OKLAHOMA BOARD OF NURSING
2915 North Classen Boulevard, Suite 524
Oklahoma City, OK 73106
(405) 962-1800

Formulary Advisory Council
AGENDA
Thursday, October 29, 2020
2:30 p.m.

This virtual Board meeting is being held consistent with the amendments to the Open Meeting Act, 25 O.S. 2011, § 301 *et seq*, signed into law by Governor Stitt on Wednesday, March 18, 2020. *See* SB661, 2020 O.S.L. 3, § 3

Website: www.nursing.ok.gov
Link to access meeting:
https://obn.webex.com/obn/onstage/g.php?MTID=e97fa9d972fec5d402697141d3cab15f1
Event Number: 146 789 6240
Password: W3Lcome2U!
Dial US: +1-415-655-0001 to join by audio
Access code: 146 789 6240

Link to access meeting materials: http://nursing.ok.gov/facag2020.pdf. The Notice of this meeting was filed with the Secretary of State's Office on November 27, 2019, and was amended on July 22, 2020, and October 13, 2020. Notice/final agenda was posted on October 15, 2020, at 3:30 PM, on the Cameron Building front entrance at 2915 N. Classen Blvd., Oklahoma City, at the Board office Suite 524, and on the Oklahoma Board of Nursing web site.

The Formulary Advisory Council members may discuss, vote to approve, vote to disapprove, vote to table, change the sequence of any agenda item, or vote to strike or not discuss any agenda item.

The following council members are participating remotely via the Cisco Webex Events electronic platform:
Leanna Harkess, APRN-CNP, CNM
Tracy Langley, APRN-CNP
Kathy O'Dell, DNP, RN
Robin Kimball-Potter, APRN-CNS
Jay Kinnard, DPh
Denton Chancey, DPh
JJ Peek, DPh
Kacee Blackwell, DPh
Dr. Jason Regan, DO
Dr. Dana Stone, MD
Dr. Edward Legako, MD

Board staff representatives are:
Gina Stafford, BSN, RN
Jackye Ward, MS, RN

In the event electronic communications are lost or compromised during the meeting, the Oklahoma Board of Nursing will attempt to restore communications for a maximum of (2) two hours. If unable to restore communications the meeting will be adjourned.

1. Call to order
    1.1 Declaration of a quorum (7 members with 2 members from each category)
    1.2 Role of the Council

2. Decision regarding approval of March 14, 2019, meeting minutes **(Attachment #1)**

3. Board Updates: Verbal reports
    3.1 Changes to the *Oklahoma Nursing Practice Act*-Jackye Ward
    3.2 Changes to the *Rules* of the Oklahoma Board of Nursing-Jackye Ward
    3.3 Optimal Regulatory Board System (ORBS)-Jackye Ward
    3.4 Executive Orders related to COVID-19- Jackye Ward
    3.5 FAC membership regarding expiration dates-G. Stafford
    3.6 FAC new membership appointments-G. Stafford

4. Review and recommendations to the Oklahoma Board of Nursing on the *Exclusionary Formulary for Advanced Practice Registered Nurses with Prescriptive Authority*, #P-50B
    - *Exclusionary Formulary for Advanced Practice Registered Nurses with Prescriptive Authority*, #P-50B **(Attachment #2)**

5. Review and recommendations to the Oklahoma Board of Nursing on the *Formulary*
    - *Advisory Council Procedure for Amending the Formulary*, #P-50 **(Attachment #3)**

6. Council decision regarding election of chairperson and vice-chairperson
    6.1 Chairperson
    6.2 Vice-Chairperson

7. Date for next meeting

8. Adjournment

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FORMULARY ADVISORY COUNCIL
Minutes – March 14, 2019

The Formulary Advisory Council to the Oklahoma Board of Nursing met on March 14, 2019. Written notice of the meeting was filed with the Secretary of State's Office on December 11, 2018. Notice was posted on the Oklahoma Board of Nursing web site. A notice agenda was also posted on the Cameron Building front entrance at 2915 North Classen Boulevard, Oklahoma City, Oklahoma, as well as the Board office, Suite 524, March 12, 2019 and not less than 24 hours prior to the meeting.

Place of Meeting: Basement Conference Room, Cameron Building

Time of Meeting: 2:35 PM

Members Present:

Tim Anderson, DPh	Oklahoma Pharmacists Association
Harold Ginzburg, MD, JD, MPH	Oklahoma State Medical Association
L. Harkess, APRN-CNM, APRN-CNP	Oklahoma Board of Nursing
Meri Hix, DPh, BCPS	Oklahoma Pharmacists Association
Susan Jones, APRN- CNS	Oklahoma Board of Nursing
Jay Kinnard, DPh	Oklahoma Pharmacists Association
Robin Potter-Kimball, APRN-CNS	Oklahoma Board of Nursing
Dana Stone, MD	Oklahoma State Medical Association

Members Absent:

Mary Jane Fry, DPh	Oklahoma Pharmacists Association
Deborah Booton-Hiser, APRN-CNP, PhD	Oklahoma Board of Nursing
Robert Holsey, DO, DPh	Oklahoma State Osteopathic Assoc.
Edward Legako, MD	Oklahoma State Medical Association

Guests:

Mandee Davis	Southwestern Oklahoma State University Pharmacy Student
Jordan Hendershot	Southwestern Oklahoma State University Pharmacy Resident

Board Staff Representative:
Jackye Ward, MS, RN
Gina Stafford, BSN, RN

1.0 Call to Order: The meeting was called to order by J. Kinnard, Vice Chairperson, at 2:35 PM.

1.1 Declaration of quorum: A quorum was declared present.

1.2 Role of the Council: J. Kinnard defined the role of the Council.

2.0 Council decision regarding approval of council meeting minutes for August 9, 2018: It was moved (H. Ginzburg) and seconded to approve the minutes of August 9, 2018.

Voting:

Yes:	(7)	T. Anderson, L. Harkess, H. Ginzburg, M. Hix, J. Kinnard, R. Potter-Kimball, D. Stone
No:	(0)	
Absent:	(4)	M. Fry, D. Booton-Hiser, R. Holsey, E. Legako,
Abstain	(1)	S. Jones

Motion carried.

3.0 Verbal reports requiring no action by committee:

3.1 Proposed changes to the *Oklahoma Nursing Practice Act*: J. Ward summarized proposed changes to the *Oklahoma Nursing Practice Act.*

3.2 Proposed changes to the *Rules* of the Oklahoma Board of Nursing: J. Ward summarized proposed changes to the *Rules of the Oklahoma Board of Nursing.*

3.3 Update on the enhanced Nurse Licensure Compact (eNLC): J. Ward provided an update on the eNLC reporting the Agency has processed 4,654 multistate applications since the implementation date for the eNLC.

3.4 FAC member expiration dates: G. Stafford reported the membership terms for Dr. Holsey and T. Anderson have expired. A notification has been sent to the appropriate associations for the appointment of representatives. D. Booton-Hiser has asked to be replaced due to increased responsibilities.

3.5 Update regarding the passage of HR 6, known as *Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act*: G. Stafford reported P.L. 115-271, also known as the *Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act,* became law October 24, 2018. Changes to the federal

law allow for all Advanced Practice Registered Nurse roles to prescribe Buprenorphine to treat Opioid Use Disorder.

3.6 Reduce Opioid Disorder: G. Stafford summarized the website update to include information and resources to help reduce Opioid overdose.

3.7 FAC member expiration dates: G. Stafford summarized the statute [59 O.S. § 567.4a (9)(c)] that allows Members of the Council to continue to serve beyond expiration of their term until a successor is appointed by the original appointing authority.

3.8 Other: no items

4.0 Review and recommendations to the Oklahoma Board of Nursing on the *Exclusionary Formulary for Advanced Practice Registered Nurses with Prescriptive Authority,#P-50B:*

- **Discussion regarding changes**: G. Stafford reported the process for reviewing the *Exclusionary Formulary.* Review included all new drugs assigned classification in the *2018 American Hospital Formulary Service Drug Information Book* since the last meeting, August 9, 2018; and review of all new drugs in the *2019 American Hospital Formulary Service Drug Information Book* to date. The Council reviewed the proposed changes to the formulary. After discussion regarding Buprenorphine related to treatment for Opioid Use Disorder and changes to the federal law, the Council determined Buprenorphine did not need to be placed on the *Exclusionary Formulary.* The *Exclusionary Formulary* authorizes for APRNs to prescribe in accordance with their scope of practice.

It was moved (H. Ginzburg) and seconded to move the *Exclusionary Formulary* with revisions forward to the Board for approval.

Voting:

Yes:	(8)	T. Anderson, H. Ginzburg, L. Harkess, M. Hix, S. Jones, J. Kinnard, R. Potter-Kimball, D. Stone
No:	(0)	
Absent:	(4)	M. Fry, D. Booton-Hiser, R. Holsey, E. Legako

Motion carried.

5.0 Review and recommendations to the Oklahoma Board of Nursing on the *Formulary Advisory Council Procedure for Amending the Formulary*, #P-50: A motion was made (J. Kinnard) and seconded to send the *Request to Amend the*

Formulary without changes to the Board for approval.

Voting:

Yes: (8) T. Anderson, H. Ginzburg, L. Harkess, M. Hix, S. Jones, J. Kinnard, R. Potter-Kimball, D. Stone

No: (0)

Absent: (4) M. Fry, D. Booton-Hiser, R. Holsey, E. Legako

Motion carried.

6.0 Council decision regarding election of chairperson and vice-chairperson:

6.1 Motion made (J. Kinnard) and seconded that Dr. Ginzburg serve as Chairperson.

Voting:

Yes: (8) T. Anderson, H. Ginzburg, L. Harkess, M. Hix, R. Holsey, J. Kinnard, R. Potter-Kimball, D. Stone

No: (0)

Absent: (4) M. Fry, D. Booton-Hiser, S. Jones, E. Legako

Motion carried.

6.2 Motion made (J. Kinnard) and seconded that R. Potter-Kimball serve as Vice Chairman

Voting:

Yes: (8) T. Anderson, H. Ginzburg, L. Harkess, M. Hix, S. Jones, J. Kinnard, R. Potter-Kimball, D. Stone

No: (0)

Absent: (4) M. Fry, D. Booton-Hiser, R. Holsey, E. Legako

Motion carried.

7.0 **Date for next meeting:** Motion made (R. Kimball-Potter) and seconded for the next meeting date for the Formulary Advisory Council to be set for **Thursday, August 13, 2020, at 2:30 PM.**

Voting:

Yes: (8) T. Anderson, H. Ginzburg, L. Harkess, M. Hix, S. Jones, J. Kinnard, R. Potter-Kimball, D. Stone

No: (0)

Absent: (4) M. Fry, D. Booton-Hiser, R. Holsey, E. Legako

Motion carried.

8.0 **Adjournment:** There being no further business, a motion was made for adjournment (R. Potter-Kimball) and seconded. The meeting adjourned at 3:35 p.m.

Voting:

Yes: (8) T. Anderson, H. Ginzburg, L. Harkess, M. Hix, S. Jones , J. Kinnard, R. Potter-Kimball, D. Stone

No: (0)

Absent: (4) M. Fry, D. Booton-Hiser, R. Holsey, E. Legako

Motion carried.

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MEMORANDUM

TO: Formulary Advisory Council

FROM: Gina Stafford, RN
Associate Director for Nursing Practice

DATE: October 5, 2020

RE: *Exclusionary Formulary for Advanced Practice Nurses with Prescriptive Authority,* #P-50B

Attached is the *Exclusionary Formulary*, #50B for your review. As a point of information, the Formulary Advisory Council is a statutory committee responsible for the development and submission to the Board recommendations for an exclusionary formulary which lists drugs or categories of drugs that shall **not** be prescribed by Advanced Practice Registered Nurses. The Board shall either accept or reject the recommendations made by the Council. No amendments to the recommended exclusionary formulary may be made by the Board without the approval of the Formulary Advisory Council [Oklahoma Nurse Practice Act, specifically 59 O.S. §567.4a.9.a]. The Council and the Board shall annually review the approved exclusionary formulary and shall make any necessary revisions utilizing the same procedures used to develop the initial exclusionary formulary. [Oklahoma Nurse Practice Act, specifically 59 O.S. §567.4a.9.d]

Revisions/Rationale: A review of the new drug assignments listed in the *American Society of Health-System Pharmacists American Hospital Formulary Service (AHFS) Drug Information Manual 2020* indicates a need for possible revisions to the *Exclusionary Formulary for Advanced Practice Nurses with Prescriptive Authority*, # 50B.

The proposed changes include:

- Removal of all asterisks, which indicate the drug has been omitted from the print version of *AHFS Drug Information.*
- Ketamine is now included in the *AHFS Drug Information 2020*; therefore, removal of "not in AHFS".
- Adding an exception regarding Ketamine, which would allow the drug to be ordered for pain control by an APRN who is appropriately certified, privileged and credentialed.
- Adding Remimazolam (Byfavo), which is indicated for the induction and maintenance of procedural sedation. Scheduling is pending at this time.

The following items are provided for your review.

- DRAFT *Exclusionary Formulary for Advanced Practice Nurses with Prescriptive Authority*, #P-50B (pages 1-2)
- *AHFS Drug Classifications 2020* (pages 3-5)
- 2020 New Drug Assignments (since our last meeting) (pages 6-13)
- 2020 Drug Reassignments (since our last meeting) (page 14)
- Ketamine 28:04.92- *AHFS Drug Information 2020* (pages 15-23)
- Remimazolam (Byfavo)-FDA Drug information (pages 24-47)

Staff and Others Involved: J. Ward and G. Stafford

Legal Implications: There are no known legal implications with the proposed revisions as attached.

Fiscal Impact: There is no fiscal impact anticipated with the proposed revisions.

Recommendations/Requested Action: The guideline is presented for review and approval with a decision to move forward for Board approval.

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EXCLUSIONARY FORMULARY FOR ADVANCED PRACTICE REGISTERED NURSES WITH PRESCRIPTIVE AUTHORITY

The Advanced Practice Registered Nurse (Certified Nurse Practitioner, Clinical Nurse Specialist and Certified Nurse Midwife) in accordance with Oklahoma Nursing Practice Act, may prescribe medications that are within the Advanced Practice Registered Nurse's scope of practice, under the medical direction of a supervising physician and an Exclusionary Formulary. The Exclusionary Formulary lists medications or categories of medications that shall not be prescribed by the Advanced Practice Registered Nurse with deemed prescriptive authority through the Board. This authorization shall not include dispensing drugs, but shall not preclude, subject to federal regulations, the receipt of, the signing for, or the dispensing of professional samples to patients, in accordance with the Advanced Practice Registered Nurse's scope of practice.

- **All Schedule I and II Controlled Dangerous Substances cannot be prescribed by the Advanced Practice Registered Nurse with prescriptive authority.** [63 O.S. § 2-312.C]
- The Advanced Practice Registered Nurse with prescriptive authority who prescribes Schedule III-IV Controlled Dangerous Substances will comply with State and Federal Drug Enforcement Agency (DEA) prior to prescribing controlled substances. **No more than a 30-day supply for Schedule III-V drugs** shall be prescribed by an Advanced Practice Registered Nurse with prescriptive authority. [485:10-16-5]
- **If prescribing an opioid, the law can be more restrictive.** The Advanced Practice Registered Nurse with prescriptive authority must follow the *Oklahoma Uniform Controlled Dangerous Substance Act* [63 O.S. § 2-309I] when prescribing an opioid.
- Prescriptions will comply with all applicable state and federal laws. [485:10-16-8(a)]

Reference for the Exclusionary Formulary for Classification Purposes: ***American Hospital Formulary Service Drug Information Book*** **(current)**

The Exclusionary Formulary includes:

All Schedule I and II Controlled Dangerous Substances
28:04 **Anesthetics, General** **A. Barbiturates** • Sodium Methohexital (Brevital)* • Sodium Thiopental (Pentothal) (not in AHFS) **B. General Anesthesia Miscellaneous** • Etomidate (Amidate) ➢ **Exception:** May be ordered ONLY for Rapid Sequence Intubation by an APRN who is appropriately certified, privileged and credentialed • Fospropofol (Lusedra) • Ketamine (Ketalar) ~~(not in AHFS)~~ ➢ **Exception**: May be ordered ONLY for pain control by an APRN who is appropriately

certified, privileged and credentialed

- Propofol (Diprivan)

C. Inhalation Anesthetics*~~*~~

All inhalation anesthetics including but not limited to the following:

- Nitrous Oxide
- Cyclopropane
- Ethylene
- Sevoflurane (Ultane)
- Desflurane (Suprane)
- Enflurane (Ethrane)
- Isoflurane (Forane)

28:08 Analgesics

Opiate Agonist

- Opium*~~*~~ (Unless less than 25 mg/dosage unit)

28:16 Psychotherapeutic Agents

- Clozapine
  - **Exception:** May be ordered by an APRN with the appropriate certification, REMS registration and supervised by a qualified physician with REMS registration.

28:24 Anxiolytics, Sedatives, Hypnotics

Benzodiazepines

- Midazolam (Versed)
  - **Exception:** May be ordered ONLY for Rapid Sequence Intubation by an APRN who is appropriately certified, privileged and credentialed
- Remimazolam (Byfavo)

60:00 Gold Compounds

All Gold Compounds including but not limited to:

- Auranofin (Ridaura)*~~*~~
- Aurothioglucose/Gold Sodium Thiomalate (Solganal, Aurolate)*~~*~~

78:00 Radioactive Agents*~~*~~

All Radioactive Agents including but not limited to: Amyvid (not in AHFS)

The Advanced Practice Registered Nurse with prescriptive authority may submit to the Formulary Advisory Council a written request to amend to the Exclusionary Formulary with documentation verifying a practice-specific prescriptive standard(s). (See the *Formulary Advisory Council Procedure for Amending the Formulary* on the Oklahoma Board of Nursing's web site at: http://www.nursing.ok.gov/prac-amndform.pdf

~~*Omitted from the print version of AHFS Drug Information because of space limitations. Updated drug information available on AHFS Drug Information website at: http://www.ahfsdruginformation.com~~

AHFS® PHARMACOLOGIC-THERAPEUTIC CLASSIFICATION©

0:01 Front Matter

4:00 Antihistamine Drugs

- 4:04 First Generation Antihistamines
  - 4:04.04 Ethanolamine Derivatives*
  - 4:04.08 Ethylenediamine Derivatives*
  - 4:04.12 Phenothiazine Derivatives*
  - 4:04.16 Piperazine Derivatives*
  - 4:04.20 Propylamine Derivatives*
  - 4:04.92 Miscellaneous Derivatives*
- 4:08 Second Generation Antihistamines
- 4:92 Other Antihistamines*

8:00 Anti-infective Agents

- 8:08 Anthelmintics
- 8:12 Antibacterials
  - 8:12.02 Aminoglycosides
  - 8:12.06 Cephalosporins
    - 8:12.06.04 First Generation Cephalosporins
    - 8:12.06.08 Second Generation Cephalosporins
    - 8:12.06.12 Third Generation Cephalosporins
    - 8:12.06.16 Fourth Generation Cephalosporins
    - 8:12.06.20 Fifth Generation Cephalosporins
    - 8:12.06.28 Siderophore Cephalosporins*
  - 8:12.07 Miscellaneous β-Lactams
    - 8:12.07.04 Carbacephems*
    - 8:12.07.08 Carbapenems
    - 8:12.07.12 Cephamycins
    - 8:12.07.16 Monobactams
  - 8:12.08 Chloramphenicol
  - 8:12.12 Macrolides
    - 8:12.12.04 Erythromycins
    - 8:12.12.12 Ketolides*
    - 8:12.12.92 Other Macrolides
  - 8:12.16 Penicillins
    - 8:12.16.04 Natural Penicillins
    - 8:12.16.08 Aminopenicillins
    - 8:12.16.12 Penicillinase-resistant Penicillins
    - 8:12.16.16 Extended-spectrum Penicillins
  - 8:12.18 Quinolones
  - 8:12.20 Sulfonamides
  - 8:12.24 Tetracyclines
    - 8:12.24.04 Aminomethylcyclines
    - 8:12.24.08 Fluorocyclines
    - 8:12.24.12 Glycylcyclines
  - 8:12.28 Antibacterials, Miscellaneous
    - 8:12.28.04 Aminocyclitols*
    - 8:12.28.08 Bacitracins
    - 8:12.28.12 Cyclic Lipopeptides
    - 8:12.28.16 Glycopeptides
    - 8:12.28.20 Lincomycins
    - 8:12.28.24 Oxazolidinones
    - 8:12.28.26 Pleuromutilins
    - 8:12.28.28 Polymyxins
    - 8:12.28.30 Rifamycins
    - 8:12.28.32 Streptogramins
    - 8:12.28.92 Other Miscellaneous Antibacterials*
- 8:14 Antifungals
  - 8:14.04 Allylamines
  - 8:14.08 Azoles
  - 8:14.16 Echinocandins
  - 8:14.28 Polyenes
  - 8:14.32 Pyrimidines
  - 8:14.92 Antifungals, Miscellaneous
- 8:16 Antimycobacterials
  - 8:16.04 Antituberculosis Agents
  - 8:16.92 Antimycobacterials, Miscellaneous
- 8:18 Antivirals
  - 8:18.04 Adamantanes
  - 8:18.08 Antiretrovirals
    - 8:18.08.04 HIV Entry and Fusion Inhibitors
    - 8:18.08.08 HIV Protease Inhibitors
    - 8:18.08.12 HIV Integrase Inhibitors
    - 8:18.08.16 HIV Nonnucleoside Reverse Transcriptase Inhibitors
    - 8:18.08.20 HIV Nucleoside and Nucleotide Reverse Transcriptase Inhibitors
    - 8:18.08.92 Antiretrovirals, Miscellaneous*
  - 8:18.20 Interferons
  - 8:18.24 Monoclonal Antibodies
  - 8:18.28 Neuraminidase Inhibitors
  - 8:18.32 Nucleosides and Nucleotides
  - 8:18.40 HCV Antivirals
    - 8:18.40.04 HCV Cyclophilin Inhibitors*
    - 8:18.40.08 HCV Entry Inhibitors*
    - 8:18.40.16 HCV Polymerase Inhibitors
    - 8:18.40.20 HCV Protease Inhibitors
    - 8:18.40.24 HCV Replication Complex Inhibitors
    - 8:18.40.92 HCV Antivirals, Miscellaneous*
  - 8:18.92 Antivirals, Miscellaneous
- 8:30 Antiprotozoals
  - 8:30.04 Amebicides
  - 8:30.08 Antimalarials
  - 8:30.92 Antiprotozoals, Miscellaneous
- 8:36 Urinary Anti-infectives
- 8:92 Anti-infectives, Miscellaneous*

10:00 Antineoplastic Agents

12:00 Autonomic Drugs

- 12:04 Parasympathomimetic (Cholinergic) Agents
- 12:08 Anticholinergic Agents
  - 12:08.04 Antiparkinsonian Agents*
  - 12:08.08 Antimuscarinics/Antispasmodics
- 12:12 Sympathomimetic (Adrenergic) Agents
  - 12:12.04 α-Adrenergic Agonists
  - 12:12.08 β-Adrenergic Agonists
    - 12:12.08.04 Nonselective β-Adrenergic Agonists
    - 12:12.08.08 Selective β_1-Adrenergic Agonists
    - 12:12.08.12 Selective β_2-Adrenergic Agonists
  - 12:12.12 α- and β-Adrenergic Agonists
- 12:16 Sympatholytic (Adrenergic Blocking) Agents
  - 12:16.04 α-Adrenergic Blocking Agents
    - 12:16.04.04 Nonselective α-Adrenergic Blocking Agents
    - 12:16.04.08 Nonselective α_1-Adrenergic Blocking Agents*
    - 12:16.04.12 Selective α_1-Adrenergic Blocking Agents
  - 12:16.08 β-Adrenergic Blocking Agents*
    - 12:16.08.04 Nonselective β-Adrenergic Blocking Agents*
    - 12:16.08.08 Selective β-Adrenergic Blocking Agents*
- 12:20 Skeletal Muscle Relaxants
  - 12:20.04 Centrally Acting Skeletal Muscle Relaxants
  - 12:20.08 Direct-acting Skeletal Muscle Relaxants
  - 12:20.12 GABA-derivative Skeletal Muscle Relaxants
  - 12:20.20 Neuromuscular Blocking Agents
  - 12:20.92 Skeletal Muscle Relaxants, Miscellaneous
- 12:92 Autonomic Drugs, Miscellaneous

16:00 Blood Derivatives

20:00 Blood Formation, Coagulation, and Thrombosis

- 20:04 Antianemia Drugs
  - 20:04.04 Iron Preparations
  - 20:04.08 Liver and Stomach Preparations*
- 20:12 Antithrombotic Agents
  - 20:12.04 Anticoagulants
    - 20:12.04.08 Coumarin Derivatives
    - 20:12.04.12 Direct Thrombin Inhibitors
    - 20:12.04.14 Direct Factor Xa Inhibitors
    - 20:12.04.16 Heparins
    - 20:12.04.92 Anticoagulants, Miscellaneous
  - 20:12.14 Platelet-reducing Agents
  - 20:12.18 Platelet-aggregation Inhibitors
  - 20:12.20 Thrombolytic Agents
  - 20:12.92 Antithrombotic Agents, Miscellaneous
- 20:16 Hematopoietic Agents
- 20:24 Hemorrheologic Agents
- 20:28 Antihemorrhagic Agents
  - 20:28.08 Antiheparin Agents
  - 20:28.16 Hemostatics
  - 20:28.92 Antihemorrhagic Agents, Miscellaneous
- 20:92 Blood Formation, Coagulation, and Thrombosis Agents, Miscellaneous

24:00 Cardiovascular Drugs

- 24:04 Cardiac Drugs
  - 24:04.04 Antiarrhythmic Agents
    - 24:04.04.04 Class Ia Antiarrhythmics
    - 24:04.04.08 Class Ib Antiarrhythmics
    - 24:04.04.12 Class Ic Antiarrhythmics
    - 24:04.04.16 Class II Antiarrhythmics*
    - 24:04.04.20 Class III Antiarrhythmics
    - 24:04.04.24 Class IV Antiarrhythmics
    - 24:04.04.92 Antiarrhythmics, Miscellaneous
  - 24:04.08 Cardiotonic Agents
  - 24:04.92 Cardiac Drugs, Miscellaneous
- 24:06 Antilipemic Agents
  - 24:06.04 Bile Acid Sequestrants
  - 24:06.05 Cholesterol Absorption Inhibitors
  - 24:06.06 Fibric Acid Derivatives
  - 24:06.08 HMG-CoA Reductase Inhibitors
  - 24:06.24 Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors
  - 24:06.92 Antilipemic Agents, Miscellaneous
- 24:08 Hypotensive Agents
  - 24:08.04 α-Adrenergic Blocking Agents*
  - 24:08.08 β-Adrenergic Blocking Agents*
  - 24:08.12 Calcium-Channel Blocking Agents*
    - 24:08.12.08 Dihydropyridines*
    - 24:08.12.92 Calcium-Channel Blocking Agents, Miscellaneous*
  - 24:08.16 Central α-Agonists
  - 24:08.20 Direct Vasodilators
  - 24:08.24 Diuretics*
    - 24:08.24.04 Carbonic Anhydrase Inhibitors*
    - 24:08.24.08 Loop Diuretics*
    - 24:08.24.12 Osmotic Diuretics*
    - 24:08.24.16 Potassium-sparing Diuretics*
    - 24:08.24.20 Thiazide Diuretics*
    - 24:08.24.24 Thiazide-like Diuretics*
    - 24:08.24.92 Diuretics, Miscellaneous*
  - 24:08.32 Peripheral Adrenergic Inhibitors

26:00 Cellular Therapy*

28:00 Central Nervous System Agents

32:00 Contraceptives (foams, devices)*

34:00 Dental Agents*

36:00 Diagnostic Agents

38:00 Disinfectants (for agents used on objects other than skin)*

40:00 Electrolytic, Caloric, and Water Balance

44:00 Enzymes

48:00 Respiratory Tract Agents

* Category is currently not in use in the printed version of *AHFS Drug Information®*.

DrugAssignments

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Alkindi® Sprinkle	hydrocortisone	Diurnal	replacement therapy in pediatric patients with adrenocortical insufficiency	2020/09/29	68:04 - Adrenals	3S	213876
Xeljanz® Oral Solution	tofacitinib citrate	Pfizer	RA, PsA, UC, JIA	2020/09/25	92:36 - Disease-modifying Antirheumatic Drugs	3P	213082
Gavreto®	pralsetinib	Blueprint Medicines	metastatic rearranged during transfection (RET) fusion- positive nonsmall cell lung cancer (NSCLC)	2020/09/04	10:00 - Antineoplastic Agents	1P/O	213721
Detectnet®	copper CU-64 dotatate	Radiomedix	with PET for localization of somatostatin receptor positive neuroendocrine tumors (NETs)	2020/09/03	36:68 - Roentgenographic and Other Imaging Agents	1P/O	213227
Onureg®	azacitidine	Celgene	acute myeloid leukemia	2020/09/01	10:00 - Antineoplastic Agents	3P/O	214120
Qdolo®	tramadol hydrochloride	Athena	pain	2020/09/01	28:08.08 - Opiate Agonists	3S	214044
Xaracoll®	bupivacaine hydrochloride	Innocoll	postsurgical analgesia for up to 24 hours following open inguinal hernia repair	2020/08/28	72:00 - Local Anesthetics	3S	209511
Sogroya®	somapacitan-beco	Novo Nordisk	growth hormone deficiency	2020/08/28	68:28 - Pituitary		761156
Winlevi®	clascoterone	Cassiopea	acne vulgaris	2020/08/26	84:92 - Skin and Mucous Membrane Agents, Misc	1S	213433
Kesimpta®	ofatumumab	Novartis	relapsing forms of multiple sclerosis (MS)	2020/08/20	92:20 - Immunomodulatory Agents		125326
Cystadrops®	cysteamine hydrochloride	Recordati	corneal cystine crystal deposits in adults and children with cystinosis	2020/08/19	52:92 - EENT Drugs, Misc	5S	211302
Enspryng®	satralizumab-mwge	Genentech	neuromyelitis optica spectrum disorder (NMOSD)	2020/08/14	92:20 - Immunomodulatory Agents		761149
Viltepso®	viltolarsen	NS Pharma	Duchenne muscular dystrophy (DMD)	2020/08/12	92:18 - Antisense Oligonucleotides	1P	212154
Olinvyk®	oliceridine	Trevena	acute pain	2020/08/07	28:08.08 - Opiate Agonists	1S	210730
Evrysdi®	risdiplam	Genentech	spinal muscular atrophy (SMA)	2020/08/07	92:92 - Other Miscellaneous Therapeutic Agents	1P/O	213535
Lampit®	nifurtimox	Bayer	Chagas disease (American Trypanosomiasis)	2020/08/06	8:30.92 - Antiprotozoals, Misc	1P	213464
Blenrep®	belantamab mafodotin-blmf	GlaxoSmithKline	relapsed or refractory multiple myeloma	2020/08/05	10:00 - Antineoplastic Agents		761158
Monjuvi®	tafasitamab-cxix	Morphosys	diffuse large B-cell lymphoma (DLBCL)	2020/07/31	10:00 - Antineoplastic Agents		761163
Xeglyze®	abametapir	Dr. Reddy's	head lice	2020/07/24	84:04.12 - Scabicides and Pediculicides	1S	206966
Tecartus®	brexucabtagene autoleucel	Kite Pharma	relapsed/refractory mantle cell lymphoma (r/r MCL)	2020/07/24	10:00 - Antineoplastic Agents; 26:12 - Gene Therapy		125703
Breztri Aerosphere®	budesonide; formoterol fumarate; glycopyrrolate	AstraZeneca	chronic obstructive pulmonary disease (COPD)	2020/07/23	68:04 - Adrenals; 12:12.08.12 - Selective beta-2-Adrenergic Agonists; 12:08.08 - Antimuscarinics/Antispasmodics	5S	212122
Xywav® (CIII)	calcium; magnesium; potassium; sodium oxybates	Jazz	cataplexy or excessive daytime sleepiness (EDS)	2020/07/21	28:92 - Central Nervous System Agents, Misc	1P	212690
Wynzora®	calcipotriene; betamethasone dipropionate	MC2 Therapeutics	plaque psoriasis	2020/07/20	84:92 - Skin and Mucous Membrane Agents, Misc; 84:06.08 - Corticosteroids	5S	213422
Upneeq®	oxymetazoline hydrochloride	RVL Pharma	acquired blepharoptosis	2020/07/08	52:32 - Vasoconstrictors	S	212520
Inqovi®	cedazuridine; decitabine	Astex	myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML)	2020/07/07	10:00 - Antineoplastic Agents	1P	212576
Qwo®	collagenase clostridium histolyticum-aaes	Endo	moderate to severe cellulite	2020/07/06	44:00 - Enzymes		761146
Hulio®	adalimumab-fkjp	Mylan	RA, JIA, PsA, AS, CD, UC, Ps	2020/07/06	92:20 - Immunomodulatory Agents		761154

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Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Byfavo®	remimazolam	Cosmo	induction and maintenance of procedural sedation	2020/07/02	28:24.08 - Benzodiazepines	1P	212295
Tralement®	trace elements 4 (cupric sulfate; manganese sulfate; selenious acid; zinc sulfate)	American Reagent	parenteral nutrition	2020/07/02	40:12 - Replacement Preparations	4S	209376
Rukobia®	fostemsavir tromethamine	Viiv	HIV-1 infection	2020/07/02	8:18.08.04 - HIV Entry and Fusion Inhibitors	1P	212950
Dojolvi®	triheptanoin	Ultragenyx	caloric and fatty acid replacement with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)	2020/06/30	40:20 - Caloric Agents	1S	213687
Phesgo®	pertuzumab; trastuzumab; hyaluronidase-zzxf	Genentech	HER2-positive breast cancer	2020/06/29	10:00 - Antineoplastic Agents		761170
Mycapssa®	octreotide	Chiasma	acromegaly	2020/06/26	68:29.04 - Somatostatin Agonists	5S/O	208232
Fintepla®	fenfluramine	Zogenix	seizures associated with Dravet syndrome	2020/06/25	28:12.92 - Anticonvulsants, Misc	3P	212102
Gimoti®	metoclopramide hydrochloride	Evoke	acute and recurrent diabetic gastroparesis	2020/06/19	56:32 - Prokinetic Agents	3/4S	209388
Zepzelca®	lurbinectedin	Pharma Mar	metastatic small cell lung cancer (SCLC)	2020/06/15	10:00 - Antineoplastic Agents	1P/O	213702
Lyumjev®	insulin lispro-aabc	Eli Lilly	diabetes mellitus	2020/06/15	68:20.08.04 - Rapid-acting Insulins		761109
Tivicay PD®	dolutegravir	Viiv	HIV-1 infection in pediatric patients	2020/06/12	8:18.08.12 - HIV Integrase Inhibitors	3P	213983
Uplizna®	inebilizumab-cdon	Viela Bio	neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive	2020/06/11	92:20 - Immunomodulatory Agents		761142
Semglee®	insulin glargine	Mylan	diabetes mellitus	2020/06/11	68:20.08.16 - Long-acting Insulins		210605
Nyvepria®	pegfilgrastim-apgf	Hospira	febrile neutropenia	2020/06/10	20:16 - Hematopoietic Agents		761111
Oriahnn®	elagolix; estradiol; norethindrone acetate	Abbvie	heavy menstrual bleeding associated with uterine leiomyomas (fibroids)	2020/05/29	68:18.04 - Antigonadotropins; 68:16.04 - Estrogens; 68:32 - Progestins	4S	213388
Tauvid®	flortaucipir F18	Avid Radiopharms	PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD)	2020/05/28	36:68 - Roentgenographic and Other Imaging Agents	1P	212123
Zilxi®	minocycline	Foamix	inflammatory lesions of rosacia	2020/05/28	84:04.04 - Antibacterials	5S	213690
Artesunate	artesunate	Amivas	acute malarial infection	2020/05/27	8:30.08 - Antimalarials	1P	213036
VESIcare LS®	solifenacin succinate	Astellas	neurogenic detrusor overactivity (bladder dysfunction)	2020/05/26	86:12.04 - Antimuscarinics	3S	209529
Phexxi®	lactic acid; citric acid; potassium bitartrate	Evofem	contraception	2020/05/22	32:00 - Nonhormonal Contraceptives	3S	208352
Kynmobi®	apomorphine hydrochloride	Sunovion	acute, intermittent treatment of "off" episodes in patients with Parkinson's disease	2020/05/21	28:36.20.08 - Nonergot-derivative Dopamine Receptor Agonists	3S	210875
Cerianna®	fluoroestradiol F18	Zionexa	PET imaging for the detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer	2020/05/20	36:68 - Roentgenographic and Other Imaging Agents	1S	212155

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Ferriprox®	deferiprone	Apopharma	transfusional iron overload due to thalassemia syndromes	2020/05/19	64:00 - Heavy Metal Antagonists	5S	212269
Impeklo®	clobetasol propionate	Mylan	inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	2020/05/19	84:06.08 - Corticosteroids	5S	213691
Qinlock®	ripretinib	Deciphera	gastrointestinal stromal tumor (GIST) (fourth-line treatment)	2020/05/15	10:00 - Antineoplastic Agents	1S	213973
Retevmo®	selpercatinib	Loxo Oncology	RET fusion-positive non-small cell lung cancer (NSCLC) or thyroid cancer; RET-mutant medullary thyroid cancer (MTC)	2020/05/08	10:00 - Antineoplastic Agents	1P	213246
Tabrecta®	capmatinib	Novartis	metastatic non-small cell lung cancer (NSCLC) (with MET exon 14 skipping mutation)	2020/05/06	10:00 - Antineoplastic Agents	1P	213591
Elyxyb®	celecoxib	Dr Reddy's	acute migraine headaches	2020/05/05	28:08.04.08 - Cyclooxygenase-2 (COX-2) Inhibitors	3S	212157
Fensolvi®	leuprolide acetate	Tolmar	central precocious puberty	2020/05/01	68:18.08 - Gonadotropins	10S	213150
Darzalex Faspro®	daratumumab; hyaluronidase-fihj	Janssen	multiple myeloma	2020/05/01	10:00 - Antineoplastic Agents		761145
Veklury®	remdesivir	Gilead	covid-19 (FDA Emergency Use Authorization)	2020/05/01	8:18.32 - Nucleosides and Nucleotides		EUA
Milprosa®	progesterone	Ferring	infertility	2020/04/29	68:32 - Progestins	3S	201110
Bafiertem™	monomethyl fumarate	Banner Life Sciences	multiple sclerosis	2020/04/28	92:20 - Immunomodulatory Agents	2S	210296
Ongentys®	opicapone	Neurocrine	Parkinson's Disease	2020/04/24	28:36.12 - Catechol-O-Methyltransferase (COMT) Inhibitors	1S	212489
Trodelvy®	sacituzumab govitecan-hziy	Immunomedics	metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease	2020/04/22	10:00 - Antineoplastic Agents		761115
Tukysa®	tucatinib	Seattle Genetics	unresectable or metastatic HER2-positive breast cancer	2020/04/17	10:00 - Antineoplastic Agents	1S	213411
Pemazyre®	pemigatinib	Incyte	previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion	2020/04/17	10:00 - Antineoplastic Agents	1S	213736
Emerphed®	ephedrine sulfate	Nexus	anesthesia-induced hypotension	2020/04/17	12:12.12 - alpha- and beta-Adrenergic Agonists	5S	213407
Jelmyto®	mitomycin	Urogen	low-grade upper tract urothelial cancer (LG-UTUC)	2020/04/15	10:00 - Antineoplastic Agents	5S	211728
Koselugo®	selumetinib	AstraZeneca	neurofibromatosis type 1 (NF1)	2020/04/10	10:00 - Antineoplastic Agents	1P	213756
Zeposia®	ozanimod	Celgene	multiple sclerosis (MS)	2020/03/25	92:20 - Immunomodulatory Agents	1S	209899
Pulmotech MAA®	technetium Tc99m albumin aggregated	Cis Bio	lung scintigraphy; scintigraphy of peritoneovenous shunt	2020/03/20	36:68 - Roentgenographic and Other Imaging Agents	5S	210089
Fluorescien; Benoxinate	fluorescien sodium; benoxinate hydrochloride	Bausch	tonometry, gonioscopy	2020/03/09	36:58 - Ocular Disorders; 52:16 - Local Anesthetics	4S	211039
Isturisa®	osilodrostat	Novartis	Cushing's disease	2020/03/06	92:92 - Other Miscellaneous Therapeutic Agents	1S	212801
Durysta®	bimatoprost	Allergan	open angle glaucoma (OAG) or ocular hypertension (OHT)	2020/03/04	52:40.28 - Prostaglandin Analogs	3S	211911
Sarclisa®	isatuximab-irfc	Sanofi Aventis	multiple myeloma	2020/03/02	10:00 - Antineoplastic Agents		761113

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Nurtec ODT®	rimegepant	Biohaven	migraine headaches	2020/02/27	28:32.12 - Calcitonin Gene-related Peptide (CGRP) Antagonists	1P	212728
Barhemsys®	amisulpride	Acacia	postoperative nausea and vomiting (PONV)	2020/02/26	56:22.92 - Antiemetics, Misc	1S	209510
Nexlizet®	bempedoic acid; ezetimibe	Esperion	heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease	2020/02/26	24:06.92 - Antilipemic Agents, Misc; 24:06.05 - Cholesterol Absorption Inhibitors	1/4S	211617
Nexletol®	bempedoic acid	Esperion	heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease	2020/02/21	24:06.92 - Antilipemic Agents, Misc	1S	211616
Vyepti®	eptinezumab-jjmr	Lundbeck	migraine headaches	2020/02/21	28:32.12 - Calcitonin Gene-related Peptide (CGRP) Antagonists		761119
Anjeso®	meloxicam	Baudax Bio	moderate-to-severe pain	2020/02/20	28:08.04.92 - Other Nonsteroidal Anti-inflammatory Agents	3S	210583
Twirla®	ethinyl estradiol; levonorgestrel	Agile	birth control	2020/02/14	68:12 - Contraceptives	3S	204017
Procysbi® Granules	cysteamine bitartrate	Horizon	nephropathic cystinosis	2020/02/14	92:92 - Other Misc Therapeutic Agents	5S	213491
Pizensy®	lactitol monohydrate	Braintree	chronic idiopathic constipation (CIC)	2020/02/12	56:12 - Cathartics and Laxatives	1S	211281
Pemfexy®	pemetrexed	Eagle Pharms	recurrent, metastatic non-squamous, non-small cell lung cancer (NSCLC); malignant pleural mesothelioma	2020/02/08	10:00 - Antineoplastic Agents	5S	209472
Palforzia®	peanut (Arachis hypogaea) allergen powder-dnfp	Aimmune Therapeutics	mitigation of allergic reactions that may occur with accidental peanut exposure	2020/01/31	80:02 - Allergenic Extracts		125696
Benfezia Pen®	octreotide	Sun Pharm	acromegaly; severe diarrhea/flushing episodes associated with metastatic carcinoid tumors; profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas)	2020/01/28	68:29.04 - Somatostatin Agonists	5S	213224
Trijardy XR®	empagliflozin; linagliptin; metformin	Boehringer Ingelheim	type 2 diabetes mellitus	2020/01/27	68:20.18 - SGLT2 Inhibitors; 68:20.05 - DPP-4 Inhibitors; 68:20.04 - Biguanides	4S	212614
Tazverik®	tazemetostat	Epizyme	metastatic or locally advanced epithelioid sarcoma not eligible for complete resection	2020/01/23	10:00 - Antineoplastic Agents	1P	211723
Tepezza®	teprotumumab-trbw	Horizon Therapeutics	thyroid eye disease	2020/01/21	52:92 - EENT Drugs, Miscellaneous	1O/P	761143
Monoferric®	ferric derisomaltose	Pharmacosmos	iron deficiency anemia	2020/01/16	20:04.04 - Iron Preparations	5S	208171
Rybelsus®	semaglutide	Novo Nordisk	diabetes mellitus	2020/01/16	68:20.06 - Incretin Mimetics	9S	213182
Numbrino®	cocaine	Cody Labs	local anesthesia	2020/01/10	52:16 - Local Anesthetics	7S	209575
Valtoco®	diazepam	Neurelis	seizures	2020/01/10	28:12.08 - Benzodiazepines	3S	211635
Ayvakit®	avapritinib	Blueprint Medicines	gastrointestinal stromal tumor (GIST)	2020/01/09	10:00 - Antineoplastic Agents	1P	212608
Ubrelvy®	ubrogepant	Allergan	migraine headaches	2019/12/23	28:32.12 - Calcitonin Gene-related Peptide (CGRP) Antagonists	1S	211765
Genosyl®	nitric oxide	Vero	hypoxic respiratory failure due to pulmonary hypertension	2019/12/20	24:12.08 - Nitrates and Nitrites	5S	202860
Caplyta®	lumateperone	Intra-cellular Therapies	schizophrenia	2019/12/20	28:16.08.04 - Atypical Antipsychotics	1S	209500
TissueBlue®	brilliant blue G (BBG)	Dutch Ophthalmic	selectively stain the internal limiting membrane	2019/12/20	36:58 - Ocular Disorders	1P	209569
Dayvigo®	lemborexant	Eisai	insomnia	2019/12/20	28:24.92 - Anxiolytics, Sedatives, and Hypnotics; Misc	1S	212028

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Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Enhertu®	fam-trastuzumab deruxtecan-nxki	Daiichi Sankyo	HER2+ breast cancer	2019/12/20	10:00 - Antineoplastic Agents		761139
Ervebo®	ebola Zaire vaccine, live	Merck	prevention of disease caused by Zaire ebolavirus	2019/12/19	80:12 - Vaccines		125690
Conjupri®	levamlodipine	CSPC Ouyi Pharma	hypertension	2019/12/19	24:28.08 - Dihydropyridines	2/3S	212895
Padcev®	enfortumab vedotin-ejfv	Astellas	advanced urothelial cancer	2019/12/18	10:00 - Antineoplastic Agents		761137
Arazlo®	tazarotene	Dow	acne vulgaris	2019/12/18	84:92 - Skin and Mucous Membrane Agents, Misc	3S	211882
Nouress®	cysteine hydrochloride	Avadel	total parenteral nutrition	2019/12/13	40:12 - Replacement Preparations	5S	212535
Vyondys 53®	golodirsen	Sarepta	Duchenne muscular dystrophy (DMD)	2019/12/12	92:18 - Antisense Oligonucleotides	1P	211970
Avsola®	infliximab-axxq	Amgen	RA, JIA, PsA, AS, CD, pCD, UC, pUC, Ps	2019/12/06	92:36 - Disease-modifying Antirheumatic Drugs; 92:20 - Immunomodulatory Agents; 56:92 - GI Drugs, Misc; 84:92 - Skin and Mucous Membrane Agents, Misc		761086
Reditrex®	methotrexate	Cumberland	RA, pJIA, PA	2019/11/27	92:20 - Immunomodulatory Agents	5S	210737
Oxbryta®	voxelotor	Global Blood Therapeutics	sickle cell disease (SCD)	2019/11/25	20:92 - Blood Formation, Coagulation, and Thrombosis Agents, Misc	1S	213137
Exservan®	riluzole	Aquestive	amyotrophic lateral sclerosis (ALS)	2019/11/22	28:92 - Central Nervous System Agents, Misc	3S/O	212640
Xcopri®	cenobamate	SK Life	partial-onset seizures	2019/11/21	28:12.92 - Anticonvulsants, Misc	1S	212839
Givlaari®	givosiran	Alnylam	acute hepatic porphyria	2019/11/20	92:92 - Other Miscellaneous Therapeutic Agents	1P/O	212194
Abrilada®	adalimumab-afzb	Pfizer	RA, JIA, PsA, AS, CD, UC, Ps	2019/11/15	92:36 - Disease-modifying Antirheumatic Drugs; 92:20 - Immunomodulatory Agents; 56:92 - GI Drugs, Misc		761118
Adakveo®	crizanlizumab-tmca	Novartis	vaso-occlusive crisis assoc with sickle cell disease	2019/11/15	20:92 - Blood Formation, Coagulation, and Thrombosis Agents, Misc		761128
Brukinsa®	zanubrutinib	Beigene	mantle cell lymphoma (MCL)	2019/11/14	10:00 - Antineoplastic Agents	1P/O	213217
Fetroja®	cefiderocol sulfate tosylate	Shionogi	complicated urinary tract infections (cUTI)	2019/11/14	8:12.06.28 - Siderophore Cephalosporins (NEW)	1P	209445
Reblozyl®	luspatercept-aamt	Celgene	anemia due to beta thalassemia	2019/11/08	20:16 - Hematopoietic Agents		761136
ExEm Foam®	air polymer-type A	Giskit	sonohysterosalpingography	2019/11/07	36:68 - Roentgenographic and Other Imaging Agents	1S	212279
Absorica®	isotretinoin	Sun	severe recalcitrant nodular acne	2019/11/05	84:92 - Skin and Mucous Membrane Agents, Misc	S	211913
Talicia®	omeprazole; amoxicillin; rifabutin	Redhill	Helicobacter pylori infection	2019/11/04	56:28.92 - Antiulcer Agents and Acid Suppressants, Misc	4P	213004
Ziextenzo®	pegfilgrastim-bmez	Sandoz	chemotherapy-induced neutropenia	2019/11/04	20:16 - Hematopoietic Agents		761045
Vumerity®	diroximel fumarate	Alkermes	relapsing-remitting multiple sclerosis (MS)	2019/10/29	92:20 - Immunomodulatory Agents	2S	211855
Trikafta®	elexacaftor, tezacaftor, ivacaftor	Vertex	cystic fibrosis (CF)	2019/10/21	48:14.04 - Cystic Fibrosis Transmembrane Conductance Regulator Correctors (1); 48:14.12 - Cystic Fibrosis Transmembrane Conductance Regulator Potentiators (2)	1P/O	212273
Biorphen®	phenylephrine	Sintetica	clinically important hypotension resulting primarily from vasodilation during anesthesia	2019/10/21	12:12.04 - alpha-Adrenergic Agonists	5S	212909
Amzeeq®	minocycline topical foam	Foamix	acne vulgaris	2019/10/18	84:04.04 - Antibacterials	3S	212379
Reyvow®	lasmiditan	Eli Lilly	migraine headaches	2019/10/11	28:32.28 - Selective Serotonin Agonists	1S	211280
Secuado®	asenapine transdermal system	Hisamitsu	schizophrenia and bipolar disorder	2019/10/11	28:16.08.04 - Atypical Antipsychotics	3S	212268

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Fluorodopa F18®	fluorodeoxyphenylalanine	Feinstein	positron emission tomography (PET) in diagnosing Parkinsonian Syndrome(PS)	2019/10/10	36:68 - Roentgenographic and Other Imaging Agents	1S	200655
Scenesse®	afamelanotide	Clinuvel	prevent phototoxic reactions related to erythropoietic protoporphyria	2019/10/08	84:92 - Skin and Mucous Membrane Agents, Misc	1P/O	210797
Beovu®	brolucizumab-dbll	Novartis	wet age-related macular degeneration (AMD)	2019/10/07	52:92 - EENT Drugs, Misc		761125
Quzyttir®	cetirizine	JDP	acute urticaria	2019/10/04	4:08 - Second Generation Antihistamines	3S	211415
Aklief®	trifarotene	Galderma	acne vulgaris	2019/10/04	84:92 - Skin and Mucous Membrane Agents, Misc	1S	211527
Bonsity®	teriparatide	Pfenex	osteoporosis	2019/10/04	68:24.08 - Parathyroid Agents	5S	211939
Hemady®	dexamethasone	Dexcel	multiple myeloma	2019/10/03	68:04 - Adrenals	1S/O	211379
Jynneos®	Smallpox and Monkeypox Vaccine Live	Bavarian Nordic	prevention of smallpox and monkeypox disease	2019/09/24	80:12 - Vaccines		125678
Rybelsus®	semaglutide	Novo Nordisk	type 2 diabetes mellitus	2019/09/20	68:20.06 - Incretin Mimetics	3P	213051
Ozobax®	baclofen	Metacel	spasticity resulting from multiple sclerosis	2019/09/18	12:20.12 - GABA-derivative Skeletal Muscle Relaxants	3S	208193
Ibsrela®	tenapanor	Ardelyx	irritable bowel syndrome with constipation (IBS-C)	2019/09/12	56:92 - GI Drugs, Misc	1S	211801
Gvoke®	glucagon	Xeris	severe hypoglycemia	2019/09/10	68:22.12 - Glycogenolytic Agents	3S	212097
Nourianz®	istradefylline	Kyowa Kirin	add-on treatment for Parkinson's disease	2019/08/27	28:92 - CNS Agents, Miscellaneous	1S	022075
Gallium Ga-68 Dotatoc	gallium Ga-68 dotatoc	University of Iowa	use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs)	2019/08/21	36:68 - Roentgenographic and Other Imaging Agents	1S	210828
Xenleta®	lefamulin acetate	Nabriva	community-acquired bacterial pneumonia (CABP)	2019/08/19	8:12.28.26 - Pleuromutilins	1P	211672
Inrebic®	fedratinib	Impact	intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)	2019/08/16	10:00 - Antineoplastic Agents	1S	212327
Rinvoq®	upadacitinib	Abbvie	rheumatoid arthritis	2019/08/16	92:36 - Disease-modifying Antirheumatic Drugs	1S	211675
Rozlytrek®	entrectinib	Genentech	cancers with NTRK gene fusion; metastatic ROS1+ non-small cell lung cancer	2019/08/15	10:00 - Antineoplastic Agents	1P	212725
Wakix®	pitolisant	Bioprojet	excessive daytime sleepiness (EDS) with narcolepsy	2019/08/14	28:20.80 - Wakefulness-promoting Agents	1S	211150
Pretomanid	pretomanid	Global Alliance for TB Drug Development	drug-resistant tuberculosis	2019/08/14	8:16.04 - Antituberculosis Agents	1P	212862
Turalio®	pexidartinib	Daiichi	symptomatic tenosynovial giant cell tumor (TGCT)	2019/08/02	10:00 - Antineoplastic Agents	1P	211810
Nubeqa®	darolutamide	Bayer	non-metastatic castration-resistant prostate cancer	2019/07/30	10:00 - Antineoplastic Agents	1P	212099
Angiomax RTU®	bivalirudin	Maia	acute ischemic complications of PCI; heparin-induced thrombocytopenia (HIT) in patients undergoing PCI or cardiac surgery	2019/07/25	20:12.04.12 - Direct Thrombin Inhibitors	5S	211215
Accrufer®	ferric maltol	Shield TX	iron deficiency	2019/07/25	20:04.04 - Iron Preparations	1S	212320
Baqsimi®	glucagon nasal powder	Eli Lilly	severe hypoglycemia	2019/07/24	68:22.12 - Glycogenolytic Agents	3S	210134

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
Ruxience®	rituximab-pvvr	Pfizer	non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)	2019/07/23	10:00 - Antineoplastic Agents		761103
Hadlima®	adalimumab-bwwd	Samsung Bioepis	RA, JIA, PsA, AS, CD, UC, Ps	2019/07/23	92:36 - Disease-modifying Antirheumatic Drugs; 92:20 - Immunomodulatory Agents; 56:92 - GI Drugs, Misc		761059
Drizalma Sprinkle®	duloxetine	Sun Pharma	major depressive disorder (MDD), generalized anxiety disorder (GAD), diabetic peripheral neuropathic pain (DPNP), chronic musculoskeletal pain	2019/07/19	28:16.04.16 - Selective Serotonin- and Norepinephrine-reuptake Inhibitors	5S	212516
Recarbrio®	imipenem-cilastatin; relebactam	Merck	complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI)	2019/07/16	8:12.07.08 - Carbapenems	1/4P	212819
Katerzia®	amlodipine oral suspension	Silvergate	hypertension; coronary artery disease (chronic stable angina, vasospastic angina)	2019/07/08	24:28.08 - Dihydropyridines; 24:12.92 - Vasodilating Agents, Misc	3S	211340
Xpovio®	selinexor	Karyopharm	relapsed refractory multiple myeloma	2019/07/03	10:00 - Antineoplastic Agents	1P	212306
Xembify®	immune globulin subcutaneous, human-klhw	Grifols	primary humoral immunodeficiency	2019/07/03	80:04 - Antitoxins and Immune Globulins		125683
Thiola EC®	tiopronin	Mission	prevention of cystine stone formation with severe homozygous cystinuria	2019/06/28	92:92 - Other Miscellaneous Therapeutic Agents	3S	211843
Zirabev®	bevacizumab-bvzr	Pfizer	metastatic colorectal cancer; non-squamous non-small cell lung cancer; recurrent glioblastoma; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; in combination with other agents	2019/06/27	10:00 - Antineoplastic Agents		761099
Vyleesi®	bremelanotide acetate	Amag	hypoactive sexual desire disorder (HSDD)	2019/06/21	28:92 - Central Nervous System Agents, Misc	1S	210557
Myxredlin®	insulin human; sodium chloride	Celerity	diabetes mellitus	2019/06/20	68:20.08.08 - Short-acting Insulins	5S	208157
Kanjinti®	trastuzumab-anns	Amgen	HER2 breast cancer; HER2 metastatic gastric or gastroesophageal junction adenocarcinoma	2019/06/13	10:00 - Antineoplastic Agents		761073
Polivy®	polatuzumab vedotin-piiq	Genentech	diffuse large B-cell lymphoma (DLBCL)	2019/06/10	10:00 - Antineoplastic Agents		761121
Piqray®	alpelisib	Novartis	HR+HER2-, PIK3CA-mutated, advanced or metastatic breast cancer	2019/05/24	10:00 - Antineoplastic Agents	1S	212526
Zolgensma®	onasemnogene abeparvovec-xioi	Novartis	spinal muscular atrophy (SMA)	2019/05/24	26:12 - Gene Therapy		125694
Slynd®	drospirenone	Exeltis	oral contraception	2019/05/23	68:12 - Contraceptives; 68:32 - Progestins	2/3S	211367
Nayzilam®	midazolam nasal spray	Proximagen	intermittent, stereotypic episodes of frequent seizure activity	2019/05/17	28:12.08 - Benzodiazepines	3S/O	211321
Ruzurgi®	amifampridine	Jacobus	Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to 17	2019/05/06	92:92 - Other Miscellaneous Therapeutic Agents	1O/P	209321

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Appl Type	No
Vyndaqel®	tafamidis meglumine	FoldRx	cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM)	2019/05/03	24:04.92 - Cardiac Drugs, Misc	1P	211996
Vyndamax®	tafamidis	FoldRx	cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM)	2019/05/03	24:04.92 - Cardiac Drugs, Misc	1S	212161
Qternmet XR®	dapagliflozin; metformin; saxagliptin	AstraZeneca AB	type 2 diabetes mellitus	2019/05/02	68:20.18 - Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors; 68:20.04 - Biguanides; 68:20.05 - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	4S	210874
Dengvaxia®	dengue tetravalent vaccine, live	Sanofi Pasteur	prevention of dengue disease caused by serotypes 1-4 in patients aged 9-16	2019/05/01	80:12 - Vaccines		125682
Zuragard®	isopropyl alcohol 70%	Zurex	skin preparation for surgery	2019/04/26	84:04.92 - Local Anti-infectives, Misc	5S	210872
Duobrii®	halobetasol propionate; tazarotene	Bausch	plaque psoriasis	2019/04/25	84:06.08 - Corticosteroids; 84:92 - Skin and Mucous Membrane Agents, Misc	5S	209354
Eticovo®	etanercept-ykro	Samsung Bioepsis	rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (PsO)	2019/04/25	92:36 - Disease-modifying Antirheumatic Drugs; 92:20 - Immunomodulatory Agents (secondary)		761066
Skyrizi®	risankizumab-rzaa	Abbvie	plaque psoriasis	2019/04/23	84:92 - Skin and Mucous Membrane Agents, Misc		761105
Elcys®	cysteine hydrochloride	Exela	total parenteral nutrition	2019/04/16	40:12 - Replacement Preparations	5P	210660
Balversa®	erdafitinib	Janssen	locally advanced or metastatic bladder cancer	2019/04/12	10:00 - Antineoplastic Agents	1P	212018
Evenity®	romosozumab-aqqg	Amgen	osteoporosis	2019/04/09	92:22 - Bone Anabolic Agents (new)		761062
Dovato®	dolutegravir; lamivudine	Viiv	HIV-1 infection	2019/04/08	8:18.08.12 - HIV Integrase Inhibitors; 8:18.08.20 - HIV Nucleoside and Nucleotide Reverse Transcriptase Inhibitors	4P	211994
Asceniv®	immune globulin intravenous, human-slra	ADMA Biologics	primary humoral immunodeficiency	2019/04/01	80:04 - Antitoxins and Immune Globulins		125590
Mavenclad®	cladribine	EMD Serono	relapsing forms of multiple sclerosis (MS)	2019/03/29	92:44 - Immunosuppressive Agents	3S	022561
Avaclyr®	acyclovir	Fera	acute herpetic keratitis (dendritic ulcers) with HSV-1 and HSV-2 infection	2019/03/29	52:04.20 - Antivirals	3S	202408
Duaklir® Pressair	aclidinium; formoterol	AstraZeneca	maintenance of COPD	2019/03/29	12:08.08 - Antimuscarinics/Antispasmodics; 12:12.08.12 - Selective beta-2-Adrenergic Agonists	4S	210595
Jatenzo®	testosterone undecanoate	Clarus	testosterone replacement therapy	2019/03/27	68:08 - Androgens	3S	206089
Mayzent®	siponimod	Novartis	multiple sclerosis	2019/03/26	92:20 - Immunomodulatory Agents	1S	209884
Sunosi®	solriamfetol	Jazz	daytime sleepiness assoc with narcolepsy or obstructive sleep apnea	2019/03/20	28:20.80 - Wakefulness-promoting Agents	1S	211230
Zulresso®	brexanolone	Sage	postpartum depression (PPD)	2019/03/19	28:16.04.92 - Antidepressants, Misc	1P	211371
Zykadia®	ceritinib	Novartis	metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) -positive	2019/03/18	10:00 - Antineoplastic Agents	3S	211225

DrugReassignments

Drug Name	Active Ingredients	Change Date	Old AHFS Class	New AHFS Class
Zelnorm®	tegaserod	2019/07/22	56:92 - GI Drugs, Misc	56:32 - Prokinetic Agents
Cambia®	diclofenac potassium for oral solution	2019/05/17	28:08.04.92 - Other Nonsteroidal Anti-inflammatory Agents (NSAIAs)	28:08.04.92 - Other Nonsteroidal Anti-inflammatory Agents (NSAIAs); 28:32.92 - Antimigraine Agents, Misc
Forteo®	teriparatide	2019/04/10	68:24.08 - Parathyroid Agents	68:24.08 - Parathyroid Agents; 92:22 - Bone Anabolic Agents
Natpara®	parathyroid hormone	2019/04/10	68:24.08 - Parathyroid Agents	68:24.08 - Parathyroid Agents; 92:22 - Bone Anabolic Agents
Tymlos®	abaloparatide	2019/04/10	68:24.08 - Parathyroid Agents	68:24.08 - Parathyroid Agents; 92:22 - Bone Anabolic Agents

decreased incidence and severity of cardiovascular effects compared with other IV anesthetic agents. Minor increases in cardiac index and slight decreases in heart rate, systemic vascular resistance, and arterial blood pressure have been reported with use of etomidate. In addition, equivalent induction doses of etomidate cause less respiratory depression than propofol or barbiturates. Increases in carbon dioxide tension (PCO_2) have been reported with administration of etomidate.

Some data suggest that etomidate usually reduces intraocular pressure (IOP).

The pharmacokinetic profile of etomidate is characterized by a rapid distribution from blood into CNS, rapid clearance from the brain, and substantial tissue uptake. Following the usual induction dose (0.3 mg/kg) of etomidate, duration of hypnosis is short (about 3–10 minutes) and dose dependent. The elimination half-life of etomidate is about 1.25–5 hours. The drug is rapidly metabolized in the liver, principally by hydrolysis, to form etomidate carboxylic acid, which appears to be pharmacologically inactive. About 75% of an administered dose is excreted in urine within 24 hours, mainly (about 80%) as the carboxylic acid metabolite, while 13 and 10% of a dose are excreted in feces and bile, respectively.

Advice to Patients

When procedures requiring general anesthetics or sedation drugs, including etomidate, are considered for young children or pregnant women, importance of discussing with the patient, parent, or caregiver the benefits, risks (including potential risk of adverse neurodevelopmental effects), and appropriate timing and duration of the procedure.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs.

Importance of women informing clinicians if they are or plan to become pregnant or are breast-feeding.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Etomidate

Parenteral		
Injection, for IV use	2 mg/mL (20 and 40 mg)*	**Amidate®**, Hospira **Etomidate Injection**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ketamine Hydrochloride

■ Ketamine hydrochloride, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is a nonbarbiturate general anesthetic that also has analgesic and antidepressant properties.

Uses

Ketamine hydrochloride has historically been used as an anesthetic agent; however, the drug also can produce profound analgesia and other pharmacologic effects, and is therefore being used for a variety of other indications such as procedural sedation in the emergency department, pain management†, sedation and analgesia in the intensive care setting†, and some psychiatric indications, including treatment-resistant depression and suicidality†.

■ **Induction and Maintenance of Anesthesia** Ketamine is used IV or IM for induction of anesthesia prior to administration of other general anesthetic agents. Ketamine also is used as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Although the drug is best suited for brief procedures, additional (i.e., maintenance) doses may be administered for longer procedures. Ketamine also may be used to supplement low-potency agents (e.g., nitrous oxide). While ketamine currently is FDA-labeled for use in adults only, the drug has been used widely in pediatric patients†.

Induction of anesthesia with ketamine is rapid and results in a trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability. This anesthetic state, known as dissociative anesthesia, is markedly different from that of other general anesthetic agents (e.g., barbiturates, benzodiazepines, propofol, inhalation anesthetics).

Efficacy of ketamine as an anesthetic agent has been evaluated in over 12,000 operative and diagnostic procedures involving over 10,000 patients from 105 studies. In these studies, ketamine was administered as the sole anesthetic agent, as an induction agent for other general anesthetics, or to supplement low-potency anesthetic agents; the anesthesia produced by ketamine was rated by anesthesiologists and surgeons, respectively, as excellent or good (90 and 93%), fair (6 and 4%), or poor (4 and 3%). Using another evaluation method, anesthesia was rated as adequate in at least 90% or inadequate in 10% or less of procedures studied. Procedures for which ketamine has been used include debridement, dressing changes, and skin grafting in burn patients; neurodiagnostic procedures (e.g., pneumoencephalograms, ventriculograms, myelograms, lumbar punctures); diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions; diagnostic and operative procedures of the pharynx, larynx, or bronchial tree; colonoscopy and minor surgery of the anus and rectum; circumcision; short gynecologic procedures (e.g., dilatation and curettage); orthopedic procedures (e.g., fracture reductions, manipulations, femoral pinning, amputation, biopsies); emergency cardioversion; and cardiac catheterization.

Due to the risk of emergence reactions (see Emergence Reactions under Cautions: Nervous System Effects) and the availability of other anesthetic agents, current use of ketamine is generally limited to certain patient populations (e.g., those with hemodynamic instability) or settings (e.g., prehospital environments that lack appropriate monitoring and respiratory support) where the drug's unique pharmacologic properties may be advantageous. Because ketamine produces sympathomimetic effects, the drug may be particularly useful for induction of anesthesia in hemodynamically unstable patients (e.g., those with traumatic injury or septic shock) or in poor-risk patients with depressed vital functions. Because of its bronchodilating effects, ketamine is generally considered the induction agent of choice in patients with reactive airway disease (e.g., asthma) or active bronchospasm.

Ketamine is commonly used as an induction agent for rapid sequence intubation, particularly in patients with reactive airway disease or hemodynamic compromise; studies have shown that ketamine may produce similar outcomes to etomidate and may be used as an alternative.

■ **Procedural Sedation** Ketamine is used to provide dissociative sedation during short painful or emotionally disturbing procedures (e.g., fracture reduction, laceration repair, abscess drainage, emergency cardioversion, chest tube insertion, central line placement) in the emergency department. Administration of a single IV or IM dose can effectively produce a dissociative state for approximately 5–10 or 20–30 minutes, respectively, while maintaining cardiovascular stability, spontaneous respiration, and protective airway reflexes.

Ketamine is commonly used for procedural sedation in pediatric patients†. Although used less frequently in adults due to an increased risk of emergence delirium, current evidence also supports the use of ketamine for procedural sedation in the adult population. Ketamine has a well-established role in the care of burn patients undergoing painful procedures (e.g., dressing changes, debridement, grafts). The drug may be administered by the IM route in patients in whom IV administration may be difficult (e.g., severely agitated or combative patients, young children, patients with extensive burns).

Ketamine has been used in combination with propofol (combined therapy commonly referred to as "ketofol") for procedural sedation in the emergency department. The rationale for the combination is to counteract the adverse effects of the drugs (i.e., ketamine mitigating propofol-induced hypotension and propofol mitigating ketamine-induced vomiting and recovery agitation).

■ **Pain** Ketamine exhibits potent analgesic properties in low (i.e., subanesthetic or subdissociative) doses and has been used for a variety of acute and chronic pain conditions†. Such conditions include acute pain† in the emergency department and prehospital settings, postoperative pain†, and chronic pain† of various etiologies. In addition to its analgesic effects, ketamine also can prevent the development of central sensitization, hyperalgesia, and opiate tolerance, which may be particularly useful in patients who are opiate tolerant or opiate dependent.

Postoperative Pain Ketamine in low (i.e., subanesthetic or subdissociative) doses has been used for the management of postoperative pain† following a variety of surgical procedures in both adults and pediatric patients. The drug should be used as part of a multimodal regimen consisting of a combination of pharmacologic and nonpharmacologic methods targeting different pain mechanisms in the peripheral and central nervous systems.

Efficacy of low-dose ketamine in the postoperative setting is well established and supported by numerous studies demonstrating reduced opiate requirements and, in some cases, additional reductions in postoperative pain when the drug was used as a component of multimodal analgesia; although some studies reported discrepant results, the inconsistency may be due to differences in patient populations, dosage regimens, and concomitant analgesics used. Because ketamine appears to be most beneficial for procedures associated with severe pain, some experts state that subanesthetic ketamine infusions should be reserved for patients undergoing surgeries in which the postoperative pain is expected to be severe; such procedures include thoracic, abdominal (upper, lower, and intra-abdominal), and orthopedic (limb and spinal) surgeries. These experts state that patients undergoing procedures associated with only mild postoperative pain (e.g., tonsillectomy, head and neck surgery) have not been shown to benefit from perioperative ketamine. For these procedures, standard analgesia with low dosages of opiates, nonsteroidal anti-inflammatory agents (NSAIAs), and local anesthetics usually can provide adequate pain

lief. However, management of post-tonsillectomy pain in children can be difficult and several studies have demonstrated that administration of a single IV dose of ketamine 0.5 mg/kg (alone or in combination with other analgesics) can provide effective postoperative pain control.

Ketamine may be particularly useful in the management of opiate-tolerant or opiate-dependent patients undergoing surgery. In a randomized controlled study in opiate-dependent patients undergoing spinal surgery, intraoperative use of ketamine was associated with reduced opiate consumption at 48 hours and reduced opiate usage at 6 weeks. Ketamine also may be considered as an adjunct to reduce postoperative opiate consumption in patients who have an increased risk of opiate-related respiratory depression (e.g., those with obstructive sleep apnea).

Acute Pain Ketamine (in subanesthetic doses) has been used alone or as an adjunct to other analgesics (e.g., opiates) for relief of acute pain† in the emergency department and prehospital settings (e.g., ambulance). Studies evaluating subanesthetic ketamine for analgesia in these settings have been conducted principally in the adult population. However, low or subanesthetic doses of ketamine also have been used for analgesia in pediatric patients 3 months of age or older presenting to the emergency department. When used as an adjunct to opiate analgesics in the emergency department or prehospital setting, ketamine has resulted in greater reduction in pain scores compared with opiate therapy alone, and/or decreased opiate requirements. When given as a single agent for acute pain in the emergency department, IV ketamine has been reported to provide comparable reductions in pain scores to IV morphine.

Although evidence is limited, ketamine may be useful in opiate-dependent patients with acute exacerbations of chronic pain conditions (e.g., sickle cell disease)†.

Chronic Pain Ketamine has been used as an adjunct analgesic for the management of chronic pain of various etiologies, including complex regional pain syndrome (CRPS)†, neuropathic pain associated with spinal cord injury†, phantom limb pain†, fibromyalgia†, ischemic pain†, cancer pain†, and migraine pain†, in adults and pediatric patients. Evidence of efficacy varies depending on the specific pain condition treated and generally is limited to small randomized controlled studies, observational studies, and case reports demonstrating short-term benefits of ketamine infusions during and for a short time following the infusion; however, ketamine dosages and administration protocols varied widely in these studies.

Ketamine has been evaluated most extensively in chronic pain conditions associated with a neuropathic component. With regard to specific conditions, some experts state that there is weak to moderate evidence that ketamine infusions are effective for reducing pain related to CRPS in adults and pediatric patients; the evidence to date includes mostly systematic reviews, case reports, and observational studies with only a few small randomized controlled studies. In one study in 19 patients with CRPS, reductions in pain were reported for up to 12 weeks with continuous IV infusion of ketamine (maximum rate of 0.35 mg/kg per hour over 4 hours daily for 10 days). There also is weak evidence supporting ketamine infusions for short-term improvements in neuropathic pain associated with spinal cord injury. Other chronic pain syndromes that have been investigated generally have not responded to or only minimally responded to ketamine therapy; experts state that the available evidence remains inconclusive for the efficacy of ketamine infusions for mixed neuropathic pain, phantom limb pain, postherpetic neuralgia, fibromyalgia, ischemic pain, migraine, and low-back pain.

Although data are limited regarding the use of ketamine as an adjuvant treatment of cancer pain, some experts state that oral or IV ketamine may be considered for the management of refractory cancer pain in adults. Evidence to date remains inconclusive for the efficacy of ketamine in chronic cancer pain and is mostly based on case reports and uncontrolled studies. While a few randomized controlled studies indicate that the drug may have some benefit as an adjunct analgesic in cancer-related pain, these studies generally were small and had short durations of follow-up relative to the chronic nature of the pain being treated. In a larger controlled clinical trial in 214 adults with cancer-related neuropathic pain inadequately treated with adjuvant analgesics, the addition of oral ketamine (up to 400 mg daily for 16 days) was no more effective than placebo in improving pain scores. In another controlled clinical trial in 185 adults in palliative care settings who had refractory cancer-related pain, adjunctive therapy with ketamine (administered as a subcutaneous infusion in escalating doses up to 500 mg every 24 hours over 5 days) also was no more effective than placebo in improving pain scores. Studies of IV and oral ketamine have been conduced in children with cancer pain; although these studies were mostly retrospective, there is some evidence suggesting that pain control can be achieved with ketamine in these patients.

Additional study is needed to establish the role of ketamine in patients with chronic pain and to determine optimum dosages, durability of response, and long-term benefits and risks of the drug. Some clinicians recommend that use of ketamine be restricted to patients with refractory pain who have failed to obtain adequate relief from standard analgesics and nonpharmacologic treatments.

■ **Treatment-resistant Depression and Suicidality** Ketamine has been used in low (i.e., subanesthetic) doses for the treatment of severe and treatment-resistant depression associated with major depressive disorder or bipolar disorder†. Although there are various definitions for treatment-resistant depression, the condition often has been defined as the failure of at least 2 trials of first-line antidepressants given in an adequate dosage for an adequate duration of therapy. In patients with refractory forms of depression, ketamine usually has been given in subanesthetic doses as an IV infusion.

Ketamine has demonstrated rapid and potent antidepressant effects when administered to depressed patients in controlled studies and case series, with improvement in depression reported within several hours to a day following a single IV infusion of the drug. In controlled studies, single, low-dose IV infusions of the drug have resulted in response rates of approximately 37–71% in patients with treatment-resistant depression.

Most depressed patients who respond to a single IV infusion of ketamine experience a relapse of depression within several days to a week or two following the initial infusion. Therefore, multiple-infusion regimens of ketamine (i.e., weekly, biweekly, 3 times weekly) have been studied in depressed patients in open-label as well as blinded studies with encouraging results suggesting that repeated infusions are more effective than a single infusion and can extend the duration of depressive symptom remission. However, the long-term efficacy and safety of repeated infusions of ketamine have not been fully determined to date and further studies are needed to evaluate relapse prevention therapy with the drug. There is some concern that multiple-infusion regimens of ketamine may cause long-term cognitive impairment or neurotoxicity, although no evidence of such impairment has been seen in preliminary studies conducted to date. Some clinicians have suggested that the optimal use of ketamine infusions may be short-term to produce rapid antidepressant and antisuicidal effects until a less invasive relapse prevention strategy for a patient can be implemented.

In addition to its antidepressant effects, randomized controlled studies suggest that ketamine may be helpful in the short-term treatment of suicidal ideation†. In a systematic review and individual participant data meta-analysis, suicidal ideation rapidly decreased (within 1 day) following a single IV infusion of ketamine and the effect lasted for up to 1 week even among patients whose depression did not fully respond to ketamine therapy, suggesting that the drug may have a partially independent antisuicidal effect.

Despite the increasingly widespread use of IV ketamine to treat patients with treatment-resistant depression and suicidality, including in outpatient ketamine infusion centers and psychiatric clinics, some clinicians currently recommend that the drug's use for these psychiatric indications be limited to controlled settings under the care of skilled clinicians. Clinicians and patients should consider enrollment in clinical studies evaluating ketamine's efficacy and safety so that further data can be collected and analyzed to improve clinical practice. (See Dosage and Administration: Administration and see also Cautions: Precautions and Contraindications.)

When considering the use of ketamine for treating mood disorders, the American Psychiatric Association's (APA's) Council of Research Task Force on Novel Biomarkers and Treatments recommends balancing the potential benefits of ketamine infusion therapy with the potential risks of long-term exposure to the drug, including neurotoxicity, cystitis, and abuse potential. (See Uses: Misuse and Abuse and see also Chronic Toxicity.) A thorough pretreatment evaluation process to determine the appropriateness of ketamine therapy is recommended in such cases. If ketamine is prescribed outside of a controlled setting, careful screening, monitoring during treatment, and follow-up of patients are necessary. (See Dosage and Administration: Administration and see also Cautions: Precautions and Contraindications.)

Since conventional oral antidepressants generally require several weeks or months to be effective, the addition of ketamine to oral antidepressant therapy has been suggested as one possible method to produce a more rapid antidepressant response in patients with depression. In a randomized, double-blind, placebo-controlled study, the efficacy and safety of single-infusion ketamine augmentation of oral escitalopram therapy (10 mg daily) were evaluated in 30 outpatients with severe major depressive disorder. Ketamine was given as a single IV infusion (0.5 mg/kg over 40 minutes) on day 1 of escitalopram therapy. At 4 weeks, response occurred in significantly more escitalopram plus ketamine-treated patients than in the escitalopram plus placebo-treated patients (approximately 92 and 57% of patients, respectively). In addition, the escitalopram plus ketamine-treated patients had a shorter mean time to response than the escitalopram plus placebo-treated patients (6 days compared with 27 days).

Some clinicians state that electroconvulsive therapy (ECT) should still be considered as a first-line therapy for patients with refractory depression, and have expressed concern that a trial of single- or multiple-dose ketamine therapy might delay patients from being referred for an ECT consultation. Preliminary experience with the adjunctive use of ketamine in the course of ECT for depression does not suggest improved efficacy or tolerability.

Preliminary evidence suggests that intranasal† ketamine given in 50-mg doses is effective in rapidly improving depressive symptoms in patients with major depressive disorder and generally is well tolerated; however, further study is needed to more clearly determine the efficacy, tolerability, and optimal dosing of this alternative route of administration. The APA's Council of Research Task Force on Novel Biomarkers and Treatments currently advises against the prescription of self-administration of ketamine at home and recommends medical supervision whenever the drug is used pending further accumulation of safety data from controlled settings.

For information on the intranasal use of esketamine hydrochloride, the *S*-enantiomer of racemic ketamine, for treatment-resistant depression, see Esketamine Hydrochloride 28:16.04.92.

■ **Sedation and Analgesia in Critical Care Settings** Ketamine has been used by continuous IV infusion to provide short-term (i.e., less than 24 hours) sedation in critically ill patients† in the intensive care unit (ICU) setting.

However, evidence supporting this use is generally lacking, and other sedative agents (e.g., propofol, midazolam, dexmedetomidine) are more commonly used.

Ketamine also has been used for the management of pain in critically ill patients† in the ICU. Although opiate analgesics generally are considered the first-line drugs of choice for non-neuropathic pain in this setting, some experts state that non-opiate analgesics such as IV ketamine may be used adjunctively to reduce opiate requirements and opiate-related adverse effects.

■ **Misuse and Abuse** Ketamine is a known drug of abuse and is subject to control under the Federal Controlled Substances Act of 1970 as a schedule III drug. The pharmacologic and behavioral effects of ketamine are similar to, but somewhat less intense and shorter in duration than those of phencyclidine (PCP). Ketamine is most commonly abused by nasal insufflation (i.e., snorting) of the powder (evaporated from the injectable liquid), although IV, IM, and oral routes also have been used. Reported desired effects of ketamine include feelings of dissociation and unreality, altered state of consciousness, enhanced sensory perception, hallucinations, intoxication, mild euphoria, and a sensation of floating. Most cases of ketamine abuse have been reported in the context of multidrug or polysubstance abuse. Surveys and studies examining the use pattern of ketamine indicate that abuse of the drug may be more prevalent in certain geographic regions (e.g., Hong Kong). The annual prevalence rate for ketamine use in adolescents (17–18 years of age) in the US was 1.5% in 2012.

Although brief exposure to ketamine in a hospital setting is not likely to cause addiction, the possibility of addiction exists and patients should be individually assessed for their risk. Abuse of ketamine can result in adverse urinary, CNS, and hepatobiliary effects. (See Chronic Toxicity.) The manufacturer states that ketamine should be prescribed and administered with caution because of the risk of abuse.

Dosage and Administration

■ **Administration** Ketamine hydrochloride usually is administered by slow (e.g., over 60 seconds) IV injection, IV infusion, or IM injection. Ketamine also has been administered by oral†, intranasal†, rectal†, subcutaneous†, and intraosseous (IO)† routes. Because of extensive first-pass metabolism, the bioavailability of ketamine following oral or rectal administration is limited (approximately 20–30%). Although ketamine has been administered epidurally† or intrathecally†, there have been concerns about potential neurotoxicity with these routes, and some experts state it may be prudent to avoid neuraxial administration of the drug (see Neurotoxicity under Cautions: Nervous System Effects).

Some experts state that IV administration of ketamine is preferred to IM administration when access can be obtained readily. IM administration is associated with a higher rate of vomiting and longer recovery times compared with IV administration. In addition, IV access can permit convenient administration of additional doses for longer procedures and allow for rapid treatment of adverse effects (e.g., IV benzodiazepines for emergence reactions). In certain patients (e.g., severely agitated or uncooperative patients, young children), IM administration may be preferred.

General Anesthesia When used for general anesthesia, ketamine should be administered by or under the supervision of clinicians experienced in the use of general anesthetic drugs and in the management of possible complications (e.g., airway or respiratory compromise). Appropriate monitoring and resuscitation facilities should be readily available. Because rapid induction of anesthesia occurs following IV injection, patients should be in a supported position during administration. Purposeless and tonic-clonic movements may occur during the course of ketamine anesthesia; however, such movements do not imply a light plane of consciousness and are not indicative of the need for additional doses.

Procedural Sedation When used for procedural sedation in the emergency department, ketamine should be administered by appropriately trained individuals who can safely administer the drug and manage any possible complications (e.g., airway or respiratory compromise). Experts recommend that 2 individuals be present during the procedure (one to perform the procedure and one to monitor the patient). Patients should be continuously observed by a dedicated healthcare professional until recovery is well established. Because ketamine dissociation occurs rapidly, the drug should be administered just prior to initiation of the procedure.

Vomiting Risk Ketamine may be administered in a patient whose stomach is not empty if the benefits outweigh the potential risks. Vomiting has been reported following administration of ketamine and aspiration of gastric contents may occur; although protective laryngeal and pharyngeal reflexes generally are preserved with ketamine, the risk of aspiration must be considered when the drug is administered with other anesthetics and muscle relaxants that may impair such reflexes.

Prophylactic use of antiemetics (e.g., ondansetron) may reduce the rate of ketamine-associated vomiting. (See Cautions: GI Effects.)

Adjunctive Benzodiazepine Therapy Concomitant administration of benzodiazepines (e.g., diazepam, midazolam) may reduce the incidence of psychotomimetic manifestations during emergence from ketamine anesthesia, and is recommended in adults; however, because such benefit has not been observed in children and because the incidence of emergence reactions is much lower in children than in adults, routine use of prophylactic benzodiazepines is not recommended in pediatric patients. Benzodiazepines may be used to terminate unpleasant psychotomimetic reactions, should they occur, in adults and children.

The manufacturer states that a reduced dosage of ketamine supplemented with diazepam may be used in conjunction with other agents (e.g., nitrous oxide, oxygen) to produce balanced anesthesia. However, if ketamine hydrochloride and diazepam are used concurrently, the drugs should be administered separately, and should *not* be admixed in the same syringe or infusion container. (See Chemistry and Stability: Stability.)

Adjunctive Anticholinergic Therapy Anticholinergic agents (e.g., atropine, glycopyrrolate) may be administered prior to or concomitantly with ketamine to reduce hypersalivation and risk of laryngospasm; however, evidence to support a clinically important benefit or harm from routine anticholinergic prophylaxis is lacking, and some experts recommend that such therapy be reserved for patients with clinically important hypersalivation or impaired ability to mobilize secretions.

Treatment-resistant Depression and Suicidality When ketamine is used by IV infusion for the treatment of severe and treatment-resistant depression and suicidality†, the drug should be administered by experienced clinicians in facilities in which adequate monitoring for possible adverse reactions (e.g., altered cardiovascular and respiratory function, acute dissociative and psychotomimetic effects) and management of such reactions are possible.

Dilution Ketamine hydrochloride is commercially available as an injection containing 10, 50, or 100 mg/mL of ketamine for IV or IM use. The 100-mg/mL concentration should *not* be administered IV without proper dilution; the commercially available injection concentrate must be diluted with an equal volume of sterile water for injection, 0.9% sodium chloride injection, or 5% dextrose injection prior to IV injection.

For IV infusion, a diluted solution containing 1 mg of ketamine per mL (1 mg/mL) may be prepared by adding 500 mg of ketamine (10 mL from a vial labeled as containing 50 mg/mL of ketamine or 5 mL from a vial labeled as containing 100 mg/mL of ketamine) to an infusion bag containing 500 mL of 0.9% sodium chloride injection or 5% dextrose injection. In patients requiring fluid restriction, a 2-mg/mL solution may be prepared by adding 500 mg of ketamine (10 mL from a vial labeled as containing 50 mg/mL of ketamine or 5 mL from a vial labeled as containing 100 mg/mL of ketamine) to an infusion bag containing 250 mL of 0.9% sodium chloride injection or 5% dextrose injection. The manufacturer states that the 10-mg/mL vial of ketamine hydrochloride is not recommended for dilution; however, some stability studies have used ketamine hydrochloride solutions prepared by diluting a 10-mg/mL solution of the drug with 0.9% sodium chloride injection.

Rate of Administration Because rapid IV administration can cause respiratory depression, IV injections of ketamine should be administered slowly (e.g., over 60 seconds).

For dissociative sedation in emergency department settings, IV administration over 30–60 seconds has been recommended.

When ketamine is administered in a regimen with diazepam for induction of anesthesia, the manufacturer states that the drug may be administered by IV injection at a rate of 0.5 mg/kg per minute; for maintenance of anesthesia, ketamine may be administered by IV infusion at a rate of 0.1–0.5 mg/minute.

When ketamine is used in subanesthetic doses for acute pain†, some clinicians have recommended that the drug be administered as a short IV infusion over 15 minutes.

When ketamine is administered in subanesthetic doses for the treatment of severe and treatment-resistant depression and/or suicidality†, the drug is usually given as an IV infusion over 40 minutes. Although shorter and longer infusion rates have been used in some patients, clinical experience is too limited to recommend an alternative infusion rate at this time.

■ **Dosage** Dosage of ketamine hydrochloride is expressed in terms of ketamine.

Dose-dependency of Effects Dosage of ketamine depends on the intended use and desired pharmacologic effect. At low doses, ketamine produces analgesia and sedation, and at higher doses, the drug produces a state of dissociative anesthesia. Ketamine has a dosing threshold at which dissociation occurs (see Anesthetic Effects under Pharmacology: CNS Effects); doses at or above the threshold are referred to as "dissociative" or "anesthetic," and doses below this threshold are referred to as "subdissociative" or "subanesthetic." Although specific dosing ranges have not been established, dissociation generally appears at an IV dose of approximately 1–1.5 mg/kg or an IM dose of approximately 3–5 mg/kg. Once the dissociative threshold has been reached, additional administration of ketamine will not enhance or deepen sedation.

Induction and Maintenance of Anesthesia As with other general anesthetics, individual response to ketamine is variable and can depend on factors such as dosage, route of administration, patient age, or concomitant drugs. Dosage should be individualized based on therapeutic response and the patient's anesthetic needs. In general, higher doses of ketamine correspond with longer times to complete recovery from anesthesia.

Adult Dosage. For induction of anesthesia in adults, the manufacturer recommends an initial IV ketamine dose of 1–4.5 mg/kg (administered by slow IV injection over 60 seconds) or an initial IM dose of 6.5–13 mg/kg. On average, an IV dose of 2 mg/kg will produce surgical anesthesia for 5–10 minutes and an IM dose of 10 mg/kg will produce surgical anesthesia for 12–25 minutes.

For maintenance of anesthesia in adults, additional IV doses of 0.5–4.5 mg/kg or IM doses of 3.25–13 mg/kg may be administered as needed. A continuous IV infusion of 1–6 mg/kg per hour also has been recommended for maintenance of anesthesia. The maintenance dosage should be adjusted based on the patient's anesthetic requirements and concomitant use of other anesthetic agents.

Alternatively, the manufacturer states that the incidence of psychologic manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by using an induction regimen consisting of ketamine (1–2 mg/kg administered IV at a rate of 0.5 mg/kg per minute) augmented with diazepam (doses of 2–5 mg administered by IV injection over 60 seconds in a separate syringe). For maintenance of anesthesia using this augmented regimen, ketamine may be administered by IV infusion at a rate of 0.1–0.5 mg/minute and diazepam (2–5 mg) may be administered by IV injection in a separate syringe as needed. A total diazepam dosage of no more than 15 mg usually is sufficient for induction, and a total diazepam dosage of no more than 20 mg usually is sufficient for combined induction and maintenance; however, higher amounts may be required depending on factors such as the type and duration of the procedure or physical status of the patient.

Pediatric Dosage. In general, pediatric patients require higher doses of ketamine compared with adults, although there is considerable interpatient variability in dosing requirements.

Some experts recommend an initial IV ketamine dose of 1–3 mg/kg for induction of anesthesia in pediatric patients†; supplemental IV doses of 0.5–1 mg/kg may be given if clinically indicated. The recommended IM dose of ketamine for induction of anesthesia in pediatric patients is 5–10 mg/kg. Because of possible airway complications, some experts state that ketamine is contraindicated in infants younger than 3 months of age.

Procedural Sedation **Adult Dosage.** For dissociative sedation in adults undergoing short painful or emotionally disturbing procedures in the emergency department, the usual IV dose of ketamine is 1 mg/kg administered by IV injection over 30–60 seconds. Dissociative sedation is usually achieved with a single IV loading dose; however, if sedation is inadequate or a prolonged period of sedation is needed for longer procedures, additional IV doses of 0.5–1 mg/kg may be administered every 5–15 minutes as needed. Lower IV doses of ketamine (e.g., 0.2–0.75 mg/kg) also have been used to produce analgesia, particularly if a dissociative effect is not required for the procedure.

Although the IM route is not preferred in adults, some experts state that an IM dose of 4–5 mg/kg may be administered; additional doses of 2–5 mg/kg may be given after 5–10 minutes if initial sedation is inadequate or additional doses are needed for longer procedures. Lower IM doses of ketamine (e.g., 0.4–2 mg/kg) also have been used, particularly if a dissociative effect is not required for the procedure.

Pediatric Dosage. For dissociative sedation in pediatric patients† 3 months of age or older undergoing short painful or emotionally disturbing procedures in the emergency department, some experts state that the usual IV dose of ketamine is 1.5–2 mg/kg administered by IV injection over 30–60 seconds. Dissociative sedation is usually achieved with a single IV loading dose; however, if initial sedation is inadequate or prolonged sedation is necessary for longer procedures, additional incremental IV doses of 0.5–1 mg/kg may be administered every 5–15 minutes as needed. These experts state that the minimum IV dose that will reliably elicit the dissociative state in children is 1.5 mg/kg; however, lower IV doses (e.g., 0.25–1 mg/kg) also have been used successfully to provide adequate procedural sedation in pediatric patients, particularly if a dissociative effect is not required for the procedure.

The recommended IM dose of ketamine for dissociative sedation in pediatric patients† 3 months of age or older undergoing short painful or emotionally disturbing procedures in the emergency department is 4–5 mg/kg. Although dissociative sedation is usually achieved with a single IM dose, additional doses of 2–5 mg/kg may be administered after 5–10 minutes if initial sedation is inadequate or additional doses are needed for longer procedures. Although some experts state that the minimum IM dose that will reliably elicit the dissociative state in children is 4–5 mg/kg, lower IM doses (e.g., 1–2 mg/kg) also have been used successfully, particularly if a dissociative effect is not required for the procedure.

Sedation and Analgesia in Critical Care Settings For sedation and analgesia in critically ill adults† with severe pain unresponsive to conventional therapies, initial IV ketamine doses of 0.1–0.5 mg/kg followed by IV infusion of 0.05–0.4 mg/kg per hour (0.83–6.67 mcg/kg per minute) have been recommended by some experts as an adjunct to opiates; other dosage regimens also have been used. If additional pain control is needed, additional IV doses may be administered up to a maximum of 0.5 mg/kg; alternatively, the infusion rate may be titrated in increments of 0.06 mg/kg per hour (1 mcg/kg per minute) every 15 minutes up to a maximum of 1.2 mg/kg per hour (20 mcg/kg per minute) as tolerated.

Pain Ketamine is used in low (i.e., subanesthetic or subdissociative) dosages for the management of pain; however, a dosage range that is considered subanesthetic has not been consistently defined. Most acute pain studies used IV bolus doses less than 0.5 mg/kg and infusion rates of 0.5 mg/kg per hour or less; however, there is wide variability in the dosage ranges and routes of administration used.

Postoperative Pain. For the management of postoperative pain† in pediatric patients and adults, IV ketamine bolus doses ranging from 0.1–0.5 mg/kg with or without continuous IV infusion (at rates usually ranging from 0.1–0.6 mg/kg per hour [1.67–10 mcg/kg per minute]) have been commonly used in clinical studies; however, dosages and timing of administration in relation to the surgical procedure varied widely in these studies and the optimum dosage regimen is not known. Some experts state that there is moderate evidence supporting the use of IV ketamine bolus doses up to 0.35 mg/kg and IV infusions up to 1 mg/kg per hour (16.67 mcg/kg per minute) as an adjunct to opiates for perioperative analgesia. In several studies, administration of a single IV ketamine dose of 0.5 mg/kg (alone or in combination with other analgesics) was effective in achieving postoperative pain control in children undergoing tonsillectomy. Because of possible airway complications, some experts state that ketamine is contraindicated in infants younger than 3 months of age.

IM administration of analgesic agents for postoperative pain is not recommended because of unreliable absorption and substantial pain at the site of injection.

Acute Pain. For the management of acute pain† in the emergency department and prehospital settings, the usual IV dose of ketamine is 0.1–0.3 mg/kg administered as a slow IV injection or short IV infusion over 10–15 minutes based on studies conducted principally in adults; although longer infusions of ketamine are rare in this setting, continuous IV infusions of 0.1–0.3 mg/kg per hour (1.67–5 mcg/kg per minute) have been used. Non-weight-based IV ketamine doses ranging from 10–20 mg also have been used in clinical studies of ketamine for the treatment of acute pain in adults. When ketamine is used for acute pain in settings without intensive monitoring, some experts state that IV bolus doses should not exceed 0.35 mg/kg and infusion rates generally should not exceed 1 mg/kg per hour (16.67 mcg/kg per minute), but also acknowledge that higher or lower doses may be necessary due to interindividual differences in response.

Because of possible airway complications, some experts state that ketamine is contraindicated in infants younger than 3 months of age.

Ketamine may be administered IM for acute pain in the emergency department or prehospital settings; however, experts state that a dosage range has not been definitively established and analgesic effects are less predictable when the drug is administered by IM injection.

Chronic Pain. Although there is no consensus on dosages or administration protocols for ketamine in patients with chronic pain†, the drug generally is administered in subanesthetic doses by IV infusion. There is some evidence suggesting that administration of higher dosages over longer periods and more frequent infusions may provide more benefit. Some experts state that it is reasonable to initiate a single outpatient infusion of ketamine at a minimum dose of 80 mg for at least 2 hours and then reassess before initiating further treatments. In a study in children and adolescents 12–17 years of age with chronic pain conditions (e.g., chronic headache, fibromyalgia, complex regional pain syndrome), ketamine was administered by continuous IV infusion at a rate of 0.1–0.3 mg/kg per hour for 4–8 hours each day up to a maximum of 16 hours (in total, up to a maximum of 3 consecutive days). Children with severe cancer-related pain have been treated with IV infusions of ketamine at 0.1–1 mg/kg per hour. Based on limited evidence, IV ketamine bolus doses up to 0.35 mg/kg followed by IV infusions of 0.5–2 mg/kg per hour have been recommended by some experts for the management of chronic pain; however, higher (e.g., up to 7 mg/kg per hour for the treatment of refractory pain) or lower (e.g., 0.1–0.5 mg/kg per hour) infusion rates also have been used.

Treatment-resistant Depression and Suicidality For severe and treatment-resistant depression and suicidality† in adults, ketamine usually is given as a low-dose (i.e., subanesthetic dose) IV infusion of 0.5 mg/kg over 40 minutes. Obese patients (i.e., body mass index [BMI] of 30 or higher) appear to be at increased risk for ketamine-associated hypertension and other adverse hemodynamic effects and potentially may benefit from adjusting the ketamine dosage to their calculated ideal body weight rather than actual body weight; further clinical experience to determine optimal dosing in such patients is needed. There is limited evidence that higher ketamine infusion dosages (e.g., 0.75 mg/kg) may be necessary in certain chronically ill and/or severely treatment-resistant patients, but further study is needed to determine the efficacy and safety of such higher-dosage regimens.

There currently is limited clinical experience with longer-term (multiple-dose) ketamine infusion therapy for treatment-resistant depression and suicidality; however, IV infusions of ketamine have been given once, twice, or 3 times weekly for the first 2 weeks during the acute treatment phase in some patients and sometimes have been continued once or twice weekly for another 2–4 weeks during the continuation phase for a total of 4–6 weeks of therapy or gradually tapered. Patients who do not initially respond to several infusions of ketamine appear unlikely to respond to subsequent infusions. Discontinuance of ketamine therapy is recommended by some experts if the interval between infusions cannot be extended to one week or longer by the second month of treatment; these experts state that the goal should be to eventually taper and discontinue ketamine treatment until additional long-term safety data with the drug become available.

Cautions

Ketamine generally is well tolerated; however, the drug can cause adverse effects as a result of its actions on a variety of receptors (e.g., *N*-methyl-D-aspartic acid [NMDA], acetylcholine, opiate, monoaminergic, histaminic).

■ **Nervous System Effects** Like phencyclidine (PCP), ketamine, a PCP derivative, may cause psychotomimetic effects. When given in low (subanes-

thetic) doses, ketamine can produce mild cognitive, psychotic, and mood disturbances that are usually transient and limited to the time of administration; symptoms that have been reported include feelings of inebriation, positive and negative schizophrenic symptoms, dissociative symptoms, mania, confusion, lowered inhibition, perceptual disturbances, and impairments in attention, learning, and memory. At higher doses, ketamine can produce more severe schizophrenic-like symptoms, vivid hallucinations, psychosis, feelings of an "out of body" experience, mental confusion, hyperexcitability, and catalepsy.

Long-term use of ketamine can cause persistent neuropsychiatric symptoms, cognitive impairment, and psychologic abnormalities.

When used for treatment-resistant depression and suicidality, acute dissociative and psychotomimetic effects (e.g., psychotic symptoms) have been reported with IV infusions of ketamine. Such effects generally occur only during and immediately following ketamine infusion and resolve within 2–4 hours following the end of the infusion, are generally mild in severity, and are well tolerated. Clinical experience to date suggests that dissociative symptoms occur more commonly than psychotomimetic effects when ketamine is used in patients with treatment-resistant depression. (See Cautions: Precautions and Contraindications.)

Increased intracranial pressure has been reported following administration of ketamine as a result of cerebral vasodilation; however, cerebral perfusion may be increased.

Emergence Reactions Emergence reactions have been reported during recovery in patients receiving ketamine anesthesia; the manufacturer reports an incidence of approximately 12% for such emergence reactions, although higher rates have been reported in the published literature. Emergence reactions occur more frequently in adults (approximately 30–50%) than in pediatric patients (approximately 5–15%). A reduced risk has been observed in geriatric patients (older than 65 years of age) relative to younger adults and in patients who have previously received the drug.

Emergence manifestations vary in severity from pleasant to unpleasant dream-like states, vivid imagery, hallucinations, alterations in mood and body image, floating sensations, extracorporeal (out-of-body) experiences, and emergence delirium; in some cases, these states have been accompanied by confusion, excitement, and irrational behavior, which some patients recall as an unpleasant experience. The duration of such reactions is generally no more than a few hours; however, recurrences have occurred up to 24 hours following anesthesia. The manufacturer states that no residual psychologic effects have been reported from ketamine use.

Emergence reactions may be less frequent when ketamine is given IM. (See Cautions: Precautions and Contraindications.)

Neurotoxicity Animal studies suggest that ketamine may be neurotoxic when given intrathecally; however, pathologic findings were not observed in studies in which the preservative was omitted from the ketamine preparation. Studies evaluating this potential adverse effect of ketamine are lacking in humans.

■ **Cardiovascular Effects** Adverse cardiovascular effects of ketamine generally are a result of the drug's sympathomimetic effects. Mild to moderate increases in blood pressure, heart rate, and cardiac output can occur following administration of anesthetic or subanesthetic doses. Palpitations also have been reported with the drug.

Elevated blood pressure and/or heart rate may occur during IV infusions of ketamine for treatment-resistant depression and suicidality; these hemodynamic effects usually are transient and subside following completion of the IV infusion. Transient but significantly elevated blood pressure occurred in nearly one-third of ketamine-treated patients in one study. Short-term antihypertensive therapy sometimes has been used to treat ketamine infusion-associated blood pressure elevations in this and other studies.

Hypotension, bradycardia, and arrhythmia have been reported infrequently with ketamine. Precipitation of angina also has been reported. (See Cautions: Precautions and Contraindications.)

■ **Respiratory Effects** Adverse respiratory effects are rare with ketamine. When given in anesthetic doses, clinically important respiratory depression usually does not occur. Respiration is frequently stimulated; however, transient respiratory depression and apnea have been reported following rapid IV administration of the drug.

Ketamine can cause excessive secretions through stimulation of central cholinergic receptors; such increased secretions may cause laryngospasm or other airway obstruction.

Airway or respiratory complications have been reported in about 3.9% of pediatric patients receiving ketamine for dissociative sedation in the emergency department; transient apnea and respiratory depression have been reported in about 0.8% and transient laryngospasm has been reported in about 0.3% of pediatric patients in this setting.

When used in subanesthetic doses for the treatment of depression in otherwise healthy individuals, ketamine usually does not cause clinically important adverse respiratory effects.

■ **Musculoskeletal Effects** Skeletal muscle hypertonicity is a common adverse effect of ketamine and may manifest as involuntary random, purposeless, and/or tonic-clonic movements resembling seizures.

Clonus, hiccups, and hyperreflexia also have been reported following ketamine administration.

■ **Genitourinary Effects** Lower urinary tract and bladder symptoms including dysuria, urinary frequency, urgency, urge incontinence, cystitis, hematuria, and postmicturition pain have been reported in patients receiving ketamine. Pathologic changes (e.g., epithelial damage) also have been observed. In most cases, urologic symptoms have been associated with chronic ketamine use or abuse. (See Chronic Toxicity.)

■ **GI Effects** Nausea and vomiting are reported frequently in patients receiving ketamine. Vomiting has been reported in approximately 8% of pediatric patients and 5–15% of adults receiving ketamine for dissociative sedation in emergency department settings. In children, a higher incidence of vomiting (up to 33% depending on the route of administration) has been reported in the postoperative setting. Vomiting generally occurs well into the recovery period when the patient is alert and can clear the airway without assistance, but also may occur after the patient is discharged. The incidence of vomiting is highest in early adolescent patients and also may be more frequent with IM compared with IV administration.

There is some evidence suggesting that prophylactic use of antiemetics (e.g., ondansetron) may reduce the risk of ketamine-associated vomiting in pediatric patients receiving ketamine for procedural sedation. However, the effect appears to be modest and has not been consistently demonstrated in clinical studies. One approach that has been recommended is to administer prophylactic antiemetics only in those patients at highest baseline risk for vomiting (i.e., early adolescents).

Ketamine increases salivary secretions, which can cause laryngospasm; however, clinically important hypersalivation resulting in airway complications has been reported rarely.

Anorexia also has been reported in patients receiving ketamine.

■ **Hepatobiliary Effects** Elevated hepatic enzyme concentrations may occur with anesthetic and subanesthetic doses of ketamine, particularly following prolonged infusion and/or repeated doses within a short time frame. Hepatotoxicity has been reported following longer-term use (e.g., more than 3–4 days). Increased hepatic enzyme concentrations have been reported in approximately 10% of patients receiving repetitive low doses or continuous high doses of ketamine infusions clinically. In a small study in patients receiving IV infusions of *S*-ketamine for chronic pain, hepatic enzyme elevations up to 3 times the upper limit of normal occurred following a second exposure to the drug. Hepatic enzyme concentrations generally return to baseline over several months. (See Chronic Toxicity.)

■ **Ocular Effects** Nystagmus and diplopia occur frequently following administration of ketamine. Elevation of intraocular pressure (IOP) also may occur. Blurred vision and pupillary dilation have been reported with subanesthetic doses of ketamine. Transient blindness also has been reported.

■ **Dermatologic and Sensitivity Reactions** Transient erythema and morbilliform rash have been reported in patients receiving ketamine. Anaphylaxis also has been reported.

■ **Local Effects** Injection-site reactions (e.g., pain, erythema, rash) have been reported infrequently in patients receiving ketamine.

■ **Precautions and Contraindications** Ketamine hydrochloride should be administered only by or under the supervision of individuals who are experienced with its use and potential complications.

When used in anesthetic doses that may render patients unresponsive, administration of ketamine should occur in a monitored setting in the presence of personnel trained in advanced airway management and cardiovascular life support; resuscitative equipment should be readily available. When used in subanesthetic doses in the emergency department, adverse effects generally are mild and self-limiting; therefore, some experts state that ketamine administration may follow the same procedures and policies used for other analgesics in the emergency department. However, local protocols should be consulted since expectations may differ by institution.

When used in subanesthetic doses for the short-term treatment of mood disorders, ketamine generally appears to be well tolerated; however, adverse cardiovascular and CNS effects may occur. Therefore, some experts recommend that ketamine infusions only be given for mood disorders in settings in which adequate monitoring for possible adverse effects (e.g., altered cardiovascular and respiratory function, acute dissociative and psychotomimetic effects) and management of such reactions are possible.

CNS Precautions Because ketamine can cause sedation and potentially impair cognitive function, patients should be cautioned not to operate hazardous machinery, including driving a motor vehicle, or engage in potentially dangerous activities for at least 24 hours after anesthesia, depending on the dosage of ketamine administered and consideration of other drugs used during the procedure. The duration of ketamine administration also should be considered, especially in cases where early discharge is possible. When repeated administration of ketamine is used in treating patients with mood disorders, some experts recommend that assessment of cognitive function be considered.

Ketamine can exacerbate schizophrenia, and generally should be avoided in patients with schizophrenia or active psychosis. Although data are limited, caution is advised when ketamine is used for procedural sedation or acute pain in patients with other psychiatric disorders, including substance abuse-induced psychosis.

Emergence Reactions Emergence reactions may occur during the recovery period in patients receiving ketamine anesthesia. The incidence of emergence reactions may be reduced if verbal and tactile stimulation of the patient

is minimized during the recovery period; however, this should not preclude appropriate monitoring of vital signs. Prophylactic administration of benzodiazepines (e.g., diazepam, midazolam) may reduce the incidence of ketamine-induced psychotomimetic manifestations during emergence and the manufacturer suggests a regimen using a decreased dosage of ketamine in conjunction with a benzodiazepine (e.g., diazepam, midazolam) during induction and maintenance of anesthesia. (See Dosage and Administration.) Benzodiazepines also may be used to terminate severe or unpleasant emergence reactions.

Patients should be informed that they may experience psychologic manifestations as the effects of ketamine wear off, and that these effects may vary in severity and range from pleasant dream-like states to hallucinations, confusion, and unpleasant experiences.

When ketamine is used on an outpatient basis, patients should not be released until complete recovery from anesthesia occurs, after which patients should then be accompanied by a responsible adult.

Cardiovascular Precautions Because ketamine has a stimulating effect on the cardiovascular system, elevations in blood pressure and heart rate can occur. Ketamine should be used with caution or avoided in patients with known or suspected cardiac conditions that may be exacerbated by the sympathomimetic effects of the drug (e.g., unstable angina, coronary artery disease, myocardial infarction [MI], congestive heart failure, hypertension).

The manufacturer states that ketamine is contraindicated in patients in whom a substantial elevation of blood pressure would constitute a serious hazard, and that cardiac function should be continuously monitored in patients who experience hypertension or cardiac decompensation during ketamine anesthesia.

Because sympathomimetic effects may be increased in patients with porphyria or hyperthyroidism, or in those receiving thyroid replacement therapy, some experts state that ketamine should be used with caution or avoided in such patients.

Respiratory Precautions Although respiration is frequently stimulated, respiratory depression or apnea may occur following rapid IV administration or overdosage of ketamine. If respiratory depression occurs, respiratory support (e.g., mechanical ventilation) should be provided. IV injections of ketamine should be administered slowly (e.g., over 60 seconds).

Laryngospasm and other forms of airway obstruction may occur during ketamine administration; therefore, clinicians should be prepared to rapidly identify and manage such complications (e.g., with assisted ventilation, oxygen, and possible intubation). Major stimulation of the posterior pharynx (e.g., endoscopy) may increase the risk of laryngospasm; therefore, the manufacturer states that ketamine should not be used alone during surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. If the drug is used alone, mechanical stimulation of the pharynx should be avoided whenever possible. Muscle relaxants, with proper maintenance of respiration, may be required in these situations.

Although the risk of laryngospasm is low with minor oropharyngeal procedures typically performed in the emergency department, efforts should be made to avoid vigorous stimulation of the posterior pharynx and accumulation of secretions or blood during these procedures.

Some experts state that ketamine should be used with caution or avoided in patients with active pulmonary infection or disease (e.g., upper respiratory infection, asthma) because such conditions may increase the risk of laryngospasm (particularly in children).

Because of a potential increased risk of airway complications, ketamine should be used with caution or avoided in patients with a history of airway instability, tracheal surgery, or tracheal stenosis.

Hepatic Precautions Prolonged effects of ketamine may occur in patients with hepatic impairment. Some experts recommend that ketamine use should be avoided or limited in patients with severe hepatic disease or cirrhosis, and that the drug should be used with caution (e.g., with monitoring of liver function tests) in patients with moderate hepatic disease. Discontinuance of ketamine therapy is recommended if hepatotoxicity occurs.

Alcohol Precautions Ketamine should be used with caution or avoided in patients with chronic alcoholism or acute alcohol intoxication.

Visceral Pain Precautions If ketamine is used in patients undergoing surgical procedures involving visceral pain pathways, the drug should be supplemented with an agent that obtunds visceral pain.

Intracranial Pressure and Head Injury Precautions The manufacturer states that ketamine should be used with extreme caution in patients with elevated intracranial pressure and some experts state that the drug should be avoided in such patients. However, there is some controversy regarding the use of ketamine in patients with head trauma. Despite concerns of increased intracranial pressure, cerebral perfusion is maintained and there is evidence that ketamine can be safely and effectively used in patients with head injuries or risk of intracranial hypertension.

Studies suggest that intracranial pressure increases are minimal in patients with normal ventilation and are associated with concomitant elevations in cerebral perfusion. In a systematic review of data from studies using ketamine in mechanically ventilated patients with traumatic brain injury, ketamine was not associated with increased intracranial pressure; in some cases, intracranial pressure was decreased.

Because of concerns about increased intracranial pressure, some experts state that ketamine should be used with caution or avoided in patients with CNS masses, abnormalities, or hydrocephalus.

Ocular Precautions Because ketamine can increase intraocular pressure (IOP), some experts state that the drug should be used with caution or avoided in patients with elevated IOP (e.g., glaucoma, acute globe injury).

Genitourinary Precautions Because ketamine has been associated with disorders of the urinary tract (including cystitis), particularly with long-term use, interruption of ketamine therapy should be considered in patients experiencing urinary symptoms (e.g., urinary frequency, urge incontinence, dysuria, hematuria, lower abdominal pain) without evidence of infection, and the patient should be evaluated by a specialist. The manufacturer states that discontinuance of ketamine should be considered if genitourinary pain continues in the setting of other genitourinary symptoms.

Some experts advise that patients receiving long-term ketamine therapy for mood disorders be assessed for urinary symptoms such as discomfort during therapy.

Misuse and Abuse The manufacturer states that ketamine should be prescribed and administered with caution because of the risk of abuse. (See Uses: Misuse and Abuse.) Tolerance and dependence may develop following prolonged administration of the drug. Because of the risk of abuse or diversion, careful monitoring and supervision are recommended during ketamine use.

Sensitivity Reactions The manufacturer states that ketamine is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** Although the manufacturer states that safety and efficacy of ketamine have not been established in patients younger than 16 years of age, the drug has been used widely in pediatric patients† in a variety of clinical settings for anesthesia, procedural sedation and analgesia, postoperative analgesia, and chronic pain management. Ketamine frequently is used in children to facilitate painful procedures in the emergency department and is considered a drug of choice for this use. Ketamine may be particularly useful in pediatric patients because the drug may be administered IM.

Ketamine may be preferred for induction of anesthesia in children with congenital heart disease with right-to-left shunt† because of its sympathomimetic effects and hemodynamic stability.

Ketamine generally should *not* be used in infants younger than 3 months of age because of the potential increased risk of airway complications (e.g., airway obstruction, laryngospasm, apnea) thought to be due to age-specific differences in airway reactivity and anatomy.

Neurodevelopmental and Cognitive Effects Prolonged use of general anesthetics and sedation drugs, including ketamine, in children younger than 3 years of age or during the third trimester of pregnancy may affect brain development. Animal studies in multiple species, including nonhuman primates, have demonstrated that use for longer than 3 hours of anesthetic and sedation drugs that block *N*-methyl-D-aspartic acid (NMDA) receptors and/or potentiate γ-aminobutyric acid (GABA) activity leads to widespread neuronal and oligodendrocyte cell loss and alterations in synaptic morphology and neurogenesis in the developing brain, resulting in long-term deficits in cognition and behavior. Across animal species, vulnerability to these neurodevelopmental changes occurs during the period of rapid brain growth or synaptogenesis; this period is thought to correlate with the third trimester of pregnancy through the first year of life in humans, but may extend to approximately 3 years of age. The clinical relevance of these animal findings to humans is not known.

While some published evidence suggests that similar deficits in cognition and behavior may occur in children following repeated or prolonged exposure to anesthesia early in life, other studies have found no association between pediatric anesthesia exposure and long-term adverse neurodevelopmental outcomes. Most studies to date have had substantial limitations, and it is not clear whether the adverse neurodevelopmental outcomes observed in children were related to the drug or to other factors (e.g., surgery, underlying illness). There is some clinical evidence that a single, relatively brief exposure to general anesthesia in generally healthy children is unlikely to cause clinically detectable deficits in global cognitive function or serious behavioral disorders; however, further research is needed to fully characterize the effects of exposure to general anesthetics in early life, particularly for prolonged or repeated exposures and in more vulnerable populations (e.g., less healthy children).

Results from an observational study (the Pediatric Anesthesia Neurodevelopment Assessment [PANDA] study) and preliminary results from an ongoing multicenter, randomized trial (the General Anesthesia Compared to Spinal Anesthesia [GAS] trial) provide some evidence that a single, relatively brief exposure to general anesthesia in generally healthy children is unlikely to cause clinically detectable deficits in global cognitive function or serious behavioral disorders. The PANDA study compared global cognitive function (as measured by intelligence quotient [IQ] score) of children 8–15 years of age who had a single anesthesia exposure for elective inguinal hernia surgery before the age of 3 years with that of a biologically related sibling who had no anesthesia exposure before the age of 3 years. All of the children had a gestational age at birth of at least 36 weeks, and sibling pairs were within 3 years of being the same age. Children who underwent the elective procedure were mostly males (90%) and generally healthy. The mean duration of anesthesia was 84 minutes; 16% of those receiving anesthesia had exposures exceeding 2 hours. The study found no substantial difference in IQ score between children who had a single anesthesia exposure before the age of 3 years and their siblings who had not. The GAS trial was designed to compare neurodevelopmental outcomes in children who received general anesthesia with those in children who received awake regional (caudal and/or spinal) anesthesia for inguinal herniorrhaphy

before they reached a postmenstrual age of 60 weeks (with a gestational age at birth of more than 26 weeks); the primary outcome was the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale IQ at 5 years of age. In an interim analysis at the age of 2 years, no difference in composite cognitive score (as measured by the Bayley Scales of Infant and Toddler Development III) was detected between children who had received sevoflurane anesthesia of less than 1 hour's duration (median duration: 54 minutes) compared with those who had received awake regional anesthesia.

Anesthetic and sedation drugs are an essential component of care for children and pregnant women who require surgery or other procedures that cannot be delayed; no specific general anesthetic or sedation drug has been shown to be less likely to cause neurocognitive deficits than any other such drug. Pending further accumulation of data in humans from well-designed studies, decisions regarding the timing of elective procedures requiring anesthesia should take into consideration both the benefits of the procedure and the potential risks. When procedures requiring the use of general anesthetics or sedation drugs are considered for young children or pregnant women, clinicians should discuss with the patient, parent, or caregiver the benefits, risks (including potential risk of adverse neurodevelopmental effects), and appropriate timing and duration of the procedure. FDA states that procedures that are considered medically necessary should not be delayed or avoided.

■ **Geriatric Precautions** While reported clinical experience to date has not revealed age-related differences in response to ketamine when used as an anesthetic agent, clinical studies have not included sufficient numbers of adults 65 years of age or older to determine whether geriatric patients respond differently than younger adults. A reduced risk of emergence reactions has been observed in geriatric patients older than 65 years of age relative to younger adults. When ketamine is used as an anesthetic agent in geriatric patients, the dosage should be selected carefully, usually starting at the low end of the dosing range, because of the greater frequency of age-related decreases in hepatic, renal, and/or cardiac function, and of concomitant disease or other drug therapy.

■ **Mutagenicity and Carcinogenicity** Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ketamine.

Data are insufficient to evaluate the genotoxic potential of ketamine. Ketamine was clastogenic in an in vitro chromosomal aberration assay. However, unpublished data using *S*-ketamine did not reveal any evidence of genotoxic effects.

■ **Pregnancy, Fertility, and Lactation** There are no adequate and well-controlled studies of ketamine in pregnant women. Although ketamine has been used for induction of anesthesia during vaginal delivery and caesarean sections, the manufacturer states that the drug is not recommended for use during pregnancy or delivery because safety has not been established. Some neonates exposed to ketamine at maternal IV doses of 1.5 mg/kg or higher during delivery have experienced respiratory depression and low Apgar scores requiring resuscitation. Marked increases in maternal blood pressure and uterine tone have been observed following administration of IV ketamine doses greater than 2 mg/kg.

In animal reproduction studies using IM ketamine doses approximately 0.3–0.6 times the usual human dose of 10 mg/kg (based on body surface area), developmental delays, skeletal hypoplasia, and increased fetal resorptions were observed.

Based on animal data, repeated or prolonged use of general anesthetics and sedation drugs, including ketamine, during the third trimester of pregnancy may result in adverse neurodevelopmental effects in the fetus. The clinical relevance of these animal findings to humans is not known; the potential risk of adverse neurodevelopmental effects should be considered and discussed with pregnant women undergoing procedures requiring general anesthetics and sedation drugs. (See Neurodevelopmental and Cognitive Effects under Cautions: Pediatric Precautions.)

Reproduction studies in female and male rats given IV ketamine doses of 10 mg/kg (approximately 0.8 times the average human ketamine induction dose of 2 mg/kg based on body surface area) prior to mating did not reveal any evidence of impaired fertility.

It is not known whether ketamine is distributed into milk. Because the drug should be undetectable in plasma approximately 11 hours after administration, nursing after this time period should not expose the infant to clinically relevant amounts of ketamine.

Drug Interactions

■ **Drugs and Foods Affecting Hepatic Microsomal Enzymes** The biotransformation of ketamine and its norketamine metabolite is mediated by cytochrome P-450 (CYP) isoenzymes, principally by CYP3A4 with lesser involvement by CYP2B6 and CYP2C9. (See Pharmacokinetics: Elimination.) Therefore, drugs that inhibit or induce these CYP isoenzymes, particularly CYP3A4, may increase or decrease, respectively, the systemic exposure of ketamine or norketamine.

Grapefruit Juice In healthy individuals, concomitant administration of the CYP3A4 inhibitor grapefruit juice (200 mL 3 times daily for 5 days) and *S*-ketamine (single oral dose of 0.2 mg/kg) increased peak plasma concentrations and area under the concentration-time curve (AUC) of ketamine by twofold and threefold, respectively. This interaction may be clinically important if ketamine is taken orally.

Itraconazole Concomitant administration of the CYP3A inhibitor itraconazole (200 mg orally once daily) and *S*-ketamine (single oral dose of 0.2 mg/kg) in healthy individuals had no effect on the AUC of ketamine.

Macrolide Antibiotics Concomitant administration of the CYP3A4 inhibitor clarithromycin and *S*-ketamine (single oral dose of 0.2 mg/kg) in healthy individuals increased peak plasma concentration and AUC of ketamine by 3.6- and 2.6-fold, respectively, and decreased the ratio of norketamine to ketamine by 54%. In addition, self-reported pharmacologic effects of ketamine were increased when *S*-ketamine was administered following pretreatment with clarithromycin. Erythromycin, but not azithromycin, is expected to have similar effects on the pharmacokinetics of *S*-ketamine.

Rifampin Concomitant use of the potent CYP3A4 and CYP2B6 inducer rifampin (600 mg orally daily for 5 days) and *S*-ketamine (0.57–1.14 mg/kg by IV infusion over 2 hours) in healthy individuals decreased the AUC of *S*-ketamine and *S*-norketamine by 10 and 50%, respectively.

St. John's Wort In healthy individuals, concomitant administration of the CYP3A4 inducer St. John's wort (*Hypericum perforatum*) and *S*-ketamine (single oral dose of 0.3 mg/kg) decreased peak plasma concentration and AUC of *S*-ketamine by 66 and 58%, respectively, and of *S*-norketamine by 18 and 23%, respectively.

Ticlopidine Concomitant use of the CYP2B6 inhibitor ticlopidine (250 mg orally twice daily) and *S*-ketamine (single oral dose of 0.2 mg/kg) in healthy individuals increased the AUC of *S*-ketamine by 2.4-fold and decreased the ratio of norketamine to ketamine.

■ **Anesthetic Agents** Ketamine is clinically compatible with commonly used general and local anesthetic agents when adequate respiration is maintained.

■ **CNS Depressants** Concomitant use of ketamine with CNS depressants (e.g., alcohol, benzodiazepines, opiate agonists, skeletal muscle relaxants) may result in additive CNS depression and increased risk of respiratory depression. Concomitant use of barbiturates and/or opiate agonists with ketamine during anesthesia may prolong recovery time. However, decreased half-life and plasma concentrations of ketamine have been observed in patients receiving long-term therapy with barbiturates, likely due to hepatic enzyme induction. (See Drug Interactions: Drugs and Foods Affecting Hepatic Microsomal Enzymes.)

Benzodiazepines *Increased* half-life of ketamine has been reported in patients who were premedicated with diazepam rectally (as a single dose) prior to anesthesia; these patients required lower doses of ketamine. However, *decreased* ketamine half-life was observed in patients who had been receiving long-term therapy with oral diazepam.

Ketamine metabolism was not substantially altered in patients who received IV clorazepate prior to anesthesia.

Administration of lorazepam has been reported to diminish the antidepressant response to repeated ketamine infusions in a patient with severe depression associated with bipolar disorder. Based on limited clinical evidence and theoretic concerns based on proposed mechanisms of action that benzodiazepines may diminish the antidepressant effects of ketamine, some clinicians recommend avoiding benzodiazepine administration for 8–12 hours prior to ketamine infusions.

■ **Ergonovine** Concomitant use of ketamine and ergonovine may result in increased blood pressure.

■ **Lamotrigine** Limited data suggest that lamotrigine, which inhibits the release of glutamate, may antagonize some of the effects of ketamine. Attenuated effects of ketamine, including perceptual abnormalities, schizophrenia-like symptoms, and learning and memory impairment, have been observed in healthy individuals who were pretreated with lamotrigine (300 mg) prior to receiving ketamine (0.26 mg/kg by IV injection or 0.65 mg/kg per hour by IV infusion). Failure of ketamine anesthesia following administration of IV doses totaling approximately 3.125 mg/kg has been reported in a patient with lamotrigine overdosage.

Lamotrigine has been reported to reduce ketamine cravings in a patient with ketamine abuse disorder.

■ **Neuromuscular Blocking Agents** Ketamine may potentiate the neuromuscular blocking effects of atracurium, resulting in respiratory depression and apnea. It is not known whether ketamine affects the duration of neuromuscular blockade of other neuromuscular blocking agents.

■ **Theophyllines** Concomitant use of ketamine and aminophylline or theophylline may result in a clinically important reduction in the seizure threshold. Tonic seizures have been reported during ketamine anesthesia in patients receiving aminophylline or theophylline.

■ **Thyroid Agents** Patients receiving thyroid replacement therapy may have an increased risk of ketamine-induced hypertension and tachycardia.

Acute Toxicity

Ketamine has a wide margin of safety. Overdosage of ketamine can result in respiratory depression, in which case respiratory support (e.g., mechanical ventilation) should be provided. Several cases of accidental ketamine overdosage (with doses up to 10 or 100 times the intended dose in adults or children, respectively) resulted in prolonged sedation, but no other clinically important adverse effects or complications; ventilator support was required rarely. Death

secondary to acute ketamine overdosage in the absence of multidrug intoxication is rare, although accidental deaths have been reported. A lethal dose of ketamine in humans has not been identified.

In animal studies, vacuolation in neuronal cells of the posterior cingulate and retrosplenial cortices was observed in adult rats following intraperitoneal administration of ketamine at doses greater than 40 mg/kg. Vacuolation appeared to be reversible and did not progress to degeneration or neuronal death at doses up to 80 mg/kg (1.2 times the human dose of 10 mg/kg based on body surface area). The period of vulnerability to these changes is thought to correlate with the onset of puberty through adulthood in humans. The clinical relevance of these animal findings to humans is not known.

Chronic Toxicity

Ketamine is a known drug of abuse. Although cases of abuse and dependence have been reported with ketamine, the abuse potential with the drug has not been clearly defined.

Tolerance to the drug's effects may develop following prolonged administration. A sevenfold increase in the dose required for a desired "high" has been reported after 2 months of continuous use in recreational users of ketamine.

Although reported rarely, dependence on ketamine is possible. Cases of ketamine abuse resulting in physical or psychologic dependence have been reported. Evidence of withdrawal symptoms following discontinuance of ketamine is lacking; however, a withdrawal syndrome with psychotic features has been described following cessation of long-term ketamine use.

Urinary tract complications have been reported in association with long-term ketamine use, generally in the setting of chronic drug abuse, but also with clinical use of the drug. Reported lower urinary tract and bladder symptoms include cystitis, hematuria, dysuria, increased urinary frequency, urgency, incontinence, and postmicturition pain; secondary renal damage also can occur in severe cases. The exact mechanism of urinary tract damage is not clear, but ketamine and/or its metabolites are thought to have a direct irritant effect on the urothelium or interstitial cells of the bladder. Decreased bladder capacity and compliance, bladder wall thickening, transmural inflammation, detrusor muscle dysfunction, vesicoureteric reflux, hydronephrosis, and papillary necrosis have been observed.

Hepatobiliary toxicity also has been associated with long-term use of ketamine for therapeutic purposes or in the setting of chronic drug abuse. Epigastric pain, bile duct dilatation, and abnormal liver function tests consistent with posthepatic obstruction have been observed in chronic ketamine abusers.

Long-term use of ketamine has been reported to cause neuropsychiatric effects including hallucinatory flashbacks, inability to concentrate, and other cognitive deficits, possibly resulting from long-term effects of *N*-methyl-D-aspartic acid (NMDA)-receptor blockade. Both short-term and long-term memory impairment have been reported in chronic ketamine users. Magnetic resonance imaging (MRI) studies in chronic ketamine abusers have found areas of degeneration in the superficial white matter as early as 1 year of ketamine abuse; cortical atrophy and substantially decreased thalamocortical connectivity in the brain also have been observed.

Pharmacology

■ **Mechanism of Action** Ketamine is a nonbarbiturate general anesthetic that also has analgesic, amnestic, anti-inflammatory, and antidepressant properties. The pharmacologic effects of ketamine are dose dependent and mediated principally by its actions on the *N*-methyl-D-aspartate (NMDA) receptor, with contributory effects from other receptor interactions.

The anesthetic, amnestic, analgesic, and psychotomimetic effects of ketamine have been attributed to the drug's noncompetitive antagonism of the NMDA receptor. The NMDA receptor is a ligand-gated channel complex that plays an important role in excitatory glutamate-mediated neurotransmission, which can affect cognition, chronic pain, opiate tolerance, and mood regulation. The receptor is blocked at resting state by extracellular magnesium. Upon neuronal depolarization, magnesium is released, resulting in ligand-induced channel opening and calcium influx. Ketamine binds to the phencyclidine (PCP) site of the NMDA receptor channel, decreasing the frequency of channel opening and duration of time in the open active state, thereby inhibiting receptor activation and excitatory glutamatergic neurotransmission.

The NMDA receptor is closely involved in the development of opiate tolerance, opiate-induced hyperalgesia, and central sensitization (a condition closely related to the development of chronic pain). Activation of the NMDA receptor enhances neuronal excitability that can lead to hyperalgesia and allodynia. In the development of opiate tolerance and opiate-induced hyperalgesia, repeated activation of opiate receptors causes phosphorylation and opening of the NMDA receptor channel, leading to downregulation of opiate receptors and a reduction in opiate responsiveness. In chronic pain states, prolonged nociceptive stimulation causes activation and upregulation of NMDA receptors at dorsal horn synapses, resulting in enhanced and amplified trafficking of pain signals to the brain (central sensitization). Therefore, antagonism of NMDA receptors by ketamine decreases amplification of the response to repeated opiate receptor stimulation and can also prevent or reduce central sensitization.

In addition to its effects on the NMDA receptor, ketamine also acts on a wide range of other targets, including opiate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-aminobutyric acid A ($GABA_A$), cholinergic, nicotinic, and muscarinic receptors; L-type voltage-dependent calcium channels, hyperpolarization-activated cyclic nucleotide (HCN) channels, voltage-gated sodium channels, and large-conductance potassium (BK) channels; and the monoaminergic system.

■ **CNS Effects** Ketamine produces dissociative anesthesia as a result of a functional and electrophysiologic dissociation between the thalamocortical and limbic systems. The drug appears to selectively depress sensory association areas in the cortex, limbic systems, and thalamus without substantially obtunding the more primitive pathways (reticular-activating and limbic systems). At anesthetic doses, ketamine disrupts frontal-to-posterior corticocortical connectivity while maintaining thalamocortical somatosensory pathways. Thus, sensory input may reach cortical receiving areas but fail to be observed in some of the association areas, effectively dissociating the CNS from outside stimuli. At subanesthetic doses, ketamine has been shown to alter functional connectivity between the subgenual anterior cingulate cortex and a network cluster involving the thalamus, hippocampus, and the retrosplenial cortex, without reported loss of consciousness.

Ketamine increases cerebral metabolism and cerebral blood flow, and can also potentially increase intracranial pressure.

Anesthetic Effects At anesthetic doses, ketamine produces a dissociative, cataleptic state characterized by profound analgesia, sedation, and amnesia. The anesthetic state produced by ketamine is distinct from that of other general anesthetic drugs (e.g., barbiturates, propofol, benzodiazepines, inhalation anesthetics). Dissociated patients are nonresponsive and unable to respond to external stimuli (including pain). Although there is some variability, ketamine dissociation usually occurs at a dosing threshold of approximately 1–1.5 mg/kg when given IV or 3–4 mg/kg when given IM. Plasma ketamine concentrations associated with dissociative anesthesia have been reported to range from approximately 1.2–3 mcg/mL; concentrations associated with hypnosis and amnesia during surgery range from 0.8–4 mcg/mL and awakening usually occurs at plasma concentrations of 0.5–1.1 mcg/mL. Unlike other anesthetic or sedative drugs, increasing the dose of ketamine beyond the dissociative threshold does not enhance or deepen sedation.

Analgesic Effects At doses and plasma concentrations lower than those used for anesthesia, ketamine produces analgesia and sedation. Although there is some variability, doses less than 1 mg/kg generally have been considered subanesthetic.

Following IV or IM administration, analgesic effects are associated with plasma ketamine concentrations ranging from 0.07–0.2 mcg/mL. Analgesic effects following oral administration occur at plasma ketamine concentrations of 0.04 mcg/mL, possibly due to a higher ratio of norketamine. (See Pharmacokinetics: Absorption.)

Antidepressant Effects The precise mechanism(s) of ketamine's antidepressant activity has not been clearly established. Considerable preclinical research suggests that the NMDA class of glutamate receptors plays a role in the pathophysiology of depression as well as in the mechanism of action of antidepressant treatments. In addition, NMDA receptor antagonists, including ketamine, have been shown to be effective in animal models of depression and in models that predict antidepressant activity in many studies. Preclinical and clinical data suggest that the antidepressant effects of ketamine may be mediated by an increase in glutamate, which leads to a cascade of events that results in synaptogenesis and reversal of the negative effects of chronic stress and depression, particularly in the prefrontal cortex.

Following IV infusion of 0.5 mg/kg of ketamine over 40 minutes in patients with treatment-resistant major depressive disorder, peak plasma ketamine concentrations of 0.07–0.2 mcg/mL are achieved. These concentrations usually are associated with antidepressant effects but not general anesthetic effects.

Psychotomimetic Effects Like PCP, ketamine may cause psychotomimetic effects as a result of NMDA-receptor antagonism; such effects can occur following anesthetic or subanesthetic doses. At higher ketamine doses used for anesthesia, psychotomimetic effects appear to be dose related; however, a dose-related effect has not been clearly established at subanesthetic doses. The analgesic properties of ketamine are closely related to its psychotomimetic effects.

Psychotomimetic effects of ketamine may occur at IV doses in the range of 0.1–1 mg/kg or IM doses in the range of 25–200 mg. The most common manifestations reported following single subanesthetic IV doses include distortions in visual, auditory, or somatosensory stimuli; alterations in the perception of self or time; conceptual disorganization; hallucinations; suspiciousness; unusual thought content; blunted affect; emotional withdrawal; and motor retardation.

Psychotomimetic manifestations appearing during awakening or emergence from ketamine-induced dissociative anesthesia have been described as disturbances in visual and audio perception, mood, body image, and time; feelings of unreality, floating, or depersonalization; conscious dreams; and hallucinations. Such effects may occur at plasma concentrations as low as 0.05 mcg/mL, with more severe effects (e.g., anxiety, paranoid feelings) occurring around plasma concentrations of 0.5 mcg/mL. A linear concentration-effect relationship has been observed in healthy individuals for plasma concentrations ranging from 0.05–0.2 mcg/mL.

Psychotomimetic effects of ketamine usually are reversible following discontinuance of the drug.

■ **Respiratory Effects** Respiratory function generally is preserved during administration of ketamine, although transient and minimal respiratory depression may occur occasionally. Arterial hypoxemia and respiratory depres-

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sion have been reported following rapid IV administration of the drug. The drug may have a respiratory stimulating effect at low doses.

Upper airway reflexes remain intact and may be slightly exaggerated during ketamine administration. Ketamine also produces bronchodilation, likely through vagolytic and other centrally mediated mechanisms.

■ **Cardiovascular Effects** Ketamine inhibits the reuptake of catecholamines and has other direct and indirect sympathomimetic effects at subanesthetic and anesthetic doses. Typical cardiovascular effects include increases in heart rate, blood pressure, cardiac output, and myocardial oxygen consumption; however, hypotension and bradycardia also have been observed. Ketamine also causes direct relaxation of vascular smooth muscle; however, systemic vascular resistance usually is unaffected. The sympathomimetic effects of ketamine often are used to therapeutic advantage (e.g., in patients with severe hypotension, sepsis, or other hemodynamically compromised state).

When ketamine is administered IV in anesthetic doses, increased blood pressure usually occurs shortly after the IV injection, reaches a maximum within a few minutes, and returns to preanesthetic levels within 15 minutes. Systolic and diastolic blood pressure usually peaks at 10–50% over baseline values, but increases can be higher or last longer in some individuals. In healthy individuals receiving subanesthetic doses of ketamine (0.5 mg/kg by IV infusion over 40 minutes), increases in blood pressure were observed 10 minutes after the start of infusion; mean maximum increases in systolic and diastolic blood pressure of 13.38 and 12.65 mm Hg, respectively, occurred approximately 28 minutes after initiation of the infusion and returned to baseline levels within 2 hours. The mean maximum increase in heart rate in these individuals was 10.69 beats per minute.

Ketamine may have negative inotropic effects in some patients.

Pharmacokinetics

■ **Absorption** Ketamine has a rapid onset of anesthetic action when given IV or IM. Following IV administration of the usual induction dose of 2 mg/kg, onset of surgical anesthesia occurs within 30 seconds and the duration of anesthetic effect is 5–10 minutes. Following IM administration of doses ranging from 9–13 mg/kg, onset of surgical anesthesia occurs within 3–4 minutes and the duration of anesthetic effect is usually 12–25 minutes. Plasma ketamine concentrations are about 1.8–2 mcg/mL at 5 minutes following IV injection of a 2-mg/kg dose and about 1.7–2.2 mcg/mL at 15 minutes following IM injection of a 6-mg/kg dose. Following IV administration of a 2.5-mg/kg dose, ketamine has an initial distribution phase (α) lasting about 45 minutes and a half-life of 10–15 minutes, which is associated with the duration of anesthetic effect (about 20 minutes).

Norketamine, the main active metabolite of ketamine, appears in the blood 2–3 minutes following IV administration of the drug and reaches peak plasma concentration in approximately 30 minutes.

Peak plasma concentrations following oral administration of ketamine occur within 20–120 minutes.

Bioavailability of ketamine following IM administration is 93% in adults; lower IM bioavailability has been reported in children. Due to extensive first-pass metabolism, bioavailability following oral or rectal administration is low (16–30 or 11–30%, respectively), with relatively higher concentrations of norketamine.

Bioavailability of ketamine following intranasal administration has been reported to be up to 45–50%, but can vary substantially.

In children 4–10 years of age, plasma ketamine concentrations are similar to those observed in adults. Plasma concentrations of norketamine are higher in children than adults following equivalent weight-adjusted doses.

■ **Distribution** Ketamine is rapidly and widely distributed into highly perfused tissues, including the CNS, with a distribution half-life of 10–15 minutes. Animal studies have shown ketamine to be highly concentrated in body fat, liver, and lung. Because ketamine is lipophilic, it has a large volume of distribution.

Termination of the anesthetic effect of ketamine occurs partly via redistribution from the CNS to peripheral tissues and partly by hepatic biotransformation.

Ketamine crosses the placenta. Following an IM dose of 250 mg (approximately 4.2 mg/kg) in parturient patients, placental transfer rate of ketamine from maternal artery to umbilical vein was 47% at the time of delivery (average of 12 minutes from the time of injection to vaginal delivery).

It is not known whether ketamine is distributed into milk.

Ketamine is less than 50% bound to plasma proteins (α_1-acid glycoprotein or albumin).

■ **Elimination** Ketamine is metabolized extensively in the liver, principally undergoing *N*-demethylation to the active metabolite norketamine, which has approximately one-third the anesthetic activity of the parent drug. *N*-demethylation of ketamine to norketamine is mediated principally by cytochrome P-450 (CYP) isoenzyme 3A4 and, to a lesser extent, by CYP2B6 and CYP2C9. Norketamine is further metabolized to hydroxynorketamines and dehydronorketamine.

Other biotransformation pathways of ketamine include hydroxylation of the cyclohexone ring, conjugation with glucuronic acid, and dehydration of the hydroxylated metabolites to form a cyclohexene derivative.

About 90% of a parenteral dose of ketamine is excreted in the urine, mostly as conjugates of hydroxylated metabolites. Less than 5% of a dose is excreted unchanged in feces and urine. Because ketamine is extensively metabolized prior to excretion, the effect of renal function on the pharmacokinetics of ketamine and norketamine is minimal. Plasma concentrations of ketamine have been reported to be 20% higher in individuals with acute renal failure than in those with normal renal function.

Ketamine is not appreciably removed by hemodialysis or hemofiltration (10 or 4%, respectively).

The elimination half-life of ketamine is approximately 2–4 hours and is shorter in children (approximately 100 minutes) than in adults. The half-life of norketamine is 12 hours.

Chemistry and Stability

■ **Chemistry** Ketamine hydrochloride is an arylcycloalkylamine general anesthetic derived from phencyclidine (PCP). Ketamine is commercially available in the US as a racemic mixture containing equal amounts of the *R*- and *S*-enantiomers. *S*-Ketamine, which is commercially available as esketamine in the US and some other countries, has a higher binding affinity for *N*-methyl-D-aspartate (NMDA) receptors and has approximately 3–4 times greater anesthetic potency than *R*-ketamine. *S*-Ketamine also appears to be associated with more frequent psychotomimetic adverse effects compared with *R*-ketamine.

Ketamine is commercially available as the hydrochloride salt. Ketamine hydrochloride injection is a sterile solution of the drug that contains benzethonium chloride as a preservative; sodium chloride has been added to the injection containing 10 mg of ketamine per mL to provide an isotonic solution. The sterile solution has a pH of 3.5–5.5.

Ketamine hydrochloride is soluble in both water and lipids.

■ **Stability** Ketamine hydrochloride injection should be stored at controlled room temperature between 20–25°C and protected from light.

The commercially available 100-mg/mL ketamine injection (as the hydrochloride) must be diluted with an equal volume of sterile water for injection, 5% dextrose, or 0.9% sodium chloride injection prior to IV injection. For IV infusion, a solution containing 1 or 2 mg/mL may be prepared by diluting an appropriate volume of ketamine from the commercially available 50- or 100-mg/mL vial with 5% dextrose or 0.9% sodium chloride injection. (See Dilution under Dosage and Administration: Administration.)

The manufacturer states that ketamine hydrochloride injection is incompatible with barbiturates and diazepam, and should *not* be mixed in the same syringe or infusion solution with these drugs due to the risk of precipitate formation. Ketamine has been reported to be compatible with several drugs when administered as additives, simultaneously in the same syringe, or when a Y-type administration set is used; specialized references should be consulted for more specific information.

Preparations

Ketamine is subject to control under the Federal Controlled Substances Act of 1970 as a schedule III (C-III) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ketamine Hydrochloride

Parenteral		
Injection	10 mg (of ketamine) per mL*	**Ketalar®** (C-III), Par
		Ketamine Hydrochloride Injection (C-III)
	50 mg (of ketamine) per mL*	**Ketalar®** (C-III), Par
		Ketamine Hydrochloride Injection (C-III)
	100 mg (of ketamine) per mL*	**Ketalar®** (C-III), Par
		Ketamine Hydrochloride Injection (C-III)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Propofol

■ Propofol is a sedative and hypnotic agent.

Uses

Propofol is used for IV induction and maintenance of anesthesia in adults and pediatric patients. Propofol also is used IV for initiation and maintenance of monitored anesthesia care (MAC) sedation in adults undergoing diagnostic procedures or in those undergoing surgical procedures who are receiving local or regional anesthesia. In addition, propofol is used IV for sedation in intubated and mechanically ventilated adults in a critical care setting (e.g., intensive care unit [ICU]).

■ **Induction and Maintenance of Anesthesia** *General Overview of Anesthesia* The IV anesthetic agents propofol, etomidate, methohexital, and thiopental (no longer commercially available in the US) are widely used

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BYFAVO safely and effectively. See full prescribing information for BYFAVO.

BYFAVO™ (remimazolam) for injection, for intravenous use, Scheduling pending
Initial U.S. Approval: 2020

WARNING: PERSONNEL AND EQUIPMENT FOR MONITORING AND RESUSCITATION, AND RISKS FROM CONCOMITANT USE WITH OPIOID ANALGESICS AND OTHER SEDATIVE-HYPNOTICS

See full prescribing information for complete boxed warning

- **Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO. (2.1, 5.1)**
- **Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation. (2.1, 5.1)**
- **BYFAVO has been associated with hypoxia, bradycardia, and hypotension. Continuously monitor vital signs during sedation and through the recovery period. (2.1, 5.1)**
- **Resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask assisted ventilation must be immediately available during administration of BYFAVO. (2.1, 5.1)**
- **Concomitant use of benzodiazepines with opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of intravenous BYFAVO can be accentuated by concomitantly administered CNS depressant medications, including other benzodiazepines and propofol. Continuously monitor patients for respiratory depression and depth of sedation. (5.2, 7.1)**

----------INDICATIONS AND USAGE----------

BYFAVO (remimazolam) for injection is a benzodiazepine indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less. (1)

----------DOSAGE AND ADMINISTRATION----------

Individualize and titrate BYFAVO dosing to desired clinical effect. (2.2)

Adult Patients:

- Administer an initial dose intravenously as a 5 mg push injection over a 1-minute time period. (2.2)
- If necessary, administer supplemental doses of 2.5 mg intravenously over a 15-second time period. At least 2 minutes must elapse prior to the administration of any supplemental dose. (2.2)

ASA-PS III-IV Patients (at the discretion of the physician):

- Based on the general condition of the patient, administer 2.5 mg to 5 mg over 1-minute time period. (2.2)
- If necessary, administer supplemental doses of 1.25 mg to 2.5 mg intravenously over a 15-second time period. At least 2 minutes must elapse prior to the administration of any supplemental dose. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Each glass, single-patient-use vial contains 20 mg BYFAVO (remimazolam) lyophilized powder for reconstitution, equivalent to 27.2 mg remimazolam besylate. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to dextran 40. (4)

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity Reactions: Hypersensitivity reactions including anaphylaxis may occur. (5.3)
Neonatal Sedation: Benzodiazepine use during pregnancy can result in neonatal sedation. Observe newborns for signs of sedation and manage accordingly. (5.4)
Pediatric Neurotoxicity: In developing animals, exposures greater than 3 hours cause neurotoxicity. Weigh benefits against potential risks when considering elective procedures in children under 3 years old. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reactions (>10%) in patients receiving BYFAVO for procedural sedation are hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Acacia Pharma at 1-877-357-9237 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

Lactation: A lactating woman may pump and discard breast milk for 5 hours after treatment with BYFAVO. (8.2)
Pediatric Use: BYFAVO should not be used in patients less than 18 years of age. (8.4)
Geriatric Use: Sedating drugs, such as BYFAVO, may cause confusion and over-sedation in the elderly; elderly patients generally should be observed closely. (8.5)
Severe Hepatic Impairment: In patients with severe hepatic impairment the dose of BYFAVO should be carefully titrated to effect. Depending on the overall status of the patient, reduced doses might be indicated. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Personnel and Equipment for Monitoring and Resuscitation

- **Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.**
- **Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.**
- **BYFAVO has been associated with hypoxia, bradycardia, and hypotension. Continuously monitor vital signs during sedation and during the recovery period *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.**
- **Resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask assisted ventilation must be immediately available during administration of BYFAVO *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.**

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

Concomitant use of benzodiazepines, including BYFAVO, and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of intravenous BYFAVO can be accentuated by concomitantly administered CNS depressant medications, including other benzodiazepines and propofol. Continuously monitor patients for respiratory depression and depth of sedation *[see Warnings and Precautions (5.2), Drug Interactions (7.1)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

BYFAVO can depress respiration. Continuously monitor patients for early signs of hypoventilation, airway obstruction, and apnea using capnography, pulse oximetry, and clinical assessment.

Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO.

Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.

Supplemental oxygen, resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask assisted ventilation must be immediately available during administration of BYFAVO. A benzodiazepine reversal agent should be immediately available.

Continuously monitor vital signs during sedation and through the recovery period *[see Warnings and*

Precautions (5.1)].

Peak sedation occurs approximately 3 to 3.5 minutes after an initial 5 mg intravenous injection of BYFAVO given over a 1-minute period *[see Clinical Pharmacology (12.2)].*

Titrate subsequent doses of BYFAVO on the basis of clinical judgment and assessment of the depth of sedation. If maintenance of procedural sedation is inadequate, consider alternative medications *[see Clinical Studies (14)].*

2.2 Basic Dosing Information

- Individualize BYFAVO dosing and titrate to desired clinical response.
- In clinical studies, fentanyl 25 to 75 mcg was administered for analgesia prior to the first dose of BYFAVO. Supplemental doses of fentanyl were administered as needed for analgesia *[see Clinical Studies (14)].*
- Recommended dosing guidelines:

Induction of Procedural Sedation	**For adult patients:** Administer 5 mg intravenously over a 1-minute time period.
	For ASA-PS (American Society of Anesthesiologists Physical Status) III and IV patients: Administer 2.5 mg to 5 mg intravenously over 1 minute based on the general condition of the patient.
Maintenance of Procedural Sedation (as needed)	**For adult patients:** Administer 2.5 mg intravenously over 15 seconds. At least 2 minutes must elapse prior to administration of any supplemental dose.
	For ASA-PS III and IV patients: Administer 1.25 mg to 2.5 mg intravenously over 15 seconds. At least 2 minutes must elapse prior to administration of any supplemental dose.

2.3 Preparation

Reconstitution of BYFAVO (remimazolam) for injection

- Strict aseptic technique must be maintained during handling of BYFAVO.
- This product does not contain preservative.
- Once removed from packaging, protect vials from light.
- Each single-patient-use vial contains 20 mg BYFAVO lyophilized powder for reconstitution. The product must be prepared immediately before use.
- To reconstitute, add 8.2 mL sterile 0.9% Sodium Chloride Injection, USP, to the vial, directing the stream of solution toward the wall of the vial. Gently swirl the vial (do not shake) until the contents are fully dissolved. The reconstituted product will deliver a final concentration of 2.5 mg/mL solution of BYFAVO.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Upon reconstitution, the solution should be a clear, colorless to pale yellow solution. Discard if particulate matter or discoloration is observed.

- If not used immediately, reconstituted BYFAVO may be stored in the vial for up to 8 hours under controlled room temperature at 20°C to 25°C (68°F to 77°F). After 8 hours, any unused portion must be discarded.

2.4 Administration with Other Fluids

- BYFAVO has been shown to be compatible with the following fluids: 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 20% Dextrose Injection, USP, 5% Dextrose and 0.45% Sodium Chloride Injection, USP, and Ringer's Solution. Do not mix BYFAVO with other drugs or fluids prior to administration.
- BYFAVO compatibility with other agents has not been adequately evaluated.

3 DOSAGE FORM AND STRENGTHS

Single-patient-use vial: Each glass, single-patient-use vial of BYFAVO (remimazolam) for injection contains 20 mg remimazolam white to off-white lyophilized powder, equivalent to 27.2 mg remimazolam besylate.

4 CONTRAINDICATIONS

BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40 *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Personnel and Equipment for Monitoring and Resuscitation

Clinically notable hypoxia, bradycardia, and hypotension were observed in Phase 3 studies of BYFAVO. Continuously monitor vital signs during sedation and through the recovery period.

Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO.

Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.

Resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask assisted ventilation must be immediately available during administration of BYFAVO *[see Dosage and Administration (2.1)]*.

Consider the potential for worsened cardiorespiratory depression prior to using BYFAVO concomitantly with other drugs that have the same potential (e.g., opioid analgesics or other sedative-hypnotics) *[see Drug Interactions (7.1)]*.

Administer supplemental oxygen to sedated patients through the recovery period.

A benzodiazepine reversal agent (flumazenil) should be immediately available during administration of BYFAVO *[see Overdosage (10)]*.

5.2 Risks from Concomitant Use with Opioid Analgesics and Other Sedative-Hypnotics

Concomitant use of benzodiazepines, including BYFAVO, and opioid analgesics may result in profound sedation, respiratory depression, coma, and death *[see Drug Interactions (7.1)]*.

The sedative effect of intravenous BYFAVO can be accentuated by concomitantly administered CNS depressant medications, including other benzodiazepines and propofol.

Titrate the dose of BYFAVO when administered with opioid analgesics and sedative-hypnotics to the desired clinical response.

Continuously monitor sedated patients for hypotension, airway obstruction, hypoventilation, apnea, and oxygen desaturation. These cardiorespiratory effects may be more likely to occur in patients with obstructive sleep apnea, the elderly, and ASA-PS III or IV patients.

5.3 Hypersensitivity Reactions

BYFAVO contains dextran 40, which can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis. BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40 *[see Contraindications (4), Adverse Reactions (6)]*.

5.4 Neonatal Sedation

Use of benzodiazepines during the later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) in the neonate. Observe newborns for signs of sedation and manage accordingly *[see Use in Specific Populations (8.1, 8.4)]*.

5.5 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 Use in Specific Populations (8.1, 8.4), Nonclinical Pharmacology (13.2)]*.

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BYFAVO was evaluated in three prospective, randomized, double-blind, multicenter, parallel group clinical studies in 630 patients undergoing colonoscopy (two studies) or bronchoscopy (one study). Colonoscopy Study 1 and the bronchoscopy study evaluated American Society of Anesthesiologists Physical Status (ASA-PS) class I to III patients, and Colonoscopy Study 2 evaluated ASA-PS class III and IV patients.

All three studies evaluated the safety of BYFAVO compared to placebo with midazolam rescue and an open-label midazolam treatment arm. Patients were administered a total dose ranging from 5 to 30 mg of BYFAVO. In these studies, the most common adverse reactions (incidence greater than 10%) following BYFAVO administration were hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension. There were two patients who experienced an adverse reaction that led to discontinuation of study drug. One patient in the BYFAVO arm in the bronchoscopy study discontinued treatment due to bradycardia, hypertension, hypotension, hypoxia, and respiratory rate increase. One patient in the open-label midazolam arm in Colonoscopy Study 2 discontinued due to respiratory acidosis. No deaths were reported during the studies.

Tables 1-3 provide a summary of the common adverse reactions observed in each of the three Phase 3 studies with BYFAVO.

Table 1: Common Adverse Reactions in Colonoscopy Study 1 (Incidence >2%), ASA-PS Class I to III

Adverse Reaction	BYFAVO N = 296 n (%)	Placebo (with Midazolam Rescue‡) N = 60 n (%)	Midazolam N = 102 n (%)
Hypotension§	115 (39%)	25 (42%)	63 (62%)
Hypertension†	59 (20%)	17 (28%)	18 (18%)
Bradycardia	33 (11%)	7 (12%)	16 (16%)
Diastolic hypertension†	29 (10%)	6 (10%)	9 (9%)
Tachycardia	23 (8%)	7 (12%)	13 (13%)
Diastolic hypotension§	23 (8%)	4 (7%)	9 (9%)
Systolic hypertension†	16 (5%)	5 (8%)	6 (6%)

‡ 57/60 (95%) patients received midazolam rescue.

§ Hypotension defined as a fall in systolic BP to ≤80 mmHg or in diastolic BP to ≤40 mmHg, or a fall in systolic or diastolic BP of 20% or more below baseline or necessitating medical intervention.

† Hypertension defined as an increase in systolic BP to ≥180 mmHg or in diastolic BP to ≥100 mmHg, or an increase of systolic or diastolic BP of 20% or more over baseline or necessitating medical intervention.

Table 2: Common Adverse Reactions in Bronchoscopy Study (Incidence >2%)

Adverse Reaction	BYFAVO N = 303 n (%)	Placebo (with Midazolam Rescue‡) N = 59 n (%)	Midazolam N = 69 n (%)
Hypotension§	99 (33%)	28 (47%)	23 (33%)
Hypertension†	85 (28%)	9 (15%)	19 (28%)
Diastolic hypertension†	77 (25%)	15 (25%)	16 (23%)
Systolic hypertension†	67 (22%)	13 (22%)	17 (25%)
Hypoxia	66 (22%)	12 (20%)	13 (19%)
Respiratory rate increased	43 (14%)	6 (10%)	10 (14%)
Diastolic hypotension§	41 (14%)	17 (29%)	16 (23%)
Nausea	12 (4%)	2 (3%)	2 (3%)
Bradycardia	11 (4%)	4 (7%)	4 (6%)
Pyrexia	11 (4%)	1 (2%)	1 (1%)
Headache	8 (3%)	0 (0%)	3 (4%)

‡ 57/59 (97%) patients received midazolam rescue.

§ Hypotension defined as a fall in systolic BP to ≤80 mmHg or in diastolic BP to ≤40 mmHg, or a fall in systolic or diastolic BP of 20% or more below baseline or necessitating medical intervention.

† Hypertension defined as an increase in systolic BP to ≥180 mmHg or in diastolic BP to ≥100 mmHg, or an increase of systolic or diastolic BP of 20% or more over baseline or necessitating medical intervention.

Table 3: Common Adverse Reactions in Colonoscopy Study 2 (Incidence >2%), ASA-PS Class III and IV

Adverse Reaction	BYFAVO N = 31 n (%)	Placebo (with Midazolam Rescue‡) N = 16 n (%)	Midazolam N = 30 n (%)
Hypotension§	18 (58%)	11 (69%)	17 (57%)
Hypertension†	13 (42%)	6 (38%)	13 (43%)
Respiratory acidosis	6 (19%)	2 (13%)	8 (27%)
Diastolic hypertension†	3 (10%)	0 (0%)	0 (0%)
Systolic hypertension†	2 (6%)	0 (0%)	0 (0%)
Bradycardia	1 (3%)	1 (6%)	4 (13%)
Respiratory rate decreased	1 (3%)	1 (6%)	2 (7%)
Diastolic hypotension§	1 (3%)	1 (6%)	0 (0%)
Blood pressure diastolic increased	1 (3%)	0 (0%)	0 (0%)
Blood pressure increased	1 (3%)	0 (0%)	0 (0%)
Blood pressure systolic increased	1 (3%)	0 (0%)	0 (0%)

Adverse Reaction	BYFAVO N = 31 n (%)	Placebo (with Midazolam Rescue‡) N = 16 n (%)	Midazolam N = 30 n (%)
Upper respiratory tract infection	1 (3%)	0 (0%)	0 (0%)

‡ 16/16 (100%) patients received midazolam rescue.

§ Hypotension defined as a fall in systolic BP to ≤80 mmHg or in diastolic BP to ≤40 mmHg, or a fall in systolic or diastolic BP of 20% or more below baseline or necessitating medical intervention.

† Hypertension defined as an increase in systolic BP to ≥80 mmHg or in diastolic BP to ≥100 mmHg, or an increase of systolic or diastolic BP of 20% or more over baseline or necessitating medical intervention.

Adverse reaction data from Colonoscopy Study 1 and the bronchoscopy study analyzed according to the cumulative dose of concomitant fentanyl (<100 mcg, 100-150 mcg and >150 mcg) suggest an increase in some adverse reactions with increasing fentanyl dose, such as hypotension, hypertension, bradycardia, hypoxia, and increased respiratory rate (see Table 4 and Table 5). There were too few patients in each fentanyl stratum in Colonoscopy Study 2 to perform this analysis.

Table 4: Common Adverse Reactions* in Colonoscopy Study 1 by Cumulative Fentanyl Dose

	BYFAVO			Placebo (with Midazolam Rescue‡)			Midazolam		
Fentanyl dose (mcg)	**<100**	**100-150**	**>150**	**<100**	**100-150**	**>150**	**<100**	**100-150**	**>150**
	N = 148	**N = 146**	**N = 2**	**N = 9**	**N = 43**	**N = 8**	**N = 31**	**N = 62**	**N = 9**
Adverse Reaction	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypotension§	49 (33%)	64 (44%)	2 (100%)	5 (56%)	17 (40%)	3 (38%)	18 (58%)	36 (58%)	9 (100%)
Hypertension†	24 (16%)	35 (24%)	0 (0%)	1 (11%)	14 (33%)	2 (25%)	3 (10%)	12 (19%)	3 (33%)
Bradycardia	12 (8%)	20 (14%)	1 (50%)	0 (0%)	5 (12%)	2 (25%)	1 (3%)	13 (21%)	2 (22%)
Diastolic hypertension†	9 (6%)	20 (14%)	0 (0%)	0 (0%)	3 (7%)	3 (38%)	2 (6%)	7 (11%)	0 (0%)
Tachycardia	10 (7%)	12 (8%)	1 (50%)	0 (0%)	6 (14%)	1 (13%)	2 (6%)	8 (13%)	3 (33%)
Diastolic hypotension§	10 (7%)	13 (9%)	0 (0%)	0 (0%)	3 (7%)	1 (13%)	3 (10%)	4 (6%)	2 (22%)
Systolic hypertension†	5 (3%)	11 (8%)	0 (0%)	0 (0%)	3 (7%)	2 (25%)	4 (13%)	2 (3%)	0 (0%)

* Incidence >2% of patients.

‡ 57/60 (95%) patients received midazolam rescue.

§ Hypotension defined as a fall in systolic BP to ≤80 mmHg or in diastolic BP to ≤40 mmHg, or a fall in systolic or diastolic BP of 20% or more below baseline or necessitating medical intervention.

† Hypertension defined as an increase in systolic BP to ≥180 mmHg or in diastolic BP to ≥100 mmHg, or an increase of systolic or diastolic BP of 20% or more over baseline or necessitating medical intervention.

Table 5: Common Adverse Reactions* in Bronchoscopy Study by Cumulative Fentanyl Dose

	BYFAVO			Placebo (with Midazolam Rescue‡)			Midazolam		
Fentanyl dose (mcg)	**<100**	**100-150**	**>150**	**<100**	**100-150**	**>150**	**<100**	**100-150**	**>150**
	N = 215	**N = 63**	**N = 25**	**N = 26**	**N = 18**	**N = 15**	**N = 29**	**N = 27**	**N = 13**
Adverse Reaction	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypotension§	52 (24%)	32 (51%)	16 (64%)	7 (27%)	9 (50%)	12 (80%)	7 (24%)	7 (26%)	9 (69%)
Hypertension†	43 (20%)	25 (40%)	18 (72%)	2 (8%)	2 (11%)	5 (33%)	3 (10%)	8 (30%)	8 (62%)
Diastolic hypertension†	65 (30%)	12 (19%)	0 (0%)	11 (42%)	3 (17%)	1 (7%)	10 (34%)	6 (22%)	0 (0%)
Systolic hypertension†	55 (26%)	11 (17%)	1 (4%)	10 (38%)	3 (17%)	0 (0%)	9 (31%)	6 (22%)	2 (15%)
Hypoxia	35 (16%)	22 (35%)	9 (36%)	6 (23%)	2 (11%)	4 (27%)	2 (7%)	5 (19%)	6 (46%)
Respiratory rate increased	22 (10%)	12 (19%)	9 (36%)	1 (4%)	2 (11%)	3 (20%)	2 (7%)	5 (19%)	3 (23%)
Diastolic hypotension§	28 (13%)	13 (21%)	0 (0%)	8 (31%)	7 (39%)	2 (13%)	7 (24%)	6 (22%)	3 (23%)
Nausea	9 (4%)	1 (2%)	2 (8%)	0 (0%)	0 (0%)	2 (13%)	1 (3%)	1 (4%)	0 (0%)
Bradycardia	3 (1%)	4 (6%)	4 (16%)	2 (8%)	1 (6%)	1 (7%)	0 (0%)	2 (7%)	2 (15%)
Pyrexia	7 (3%)	2 (3%)	2 (8%)	0 (0%)	0 (0%)	1 (7%)	1 (3%)	0 (0%)	0 (0%)
Headache	5 (2%)	2 (3%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (11%)	0 (0)%

* Incidence >2% of patients.

‡ 57/59 (97%) patients received midazolam rescue.

§ Hypotension defined as a fall in systolic BP to ≤ 80 mmHg or in diastolic BP to ≤40 mmHg, or a fall in systolic or diastolic BP of 20% or more below baseline or necessitating medical intervention.

† Hypertension defined as an increase in systolic BP to ≥180 mmHg or in diastolic BP to ≥100 mmHg, or an increase of systolic or diastolic BP of 20% or more over baseline or necessitating medical intervention.

7 DRUG INTERACTIONS

7.1 Opioid Analgesics and Other Sedative-Hypnotics

The sedative effect of intravenous BYFAVO can be accentuated by concomitantly administered CNS depressant medications, including opioid analgesics, other benzodiazepines, and propofol. Continuously monitor vital signs during sedation and through the recovery period. Titrate the dose of BYFAVO when administered with opioid analgesics and sedative-hypnotics to the desired clinical response *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Infants born to mothers using benzodiazepines during the later stages of pregnancy have been reported to experience symptoms of sedation *[see Warnings and Precautions (5.4), Clinical Considerations].* Although there are no data on the effects of BYFAVO use in pregnant women, available data from published observational studies of pregnant women exposed to other benzodiazepines have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).*

In animal studies, reduced fetal weights but no evidence of malformations or embryofetal lethality were noted in a study in which pregnant rabbits were treated intravenously with 4 times the maximum recommended human dose (MRHD) of 30 mg during organogenesis. Adequate rodent reproductive and developmental toxicology studies have not been completed to fully evaluate the effects of BYFAVO.

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).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation and respiratory depression and manage accordingly *[see Warnings and Precautions (5.4)].*

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of more recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco, and other medications, have not confirmed these findings. There are no data on the specific effects of remimazolam on pregnancy. Infants exposed to benzodiazepines during the late third trimester of pregnancy or during labor have been reported to exhibit sedation and neonatal withdrawal symptoms.

Animal Data

Reduced fetal weights but no evidence of malformation or embryofetal lethality were noted in a study in which pregnant rabbits were treated intravenously with 5 mg/kg remimazolam (approximately 4 times the MRHD of 30 mg/day based on AUC) from Gestation Day 6 to 20 in the presence of maternal toxicity (reduced food intake and body weights).

In a study that did not test exposures comparable to the MRHD of 30 mg/day over the full period of organogenesis, there was an increase in early resorptions (embryolethality) but no evidence of malformations when female rats were treated from Gestation Day 6 through 17 with up to 30 mg/kg remimazolam via intravenous bolus (approximately 0.3 times the MRHD based on AUC by the end of the dosing interval) in the presence of maternal toxicity (convulsion in one mid dose and one high dose dam).

In a pre- and postnatal development study that did not test exposures comparable to the MRHD of 30 mg/day over the full treatment period, there were no adverse effects on survival or development of offspring when pregnant rats were treated with up to 30 mg/kg remimazolam (<0.3 times the MRHD by the end of the gestational period) by intravenous bolus injection from Gestation Day 6 through Lactation Day 20 with minimal evidence of maternal toxicity (sedation).

No evidence of adverse effects on physical development, a functional observational battery of behavioral assessments, or fertility were noted in pups born to pregnant rabbits that were treated by intravenous infusion of up to 20 mg/kg/day remimazolam (approximately 19 times the MRHD based on AUC) from 14 days prior to mating until Lactation Day 30 despite the presence of maternal toxicity (sedation, convulsions, and mortality). Learning and memory of the first-generation offspring was not evaluated in this study.

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 and Precautions (5.4), Use in Specific Populations (8.4), Nonclinical Toxicology (13.2)].*

8.2 Lactation

Risk Summary

There are no data on the effects of remimazolam in human milk, the effects on the breastfed infant or the effects on milk production. Remimazolam is present in animal milk *(see Data)*. When a drug is present in animal milk, it is likely that it will be present in human milk. There are reports of sedation in infants exposed to benzodiazepines through breast milk. Monitor infants exposed to BYFAVO through breast milk for sedation, respiratory depression, and feeding problems. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 5 hours (approximately 5 elimination half-lives) after BYFAVO administration in order to minimize drug exposure to a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BYFAVO and any potential adverse effects on the breastfed child from BYFAVO or from the underlying maternal condition.

Data

In rabbits administered daily intravenous infusions of remimazolam at 12.5 and 20 mg/kg/day from 14 days before mating until Lactation Day 30, remimazolam and the metabolite CNS7054 were present in milk samples obtained after the end of an infusion on Day 10 or 11 of lactation. Remimazolam was not quantifiable in plasma samples obtained from rabbit kits taken in the morning on Day 10 or 11 of lactation. However, metabolite CNS7054 was present at low levels in 2 of the 5 kits sampled.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. No studies are available in any pediatric population and extrapolation of adult effectiveness data to the pediatric population is not possible.

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as BYFAVO, 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 and Precautions (5.4), Use in Specific Populations (8.1), Nonclinical Toxicology (13.2)].*

8.5 Geriatric Use

Of the total number of subjects treated with BYFAVO in clinical studies for procedural sedation, there were 649 subjects <65 years of age, 221 subjects >65 years of age, 171 subjects between 65-74 years of age, and 50 subjects >75 years of age.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. Some data suggest a potential of greater sensitivity (a faster onset of loss of consciousness and a longer duration of sedation) of some older individuals.

Administer supplemental doses of BYFAVO slowly to achieve the level of sedation required for the procedure, and monitor all patients for cardiorespiratory complications.

8.6 Hepatic Impairment

In patients with severe hepatic impairment, the dose of BYFAVO should be carefully titrated to effect. Depending on the overall status of the patient, lower frequency of supplemental doses may be needed to achieve the level of sedation required for the procedure. All patients should be monitored for sedation-related cardiorespiratory complications *[see Clinical Pharmacology (12.3)].*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

[This section cannot be completed until the Drug Enforcement Administration completes a scheduling action under the Controlled Substances Act.]

9.2 Abuse

BYFAVO contains the benzodiazepine, remimazolam. Benzodiazepines are a class of sedative drugs with a known potential for abuse. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. In a human abuse potential study conducted in recreational sedative abusers (n = 39), remimazolam (5 and 10 mg, IV) produced responses on positive subjective measures such as "Drug Liking," "Overall Drug Liking," "Take Drug Again," and "Good Drug Effects" that were statistically similar to those produced by the sedative midazolam (2.5 and 5 mg), and statistically greater than the responses on these measures that were produced by placebo.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. In a monkey physical dependence study, chronic administration of remimazolam produced withdrawal signs such as tremors, muscle rigidity, restlessness, impaired motor activity, and a reduction in food consumption upon drug discontinuation. One monkey of six in this study exhibited systemic convulsions and dissociation from the environment. These behaviors are consistent with benzodiazepine withdrawal, which suggests that remimazolam produces physical dependence.

10 OVERDOSAGE

Clinical Presentation

Overdose may lead to CNS depression, associated with drowsiness, confusion, and lethargy, with possible progression to ataxia, respiratory depression, and hypotension.

Management of Overdosage

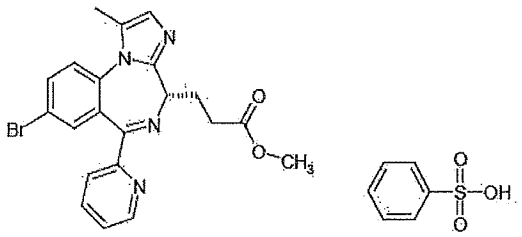
Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with BYFAVO is known or suspected. Prior to the administration of flumazenil, institute necessary measures to secure the airway, and ensure adequate ventilation and oxygenation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Flumazenil will only reverse benzodiazepine-induced effects and will not reverse the effects of other medications, such as opioid analgesics. Consult the complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, prior to use.

Monitor patients treated with flumazenil for re-sedation, respiratory depression, and other residual benzodiazepine effects. Re-sedation by BYFAVO has not been observed after administration of flumazenil in clinical trials.

11 DESCRIPTION

Each glass, single-patient-use, sterile vial of BYFAVO (remimazolam) for injection contains 20 mg remimazolam, equivalent to 27.2 mg remimazolam besylate.

Remimazolam is a benzodiazepine. Its chemical description is 4H-imidazol[1,2-a][1,4]benzodiazepine-4-propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-, methyl ester, benzenesulfonate (1:1). The structural formulas are shown below.



Molecular weight of BYFAVO (free base): 439.3 g/mol.

Molecular weight of BYFAVO besylate: 597.5 g/mol.

BYFAVO besylate powder is sparingly soluble in water.

BYFAVO 20 mg contains: 82 mg dextran 40 and 55 mg lactose monohydrate as bulking agents/stabilizers. The pH is adjusted with hydrochloride/sodium hydroxide. Upon reconstitution with saline, BYFAVO has a pH of 2.9 to 3.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BYFAVO is a benzodiazepine. BYFAVO binds to brain benzodiazepine sites (gamma amino butyric acid type A [$GABA_A$] receptors), while its carboxylic acid metabolite (CNS7054) has a 300 times lower affinity for the receptor. BYFAVO, like other benzodiazepines, did not show clear selectivity between subtypes of the $GABA_A$ receptor.

12.2 Pharmacodynamics

Dose finding studies determined the IV dosing recommendation of the initial 5 mg bolus, followed by 2.5 mg top-up doses. Median time to peak sedation, defined as the lowest Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score after the initial dose, in the Phase 3 trials was 3 to 3.5 minutes and median time to fully alert, defined as time to the first of three consecutive MOAA/S scores of five, following the last dose of BYFAVO was 11 to 14 minutes.

Cardiac Electrophysiology

In a thorough QT study, 57 healthy volunteers were given an IV push of 10 mg or 20 mg BYFAVO, intravenous midazolam (2.5 mg or 7.5 mg) or placebo, or a single tablet of moxifloxacin 400 mg given orally. The largest mean placebo-adjusted change-from-baseline QTc (upper bound of 2-sided 90% confidence interval) was 6.7 (9.5) ms, 10.7 (13.4) ms, 4.5 (7.3) ms, and 8.1 (10.8) ms, respectively, after treatment with 10 mg or 20 mg BYFAVO, or 2.5 mg or 7.5 mg midazolam.

BYFAVO treatment is associated with increases in heart rate. The largest mean placebo-adjusted change-from-baseline HR (upper bound of 2-sided 90% confidence interval) was 12.3 (14.2) bpm and 15.2 (17.1) bpm, respectively, after treatment with 10 mg and 20 mg BYFAVO.

12.3 Pharmacokinetics

- BYFAVO has a terminal elimination half-life from plasma of 37 to 53 minutes.
- Mean distribution half-life ($t_{1/2\alpha}$) is between 0.5 and 2 minutes.
- Half-life ($t_{1/2}$) is prolonged with increasing severity of hepatic impairment leading to a need for careful dose titration in patients with severe hepatic impairment.
- Clearance (54 to 75 L/h) is not related to body weight.
- In healthy subjects at least 80% and in colonoscopy patients 50% to 60% of dose is excreted in urine as inactive metabolite.

Absorption

BYFAVO is administered intravenously. BYFAVO overall maximum plasma concentration (C_{max}) after IV administration of 0.01 to 0.5 mg/kg was 189 to 6,960 ng/mL, and overall area under the concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) was 12.1 to 452 ng·h/mL; BYFAVO cumulative dose versus BYFAVO total exposure ($AUC_{0-\infty}$) suggested a close to dose-proportional relationship. Metabolite C_{max} was achieved approximately 20-30 minutes post dose. Metabolite $AUC_{0-\infty}$ was 231 to 7,090 ng·h/mL.

Distribution

BYFAVO volume of distribution (V_z) was 0.76 to 0.98 L/kg. Plasma protein binding of BYFAVO was >91%, primarily to human serum albumin.

Elimination

BYFAVO has a terminal elimination half-life from plasma of 37 to 53 minutes and mean distribution half-life ($t_{1/2\alpha}$) is between 0.5 and 2 minutes.

Metabolism

The main route of metabolism of BYFAVO is via conversion to primary inactive metabolite CNS7054, which is then subject to hydroxylation and glucuronidation. Conversion to CNS7054 is mediated by tissue carboxylesterases (primarily type 1A), with no meaningful contribution by cytochrome P450 enzymes. The $t_{1/2}$ of the metabolite was 2.4 to 3.8 hours.

Excretion

In colonoscopy patients, approximately 0.003% BYFAVO is excreted unchanged in urine, and 50% to 60% is excreted in urine as the metabolite CNS7054.

Specific Populations

Pediatric Patients

There were no pediatric patients who received BYFAVO.

Patients with Renal Impairment

The pharmacokinetics of BYFAVO were not altered in patients with mild to end stage renal disease not requiring dialysis. In a renal impairment study, BYFAVO PK parameters (e.g., AUC and C_{max}) were not statistically different in subjects with varying degrees of renal function (from normal to severely impaired). Increased exposure to inactive metabolite CNS7054 was observed with increasing degree of renal impairment.

Patients with Hepatic Impairment

A Phase 1 open-label, single-dose trial evaluated the PK and safety of BYFAVO given as an IV bolus of 0.1 mg/kg over 1 minute in subjects with hepatic impairment (8 moderately hepatically impaired subjects and 3 severely hepatically impaired subjects) and 9 matched healthy subjects.

The C_{max} values of total BYFAVO were 10% to 20% lower in subjects with hepatic impairment than in healthy subjects. Larger V_z (33% increase in moderately impaired and 41% increase in severely impaired) and V_{ss} (50% increase in moderately impaired and 115% increase in severely impaired), and prolonged $t_{1/2}$ (60 minutes in moderately impaired and 105 minutes in severely impaired as compared to 42 minutes in healthy subjects), of BYFAVO were observed with increasing severity of hepatic impairment. Sedation lasted longer and recovery took longer for subjects with hepatic impairment compared to healthy subjects. The average duration of loss of consciousness and recovery time was 3.2 minutes and 12.1 minutes, respectively for subjects in the moderately hepatically impaired group. These times were 2.0 minutes and 16.7 minutes, respectively, for the subjects in the severely hepatically impaired group. Healthy control subjects had a loss of consciousness of 1.6 minutes and a recovery time of 8.0 minutes.

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

Other Specific Populations

Age, sex, race, and weight had no clinically relevant effect on BYFAVO pharmacokinetics.

Drug Interactions

BYFAVO and the metabolite CNS7054 caused no relevant inhibition of cytochrome P450 isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4. There were no inducing effects on CYP1A2, 2B6, and 3A4. BYFAVO was not a relevant substrate of a panel of human drug transporters (OATP1B1, OATP1B3, BCRP).

No relevant inhibition of human drug transporters (OAT3, OCT2, OATP1B1, OATP1B3, OAT1, BCRP) was seen with BYFAVO or CNS7054. Remifentanil did not influence the hydrolysis of BYFAVO by human liver S9 fractions, reducing the possibility of an interaction by competition for liver carboxylesterases.

These results together show a very low potential of BYFAVO for pharmacokinetic drug interactions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies have not been performed to evaluate the carcinogenic potential of remimazolam.

Mutagenesis

Remimazolam was not mutagenic or clastogenic when evaluated in an in vitro bacterial reverse mutation assay (Ames test), an in vivo rat micronucleus assay, mouse lymphoma cells, in vivo rat bone marrow micronucleus assay, or comet assay.

Impairment of Fertility

In a study that did not test exposures comparable to the MRHD of 30 mg/day, there were no adverse effects on male or female fertility when male rats were treated for 28 days prior to mating and female rats were treated for 14 days prior to mating with up to 30 mg/kg remimazolam via intravenous bolus (approximately 0.03 times the MRHD based on AUC).

There was no impact on female fertility when female rabbits were administered remimazolam by intravenous infusion (up to 4 hours/day) up to 20 mg/kg/day (approximately 17 times the MRHD of 30 mg/day based on AUC) from 14 days prior to mating.

No adverse effects on histology of the testes and epididymides or evaluation of spermatid count, sperm motility, and sperm morphology were reported in a repeat-dose toxicity study in which male minipigs were administered remimazolam by intravenous infusion (6 hours) up to 120 mg/kg/day (approximately 400 times the MRHD based on AUC) for 28 days followed by a 14-day recovery period.

13.2 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 and Precautions (5.4), Use in Specific Populations (8.1, 8.4)]*.

14 CLINICAL STUDIES

The safety and efficacy of BYFAVO compared to a saline placebo with midazolam rescue treatment group and an open-label midazolam treatment group was evaluated in three randomized, double-blind, multicenter Phase 3 studies conducted in 969 adult patients receiving procedural sedation.

14.1 Colonoscopy Study 1 (NCT 02290873)

This Phase 3 study was conducted in 461 ASA-PS class I to III patients undergoing colonoscopy. BYFAVO 5 mg (2 mL) IV was administered as an initial bolus, followed by 2.5 mg (1 mL) top-up doses versus placebo 2 mL administered as an initial bolus, followed by 1 mL top-up doses. Midazolam rescue was dosed per investigator discretion in both treatment groups. Fentanyl was administered as an analgesic pre-treatment at an initial dose of 50 to 75 mcg IV (or a reduced dose for ASA-PS Class III patients) immediately prior to administration of the initial dose of study medication. Top-up doses of fentanyl 25 mcg every 5 to 10 minutes were allowed until analgesia was adequate or a maximum dose of 200 mcg had been administered. Supplemental oxygen was administered prior to the start of the procedure and continued at a rate of 1 to 5 L/minute until the patient was fully alert after procedure completion. Colonoscopy started when adequate sedation was achieved, defined as an MOAA/S score ≤3. The primary efficacy endpoint for BYFAVO versus placebo was success of the colonoscopy procedure, defined as a composite of the following:

- Completion of the colonoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement for more than 5 doses of study medication within any 15-minute window.

There were 63 patients (13.8%) who were aged 65 years or older, 218 patients (47.6%) who were male, 339 (74.0%) who were white, 80 (17.5%) who were Black or African American, 31 (6.8%) who were Asian, and 73 (15.9%) who were Hispanic or Latino. There were 143 patients in ASA-PS class I, 285 in ASA-PS class II, and 30 in ASA-PS class III. As shown in Table 6, the colonoscopy sedation success rate was statistically significantly higher in the BYFAVO group than in the placebo group.

Table 6. Colonoscopy Sedation Success Rate – Colonoscopy Study 1

Cohort	Sedation Success Rate n/N (%)
Remimazolam	272/298 (91.3%)
Placebo	1/60 (1.7%)

n/N = number of successes/number of subjects in group.

The reasons for procedural sedation failure are shown in Table 7.

Table 7. Reasons for Procedural Sedation Failure – Colonoscopy Study 1

Reason	Remimazolam N = 298 n (%)	Placebo N = 60 n (%)
Rescue sedative medication taken	10 (3.4%)	57 (95%)
Too many doses within the predefined time window	18 (6.0%)	44 (73.3%)
Procedure not completed	7 (2.3%)	1 (1.7%)

Table 8 shows the number of top-up doses required, and the total doses of study medication, fentanyl, and rescue medication administered.

Table 8. Number of Top-up Doses and Total Doses of Study Medication, Fentanyl, and Rescue Medication – Colonoscopy Study 1

	Number of Top-up Doses of Study Drug (Mean ± SD)	Total Amount of Study Drug (mg) (Mean ± SD)	Total Amount of Fentanyl (mcg) (Mean ± SD)	Total Amount of Midazolam Rescue Medication (mg) (Mean ± SD)
Remimazolam	2.2 ± 1.6	10.5 ± 4.0	88.9 ± 21.7	0.3 ± 2.1
Placebo	5.1 ± 0.5	0	121.3 ± 34.4	6.8 ± 4.2

Summaries of the time to start procedure, duration of procedure, time to fully alert, and time to ready for discharge are shown in Table 9.

Table 9. Time to Start Procedure, Duration of Procedure, Time to Fully Alert, and Time to Ready for Discharge for the Remimazolam Cohort – Colonoscopy Study 1

Time to start procedure (minutes)†	
Median (95% confidence interval)	4.0 (4.0, 4.0)
Min, Max	0, 26
Duration of procedure (minutes)‡	
Median (95% confidence interval)	12.0 (11.0, 13.0)
Min, Max	3, 33
Number (proportion) of procedures lasting longer than 30 minutes	1/291 (0.3%)
Time to fully alert after end of colonoscopy (minutes)‡	
Median (95% confidence interval)	6.0 (5.0, 7.0)
Min, Max	0, 44
Time to ready to discharge after end of colonoscopy (minutes)‡	
Median (95% confidence interval)	44.0 (42.0, 46.0)
Min, Max	3, 79

† Patients who were unable to start the procedure were excluded.

‡ Patients who did not successfully complete the procedure were excluded.

14.2 Bronchoscopy Study (NCT 02296892)

This Phase 3 study was conducted in 431 ASA-PS class I to III patients undergoing bronchoscopy. BYFAVO 5 mg (2 mL) IV was administered as an initial bolus, followed by 2.5 mg (1 mL) top-up doses versus placebo 2 mL administered as an initial bolus, followed by 1 mL top-up doses. Midazolam rescue was dosed per investigator discretion in both treatment groups. Fentanyl was administered as an analgesic pre-treatment at an initial dose of 25 to 50 mcg IV immediately prior to administration of the initial dose of study medication. Top-up doses of fentanyl 25 mcg every 5 to 10 minutes were allowed until analgesia was adequate. A maximum dose of fentanyl 200 mcg was recommended. Supplemental oxygen was administered prior to the start of the procedure and continued at a rate of 1 to 15 L/minute until the patient was fully alert after procedure completion. Bronchoscopy started when adequate sedation was achieved, defined as an MOAA/S score ≤3. The primary efficacy endpoint for BYFAVO versus placebo was successful sedation for the bronchoscopy procedure, defined as a composite of the following:

- Completion of the bronchoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement for more than 5 doses of study medication within any 15-minute window.

There were 209 patients (48.5%) who were 65 years or older, 198 patients (45.9%) who were male, 358 (83.1%) who were white, 62 (14.4%) who were Black or African American, 5 (1.2%) who were Asian, and 8 (1.9%) who were Hispanic or Latino. There were 15 patients in ASA-PS class I, 254 in ASA-PS class II, and 162 in ASA-PS class III. As shown in Table 10, the bronchoscopy sedation success rate was statistically significantly higher for the BYFAVO group than for the placebo group.

Table 10. Bronchoscopy Success Rates

Cohort	Total Success Rate n/N (%)
Remimazolam	250/310 (80.6%)
Placebo	3/63 (4.8%)

n/N = number of successes/number of subjects in group.

The reasons for procedural sedation failure are shown in Table 11.

Table 11. Reasons for Procedural Sedation Failure – Bronchoscopy Study

Reason	Remimazolam N = 310 n (%)	Placebo N = 63 n (%)
Rescue sedative medication taken	49 (15.8%)	57 (90.5%)
Too many doses within the predefined time window	14 (4.5%)	10 (15.9%)
Procedure not completed	9 (2.9%)	3 (4.8%)

Table 12 shows the number of top-up doses required, and the total doses of study medication, fentanyl, and rescue medication administered.

Table 12. Number of Top-up Doses and Total Doses of Study Medication, Fentanyl, and Rescue Medication – Bronchoscopy Study

	Number of Top-up Doses of Study Drug (Mean ± SD)	Total Amount of Study Drug (mg) (Mean ± SD)	Total Amount of Fentanyl (mcg) (Mean ± SD)	Total Amount of Midazolam Rescue Medication (mg) (Mean ± SD)
Remimazolam	2.6 ± 2.0	11.47 ± 5.1	81.8 ± 54.3	1.3 ± 3.5
Placebo	4.1 ± 0.8	5.87 ± 3.7	118.8 ± 79.1	5.8 ± 3.7

Summaries of the time to start procedure, duration of procedure, time to fully alert, and time to ready for discharge are shown in Table 13.

Table 13. Time to Start Procedure, Duration of Procedure, Time to Fully Alert and Time to Ready for Discharge for the Remimazolam Cohort – Bronchoscopy Study

Time to start procedure (minutes)†	
Median (95% confidence interval)	4.1 (4.0, 4.8)
Min, Max	1,41
Duration of procedure (minutes)‡	
Median (95% confidence interval)	10.0 (8.0, 11.0)
Min, Max	1, 68
Number (proportion) of procedures lasting longer than 30 minutes‡	28/299 (9.4%)
Time to fully alert after end of bronchoscopy (minutes)‡	
Median (95% confidence interval)	6.0 (5.2, 7.1)
Min, Max	1.1, 107
Time to ready to discharge after end of bronchoscopy (minutes)‡	
Median (95% confidence interval)	60.0 (57.0, 63.0)
Min, Max	6.6, 284

† Patients who were unable to start the procedure were excluded.

‡ Patients who did not successfully complete the procedure were excluded.

14.3 Colonoscopy Study 2 (NCT 02532647)

This Phase 3 study was conducted in 77 ASA-PS class III and IV patients undergoing colonoscopy. BYFAVO 2.5 mg (1 mL) to 5 mg (2 mL) IV was administered as an initial bolus, followed by 1.25 mg (0.5 mL) to 2.5 mg (1 mL) top-up doses versus placebo 1 to 2 mL administered with midazolam rescue, dosed per investigator discretion. Fentanyl was administered as an analgesic pre-treatment at an initial maximum dose of 50 mcg (with dose reduction for debilitated patients), immediately prior to administration of the initial dose of study medication. Top-up doses of fentanyl 25 mcg every 5 to 10 minutes were allowed until analgesia was adequate or a maximum dose of 200 mcg had been administered. Supplemental oxygen was administered prior to the start of the procedure and continued at a rate of up to 4 L/minute until the patient was fully alert after procedure completion. Colonoscopy started when adequate sedation was achieved, defined as an MOAA/S score ≤3.

The primary objective of the study was to assess the safety of multiple doses of BYFAVO compared to placebo and midazolam. Procedure success was a secondary objective and was defined as follows:

- Completion of the colonoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement for more than 5 doses of study medication within any 15-minute window.

The total patient population, including all randomized patients who received any amount of study medication, comprised 31 patients in the remimazolam group, 16 patients in the placebo group, and 30 patients in the midazolam group. There were two patients, one each in the remimazolam and midazolam treatment groups, who were randomized, but did not receive a dose of study medication.

There were 31 patients (40.2%) who were aged 65 years or older, 43 patients (55.8%) who were male, 57 (74.0%) who were white, 19 (24.7%) who were Black or African American, 1 (1.30%) who was Asian, and none who were Hispanic or Latino. There were 40 patients in ASA-PS class III and 37 patients in ASA-PS class IV.

Patients in the remimazolam group received a mean (± SD) of 9.0 (± 3.7) mg of remimazolam and a mean (± SD) of 2.5 (± 10.2) mg of midazolam compared to 7.2 (± 2.5) mg in the placebo group. The mean total dose of fentanyl was lower in the remimazolam group (mean ± SD: 59.7 ± 15.4 mcg) than in the placebo group (mean ± SD: 67.2 ± 21.8 mcg).

In the remimazolam group, 90.3% of patients did not receive any rescue sedative medication, compared to 0.0% in the placebo group.

There were no serious adverse reactions and no discontinuations due to adverse reactions observed in the remimazolam group. The incidence of hypotension (SMQ) was 61.3% in the remimazolam group and 75% in the placebo group.

No inferential statistical tests were performed in this trial. Patients who received BYFAVO for sedation during scheduled colonoscopy responded at a numerically greater rate than patients who received placebo (randomized analysis population – remimazolam: 27/32 [84.4%]; placebo: 0/16 [0%]).

16 HOW SUPPLIED/STORAGE AND HANDLING

BYFAVO (remimazolam) for injection, for intravenous use is supplied as follows:

NDC 71390-011-11: Carton of 10 x 12 mL vials. Each 12 mL glass vial of BYFAVO (NDC 71390-011-00) provides a sterile lyophilized white to off-white powder intended for single-patient use only and contains 20 mg remimazolam (equivalent to 27.2 mg remimazolam besylate) ready for reconstitution.

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) excursions between 15° and 30°C (59° and 86°F) are allowed.

Reconstituted BYFAVO can be stored in the vial for up to 8 hours under controlled room temperature at 20°C to 25°C (68°F to 77°F).

Protect vials from light once they are removed from packaging.

Discard unused portion.

17 PATIENT COUNSELING INFORMATION

Alcohol and Current Medications

Advise patients to notify their healthcare provider about alcohol or medication use. Alcohol and other CNS depressants, such as opioid analgesics and benzodiazepines, can have an additive effect when administered with BYFAVO *[see Warnings and Precautions (5.1), Drug Interactions (7.1)].*

Pregnancy

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Advise mothers exposed to BYFAVO during pregnancy to monitor neonates for signs of sedation, respiratory depression, and feeding problems. Instruct patients to inform their healthcare

provider if they are pregnant during treatment with remimazolam *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

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 *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.4), Nonclinical Toxicology (13.2)]*.

Lactation

Advise women to consider reducing infant exposure by pumping and discarding breast milk for 5 hours after receiving BYFAVO during procedural sedation *[see Use in Specific Populations (8.2)]*.

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8440 Allison Pointe Blvd., Suite 100
Indianapolis, IN 46250 USA

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OKLAHOMA BOARD OF NURSING
2915 N. Classen Boulevard, Suite 524
Oklahoma City, OK 73106
(405) 962-1800
www.ok.gov/nursing

MEMORANDUM

TO: Formulary Advisory Council

FROM: Gina Stafford, RN
Associate Director for Nursing Practice

DATE: October 4, 2020

RE: *Formulary Advisory Council Procedure for Amending the Formulary*, #P-50

Attached is the current guideline, *Formulary Advisory Council Procedure for Amending the Formulary*, #P-50, for your review. No changes have been made to the guideline.

Revisions/Rationale: The current procedure has been implemented without problems; therefore, no revisions have been made to the guideline.

Staff and Others Involved: J. Ward and G. Stafford

Legal Implications: There are no known legal implications with the proposed revisions as attached.

Fiscal Impact: There is no fiscal impact anticipated with the proposed revisions.

Recommendations/Requested Action: The guideline is presented for review and approval with a decision to move forward for Board approval.

OKLAHOMA BOARD OF NURSING
2915 North Classen Boulevard, Suite 524
Oklahoma City, OK 73106
405-962-1800

Formulary Advisory Council
Procedure for Amending the Formulary

The following is a procedure for submission of requests for revision to the Exclusionary and Inclusionary Formularies to the Formulary Advisory Council for review and consideration.

I. Individuals requesting a revision to the Inclusionary or Exclusionary Formulary must submit a completed written request to the Oklahoma Board of Nursing ("Board") office on a form approved by the Board. The request will include the rationale for the request, the individual's position, literature to support the position, and information on the drug from the drug manufacturer.

Such information must be received in the Board office at least 30 calendar days prior to the scheduled Formulary Advisory Council Meeting, to allow all Formulary Advisory Council members to review the information prior to the Formulary Advisory Council meeting.

II. Recommendations for revision of the Inclusionary Formulary and Exclusionary Formulary approved by the Formulary Advisory Council will be considered by the Board during the next regularly scheduled meeting of the Board in accordance with 59 O.S. §567.4a.9. a. and d. and 59 O.S. §567.4b.A. and C.

III. The Formulary Advisory Council, during a scheduled annual meeting and in the course of review and discussion of the current Inclusionary and Exclusionary Formularies, may recommend revisions to the Formularies to the Board, without following this procedure, if Council Members are in agreement of the recommendation and a member of the Formulary Advisory Council does not request review of additional information concerning the revision.

IV. **Regulatory Authority**

59 O.S. §§567.4a. 9. a. and d., and 567.4.b. A. and C.

REQUEST TO AMEND THE FORMULARY

Individual Making Request:

1. NAME_____

2. ADDRESS _____ _____ ____ _____
   Street City State Zip Code

3. (___)_____ (___)_____ _____
   Area Code/***Home Phone #*** Area Code/***Cell Phone #*** E-Mail Address

4. TITLE _____
   (CNP, CNM, CNS, CRNA, MD, DO, Pharmacist, Other- specify_____)

I am requesting a change to the following formulary:

4. ____ Exclusionary Formulary (Formulary Advisory Council) ARNPs, CNMs, CNSs
5. ____ Inclusionary Formulary (CRNA Formulary Advisory Council) CRNAs

6. Name of Drug(s):_____

7. Drug Classification and AHFS Reference Number(s):_____

(Please contact the Associate Director for Nursing Practice at 405/962-1800 for assistance with AHFS Classification//Reference Numbers)

8. _____ Delete from Formulary
   _____ Add to Formulary
   _____ Add precaution and/or restriction

9. Rationale for request to amend formulary: _____

Please attach the following information:
1. Literature to support your position
2. Drug Manufacturer's Information

SUBMIT ALL INFORMATION TO: Associate Director for Nursing Practice
Oklahoma Board of Nursing
2915 North Classen Boulevard, Suite 524
Oklahoma City, Oklahoma 73106
Phone - (405) 962-1800 FAX - (405) 962-1821

Information must be received in the Board office at least 30 calendar days prior to a meeting of the Formulary Advisory Council.