under Nevada law, a person who "knowingly and unlawfully services, sells or otherwise furnishes a controlled substance to another person" is liable for wrongdoing or damage caused as a result of the use of the controlled substance. NRS 41.700(1)(a)-(b).

83. Defendants' furnishing of the Alvogen Midazolam Product to John Doe I and/or non-physician administrators is unlawful because, *inter alia*, it was obtained from Alvogen and/or Cardinal Health by way of deception, evasion, deceit, and/or subterfuge, in violation of NRS § 453.331(1)(d); NAC § 630.230(d).

84. Further, Defendants' furnishing of the Alvogen Midazolam Product to John Doe I and/or non-physician administrators is unlawful for the reasons set forth in Counts VI - VIII, as

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Defendants' acquisition of the Alvogen Midazolam Product is in derogation of, and violates, Alvogen's property rights.

85. Further, Defendants' furnishing of the Alvogen Midazolam Product to John Doe I and/or non-physician administrators is unlawful because Defendants' acquisition of the Alvogen Midazolam Product was undertaken for purposes of unlawfully administering it for a non-therapeutic use (an execution) as well as for unlawfully furnishing it to non-physician administrators.

86. Under Nevada law, a person who "knowingly allows another person to use a controlled substance in an unlawful manner on premises or in a conveyance bellowing to the person allowing the use or over which the person has control," is liable for any wrongdoing or damage caused as a result of the use of the controlled substance. NRS § 41.700(1)(b).

87. Defendants intend to imminently allow another person – John Doe I and/or non-physician administrators – to use a controlled substance (the Alvogen Midazolam Product) on their premises. Defendants' proposed conduct is unlawful for the reasons set forth *supra*. Defendant's imminently threatened wrongdoing will be in violation of Nevada law for this independent reason.

88. Unless enjoined, Defendants' threatened and imminent wrongdoing will cause Alvogen to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor and prospective investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT VI: REPLEVIN

89. Alvogen incorporates paragraphs 1 through 88 above as if fully set forth herein.

90. On information and belief, Defendants sought to circumvent Alvogen's controls by issuing purchase orders for the Alvogen Midazolam Product for completion in June 2018 with an unsuspecting distributor, Cardinal Health. Based on those purchase orders to be completed in June 2018, Cardinal Health shipped to Defendants a total of 60 10ml vials of 5mg/ml midazolam and 30 5ml vials of 5mg/ml.

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91. As set forth above, Defendants knew or should have known that the distributor was not permitted, allowed, or authorized to sell the Alvogen Midazolam Products to NDOC and the remaining Defendants, let alone for the purpose of an execution. Indeed, Alvogen had written to Defendants in April of 2018 – prior to their illicit acquisition of the Midazolam products – to warn them that Alvogen has various controls in place to "ensure our products are not purchased for use in lethal injection executions," including its refusal to "accept orders from any state departments of corrections" as well as various "controls in place [to] direct[] its customers not to sell its medicines to correctional facilities or otherwise for use in connection with lethal injection executions."

92. On information and belief, NDOC wrongfully took possession of the Alvogen Midazolam Product by tacitly misrepresenting that it would be used for a legitimate medical purpose.

93. As set forth in its April 2018 letters to Defendants, in light of its clear and unambiguous communications and restrictions regarding the sale of its Midazolam Product, Alvogen is the rightful owner of the Midazolam Product and has a present and immediate right of possession to said property.

94. Given the unambiguous contents of the April Alvogen Letters, Defendants were on actual and/or constructive notice that they could not purchase the Alvogen Midazolam Product directly from Alvogen and that Alvogen's distributors were not authorized to transfer the Alvogen Midazolam Product to Defendants for purposes of utilizing it in an execution. Thus, Defendants had actual and/or constructive notice that they could not in good faith acquire title to the Alvogen Midazolam Product. Hence, the Alvogen Midazolam Product is neither the property of NDOC nor the State of Nevada.

95. Alvogen has a specific interest in the Alvogen Midazolam Product vials that are in the possession of the NDOC because the NDOC intends to use Alvogen's property for the administration of capital punishment, in violation of Alvogen's policies and agreements between Alvogen and its distributor(s).

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96. In its April 2018 letter, Alvogen specifically demanded that should Defendants somehow circumvent Alvogen's controls, intentions, and property rights to illicitly obtain any of Alvogen's Midazolam product, Defendants should immediately return said Midazolam products in exchange for a full refund.

97. In spite of said demand, Defendants have refused to return the Midazolam products that they illicitly and improperly obtained.

98. Alvogen's Midazolam Product is approved by the FDA solely for the following therapeutic uses: intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia; intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants; intravenously for induction of general anesthesia, before administration of other anesthetic agents; and for continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

99. Defendants have announced plans to utilize Alvogen's Midazolam Product for a purpose for which it is neither indicated nor intended to be used – to wit, to intentionally cause death. Defendants' proposed use for Alvogen's Midazolam Product clearly runs counter to the FDA-approved indications for this product. While Alvogen takes no position on the death penalty itself, Alvogen's products were developed to save and improve patients' lives and their use in executions is fundamentally contrary to this purpose.

100. Alvogen has a property right in both its Midazolam product and its right to deal – or refuse to deal – with particular prospective customers with respect to said drug. The Supreme Court of the United States long ago recognized the "right of [a] trader or manufacturer engaged in an entirely private business freely to exercise his own independent discretion as to parties with whom he will deal, and, of course, [to] announce in advance the circumstances under which he will refuse to sell." *United States v. Colgate & Co.*, 250 U.S. 300, 307 (1919). Alvogen has exercised those rights both generally in its statements to the public and to prison

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officials and specifically in communications with Defendants. Thus, as set forth *supra*, Alvogen specifically wrote to the Nevada Department of Corrections (through the Warden at the prison at which the Execution is to take place) and the Nevada Attorney General to specifically warn them that they were customers with whom Alvogen refused to deal – both directly and indirectly – with regard to the acquisition of its Midazolam Product.

101. Defendants' actions are wrongful vis-à-vis Alvogen because, *inter alia*, they are inconsistent with Alvogen's property rights, they do not constitute the appropriate and therapeutic use for the Midazolam Product for a legitimate medical purpose, they are contrary to the therapeutic uses for which the drug can be utilized, and they risk grave harm to Alvogen's reputation and goodwill.

102. Because of Defendants' wrongdoing, Alvogen has suffered and continues to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT VII: CONVERSION

103. Alvogen incorporates paragraphs 1 through 102 above as if fully set forth herein.

104. NDOC has undertaken a distinct act of dominion wrongfully exerted over Alvogen's personal property, the Midazolam product, in denial of, or inconsistent with his title or rights therein or in derogation, exclusion, or defiance of such title or rights.

105. NDOC has dominion over the Midazolam product because NDOC is currently in possession of the Alvogen Midazolam Product.

106. Given the unambiguous contents of the April Alvogen Letters, Defendants were on actual and/or constructive notice that they could not purchase the Alvogen Midazolam Product directly from Alvogen and that Alvogen's distributors were not authorized to transfer the Alvogen Midazolam Product to Defendants for purposes of utilizing it in an execution. Thus, Defendants had actual and/or constructive notice that they could not in good faith acquire title to the Alvogen Midazolam Product.

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107. Alvogen has true right or title to the Midazolam Product because, *inter alia*, they were sold without authorization, in direct contravention of Alvogen's stated policy of not selling midazolam to prisons and not allowing its distributors to sell midazolam to prisoners, in violation of Alvogen's fundamental property right to refuse to sell to Defendants (either directly or indirectly), and because Defendants' obtained possession of said product by way of deceit, subterfuge, evasion, and/or fraud by omission.

108. NDOC's dominion is wrongfully exerted because, according to the press report attached as Exhibit 1, NDOC was aware of Alvogen's policy of not selling midazolam to prisoners. Indeed on April 20, 2018, Alvogen sent a letter to NDOC informing them "in the clearest possible terms that Alvogen strongly objects to the use of its products in capital punishment." As described in Paragraph 9 above, the NDOC's own statements in other litigation related to this execution further show that the NDOC was aware of and actively fought disclosure of certain execution-related information because such information had been used to persuade manufacturers to cease selling their products for executions.

109. NDOC's dominion is wrongfully exerted for the additional reasons set forth *supra*, in Counts I through V.

110. On information and belief, following their receipt of the April Alvogen Letters, Defendants thereafter sought to circumvent Alvogen's policy by purchasing the Alvogen Midazolam Product through an unsuspecting intermediary and without disclosing to said intermediary the contents of the April Alvogen Letters and/or the fact that they sought to obtain the Alvogen Midazolam Product for purposes of a non-therapeutic use (i.e., an execution). Defendants were thus able to illicitly and through subterfuge obtain the Alvogen Midazolam Product in a manner that they would not have been able to accomplish had they disclosed the contents of said letter and/or their intended non-therapeutic use of the Alvogen Midazolam Product to the intermediary.

111. In its April 2018 letter, Alvogen specifically demanded that should Defendants somehow circumvent Alvogen's controls, intentions, and property rights to illicitly obtain any of Alvogen's Midazolam Product, Defendants should immediately return said Midazolam products

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in exchange for a full refund. In spite of said demand, Defendants have refused to return the Midazolam products that they illicitly and improperly obtained.

112. Defendants have announced plans to utilize Alvogen's Midazolam Product for a purpose for which it is neither indicated nor intended to be used – to wit, to intentionally cause death. Defendants' proposed use for Alvogen's Midazolam Product clearly runs counter to the FDA-approved indications for this product. While Alvogen takes no position on the death penalty itself, Alvogen's products were developed to save and improve patients' lives and their use in executions is fundamentally contrary to this purpose.

113. Alvogen has a property right in both its Midazolam Product and its right to deal – or refuse to deal – with particular prospective customers with respect to said drug. The Supreme Court of the United States long ago recognized the "right of [a] trader or manufacturer engaged in an entirely private business freely to exercise his own independent discretion as to parties with whom he will deal, and, of course, [to] announce in advance the circumstances under which he will refuse to sell." *United States v. Colgate & Co.*, 250 U.S. 300, 307 (1919). Alvogen has exercised those rights both generally in its statements to the public and to prison officials and specifically in communications with Defendants. Thus, as set forth *supra*, Alvogen specifically wrote to the Nevada Department of Corrections (through the Warden at the prison at which the Execution is to take place) and the Attorney General to specifically warn them that they were customers with whom Alvogen refused to deal – both directly and indirectly – with regard to the acquisition of its Midazolam Product.

114. Defendants' actions are wrongful vis-à-vis Alvogen because, *inter alia*, they are inconsistent with Alvogen's property rights, they do not constitute the appropriate and therapeutic use for the Midazolam product for a legitimate medical purpose, they are contrary to the therapeutic uses for which the drug can be utilized, and they risk grave harm to Alvogen's reputation and goodwill.

115. Because of Defendants' wrongdoing, Alvogen has suffered and continues to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the

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manufacture of drugs used for executions, (ii) the corresponding damage to business and investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

COUNT VIII: FALSE PRETENSES

116. Alvogen incorporates paragraphs 1 through 115 above as if fully set forth herein.

117. Defendants were aware from the April 2018 letter "that Alvogen strongly objects to the use of its products in capital punishment." The April 2018 letter went on to explain that "Alvogen does not accept orders from any state departments of corrections. Further, Alvogen has controls in place and directs its customers not to sell its medicines to correctional facilities or otherwise for use in connection with lethal injection executions."

118. Despite this awareness, Defendants intentionally defrauded Alvogen's distributor by, on information and belief, concealing the April 2018 letter from the distributor and/or the fact that Defendants intended to use the Alvogen Midazolam Product for purposes of an execution. In failing to disclose the April 2018 letter and/or their intent to use the Alvogen Midazolam Product for purposes of an execution and proceeding to order the Midazolam product, Defendants omitted relevant information and implicitly made the false representation that they had legitimate therapeutic rationale to purchase the Alvogen Midazolam Product.

119. Alvogen's distributor justifiably relied on the false pretense(s) because they had no reason to suspect that Defendants were not authorized to purchase the Midazolam product or that the Midazolam product would not be used for a legitimate medical purpose.

120. Defendants were thus able to illicitly and through subterfuge obtain the Alvogen Midazolam Product by defrauding the intermediary, and in doing so, causing grave reputational harm to Alvogen.

121. Defendants have announced plans to utilize the Alvogen Midazolam Product for a purpose for which it is neither indicated nor intended to be used – to wit, to intentionally cause death. Defendants' proposed use for Alvogen's Midazolam Product clearly runs counter to the FDA-approved indications for this product. While Alvogen takes no position on the death penalty itself, Alvogen's products were developed to save and improve patients' lives and their use in executions is fundamentally contrary to this purpose.

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122. Defendants' actions are wrongful vis-à-vis Alvogen because, *inter alia*, they are inconsistent with Alvogen's property rights insofar as Defendants obtained Alvogen's products by defrauding Alvogen's distributor, they do not constitute the appropriate and therapeutic use for the Midazolam product, they are contrary to the therapeutic uses for which the drug can be utilized, and they risk grave harm to Alvogen's reputation and goodwill.

123. Because of Defendants' wrongdoing, Alvogen has suffered and continues to suffer injuries, including, but not limited to reputational injury arising out of (i) association with the manufacture of drugs used for executions, (ii) the corresponding damage to business and investor relationships, (iii) damage to goodwill, and (iii) other irreparable harm to be proven at trial.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for relief as follows:

1. Alvogen requests a temporary restraining order and preliminary/permanent injunctive relief precluding the use of any Alvogen drug, including Midazolam, in carrying out any capital punishment and further ordering NDOC to return immediately all of the Midazolam product to Alvogen, as well as requiring an impoundment of the 90 vials of midazolam pending a hearing on its status

2. For declaratory relief as requested herein;

3. For an award of attorneys' fees and costs of suit as allowed by law; and

4. For such other and further relief as this Court deems appropriate under the circumstances.

DATED this 10th day of July, 2018.

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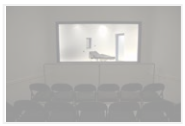
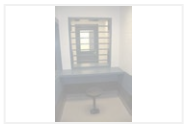
EXHIBIT 1

Nevada’s new $860,000 execution chamber is finished but gathering dust

A view of the gurney inside the newly completed execution chamber at Ely State Prison on Nov. 10, 2016. Courtesy the Nevada Department of Corrections




By SEAN WHALEY LAS VEGAS REVIEW-JOURNAL

November 27, 2016 - 11:55 pm

More in Crime

Henderson judge orders 2 teens to stand trial in shooting death

Henderson woman shot in head, left in burning apartment

Adult, not teen was victim of sex assault in Las Vegas underpass

Las Vegas lawyer linked to death of drug informant

Man, 39, fatally shot in North Las Vegas

Las inve airli

Nevada has the death penalty and is required by law to use lethal injection for executions, but its supply of one of the drugs has expired and drug companies will no longer provide the chemicals to the state for such purposes.

The new execution chamber and related facilities take up 1,900 square feet of the administration wing at the Ely State Prison, the state’s maximum security prison where Nevada’s death row population of 81 men is housed.

There are no pending executions because of legal appeals in progress by the inmates. The execution space at the prison will be used for other purposes in the meantime.

State Senate Judiciary Chairman Tick Segerblom, D-Las Vegas, said he does not plan to propose legislation to do away with the death penalty given the de facto moratorium on the process. While there might be support to abolish the death penalty in the Legislature, any bill would likely be vetoed by Gov. Brian Sandoval, he said.

Sandoval supports the death penalty.

Segerblom said he has no interest in pursuing legislation to change the method of execution, either.

VOTERS MAY WEIGH IN

But Assemblyman James Ohrenschall, D-Las Vegas, named last week as chairman of the Corrections, Probation and Parole Committee, said he plans to ask voters to weigh in on whether to repeal capital punishment.

“Given the state audit that documented the high financial costs of having capital punishment as a penalty in Nevada along with the practical matter of the lack of availability of the lethal chemical cocktail used to carry out the executions, I think it’s time that Nevadans are asked to weigh in on whether they still want capital punishment on the books,” he said.

Ohrenschall said he will introduce legislation to amend the state Constitution to abolish capital punishment and make life without parole the maximum sentence. The measure would have to pass the Legislature in both 2017 and 2019 and then go to the voters in 2020.

He will also propose legislation for a moratorium on capital punishment until voters can have the final say on the issue.

The 105-page audit cited by Ohrenschall, presented to lawmakers in 2014, showed that the cost to prosecute and litigate death penalty cases is higher than if convicted murderers were given life in prison.

Death penalty cases cost the public on average $1.03 million to $1.31 million, according to the audit. In a murder case in which capital punishment is not sought, the average cost is $775,000. In those cases, prosecutors typically seek life in prison without parole.

The 2013 Legislature ordered auditors to review the costs of capital punishment. The audit, which took 18 months, looked at the price of trials, appeals and jail time for 28 Nevada cases.

DRUG COMPANIES SIT OUT

Nevada prison officials said last month that the state will have to explore its options to carry out executions after it received no bids from pharmaceutical companies to supply drugs for lethal injections.

The state issued 247 requests for proposals on Sept. 2 after its stockpile of at least one drug used in executions expired. Not one response was received.

Nevada has used the drugs midazolam and hydromorphone to administer a lethal injection. Both are manufactured by Pfizer.

Nevada’s last execution, by lethal injection, occurred at the Nevada State Prison on April 26, 2006, when Daryl Mack was put to death. Mack was executed for the rape and murder of a Reno woman, Betty Jane May, in 1988.

Nevada has executed 12 inmates since capital punishment was reinstated by the state Legislature in 1977. All but one have been “volunteers,” or inmates who have voluntarily given up their appeals.

Contact Sean Whaley at swhaley@reviewjournal.com or 775-461-3820. Follow @seanw801 on Twitter.

RELATED

Architecture contract OK’d for Nevada execution chamber

Nevada pursues death chamber, controversial drug

Nevada has 80 on death row, but no place to execute

Nevada legislators question need for new death chamber

News

EXHIBIT 2

DAILYMED

LABEL: MIDAZOLAM- midazolam hydrochloride injection, solution

VIEW PACKAGE PHOTOS

NDC Code(s): 47781-589-17, 47781-589-20, 47781-589-22, 47781-589-91
Packager: Alvogen Inc.

Category: HUMAN PRESCRIPTION DRUG LABEL
DEA Schedule: CIV
Marketing Status: Abbreviated New Drug Application

DRUG LABEL INFORMATION

Updated May 31, 2017

If you are a consumer or patient please visit this version.

VIEW ALL SECTIONS

BOXED WARNING (WHAT IS THIS?)

Personnel and Equipment for Monitoring and Resuscitation Adults and Pediatrics: Intravenous midazolam hydrochloride has been associated with respiratory depression and ...

WARNINGS

Personnel and Equipment for Monitoring and Resuscitation

Adults and Pediatrics: Intravenous midazolam hydrochloride has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam hydrochloride should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function, e.g., pulse oximetry. Immediate availability of resuscitative drugs and age- and

size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see WARNINGS). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Risks From Concomitant Use With Opioids

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation (see WARNINGS and PRECAUTIONS, DRUG INTERACTIONS).

Individualization of Dosage

Midazolam hydrochloride must never be used without individualization of dosage. The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia is age, procedure, and route dependent (see DOSAGE AND ADMINISTRATION for complete dosing information).

Neonates: Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl (see DOSAGE AND ADMINISTRATION for complete information).

CLOSE

SPL UNCLASSIFIED SECTION

NOT FOR USE IN NEONATES

CONTAINS BENZYL ALCOHOL

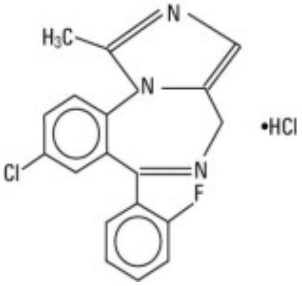
Rx only

CLOSE

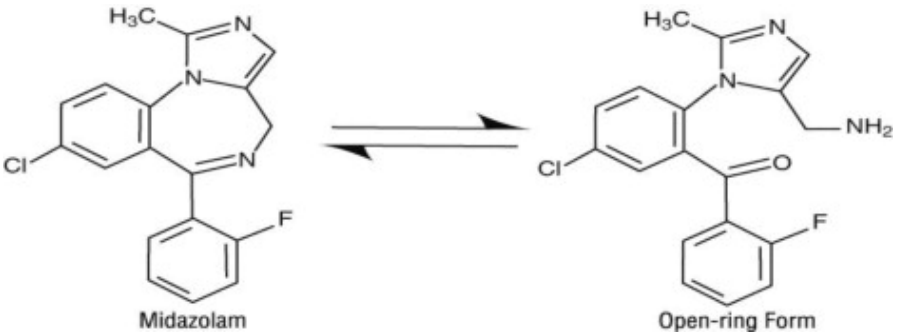
DESCRIPTION

Midazolam hydrochloride is a water-soluble benzodiazepine available as a sterile, nonpyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% edetate disodium, with 1% benzyl alcohol as preservative; the pH is adjusted to 2.9 to 3.5 with hydrochloric acid and, if necessary, sodium hydroxide.

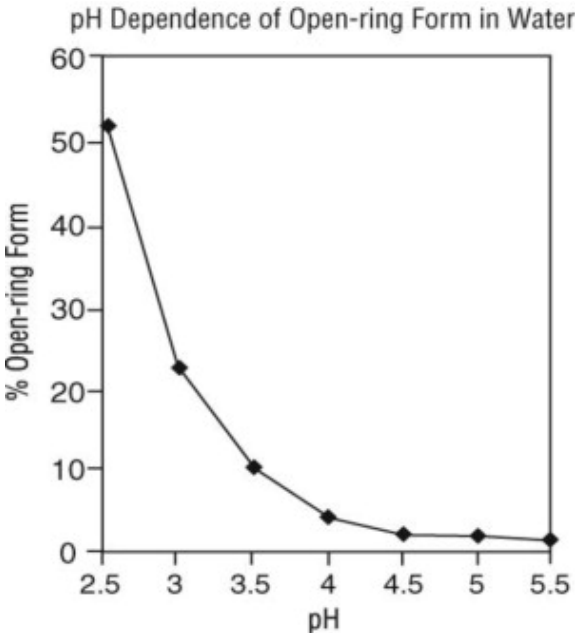
Midazolam is a white or yellowish crystalline powder, insoluble in water. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine hydrochloride. Midazolam hydrochloride has the empirical formula C18H13ClFN3•HCl, a calculated molecular weight of 362.25 and the following structural formula:



Under the acidic conditions required to solubilize midazolam in the product, midazolam is present as an equilibrium mixture (shown below) of the closed ring form shown above and an open-ring structure formed by the acid-catalyzed ring opening of the 4,5-double bond of the diazepine ring. The amount of open-ring form is dependent upon the pH of the solution. At the specified pH of the product, the solution may contain up to about 25% of the open-ring compound. At the physiologic conditions under which the product is absorbed (pH of 5 to 8) into the systemic circulation, any open-ring form present reverts to the physiologically active, lipophilic, closed-ring form (midazolam) and is absorbed as such.



The following chart plots the percentage of midazolam present as the open-ring form as a function of pH in aqueous solutions. As indicated in the graph, the amount of open-ring compound present in solution is sensitive to changes in pH over the pH range specified for the product: 3.0 to 3.6 for the 5 mg/mL concentration. Above pH 5, at least 99% of the mixture is present in the closed-ring form.



CLOSE

CLINICAL PHARMACOLOGY

Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.

Pharmacodynamics

The effects of midazolam hydrochloride on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Onset time of sedative effects after IM administration in adults is 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one adult study, when tested the following day, 73% of the patients who received midazolam hydrochloride intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration. Onset time of sedative effects in the pediatric population begins within 5 minutes and peaks at 15 to 30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving intramuscular midazolam compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after intravenous (IV) injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the adult patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% of patients had impaired recall vs 9% of the placebo controls. In another pediatric oncology study, 91% of midazolam treated patients were amnestic compared with 35% of patients who had received fentanyl alone.

When midazolam hydrochloride is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied. A dose response study of pediatric patients premedicated with 1 mg/kg intramuscular (IM) meperidine found that only 4 out of 6 pediatric patients who received 600 mcg/kg IV midazolam lost consciousness, with eye closing at 108 to 140 seconds. This

group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at 20 ± 3.2 seconds. Midazolam did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

Midazolam, used as directed, does not delay awakening from general anesthesia in adults. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Recovery from anesthesia or sedation for procedures in pediatric patients depends on the dose of midazolam administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV midazolam hydrochloride is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with midazolam and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of midazolam hydrochloride do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of midazolam hydrochloride depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (Vmax) increase. In one study of pediatric patients under general anesthesia, intramuscular midazolam (100 mcg/kg or 200 mcg/kg) was shown to depress the response to carbon dioxide in a dose-related manner.

In cardiac hemodynamic studies in adults, IV induction of general anesthesia with midazolam hydrochloride was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly. In pediatric patients, a comparison of IV midazolam hydrochloride (500 mcg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV midazolam vs a mean 25% decrease in systolic blood pressure following propofol.

Pharmacokinetics

Midazolam's activity is primarily due to the parent drug. Elimination of the parent drug takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Six single-dose pharmacokinetic studies involving healthy adults yield pharmacokinetic parameters for midazolam in the following ranges: volume of distribution (Vd), 1.0 to 3.1 L/kg; elimination half-life, 1.8 to 6.4 hours (mean approximately 3 hours); total clearance (Cl), 0.25 to 0.54 L/hr/kg. In a parallel group study, there was no difference in the clearance, in subjects administered 0.15 mg/kg (n=4) and 0.30 mg/kg

(n=4) IV doses indicating linear kinetics. The clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg (n=4) and 0.6 mg/kg (n=5) indicating non-linear kinetics in this dose range.

Absorption

The absolute bioavailability of the intramuscular route was greater than 90% in a crossover study in which healthy subjects (n=17) were administered a 7.5 mg IV or IM dose. The mean peak concentration (Cmax) and time to peak (Tmax) following the IM dose was 90 ng/mL (20% CV) and 0.5 hour (50% CV). Cmax for the 1-hydroxy metabolite following the IM dose was 8 ng/mL (Tmax=1.0 hour).

Following IM administration, Cmax for midazolam and its 1-hydroxy metabolite were approximately one-half of those achieved after intravenous injection.

Distribution

The volume of distribution (Vd) determined from six single-dose pharmacokinetic studies involving healthy adults ranged from 1.0 to 3.1 L/kg. Female gender, old age, and obesity are associated with increased values of midazolam Vd. In humans, midazolam has been shown to cross the placenta and enter into fetal circulation and has been detected in human milk and CSF (see SPECIAL POPULATIONS).

In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin and that for 1-hydroxy metabolite is about 89%.

Metabolism

In vitro studies with human liver microsomes indicate that the biotransformation of midazolam is mediated by cytochrome P450-3A4. This cytochrome also appears to be present in gastrointestinal tract mucosa as well as liver. Sixty to seventy percent of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxy-midazolam) while 4-hydroxy-midazolam constitutes 5% or less. Small amounts of a dihydroxy derivative have also been detected but not quantified. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Drugs that inhibit the activity of cytochrome P450-3A4 may inhibit midazolam clearance and elevate steady-state midazolam concentrations.

Studies of the intravenous administration of 1-hydroxy-midazolam in humans suggest that 1-hydroxy-midazolam is at least as potent as the parent compound and may contribute to the net pharmacologic activity of midazolam. *In vitro* studies have demonstrated that the affinities of 1- and 4-hydroxy-midazolam for the benzodiazepine receptor are approximately 20% and 7%, respectively, relative to midazolam.

Excretion

Clearance of midazolam is reduced in association with old age, congestive heart failure, liver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood flow.

The principal urinary excretion product is 1-hydroxy-midazolam in the form of a glucuronide conjugate; smaller amounts of the glucuronide conjugates of 4-hydroxy- and dihydroxy-midazolam are detected as well. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 0.5% (n=5). Following a single IV infusion in 5 healthy volunteers, 45% to 57% of the dose was excreted in the urine as 1-hydroxymethyl midazolam conjugate.

Pharmacokinetics-Continuous Infusion

The pharmacokinetic profile of midazolam following continuous infusion, based on 282 adult subjects, has been shown to be similar to that following single-dose administration for subjects of comparable age, gender, body habitus and health status. However, midazolam can accumulate in peripheral tissues with continuous infusion. The effects of accumulation are greater after long-term infusions than after short-term infusions. The effects of accumulation can be reduced by maintaining the lowest midazolam infusion rate that produces satisfactory sedation.

Infrequent hypotensive episodes have occurred during continuous infusion; however, neither the time to onset nor the duration of the episode appeared to be related to plasma concentrations of midazolam or alpha-hydroxy-midazolam. Further, there does not appear to be an increased chance of occurrence of a hypotensive episode with increased loading doses.

Patients with renal impairment may have longer elimination half-lives for midazolam (see SPECIAL POPULATIONS, RENAL IMPAIRMENT).

Special Populations

Changes in the pharmacokinetic profile of midazolam due to drug interactions, physiological variables, etc., may result in changes in the plasma concentration-time profile and pharmacological response to midazolam in these patients. For example, patients with acute renal failure appear to have a longer elimination half-life for midazolam and may experience delayed recovery (see SPECIAL POPULATIONS, RENAL IMPAIRMENT). In other groups, the relationship between prolonged half-life and duration of effect has not been established.

Pediatrics and Neonates

In pediatric patients aged 1 year and older, the pharmacokinetic properties following a single dose of midazolam reported in 10 separate studies of midazolam are similar to those in adults. Weight-normalized clearance is similar or higher (0.19 to 0.80 L/hr/kg) than in adults and the terminal elimination half-life (0.78 to 3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties during and following continuous intravenous infusion in pediatric patients in the operating room as an adjunct to general anesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults or other groups of pediatric patients. It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.

Obese

In a study comparing normals (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.9 vs 2.3 hours). This was due to an increase of approximately 50% in the Vd corrected for total body weight. The clearance was not significantly different between groups.

Geriatric

In three parallel group studies, the pharmacokinetics of midazolam administered IV or IM were compared in young (mean age 29, n=52) and healthy elderly subjects (mean age 73, n=53). Plasma half-life was approximately two-fold higher in the elderly. The mean Vd based on total body weight increased

consistently between 15% to 100% in the elderly. The mean Cl decreased approximately 25% in the elderly in two studies and was similar to that of the younger patients in the other.

Congestive Heart Failure

In patients suffering from congestive heart failure, there appeared to be a two-fold increase in the elimination half-life, a 25% decrease in the plasma clearance and a 40% increase in the volume of distribution of midazolam.

Hepatic Impairment

Midazolam pharmacokinetics were studied after an IV single dose (0.075 mg/kg) was administered to 7 patients with biopsy proven alcoholic cirrhosis and 8 control patients. The mean half-life of midazolam increased 2.5-fold in the alcoholic patients. Clearance was reduced by 50% and the Vd increased by 20%. In another study in 21 male patients with cirrhosis, without ascites and with normal kidney function as determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxy-midazolam were observed when compared to healthy individuals.

Renal Impairment

Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites which may result in slower recovery.

Midazolam and 1-hydroxy-midazolam pharmacokinetics in 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 mL/min/kg) and the half-life was prolonged (7.6 vs 13 hours) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 136 mL/min) and the half-life was prolonged (12 vs >25 hours). Plasma levels accumulated in all ARF patients to about ten times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In a study of chronic renal failure patients (n=15) receiving a single IV dose, there was a two-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Plasma Concentration-Effect Relationship

Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of pharmacodynamic measures (e.g., reaction time, eye movement, sedation) and are associated with extensive intersubject variability. Logistic regression analysis of sedation scores and steady-state plasma concentration indicated that at plasma concentrations greater than 100 ng/mL there was at least a 50% probability that patients would be sedated, but respond to verbal commands (sedation score = 3). At 200 ng/mL there was at least a 50% probability that patients would be asleep, but respond to glabellar tap (sedation score = 4).

Drug Interactions

For information concerning pharmacokinetic drug interactions with midazolam (see PRECAUTIONS).

CLOSE

INDICATIONS AND USAGE

Midazolam Injection, USP is indicated:

intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;

intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;

intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);

continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

CLOSE

CONTRAINDICATIONS

Injectable midazolam hydrochloride is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam hydrochloride; patients with glaucoma have not been studied.

Midazolam hydrochloride is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form. Midazolam hydrochloride is contraindicated for use in premature infants because the formulation contains benzyl alcohol (see WARNINGS and PRECAUTIONS, PEDIATRIC USE).

CLOSE

WARNINGS

Personnel and Equipment for Monitoring and Resuscitation

Prior to the intravenous administration of midazolam hydrochloride in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored for early signs of hypoventilation, airway obstruction, or apnea with means readily available (e.g., pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because intravenous midazolam can depress respiration (see CLINICAL PHARMACOLOGY), especially when used concomitantly with opioid agonists and other sedatives (see DOSAGE AND ADMINISTRATION), it should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway, and supporting ventilation. When used for

sedation/anxiolysis/amnesia, midazolam should always be titrated slowly in adult or pediatric patients. Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population (see DOSAGE AND ADMINISTRATION for complete information).

Risks From Concomitant Use With Opioids

Concomitant use of benzodiazepines, including midazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. If a decision is made to use midazolam concomitantly with opioids, monitor patients closely for respiratory depression and sedation (see PRECAUTIONS, DRUG INTERACTIONS).

Risk of Respiratory Adverse Events

Serious cardiorespiratory adverse events have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations particularly in adult or pediatric patients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

Individualization of Dosage

Midazolam hydrochloride must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression (see DOSAGE AND ADMINISTRATION for complete information).

Other Adverse Events

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam hydrochloride; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam hydrochloride and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients.

Concomitant Use of Central Nervous System Depressants

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Debilitation and Comorbid Considerations

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam hydrochloride. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (see CLINICAL PHARMACOLOGY). Because elderly patients frequently have inefficient function of one or more

organ systems and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam hydrochloride is recommended, and the possibility of profound and/or prolonged effect should be considered.

Injectable midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of intravenous midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Risk of Intra-Arterial Injection

There have been limited reports of intra-arterial injection of midazolam hydrochloride. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

The safety and efficacy of midazolam following non-intravenous and non-intramuscular routes of administration have not been established. Midazolam hydrochloride should only be administered intramuscularly or intravenously.

Return to Full Cognitive Function

Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours. The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam (see CLINICAL PHARMACOLOGY) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until 1 full day after anesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

Usage in Pregnancy

An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

Usage in Preterm Infants and Neonates

Rapid injection should be avoided in the neonatal population. Midazolam hydrochloride administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including midazolam hydrochloride) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of midazolam hydrochloride for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see WARNINGS and PRECAUTIONS, PEDIATRIC USE).

Pediatric Neurotoxicity

Published animal studies demonstrate that the administration of 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 these findings is not clear. However, based on the available data, 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 three years of age in humans (see PRECAUTIONS, PREGNANCY and PEDIATRIC USE, and ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY).

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anesthetic agents early in life and may result in adverse cognitive or behavioral effects. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

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.

CLOSE

PRECAUTIONS

General

Intravenous doses of midazolam hydrochloride should be decreased for elderly and for debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION). These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

The efficacy and safety of midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient, and the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deep levels of sedation virtually equivalent to a state of general anesthesia where the patient may require external support of vital functions. Care must be taken

to individualize and carefully titrate the dose of midazolam hydrochloride to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for peak CNS effects of both midazolam hydrochloride and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention (see BOXED WARNING, WARNINGS and DOSAGE AND ADMINISTRATION). Practitioners administering midazolam hydrochloride must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.

Inform your physician if you are pregnant or are planning to become pregnant.

Inform your physician if you are nursing.

Patients should be informed of the pharmacological effects of midazolam, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable midazolam hydrochloride, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized.

Patients receiving continuous infusion of midazolam in critical care settings over an extended period of time, may experience symptoms of withdrawal following abrupt discontinuation.

Effect of anesthetic and sedation drugs on early brain development
Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains. Discuss with parents and caregivers the benefits, risks, and timing and duration of surgery or procedures requiring anesthetic and sedation drugs.

Drug Interactions

Effect of Concomitant Use of Benzodiazepines and Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are

combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Monitor patients closely for respiratory depression and sedation.

Other CNS Depressants

The sedative effect of intravenous midazolam is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly opioids (e.g., morphine, meperidine and fentanyl) and also secobarbital and droperidol. Consequently, the dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see DOSAGE AND ADMINISTRATION).

Other Drug Interactions

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

The effect of single oral doses of 800 mg cimetidine and 300 mg ranitidine on steady-state concentrations of oral midazolam was examined in a randomized crossover study (n=8). Cimetidine increased the mean midazolam steady-state concentration from 57 to 71 ng/mL. Ranitidine increased the mean steady-state concentration to 62 ng/mL. No change in choice reaction time or sedation index was detected after dosing with the H2 receptor antagonists.

In a placebo-controlled study, erythromycin administered as a 500 mg dose, three times a day, for 1 week (n=6), reduced the clearance of midazolam following a single 0.5 mg/kg IV dose. The half-life was approximately doubled.

Caution is advised when midazolam is administered to patients receiving erythromycin since this may result in a decrease in the plasma clearance of midazolam.

The effects of diltiazem (60 mg three times a day) and verapamil (80 mg three times a day) on the pharmacokinetics and pharmacodynamics of oral midazolam were investigated in a three-way crossover study (n=9).

The half-life of midazolam increased from 5 to 7 hours when midazolam was taken in conjunction with verapamil or diltiazem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study where saquinavir or placebo was administered orally as a 1200 mg dose, three times a day, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 mg/kg IV dose was observed. The half–life was approximately doubled.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular midazolam hydrochloride for premedication in adults.

The intravenous administration of midazolam hydrochloride decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam hydrochloride administered; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

Although the possibility of minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam hydrochloride does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

Drug/Laboratory Test Interactions

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (4 times a human induction dose of 0.35 mg/kg based on body surface area comparison) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

Impairment of Fertility

Male rats were treated orally with 1, 4, or 16 mg/kg midazolam beginning 62 days prior to mating with female rats treated with the same doses for 14 days prior to mating to Gestation Day 13 or Lactation Day 21. The high dose produced an equivalent exposure (AUC) as 4 mg/kg intravenous midazolam (1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparison). There were no adverse effects on either male or female fertility noted.

Pregnancy

Teratogenic Effects: Pregnancy Category D (see WARNINGS).

Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of peak brain

development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see DATA).

Data

Animal Data

Pregnant rats were treated with midazolam using intravenous doses of 0.2, 1, and 4 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons) during the period of organogenesis (Gestation Day 7 through 15). Midazolam did not cause adverse effects to the fetus at doses of up to 1.85 times the human induction dose. All doses produced slight to moderate ataxia. The high dose produced a 5% decrease in maternal body weight gain compared to control.

Pregnant rabbits were treated with midazolam using intravenous doses of 0.2, 0.6, and 2 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons) during the period of organogenesis (Gestation Day 7 to 18). Midazolam did not cause adverse effects to the fetus at doses of up to 1.85 times the human induction dose. The high dose was associated with findings of ataxia and sedation but no evidence of maternal toxicity.

Pregnant rats were administered midazolam using intravenous doses of 0.2, 1, and 4 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons) during late gestation and through lactation (Gestation Day 15 through Lactation Day 21). All doses produced ataxia. The high dose produced a slight decrease in maternal body weight gain compared to control. There were no clear adverse effects noted in the offspring. The study included no functional assessments of the pups, such as learning and memory testing or reproductive capacity.

In a published study in primates, administration of an anesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the fetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits (see WARNINGS, PEDIATRIC NEUROTOXICITY, PRECAUTIONS, PEDIATRIC USE, and ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY).

Labor and Delivery

In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of injectable midazolam in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam is not recommended for obstetrical use.

Nursing Mothers

Midazolam is excreted in human milk. Caution should be exercised when midazolam hydrochloride is administered to a nursing woman.

Pediatric Use

The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. For specific safety monitoring and dosage guidelines (see BOXED WARNING, CLINICAL PHARMACOLOGY, INDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE and DOSAGE AND ADMINISTRATION). UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Midazolam hydrochloride should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly, with concomitant use of fentanyl.

Midazolam contain benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages greater than 99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Animal Data

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as Midazolam Injection USP, that either block NMDA receptors or potentiate the activity of GABA during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, 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.

In primates, exposure to 3 hours of ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer of isoflurane increased neuronal cell loss. Data from isoflurane-treated rodents and ketamine-treated primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers

should balance the benefits of appropriate anesthesia in pregnant women, neonates, and young children who require procedures with the potential risks suggested by the nonclinical data (see WARNINGS, PEDIATRIC NEUROTOXICITY, PRECAUTIONS, PREGNANCY, and ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY).

Geriatric Use

Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular doses of midazolam should be decreased for elderly and for debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION) and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of IM and IV midazolam to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see DOSAGE AND ADMINISTRATION).

Specific dosing and monitoring guidelines for geriatric patients are provided in the DOSAGE AND ADMINISTRATION section for premedicated patients for sedation/anxiolysis/amnesia following IV and IM administration, for induction of anesthesia following IV administration and for continuous infusion.

CLOSE

ADVERSE REACTIONS

See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam hydrochloride is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube (e.g., upper endoscopy and dental procedures).

Adults

The following additional adverse reactions were reported after intramuscular administration:

headache (1.3%)	*Local effects at IM Injection site*
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

Administration of IM midazolam hydrochloride to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see DOSAGE AND ADMINISTRATION). The following additional adverse reactions were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:

hiccoughs (3.9%)	*Local effects at the IV site*
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.6%)
"oversedation" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Pediatric Patients

The following adverse events related to the use of IV midazolam hydrochloride in pediatric patients were reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7%, paradoxical reactions 2.0%, hiccough 1.2%, seizure-like activity 1.1% and nystagmus 1.1%. The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Neonates

For information concerning hypotensive episodes and seizures following the administration of midazolam hydrochloride to neonates (see BOXED WARNING, CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Other adverse experiences, observed mainly following IV injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of 1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm

Gastrointestinal: Acid taste, excessive salivation, retching

CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia

Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness

Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site

Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma

To report SUSPECTED ADVERSE REACTIONS, contact Alvogen at 1-866-770-3024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

CLOSE

DRUG ABUSE AND DEPENDENCE

Midazolam hydrochloride contains midazolam, a Schedule IV control substance.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam. Abdominal distention, nausea, vomiting, and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient's needs. In some case reports, patients who have had severe withdrawal reactions due to abrupt discontinuation of high-dose long-term midazolam, have been successfully weaned off of midazolam over a period of several days.

CLOSE

OVERDOSAGE

Symptoms

The manifestations of midazolam overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from midazolam hydrochloride overdosage has been reported.

Treatment

Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with midazolam hydrochloride following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant medications. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

CLOSE

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see WARNINGS and PRECAUTIONS, PEDIATRIC USE).

Midazolam injection is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam hydrochloride to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergoing a procedure involving the upper airway such as endoscopy or dental (see BOXED WARNING and WARNINGS).

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, caution should be exercised before continuing administration of midazolam hydrochloride (see WARNINGS).

Midazolam injection should only be administered IM or IV (see WARNINGS).

Care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

Midazolam injection may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Midazolam, at a concentration of 0.5 mg/mL, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. The 5 mg/mL formulation of midazolam may be diluted with 0.9% sodium chloride or 5% dextrose in water.

Monitoring

Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

Adults and Pediatrics

Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3 to 5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive intravenous midazolam.

Immediate availability of resuscitative drugs and *age- and size-appropriate* equipment and personnel trained in their use and skilled in airway management should be assured (see WARNINGS).

Pediatrics

For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

USUAL ADULT DOSE INTRAMUSCULARLY FOR PREOPERATIVE SEDATION/ANXIOLYSIS/AMNESIA	THE RECOMMENDED PREMEDICATION DOSE OF MIDAZOLAM FOR GOOD RISK (ASA PHYSICAL STATUS

(INDUCTION OF SLEEPINESS OR DROWSINESS AND RELIEF OF APPREHENSION AND TO IMPAIR MEMORY OF PERIOPERATIVE EVENTS). FOR INTRAMUSCULAR USE, MIDAZOLAM HYDROCHLORIDE SHOULD BE INJECTED DEEP IN A LARGE MUSCLE MASS.	I & II) ADULT PATIENTS BELOW THE AGE OF 60 YEARS IS 0.07 TO 0.08 MG/KG IM (APPROXIMATELY 5 MG IM) ADMINISTERED UP TO 1 HOUR BEFORE SURGERY. THE DOSE MUST BE INDIVIDUALIZED AND REDUCED WHEN IM MIDAZOLAM IS ADMINISTERED TO PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE, OTHER HIGHER RISK SURGICAL PATIENTS, PATIENTS 60 OR MORE YEARS OF AGE, AND PATIENTS WHO HAVE RECEIVED CONCOMITANT NARCOTICS OR OTHER CNS DEPRESSANTS (SEE ADVERSE REACTIONS). IN A STUDY OF PATIENTS 60 YEARS OR OLDER, WHO DID NOT RECEIVE CONCOMITANT ADMINISTRATION OF NARCOTICS, 2 TO 3 MG (0.02 TO 0.05 MG/KG) OF MIDAZOLAM PRODUCED ADEQUATE SEDATION DURING THE PREOPERATIVE PERIOD. THE DOSE OF 1 MG IM MIDAZOLAM HYDROCHLORIDE MAY SUFFICE FOR SOME OLDER PATIENTS IF THE ANTICIPATED INTENSITY AND DURATION OF SEDATION IS LESS CRITICAL. AS WITH ANY POTENTIAL RESPIRATORY DEPRESSANT, THESE PATIENTS REQUIRE OBSERVATION FOR SIGNS OF CARDIORESPIRATORY DEPRESSION AFTER RECEIVING IM MIDAZOLAM.
INTRAVENOUSLY Sedation/anxiolysis/amnesia for procedures (see INDICATIONS): Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.	When used for sedation/anxiolysis/amnesia for a procedure, dosage must be individualized and titrated. Midazolam hydrochloride should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors (see WARNINGS concerning cardiac/respiratory arrest/airway obstruction/hypoventilation.)
Midazolam hydrochloride 1 mg/mL formulation is recommended for sedation/anxiolysis/amnesia for procedures to facilitate slower injection. The 5 mg/mL formulation may be diluted with 0.9% sodium chloride or 5% dextrose in water.	ONSET IS WITHIN 15 MINUTES, PEAKING AT 30 TO 60 MINUTES. IT CAN BE ADMINISTERED CONCOMITANTLY WITH ATROPINE SULFATE OR SCOPOLAMINE HYDROCHLORIDE AND REDUCED DOSES OF NARCOTICS. *Healthy Adults Below the Age of 60:* Titrate slowly to the desired effect (e.g., the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using small increments, to the appropriate level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. If narcotic premedication or other CNS depressants are used, patients will require approximately 30% less midazolam than unpremedicated patients. *Patients Age 60 or Older, and Debilitated or Chronically Ill Patients:* Because the danger of

	hypoventilation, airway obstruction, or apnea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve, and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower. Titrate slowly to the desired effect (e.g., the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary. If concomitant CNS depressant premedications are used in these patients, they will require at least 50% less midazolam than healthy young unpremedicated patients. *Maintenance Dose:* Additional doses to maintain the desired level of sedation may be given in increments of 25% of the dose used to first reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated patient. These additional doses should be given only after a thorough clinical evaluation clearly indicates the need for additional sedation.
Induction of Anesthesia: For induction of general anesthesia, before administration of other anesthetic agents.	Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

Unpremedicated Patients: In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less midazolam for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

Premedicated Patients: When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg.

In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years.

In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included fentanyl (1.5 to 2 mcg/kg IV, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), and meperidine (dosage individualized, up to 1 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered

	5 minutes before induction, all other premedications should be administered approximately 1 hour prior to the time anticipated for midazolam induction.
Injectable midazolam hydrochloride can also be used during maintenance of anesthesia, for surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases.	Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.
CONTINUOUS INFUSION For continuous infusion, midazolam hydrochloride 5 mg/mL formulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% sodium chloride or 5% dextrose in water.	*Usual Adult Dose:* If a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg (approximately 0.5 to 4.0 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10 to 15 minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 to 0.10 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids. Individual response to midazolam is variable. The infusion rate should be titrated to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam should be infused at the lowest rate that produces the desired level of sedation. Assessment of sedation should be performed at regular intervals and the midazolam infusion rate adjusted up or down by 25% to 50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger adjustments or even a small incremental dose may be necessary if rapid changes in the level of sedation are indicated. In addition, the infusion rate should be decreased by 10% to 25% every few hours to find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated.

	Patients who exhibit agitation, hypertension, or tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective midazolam hydrochloride infusion rate.
PEDIATRIC PATIENTS	UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM HYDROCHLORIDE ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam hydrochloride (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring (see tables below). In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. For appropriate patient monitoring, see BOXED WARNING, WARNINGS, MONITORING subsection of DOSAGE AND ADMINISTRATION. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (OAA/S)				
Assessment Categories				
Responsiveness	Speech	Facial Expression	Eyes	Composite Score
Responds readily to name spoken in normal tone	normal	normal	clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	mild slowing or thickening	mild relaxation	glazed or mild ptosis (less than half the eye)	4

Responds only after name is called loudly and/or repeatedly	slurring or prominent slowing	marked relaxation (slack jaw)	glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	few recognizable words	–	–	2
Does not respond to mild prodding or shaking	–	–	–	1 (deep sleep)

FREQUENCY OF OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION COMPOSITE SCORES IN ONE STUDY OF PEDIATRIC PATIENTS UNDERGOING PROCEDURES WITH INTRAVENOUS MIDAZOLAM FOR SEDATION

Age Range (years)	n	OAA/S Score				
		1 (deep sleep)	2	3	4	5 (alert)
1-2	16	6 (38%)	4 (25%)	3 (19%)	3 (19%)	0
>2-5	22	9 (41%)	5 (23%)	8 (36%)	0	0
>5-12	34	1 (3%)	6 (18%)	22 (65%)	5 (15%)	0
>12-17	18	0	4 (22%)	14 (78%)	0	0
Total (1-17)	90	16 (18%)	19 (21%)	47 (52%)	8 (9%)	0

INTRAMUSCULARLY	USUAL PEDIATRIC DOSE (NON-NEONATAL)
FOR SEDATION/ANXIOLYSIS/AMNESIA PRIOR TO ANESTHESIA OR FOR PROCEDURES, INTRAMUSCULAR	SEDATION AFTER INTRAMUSCULAR MIDAZOLAM IS AGE AND DOSE DEPENDENT: HIGHER DOSES MAY RESULT IN DEEPER AND MORE PROLONGED

MIDAZOLAM CAN BE USED TO SEDATE PEDIATRIC PATIENTS TO FACILITATE LESS TRAUMATIC INSERTION OF AN INTRAVENOUS CATHETER FOR TITRATION OF ADDITIONAL MEDICATION.	SEDATION. DOSES OF 0.1 TO 0.15 MG/KG ARE USUALLY EFFECTIVE AND DO NOT PROLONG EMERGENCE FROM GENERAL ANESTHESIA. FOR MORE ANXIOUS PATIENTS, DOSES UP TO 0.5 MG/KG HAVE BEEN USED. ALTHOUGH NOT SYSTEMATICALLY STUDIED, THE TOTAL DOSE USUALLY DOES NOT EXCEED 10 MG. IF MIDAZOLAM IS GIVEN WITH AN OPIOID, THE INITIAL DOSE OF EACH MUST BE REDUCED.
INTRAVENOUSLY BY INTERMITTENT INJECTION For sedation/anxiolysis/amnesia prior to and during procedures or prior to anesthesia.	USUAL PEDIATRIC DOSE (NON-NEONATAL) It should be recognized that the depth of sedation/anxiolysis needed for pediatric patients depends on the type of procedure to be performed. For example, simple light sedation/anxiolysis in the preoperative period is quite different from the deep sedation and analgesia required for an endoscopic procedure in a child. For this reason, there is a broad range of dosage. For all pediatric patients, regardless of the indications for sedation/anxiolysis, it is vital to titrate midazolam hydrochloride and other concomitant medications slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. Since midazolam hydrochloride is water soluble, it takes approximately three times longer than diazepam to achieve peak EEG effects, therefore one must wait an additional 2 to 3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. If other medications capable of depressing the CNS are coadministered, the peak effect of those concomitant medications must be considered and the dose of midazolam adjusted. The importance of drug titration to effect is vital to the safe sedation/anxiolysis of the pediatric patient. The total dose of midazolam will depend on patient response, the type and duration of the procedure, as well as the type and dose of concomitant medications. *Pediatric Patients Less Than 6 Months of Age:* Limited information is available in non-intubated pediatric patients less than 6 months of age. It is uncertain

	when the patient transfers from neonatal physiology to pediatric physiology, therefore the dosing recommendations are unclear. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful monitoring are essential. *Pediatric Patients 6 Months to 5 Years of Age:* Initial dose 0.05 to 0.1 mg/kg; a total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses. *Pediatric Patients 6 to 12 Years of Age:* Initial dose 0.025 to 0.05 mg/kg; total dose up to 0.4 mg/kg may be needed to reach the desired endpoint but usually does not exceed 10 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses. *Pediatric Patients 12 to 16 Years of Age:* Should be dosed as adults. Prolonged sedation may be associated with higher doses; some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg. The dose of midazolam hydrochloride must be reduced in patients premedicated with opioid or other sedative agents including midazolam. Higher risk or debilitated patients may require lower dosages whether or not concomitant sedating medications have been administered (see WARNINGS).
CONTINUOUS INTRAVENOUS INFUSION For sedation/anxiolysis/amnesia in critical care settings.	USUAL PEDIATRIC DOSE (NON-NEONATAL) To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect IN PATIENTS WHOSE TRACHEA IS INTUBATED. (Midazolam should not be administered as a rapid intravenous dose.) This loading dose may be followed

	by a continuous intravenous infusion to maintain the effect. An infusion of midazolam injection has been used in patients whose trachea was intubated but who were allowed to breathe spontaneously. Assisted ventilation is recommended for pediatric patients who are receiving other central nervous system depressant medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of midazolam should be initiated at a rate of 0.06 to 0.12 mg/kg/hr (1 to 2 mcg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental intravenous doses of midazolam hydrochloride can be administered to increase or maintain the desired effect. Frequent assessment at regular intervals using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythromycin and/or other P450-3A4 enzyme inhibitors (see PRECAUTIONS, DRUG INTERACTIONS) and in patients with liver dysfunction, low cardiac output (especially those requiring inotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when midazolam is rapidly administered. When initiating an infusion with midazolam in hemodynamically compromised patients, the usual loading dose of midazolam hydrochloride should be titrated in small increments and the patient monitored for hemodynamic instability (e.g., hypotension). These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.
CONTINUOUS INTRAVENOUS INFUSION For sedation in critical care settings.	USUAL NEONATAL DOSE Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates WHOSE TRACHEA WAS INTUBATED, continuous intravenous infusions of midazolam injection should be initiated at a rate of 0.03 mg/kg/hr (0.5 mcg/kg/min) in neonates <32 weeks and 0.06

	mg/kg/hr (1 mcg/kg/min) in neonates >32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol (see WARNINGS, USAGE IN PRETERM INFANTS AND NEONATES). Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CLOSE

HOW SUPPLIED

Midazolam Injection, USP is supplied as follows:

NDC	Midazolam Injection, USP (5 mg per mL)	Package Factor
47781-589-17	25 mg per 5 mL Multi-Dose Vial	10 vials per carton
47781-589-91	50 mg per 10 mL Multi-Dose Vial	10 vials per carton

Storage Conditions

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light.

Sterile, Nonpyrogenic.

The container closure is not made with natural rubber latex.

CLOSE

ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY

Published studies in animals demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in neonates and young children who require procedures against the potential risks suggested by the nonclinical data (see WARNINGS, PEDIATRIC NEUROTOXICITY and PRECAUTIONS, PREGNANCY and PEDIATRIC USE).

Manufactured by:
Gland Pharma Limited
D.P.Pally, Dundigal Post
Hyderabad-500 043, India

Product of India

Distributed by:
Alvogen, Inc.
Pine Brook, NJ 07058 USA

Revised: May 2017
PI589-00

CLOSE

PRINCIPAL DISPLAY PANEL

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – Carton

NDC 47781-589-17

Midazolam Injection, USP

C-IV

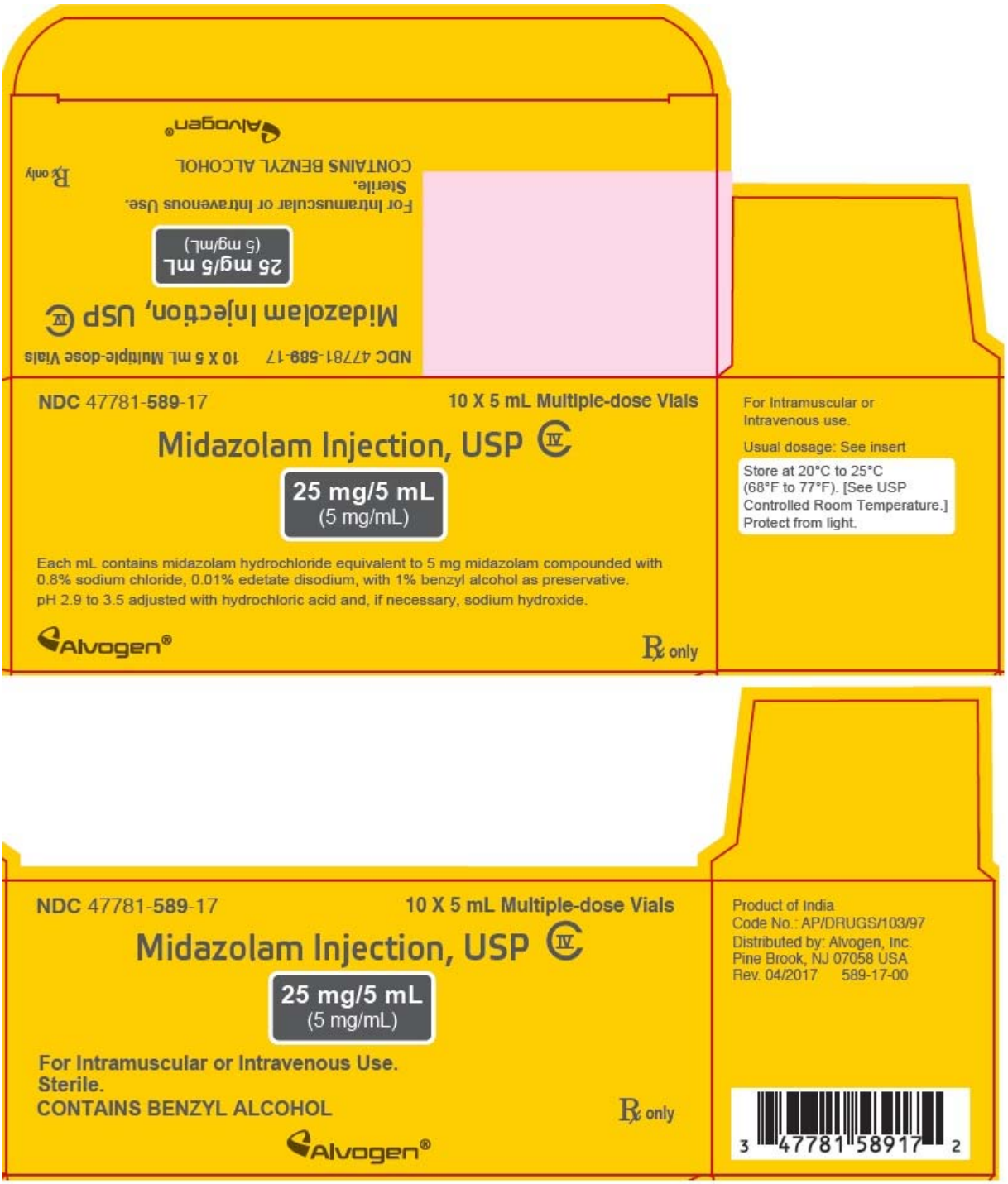
25 mg/5 mL

(5 mg/mL)

For Intramuscular or Intravenous Use. Sterile.

Rx only

CONTAINS BENZYL ALCOHOL



CLOSE

PRINCIPAL DISPLAY PANEL

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – Carton

NDC 47781-589-91

Midazolam Injection, USP

C-IV

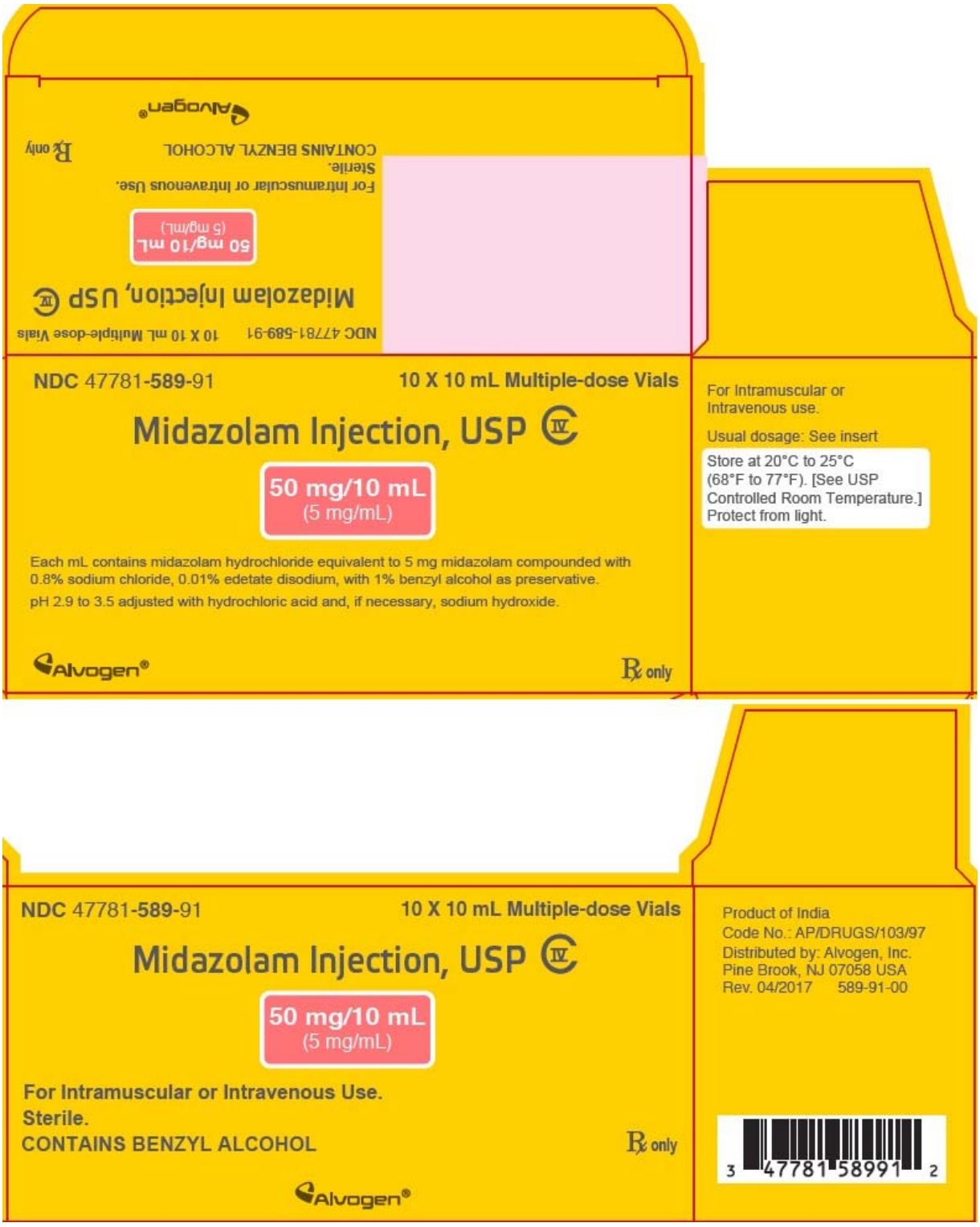
50 mg/10 mL

(5 mg/mL)

For Intramuscular or Intravenous Use. Sterile.

Rx only

CONTAINS BENZYL ALCOHOL



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INGREDIENTS AND APPEARANCE

MIDAZOLAM
midazolam hydrochloride injection, solution

PRODUCT INFORMATION

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:47781-589
Route of Administration	INTRAVENOUS, INTRAMUSCULAR	**DEA Schedule**	CIV

ACTIVE INGREDIENT/ACTIVE MOIETY

Ingredient Name	Basis of Strength	Strength
midazolam hydrochloride (UNII: W7TTW573JJ) (midazolam - UNII:R60L0SM5BC)	midazolam	5 mg in 1 mL

INACTIVE INGREDIENTS

Ingredient Name	Strength
sodium chloride (UNII: 451W47IQ8X)	
edetate disodium (UNII: 7FLD91C86K)	
benzyl alcohol (UNII: LKG8494WBH)	
sodium hydroxide (UNII: 55X04QC32I)	
hydrochloric acid (UNII: QTT17582CB)	

PACKAGING

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:47781-589-17	10 in 1 CARTON	08/11/2017	
1	NDC:47781-589-20	5 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		
2	NDC:47781-589-91	10 in 1 CARTON	08/11/2017	
2	NDC:47781-589-22	10 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		

MARKETING INFORMATION

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA090850	08/11/2017	

LABELER - ALVOGEN INC. (008057330)

CLOSE

VIEW ALL SECTIONS

FIND ADDITIONAL RESOURCES (also available in the left menu)

SAFETY

Boxed Warnings, Report Adverse Events, FDA Safety Recalls, Presence in Breast Milk

RELATED RESOURCES

Medline Plus, Clinical Trials, PubMed, Biochemical Data Summary

MORE INFO ON THIS DRUG

View Label Archives, RxNorm, Get Label RSS Feed

EXHIBIT 3

State Governor
State Attorney General
Director of the State Department of Corrections

April 20, 2018

Dear Warden Filson,

My name is Andrea Sweet and I am a Vice President, Legal Affairs at Alvogen, Inc.

Alvogen is aware that certain medicines we manufacture for specific healthcare applications are currently sought by some correctional facilities in the US for use in lethal injection executions.

I am writing to communicate in the clearest possible terms that Alvogen strongly objects to the use of its products in capital punishment. While Alvogen takes no position on the death penalty itself, our products were developed to save and improve patients' lives and their use in executions is fundamentally contrary to this purpose.

To ensure our products are not purchased for use in lethal injection executions, Alvogen does not accept orders from any state departments of corrections. Further, Alvogen has controls in place and directs its customers not to sell its medicines to correctional facilities or otherwise for use in connection with lethal injection executions. These controls reflect our company's policy of ensuring the appropriate use of our medicines.

The use of Alvogen products, such as midazolam or rocuronium, in executions clearly runs counter to the FDA-approved indication for these products. If your state has purchased products manufactured by Alvogen for use in capital punishment procedures – either directly or indirectly – we ask that you immediately return our products in exchange for a full refund.

Finally, I have been informed that some states have implemented "secrecy policies/laws" which they hope will enable them to bypass company control systems and purchase manufactured medicines for use in executions. Alvogen closely tracks the distribution of its medicines as required by law and will take action in case of such diversions. Transparency across the supply chain is important to protect public health and the commercial interests of healthcare companies.

If you require further clarification regarding our opposition to the misuse of medicines in executions or have questions about specific products you have purchased from Alvogen, please do not hesitate to contact me; I would be glad to discuss these issues further.

Sincerely,

Andrea Sweet
Vice President, Legal Affairs

10 Bloomfield Avenue
Building B
Pine Brook, NJ 07058

Phone 973 796 3400
Fax 973 796 3439

info@alvogen.com
www.alvogen.com

EXHIBIT 4

State Governor
State Attorney General
Director of the State Department of Corrections

April 20, 2018

Dear Mr. Dzurenda,

My name is Andrea Sweet and I am a Vice President, Legal Affairs at Alvogen, Inc.

Alvogen is aware that certain medicines we manufacture for specific healthcare applications are currently sought by some correctional facilities in the US for use in lethal injection executions.

I am writing to communicate in the clearest possible terms that Alvogen strongly objects to the use of its products in capital punishment. While Alvogen takes no position on the death penalty itself, our products were developed to save and improve patients' lives and their use in executions is fundamentally contrary to this purpose.

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If you require further clarification regarding our opposition to the misuse of medicines in executions or have questions about specific products you have purchased from Alvogen, please do not hesitate to contact me; I would be glad to discuss these issues further.

Sincerely,

Andrea Sweet
Vice President, Legal Affairs

10 Bloomfield Avenue
Building B
Pine Brook, NJ 07058

Phone 973 796 3400
Fax 973 796 3439

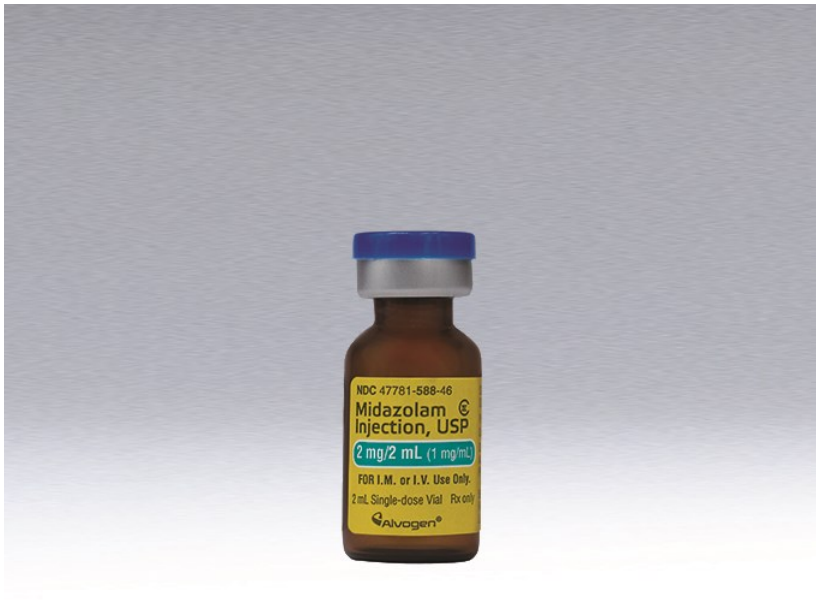
info@alvogen.com
www.alvogen.com

EXHIBIT 5

Midazolam Injection, USP C-IV Single Dose Vial

This product contains boxed warnings. See full prescribing information for this product.

Alvogen endorses the use of its products in accordance with FDA-approved indications. To this end, Alvogen has undertaken controls to avoid diversion of this product for use in execution protocols. In furtherance of this effort, Alvogen does not accept direct orders from prison systems or departments of correction. In addition, Alvogen is working to ensure that its distributors and wholesalers do not resell, either directly or indirectly this product, to prison systems or departments of correction.



MIDAZOLAM INJECTION, USP C-IV SINGLE DOSE VIAL

	NDC#	STRENGTH	PKG SIZE	GCN	GCN SEQ#	
	47781-588-68	2 mg/2 mL (1 mg/mL)	25			PRESCRIBING INFO With Boxed Warnings

EXHIBIT 6

Drug company threatens legal action to prevent drug from being used in Dozier's execution

foxreno.com/news/local/new-drug-in-nevada-execution-plan-linked-to-botched-executions-in-other-states

by Ben Margiott

Thursday, July 5th 2018

New drug in Nevada execution plan linked to botched executions in other states

RENO, Nev. (News 4 & Fox 11) — UPDATE: According to an Alvogen spokesperson, the company is considering taking legal action to prevent their drug from being used in Wednesday's scheduled execution in Ely.

Alvogen makes one of the drugs used that will be used in Scott Dozier's execution.

Statement from spokesperson Halldór Kristmannsson:

> "Alvogen does not market, promote or condone the use of any of its approved prescription drug products, including midazolam, for use in state sponsored executions. To avoid any improper, off label use of our products, Alvogen does not accept direct orders from prison systems or departments of correction. Alvogen works with our distributors and wholesalers to restrict any resale, either directly or indirectly, of our midazolam product to any prison system or department of correction.

> With respect to the alleged intent of the State of Nevada Department of Corrections to use our midazolam product in an execution, we are exploring all potential avenues, including legal recourse, to prevent the improper use of our product in this particular execution."

Nevada is just two days away from executing its first inmate in over a decade, but questions still linger about the controversial three-drug lethal injection combination the Department of Corrections plans to use.

After NDOC's supply of the sedative Diazepam recently expired, the state obtained adequate dosages of the sedative Midazolam, which has been linked to multiple botched executions in other states.

The new sedative drug Midazolam was made by the pharmaceutical company Alvogen, and distributed by Cardinal Health, according to a sales invoice obtained by News 4.

According to the Lethal Injection Information Center, "Alvogen is working to ensure that its distributors and wholesalers do not resell, either directly or indirectly, [Alvogen products] to prison systems or departments of correction."

Midazolam has factored into botched executions in Ohio, Oklahoma, Arizona and Alabama, according to the nonprofit and nonpartisan Death Penalty Information Center.

The sedative was also used in an April 2017 Arkansas execution where witnesses described the inmate "coughing, convulsing, lurching and jerking."

Kelly Kissel, a longtime Associated Press news editor and the current metro editor at The Advocate, has witnessed over 10 executions, including the recent Arkansas one.

"Three or four minutes into the execution was when he started lurching forward. His forehead was pressing against the restraint that was around his forehead," Kissel said.

> "For lack of a better term, it was the most violent execution that I had seen."

According to DPIC, the use of Midazolam factored into an Alabama inmate "heaving and gasping for breath" for about 15 minutes.

Both Florida and Arizona recently abandoned the use of Midazolam in three-drug lethal injection combinations.

Questions remain about the other drugs in the lethal injection combination — the opioid Fentanyl and the paralytic Cisatracurium.

The paralytic element Cisatracurium was the focus of court challenges late last year, with critics arguing that the drug would mask signs of possible suffering, or lead to so-called air hunger.

Fentanyl is in both Nevada and Nebraska's execution protocols, but has never been used in an execution in the United States.

Nevada plans to execute convicted murderer Scott Dozier, now 47, on July 11th at 8:00 p.m. at the Ely State Prison.

Dozier has voluntarily waived all his appeals and maintains that he wants to be executed.

EXHIBIT 7

Nevada releases records on sedative to be used in execution

AP apnews.com/79a2e272ac954e5bae7c0e63218fa51e

LAS VEGAS (AP) — Nevada prison officials released records Friday afternoon about where and when a sedative was obtained for use next week in the state's first execution since 2006.

Records from the Nevada Department of Corrections show midazolam slated for use in Scott Raymond Dozier's lethal injection Wednesday was purchased in May from the state's regular pharmaceutical distributor, Cardinal Health, and manufactured by pharmaceutical company Alvogen.

The U.S. Supreme Court ruled in 2015 that midazolam can be used in lethal injections. But the drug has been blamed in recent years for problem executions in several other states.

Messages seeking comment from Alvogen on Friday afternoon were not immediately returned. The company, however, said on a webpage for the product that it opposes the drug's use in lethal injections.

The company says it has taken steps to try to avoid having midazolam be used in executions and does not accept orders from prison systems or corrections departments. The company says it is also working to ensure its distributors and wholesalers do not directly or indirectly resell the drug to prisons or corrections departments.

A message seeking comment from Cardinal Health was not immediately returned Friday.

The American Civil Liberties Union of Nevada points to Arizona's decision to stop using the drug after a 2014 lethal injection that took nearly two hours to kill Joseph Rudolph Wood. The organization has criticized the plan for Dozier's lethal injection as being less human than putting down a pet.

Nevada plans to use midazolam injections to be followed by high doses of the powerful synthetic opioid fentanyl and muscle-paralyzing drug cisatracurium. Fentanyl and cisatracurium have never before been used for executions.

Dozier has been on death row since 2007 after being convicted in murders in Phoenix and Las Vegas. The 47-year-old has waived appeals in his case and has said he wants to die and doesn't care if he suffers.

ACLU of Nevada spokesman Wesley Juhl said the organization was reviewing the Nevada records Friday afternoon and figuring out its next steps.