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

CRNA Formulary Advisory Council
AGENDA
Monday, September 28, 2020
3:30 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=e5d5a4a0694f1984ac4392f3fb597d856
Event Number: 146 864 1949
Password: jqWNuPjr565

Dial US: +1-415-655-0001 to join by audio
Access code: 146 864 1949

Link to access meeting materials: http://nursing.ok.gov/agcrna20.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 September 15, 2020. Notice/final agenda was posted on September 17, 2020, at 1:00 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 CRNA 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:

Victor Long, APRN-CRNA
Bruce Kennedy, APRN-CRNA
Brian Seacat, MD
Jeremy Almon, MD
Mark St. Cyr, DPh
Jan Palovik, MSA, APRN-CRNA, Oklahoma Board of Nursing Vice-President
Liz Massey, DNP, RN, Oklahoma Board of Nursing President (Ex-Officio Member)

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 (minimum of three members)
   1.2. Reminder that voting members include 2 anesthesiologists, 1 pharmacist, and 2 CRNAs 59 O.S. §567.4b B.1.

2. Committee decision regarding approval of April 22, 2019, committee meeting minutes **(Attachment #1)**

3. Board Update: Verbal reports only, requiring no action or discussion by committee (verbal reports only)
   3.1 Changes to the *Oklahoma Nursing Practice Act* – Jackye Ward
   3.2 Changes to the *Oklahoma Board of Nursing Practice Rules* – Jackye Ward
   3.3 Optimal Regulatory Board System (ORBS) – Jackye Ward
   3.4 Governor Kevin Stitt's request for exemption from the federal regulation requiring the CRNA to be supervised by a physician – Gina Stafford
   3.5 Executive Orders related to COVID-19 – Jackye Ward
   3.6 CRNA Formulary Advisory Council members – expiration of appointments (Dr. Tinker 7/2020)

4. Committee review and recommendations of the DRAFT *CRNA Inclusionary Formulary* **(Attachment #2)**

5. Committee election of Chairperson and Vice Chairperson for 2020

6. Committee member determination for date of next meeting
   6.1 Date and time

7. Adjournment

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CRNA Formulary Advisory Committee
Minutes-April 22, 2019

The CRNA Formulary Advisory Council ("Council") to the Oklahoma Board of Nursing ("Board") met on April 22, 2019. Notice of the meeting was initially filed with the Secretary of State's Office on December 11, 2018. Notice of the meeting was posted on the Oklahoma Board of Nursing web site not less than 24 hours prior to the meeting. 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 at 2915 North Classen, Suite 524, at 4 PM on April 5, 2019 and not less than 24 hours prior to the meeting.

Place of Meeting: Basement Conference Room, Cameron Building

Time of Meeting: 3:30 PM

Members Present: Mark St Cyr, D.Ph.
Oklahoma Pharmacists Association

Lad Yates, MD
Oklahoma Society of Anesthesiologists

Thomas Tinker, MD
Oklahoma Society of Anesthesiologists

Victor Long, APRN-CRNA
Oklahoma Association of Nurse Anesthetists

Bruce Kennedy, APRN-CRNA
Oklahoma Association of Nurse Anesthetists

Members Absent: None

Board Representative: Jan Palovik, MS, APRN-CRNA

Staff Representatives: Jackye Ward, MS, RN
Gina Stafford, RN

Guest: None

1.0 Call to order: The meeting was called to order at 3:30 PM by Dr. Tinker, Chairperson.

1.1 Declaration of a quorum: A quorum was declared present.

2.0 Minutes of the previous meeting – April 23, 2018: The minutes were reviewed. A motion was made (V. Long) and seconded to approve the minutes of April 23, 2018.

Voting:

Yes:	(5)	B. Kennedy, V. Long, M. St Cyr, T. Tinker, L. Yates
No:	(0)	
Absent:	(0)	

Motion Carried.

3.0 Board of Nursing update (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 *Oklahoma Board of Nursing Rules*: J. Ward summarized proposed changes to the *Rules.*

3.3 New Enhanced Nurse Licensure Compact (NLC): J. Ward provided an update regarding multistate licenses. The Agency has licensed over 5,000 RN/LPN applicants since the implementation of the NLC.

3.4 Formulary Advisory Council: G. Stafford provided proposed changes to the *Exclusionary Formulary for Advanced Practice Registered Nurses with Prescriptive Authority.* The Formulary will move forward for Board approval in May.

3.5 Board approved guideline: G. Stafford reviewed changes to the *Rapid Sequence Intubation Guideline for Registered Nurses.*

3.6 Updated regarding the passage of HR 6: G. Stafford reviewed HR 6, known as the *Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act.* The Act was signed into law on October 24, 2018.

3.7 CRNA Formulary Advisory Council membership: G. Stafford reported the appointment term for Dr. Lad Yates will expire 4/30/2019. The Oklahoma Medical Association will be contacted for the appointment of a representative.

3.8 Other: no other reports

4.0 Review and committee recommendations on revisions to *CRNA Inclusionary Formulary*: Council members reviewed the DRAFT *CRNA Inclusionary Formulary*, #P-50A with proposed revisions. A list of new and updated monographs was provided to committee members. The proposed revisions include language changes to warnings, title change to 20:20 category, removal of two discontinued drugs, addition of two new drugs, correction to category 56:22.32, organize insulins to match the current edition of the *AHFS Drug Classification* and update to references. Additional revisions were discussed. These changes include removal of all warnings, references to warnings, asterisks and addition of one more drug. After discussion, it was moved (M. St Cyr) and seconded to recommend the following revisions to the *CRNA Inclusionary Formulary*, #P-50A to the Board for approval:

- Remove asterisks from the formulary, no need to identify which drugs are not in the print version on the *AHFS Drug Information*
- Remove all warnings and references to warnings
- Remove category 56:22.93
- Revise title for 20:00
- Identify Citrates
- Add three drugs:
  Andexanet Alfa 20:28.92
  Meloxicam 28:08.04.92
  Insulin Glulisine 68:20.08.04
- Remove three drugs:
  Metaraminol 12:12.12
  Dextran 75 40:12
  Insulin Zinc 68:20.08
- Update the reference for *AHFS Drug Information* to the current edition (2019)

Voting:

Yes:	(5)	B. Kennedy, V. Long, M. St Cyr, T. Tinker, L. Yates
No:	(0)	
Absent:	(0)	

Motion Carried.

5.0 **Election of Chairperson and Vice Chairperson for 2020:** It was moved (L. Yates) and seconded to appoint Dr. Tinker as Chairperson and to appoint Bruce Kennedy as Vice Chairperson for the next CRNA Formulary Advisory Council Meeting.

Voting:

Yes:	(5)	B. Kennedy, V. Long, M. St Cyr, T. Tinker, L. Yates
No:	(0)	
Absent:	(0)	

Motion Carried.

6.0 **Date for next meeting:** The members discussed possible dates and times for the next meeting.
6.1 Selected date and time for the next meeting will be Monday, April 20, 2020 at 3:30 PM.

Voting:

Yes:	(5)	B. Kennedy, V. Long, M. St Cyr, T. Tinker, L. Yates
No:	(0)	

Absent: (0)

Motion Carried.

7.0 Adjournment: There being no further business, the meeting was adjourned at 4:31 PM.

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MEMORANDUM

TO: CRNA Inclusionary Formulary Advisory Council

FROM: Gina Stafford, RN
Associate Director for Nursing Practice

DATE: August 30, 2020

RE: *CRNA Inclusionary Formulary,* #P-50A

Attached are draft revisions to the *CRNA Inclusionary Formulary*, # P-50A 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 inclusionary formulary which lists drugs or categories of drugs that shall be ordered or administered by Certified Registered Nurse Anesthetists. "The Board shall either accept or reject the recommendations made by the Council. No amendments to the recommended inclusionary formulary may be made by the Board without the approval of the Formulary Advisory Council." [Oklahoma Nurse Practice Act, specifically 59 O.S. §567.4b A.3]

Revisions/Rationale: Changes include additional language to define a CRNA, addition of the statute regarding the Formulary Advisory Council, addition of three new drugs, removal of one discontinued drug and a date change to the reference.

The proposed revisions are noted in the DRAFT policy attached. Revisions are indicated using strikethrough for deletions and double underlining for additions. I have highlighted the changes for easy identification.

Information attached for your review includes:

- DRAFT *CRNA Inclusionary Formulary*, #P-50A **[Attachment #2]**
- A complete listing of categories/drugs as listed in the current (2020) edition of the *AHFS Drug Information Manual* **[Attachment A]**
- *AHFS Classification Drug Assignments 2019-2020* (The list includes new drugs since our last meeting.) **[Attachment B]**
- FDA drug information on Byfavo (Remimazolam) (new drug) **[Attachment C]**
- FDA drug information on Barhemsys (Amisulpride) (new drug) **[Attachment D]**
- FDA drug information on Angiomax RTU (Bivalirudin) **[Attachment E]**
- FDA drug discontinued on Zantac (Ranitidine) **[Attachment F]**

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

Legal Implications: There are no known legal implications.

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

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

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CRNA Inclusionary Formulary

To be granted authority to select, order, obtain and administer drugs, Certified Registered Nurse Anesthetists (CRNAs) must hold a current Registered Nurse license, be recognized as a CRNA in Oklahoma and meet the continuing education requirements noted in the *Rules of the Oklahoma Board of Nursing*, specifically 485:10-18-2. Pursuant to 59 O.S. § 567.3a.10 [*Oklahoma Nursing Practice Act*], a CRNA is an Advanced Practice Registered Nurse who administers anesthesia in collaboration with a medical doctor, an osteopathic physician, a podiatric physician or a dentist licensed in this state and under conditions in which timely onsite consultation by such doctor, osteopath, podiatric physician or dentist is available. The Formulary Advisory Council has been established to develop and submit to the Board recommendations for an inclusionary formulary ~~,~~ pursuant to 59 O.S. § 567.4b. [*Oklahoma Nursing Practice Act*].

The following Board-approved *CRNA Inclusionary Formulary* lists drugs that may be ordered, selected, obtained or administered during the **perioperative** and **periobstetrical** periods by CRNAs who have been granted authority by the Board to select, order, obtain, and administer drugs.

4:00 Antihistamine Drugs
- 4:04 First Generation Antihistamines
  - Diphenhydramine Hydrochloride
  - Promethazine Hydrochloride (see also 28:24.92 and 28:16.08.24)

12:00 Autonomic Drugs
- 12:04 Parasympathomimetic (Cholinergic) Agents
  - Neostigmine Bromide
  - Physotigmine Salicylate
  - Pyridostigmine Bromide
- 12:08 Anticholinergic Agents
  - 12:08.08 Antimuscarinics/antispasmodics
    - Atropine
    - Glycopyrrolate
    - Ipratropium Bromide
    - Scopolomine
- 12:12 Sympathomimetic (Adrenergic) Agents
  - 12:12.04 α-Adrenergic Agents
    - Midodrine
    - Phenylephrine
  - 12:12.08 β-Adrenergic Agonists
    - 12:12.08.04 Non-selective β-Adrenergic Agonists
      - Isoproterenol

12:12.08.08 Selective β_1-Adrenergic Agonists
Dobutamine
Dopamine

12:12.08.12 Selective β_2-Adrenergic Agonists
Albuterol/Levalbuterol
Formoterol
Indacterol
Metaproterenol
Salmeterol
Terbutaline Sulfate

12:12.12 α- and β-Adrenergic Agonists
Ephedrine
Epinephrine
Norepinephrine
Pseudoephedrine

12:16 Sympatholytic (Adrenergic Blocking) Agents
12:16.04 α-Adrenergic Blocking Agents
12:16.04.04 Non-selective α-Adrenergic Blocking Agents
Phentolamine

12:20 Skeletal Muscle Relaxants (all intravenous future new drugs approved)
12:20.04 Centrally Acting Skeletal Muscle Relaxants
Carisoprodol
Cyclobenzaprine
Metaxalone
Methocarbamol
Tizanidine
12:20.08 Direct-acting Skeletal Muscle Relaxants
Dantrolene Sodium
12:20.12 GABA-derivative Skeletal Muscle Relaxants
Baclofen
12:20.20 Neuromuscular Blocking Agents
Atracurium Besylate
Cisatracurium
Pancuronium Bromide
Rocuronium Bromide
Succinylcholine Chloride
Vecuronium Bromide

16:00 Blood Derivatives
Albumin Human
Plasma Protein Fraction

Blood and Blood Components (not in AHFS)

20:00 Blood Formation, Coagulation, and Thrombosis

20:12 Antithrombotic Agents
20:12.04 Anticoagulants
20:12.04.12 Direct Thrombin Inhibitors
Bivalirudin
20:12.04.16 Heparins
Enoxaparin
Heparin
20:28 Antihemorrhagic Agents
20:28.08 Antiheparin Agents
Protamine Sulfate
20:28.16 Hemostatics
Aminocaproic Acid
Tranexamic Acid (TXA) (not in AHFS)
20:28.92 Antihemorrhagic Agents, Misc.
Idarucizumab
Andexanet Alfa

24:00 Cardiovascular Drugs
24:04 Cardiac Drugs
24:04.04 Antiarrhythmic Agents
24:04.04.04 Class Ia Antiarrhythmics
Disopyramide
Procainamide
Quinidine
24:04.04.08 Class Ib Antiarrhythmics
Lidocaine
24:04.04.20 Class III Antiarrhythmics
Amiodarone
24:04.04.24 Class IV Antiarrhythmics
Adenosine
24:04.08 Cardiotonic Agents
Digoxin
24:08 Hypotensive Agents
24:08.16 Central α-Agonists
Clonidine
Methyldopa
24:08.20 Direct Vasodilators
Hydralazine
Sodium Nitroprusside
24:12 Vasodilating Agents
24:12.08 Nitrates and Nitrites
Nitroglycerine
24:24 β-Adrenergic Blocking Agents
Atenolol
Esmolol Hydrochloride
Labetalol

Metoprolol
Nadolol
Propranolol

24:28 Calcium-Channel Blocking Agents

24:28.08 Dihydropyridines
Nicardipine
Nifedipine

24:28.92 Calcium-Channel Blocking Agents, Miscellaneous
Verapamil

24:32 Renin-Angiotensin-Aldosterone System Inhibitors

24:32.04 Angiotensin-Converting Enzyme Inhibitors
Captopril
Enalaprilat/Enalapril

28:00 Central Nervous System Agents

28:04 General Anesthetics (all in this class approved including future new drugs)

28:04.04 Barbiturates
Methohexital

28:04.16 Inhalation Anesthetics (not in AHFS)

28:04.92 General Anesthetics, Miscellaneous
Etomidate
Ketamine (not in AHFS)
Fospropofol
Propofol

28:08 Analgesics and Antipyretics

28:08.04 Nonsteroidal Antiflammatory Agents

28:08.04.08 Cyclooxygenase-2 (COX-2) Inhibitors
Celecoxib

28:08.04.24 Salicylates
Aspirin

28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents
Ibuprofen (PO or IV)
Indomethacin
Ketorolac
Meloxicam

28:08.08 Opiate Agonists (all in this class approved including future new drugs)
Codeine
Fentanyl
Hydrocodone
Hydromorphone
Levorphanol
Meperidine
Morphine
Remifentanil
Sufentanil Citrate
Tramadol

28:08.12 Opiate Partial Agonists (all in this class approved including future new drugs)
Buprenorphine
Butorphanol
Nalbuphine
28:08.92 Analgesics and Antipyretic, Miscellaneous
Acetaminophen (PO or IV)
Sodium Thiosalicylate

28:10 Opiate Antagonists (all in this class approved including future new drugs)
Nalmefene
Naloxone
Naltrexone

28:12 Anticonvulsants
28:12.04 Barbituates
Phenobarbital
28:12.08 Benzodiazepines
Clonazepam (see also 28:24.08)
28:12:12 Hydantoins
Ethotoin
Fosphenytoin
Phenytoin
28:12.92 Anticonvulsants, Miscellaneous
Carbamazepine
Felbamate
Gabapentin
Lamotrigine
Magnesium Sulfate
Valproate/Divalproex

28:16 Psychotherapeutic Agents
28:16.08 Antipsychotics
28:16.08.04 Atypical Antipsychotics
28:16.08.08 Butyrophenones
Haloperidol
28:16.08.24 Phenothiazines
Perphenazine
Prochlorperazine

28:20 Anorexigenic Agents and Respiratory and CNS Stimulants
28:20.32 Respiratory and CNS Stimulants
Caffeine/Caffeine and Sodium Benzoate
Doxapram

28:24 Anxiolytics, Sedatives, and Hypnotics
28:24.04 Barbiturates (all in this class approved including future new drugs)
Phenobarbital
28:24.08 Benzodiazepines (all in this class approved including future new drugs)
Alprazolam
Chlordiazepoxide

Diazepam
Lorazepam
Midazolam
Remimazolam
Temazepam

28:24.92 Anxiolytics, Sedatives, and Hypnotics, Miscellaneous
Dexmedetomidine
Hydroxyzine
Promethazine

28:36 Antiparkinsonian Agents

28:36.08 Anticholinergic Agents
Benztropine Mesylate

28:92 Central Nervous System Agents, Miscellaneous
Flumazenil

36:00 Diagnostic Agents

36:40 Kidney Function
Indigo Carmine (Indigotindisulfonate)

36:56 Myasthenia Gravis
Edrophonium Chloride

40:00 Electrolytic, Caloric, and Water Balance

40:08 Alkalinizing Agents
Citrates (i.e., potassium citrate and citric acid, sodium citrate and citric acid, tricitrates)
Sodium Bicarbonate
Sodium Lactate

40:12 Replacement Preparations
Calcium Salts
Dextran 40
Electrolyte Solutions
Hetastarch
Potassium Supplements
Sodium Chloride

40:20 Caloric Agents
Dextrose
Invert Sugar

40:24 Salt and Sugar Substitutes (not in AHFS)

40:28 Diuretics

40:28.08 Loop Diuretics
Bumetanide
Furosemide

40:28.12 Osmotic Diuretics
Mannitol

40:28.20 Thiazide Diuretics
Chlorothiazide

48:00 Respiratory Tract Agents (all in this class approved including future new drugs)

48:08 Antitussives
- Benzonatate
- Codeine
- Dextromethorphan
- Hydrocodone

48:16 Expectorants
- Guaifenesin
- Potassium Iodide (see also 68:36.08)

48:24 Mucolytic Agents
- Acetylcysteine (see also 92:12)

52:00 Eye, Ear, Nose, and Throat (EENT) Preparations

52:16 Local Anesthetics
- Benzocaine
- Dyclonine
- Proparacaine
- Tetracaine

52:32 Vasoconstrictors
- Epinephrine
- Naphazoline
- Oxymetazoline
- Phenylephrine
- Propylhexedrine
- Tetrahydrolozine

52:40 Antiglaucoma Agents

52:40.12 Carbonic Anhydrase Inhibitors
- Acetazolamide

56:00 Gastrointestinal Drugs

56:04 Antacids and Adsorbents
- Aluminum Carbonate
- Aluminum Hydroxide
- Aluminum Phosphate
- Antacids
- Calcium Carbonate
- Charcoal, Activated
- Dihydroxyaluminum Aminoacetate
- Dihydroxyaluminum Sodium Carbonate
- Magaldrate
- Magnesium Carbonate
- Magnesium Hydroxide
- Magnesium Oxide
- Magnesium Trisilicate
- Sodium Bicarbonate

56:22 Antiemetics
56:22.08 Antihistamines
Dimenhydrinate
Meclizine
Prochlorperazine
Trimethobenzamide
56:22.20 5-HT_3 Receptor Antagonists
Dolasetron
Granisetron
Ondansetron
56:22.92 Antiemetics, Miscellaneous
Amisulpride
56:28 Antiulcer Agents and Acid Suppressants
56:28.12 Histamine H2-Antagonists
Cimetidine
Famotidine
Nizatidine
~~Ranitidine~~
56:28.32 Protectants
Sucralfate
56:28.36 Proton-pump Inhibitors
Dexlansoprazole
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole
56:32 Prokinetic Agents
Metoclopramide

68:00 Hormones and Synthetic Substitutes
68:04 Adrenals (all in this class approved including future new drugs)
Beclomethasone
Betamethasone
Cortisone Acetate
Dexamethasone
Fludrocortisone
Flunisolide
Hydrocortisone
Methlyprednisolone
Prednisolone
Prednisone
Triamcinolone
68:20 Antidiabetic Agents
68:20.08 Insulins
68:20.08.04 Rapid-acting Insulins

Insulin Aspart
Insulin Glulisine
Insulin Lispro

68:20.08.08 Short-acting Insulins
Insulin Human
Insulin Isophane (not in AHFS)

68:20.08.16 Long-acting Insulins
Insulin Glargine

68:20.20 Sulfonylureas
Chlorpropamide
Glimepiride
Glipizide
Glyburide
Tolazamide
Tolbutamide

68:22 Antihypoglycemic Agents

68:22.12 Glycogenolytic Agents
Glucagon

68:28 Pituitary
Corticotropin
Desmopressin
Vasopressin

68:44 Renin-Angiotensin-Aldosterone System (RAAS)
Angiotensin II (not in AHFS)

72:00 Local Anesthetics (all in this class approved including future new drugs)
Articaine
Bupivacaine
Chloroprocaine
Lidocaine
Mepivacaine
Prilocaine
Procaine (not in AHFS)
Ropivacaine (not in AHFS)
Tetracaine

76:00 Oxytocics
Carboprost Tromethamine
Dinoprostone
Ergonovine/Methergonovine
Oxytocin
Sodium Chloride 20% Injection
Urea 40-50% Injection

84:00 Skin and Mucous Membrane Agents

84:04 Anti-infective

84:04.92 Local Anti-Infectives, Miscellaneous
Chlorhexidine gluconate

84:08 Antipruritics and Local Anesthetics (all in this class approved including future new drugs)
Benzocaine
Dibucaine
Doxepin
Ethyl Chloride
Phenazopyridine
Pramoxine

86:00 Smooth Muscle Relaxants

86:16 Respiratory Smooth Muscle Relaxants
Aminophylline
Theophyllines

92:00 Miscellaneous Therapeutic Agents

92:12 Antidotes
Acetylcysteine
Methylene Blue
Sugammadex

[NOTE: ACLS Algorithm medications are listed according to the classification system in the AHFS Drug Information resource.]

Regulatory Authority:

59 O.S. §567.4b. C.

Reference:

American Hospital Formulary Service®. *AHFS Drug Information* (~~2019~~2020). Published by Authority of the Board of the American Society of Health-System Pharmacists®, Bethesda, MD.

Attachment A

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_2-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

- 48:14.12 Cystic Fibrosis Transmembrane Conductance Regulator Potentiators
- 48:16 Expectorants
- 48:24 Mucolytic Agents
- 48:32 Phosphodiesterase Type 4 Inhibitors
- 48:36 Pulmonary Surfactants
- 48:48 Vasodilating Agents
- 48:92 Respiratory Agents, Miscellaneous

52:00 Eye, Ear, Nose, and Throat (EENT) Preparations

- 52:02 Antiallergic Agents
- 52:04 Anti-infectives
  - 52:04.04 Antibacterials
  - 52:04.16 Antifungals
  - 52:04.20 Antivirals
  - 52:04.92 Anti-infectives, Miscellaneous
- 52:08 Anti-inflammatory Agents
  - 52:08.08 Corticosteroids
  - 52:08.20 Nonsteroidal Anti-inflammatory Agents
  - 52:08.92 Anti-inflammatory Agents, Miscellaneous
- 52:12 Contact Lens Solutions*
- 52:16 Local Anesthetics
- 52:24 Mydriatics
- 52:28 Mouthwashes and Gargles
- 52:32 Vasoconstrictors
- 52:40 Antiglaucoma Agents
  - 52:40.04 α-Adrenergic Agonists
  - 52:40.08 β-Adrenergic Blocking Agents
  - 52:40.12 Carbonic Anhydrase Inhibitors
  - 52:40.20 Miotics
  - 52:40.24 Osmotic Agents*
  - 52:40.28 Prostaglandin Analogs
  - 52:40.32 Rho Kinase Inhibitors
  - 52:40.92 Antiglaucoma Agents, Miscellaneous*
- 52:92 EENT Drugs, Miscellaneous

56:00 Gastrointestinal Drugs

- 56:04 Antacids and Adsorbents
- 56:08 Antidiarrhea Agents
- 56:10 Antiflatulents
- 56:12 Cathartics and Laxatives
- 56:14 Cholelitholytic Agents
- 56:16 Digestants
- 56:20 Emetics*
- 56:22 Antiemetics
  - 56:22.08 Antihistamines
  - 56:22.20 5-HT_3 Receptor Antagonists
  - 56:22.32 Neurokinin-1 Receptor Antagonists
  - 56:22.92 Antiemetics, Miscellaneous
- 56:24 Lipotropic Agents*
- 56:28 Antiulcer Agents and Acid Suppressants
  - 56:28.12 Histamine H_2-Antagonists
  - 56:28.28 Prostaglandins
  - 56:28.32 Protectants
  - 56:28.36 Proton-pump Inhibitors
  - 56:28.92 Antiulcer Agents and Acid Suppressants, Miscellaneous*
- 56:32 Prokinetic Agents
- 56:36 Anti-inflammatory Agents
- 56:92 GI Drugs, Miscellaneous

60:00 Gold Compounds

64:00 Heavy Metal Antagonists

68:00 Hormones and Synthetic Substitutes

- 68:04 Adrenals
- 68:08 Androgens
- 68:12 Contraceptives
- 68:16 Estrogens, Antiestrogens, and Estrogen Agonist-Antagonists
  - 68:16.04 Estrogens
  - 68:16.08 Antiestrogens
  - 68:16.12 Estrogen Agonist-Antagonists
- 68:18 Gonadotropins and Antigonadotropins
  - 68:18.04 Antigonadotropins
  - 68:18.08 Gonadotropins
- 68:20 Antidiabetic Agents
  - 68:20.02 α-Glucosidase Inhibitors
  - 68:20.03 Amylinomimetics
  - 68:20.04 Biguanides
  - 68:20.05 Dipeptidyl Peptidase IV (DDP-4) Inhibitors
  - 68:20.06 Incretin Mimetics
  - 68:20.08 Insulins
  - 68:20.16 Meglitinides
  - 68:20.17 Sodium-glucose Cotransporter 1 (SGLT1) Inhibitors*
  - 68:20.18 Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors
  - 68:20.20 Sulfonylureas
  - 68:20.28 Thiazolidinediones
  - 68:20.92 Antidiabetic Agents, Miscellaneous*
- 68:22 Antihypoglycemic Agents
  - 68:22.12 Glycogenolytic Agents
  - 68:22.92 Antihypoglycemic Agents, Miscellaneous
- 68:24 Parathyroid and Antiparathyroid Agents
  - 68:24.04 Antiparathyroid Agents
  - 68:24.08 Parathyroid Agents
- 68:28 Pituitary
- 68:29 Somatostatin Agonists and Antagonists
  - 68:29.04 Somatostatin Agonists
  - 68:29.08 Somatostatin Antagonists*
- 68:30 Somatotropin Agonists and Antagonists
  - 68:30.04 Somatotropin Agonists
  - 68:30.08 Somatotropin Antagonists
- 68:32 Progestins
- 68:34 Other Corpus Luteum Hormones*
- 68:36 Thyroid and Antithyroid Agents
  - 68:36.04 Thyroid Agents
  - 68:36.08 Antithyroid Agents
- 68:40 Leptins
- 68:44 Renin-Angiotensin-Aldosterone System

72:00 Local Anesthetics

76:00 Oxytocics

78:00 Radioactive Agents*

80:00 Antitoxins, Immune Globulins, Toxoids, and Vaccines

- 80:02 Allergenic Extracts*
- 80:04 Antitoxins and Immune Globulins
- 80:08 Toxoids
- 80:12 Vaccines

84:00 Skin and Mucous Membrane Agents

- 84:04 Anti-infectives
  - 84:04.04 Antibacterials
  - 84:04.06 Antivirals
  - 84:04.08 Antifungals
    - 84:04.08.04 Allylamines
    - 84:04.08.08 Azoles
    - 84:04.08.12 Benzylamines
    - 84:04.08.16 Echinocandins*
    - 84:04.08.20 Hydroxypyridones
    - 84:04.08.24 Oxaboroles
    - 84:04.08.28 Polyenes
    - 84:04.08.32 Pyrimidines*
    - 84:04.08.40 Thiocarbamates
    - 84:04.08.92 Antifungals, Miscellaneous
  - 84:04.12 Scabicides and Pediculicides
  - 84:04.92 Local Anti-infectives, Miscellaneous
- 84:06 Anti-inflammatory Agents
  - 84:06.08 Corticosteroids
  - 84:06.20 Nonsteroidal Anti-inflammatory Agents
  - 84:06.92 Anti-inflammatory Agents, Miscellaneous
- 84:08 Antipruritics and Local Anesthetics
- 84:12 Astringents
- 84:16 Cell Stimulants and Proliferants
- 84:20 Detergents
- 84:24 Emollients, Demulcents, and Protectants*
  - 84:24.04 Basic Lotions and Liniments*
  - 84:24.08 Basic Oils and Other Solvents*
  - 84:24.12 Basic Ointments and Protectants*
  - 84:24.16 Basic Powders and Demulcents*
- 84:28 Keratolytic Agents
- 84:32 Keratoplastic Agents
- 84:50 Depigmenting and Pigmenting Agents
  - 84:50.04 Depigmenting Agents
  - 84:50.06 Pigmenting Agents
- 84:80 Sunscreen Agents
- 84:92 Skin and Mucous Membrane Agents, Miscellaneous

86:00 Smooth Muscle Relaxants

- 86:08 Gastrointestinal Smooth Muscle Relaxants*
- 86:12 Genitourinary Smooth Muscle Relaxants
  - 86:12.04 Antimuscarinics
  - 86:12.08 β_3-Adrenergic Agonists
    - 86:12.08.12 Selective β_3-Adrenergic Agonists
- 86:16 Respiratory Smooth Muscle Relaxants

88:00 Vitamins

- 88:04 Vitamin A
- 88:08 Vitamin B Complex
- 88:12 Vitamin C
- 88:16 Vitamin D
- 88:20 Vitamin E
- 88:24 Vitamin K Activity
- 88:28 Multivitamin Preparations

92:00 Miscellaneous Therapeutic Agents

- 92:04 Alcohol Deterrents
- 92:08 5-α-Reductase Inhibitors
- 92:12 Antidotes
- 92:16 Antigout Agents
- 92:18 Antisense Oligonucleotides
- 92:20 Immunomodulatory Agents
- 92:22 Bone Anabolic Agents
- 92:24 Bone Resorption Inhibitors
- 92:26 Carbonic Anhydrase Inhibitors
- 92:28 Cariostatic Agents
- 92:32 Complement Inhibitors
- 92:36 Disease-Modifying Antirheumatic Drugs
- 92:40 Gonadotropin-releasing Hormone Antagonists*
- 92:44 Immunosuppressive Agents
- 92:56 Protective Agents
- 92:92 Other Miscellaneous Therapeutic Agents

94:00 Devices*

96:00 Pharmaceutical Aids*

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

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

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Attachment B

DrugAssignments

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
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
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

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Appl Type	No
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
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

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Appl Type	No
Darzalex Faspro®	daratumumab; hyaluronidase-fihj	Janssen	multiple myeloma	2020/05/01	10:00 - Antineoplastic Agents		761145
Remdesivir	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
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

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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
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

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
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
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

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
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 - Antioneoplastic Agents	1P	211810
Nubeqa®	darolutamide	Bayer	non-metastatic castration-resistant prostate cancer	2019/07/30	10:00 - Antioneoplastic 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
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

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Type	Appl No
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
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

Drug Name	Active Ingredients	Company	Indication	Approval Date	AHFS Class	NDA Appl Type No
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

Attachment C

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

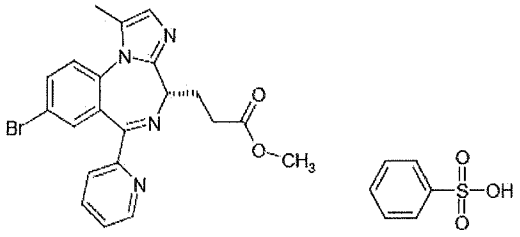
Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with BYFAVO is known or suspected. Prior to the administration of flumazenil, institute necessary measures to secure the airway, 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)]*.

Distributed by Acacia Pharma, Inc.
8440 Allison Pointe Blvd., Suite 100
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BYF-0001-USPI-07/2020

Attachment D

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BARHEMSYS safely and effectively. See full prescribing information for BARHEMSYS.

BARHEMSYS® (amisulpride) injection, for intravenous use
Initial U.S. Approval: 2020

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

BARHEMSYS is a dopamine-2 (D_2) antagonist indicated in adults for:

- Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class. (1)
- Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis. (1)

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

The recommended dosage of BARHEMSYS:

- Prevention of PONV, either alone or in combination with another antiemetic: 5 mg as a single intravenous dose infused over 1 to 2 minutes at the time of induction of anesthesia. (2.1)
- Treatment of PONV: 10 mg as a single intravenous dose infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure. (2.1)
- See full prescribing information for preparation and administration instructions. (2.2)

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

Injection: 5 mg/2 mL (2.5 mg/mL) in a single-dose vial. (3)

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

Known hypersensitivity to amisulpride. (4)

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

QT Prolongation: Occurs in a dose- and concentration-dependent manner. Avoid use in patients with congenital long QT syndrome and in patients taking droperidol. ECG monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders; electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia); congestive heart failure; and in patients taking other medicinal products (e.g., ondansetron) or with other medical conditions known to prolong the QT interval. (5.1, 7.2)

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

Most common adverse reactions (≥ 2%) are:

- Prevention of PONV: increased blood prolactin concentrations, chills, hypokalemia, procedural hypotension, and abdominal distension. (6.1)
- Treatment of PONV: infusion site pain. (6.1)

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 48 hours after BARHEMSYS administration. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BARHEMSYS® is indicated in adults for:

- prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class.
- treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended adult dosage of BARHEMSYS and infusion rate by indication is shown in the table below:

Indication	Adult Dosage Regimen
Prevention of PONV	5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia *[see Dosage and Administration (2.2)]*.
Treatment of PONV	10 mg as a single intravenous injection infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure *[see Dosage and Administration (2.2)]*.

2.2 Preparation and Administration

- Dilution of BARHEMSYS is not required before administration. BARHEMSYS is chemically and physically compatible with Water for Injection, 5% Dextrose Injection and 0.9% Sodium Chloride Injection, which may be used to flush an intravenous line before or after administration of BARHEMSYS.
- Protect from light. BARHEMSYS is subject to photodegradation. Administer BARHEMSYS within 12 hours of removal of the vial from the protective carton.
- Prior to administration, inspect the BARHEMSYS solution visually for particulate matter and discoloration. Discard if particulate matter or discoloration is observed.

3 DOSAGE FORMS AND STRENGTHS

Injection: 5 mg/2 mL (2.5 mg/mL) as a clear, colorless sterile solution in a single-dose vial.

4 CONTRAINDICATIONS

BARHEMSYS is contraindicated in patients with known hypersensitivity to amisulpride *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 QT Prolongation

BARHEMSYS causes dose- and concentration-dependent prolongation of the QT interval *[see Clinical Pharmacology (12.2)]*. The recommended dosage is 5 or 10 mg as a single intravenous dose infused over 1 to 2 minutes *[see Dosage and Administration (2.1)]*.

Avoid BARHEMSYS in patients with congenital long QT syndrome and in patients taking droperidol.

Electrocardiogram (ECG) monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders; electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia); congestive heart failure; and in patients taking other medicinal products (e.g., ondansetron) or with other medical conditions known to prolong the QT interval *[see Drug Interactions (7.2)]*.

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 data described below reflect exposure to BARHEMSYS in 1,166 patients treated in placebo-controlled trials. 748 of these patients received a dose of 5 mg for prevention of PONV (of whom 572 received another antiemetic concomitantly) and 418 patients received 10 mg for treatment of PONV *[see Clinical Studies (14.1, 14.2)]*. The mean age of the population was 49 years (range 18 to 91 years), 87% female, 80% White/Caucasian, 9% Black, and 1% Asian.

Prevention of PONV

Common adverse reactions reported in at least 2% of adult patients who received BARHEMSYS 5 mg and at a higher rate than placebo in Studies 1 and 2 for the prevention of PONV are shown in Table 1.

Table 1. Common Adverse Reactions* in Adult Patients in Studies 1 and 2 of BARHEMSYS for Prevention of PONV

	BARHEMSYS 5 mg	Placebo
	N=748	N=741
Chills	4%	3%
Hypokalemia	4%	2%
Procedural hypotension	3%	2%
Abdominal distension	2%	1%

*Reported in at least 2% of patients treated with BARHEMSYS and at a higher rate than placebo

Serum prolactin concentrations were measured in Study 1 where 5% (9/176) of BARHEMSYS-treated patients vs 1% (1/166) of placebo-treated patients had increased blood prolactin reported as an adverse reaction. Serum prolactin concentrations increased from a mean of 10 ng/mL at baseline to 32 ng/mL after

BARHEMSYS treatment in 112 females (upper limit of normal 29 ng/mL) and from 10 ng/mL to 19 ng/mL in 61 males (upper limit of normal 18 ng/mL). No clinical consequences due to elevated prolactin levels were reported.

Treatment of PONV

The most common adverse reaction, reported in at least 2% of adult patients who received BARHEMSYS 10 mg (N=418) and at a higher rate than placebo (N=416), in clinical trials for the treatment of PONV (Studies 3 and 4) was infusion site pain (BARHEMSYS 6%; placebo 4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval chronic oral use of amisulpride outside of the United States (BARHEMSYS is not approved for oral dosing or chronic use). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders*: agranulocytosis
- *Cardiac disorders*: bradycardia, torsades de pointes, ventricular tachycardia, prolonged QT by electrocardiogram
- *General disorders*: neuroleptic malignant syndrome
- *Immune system disorders*: angioedema, hypersensitivity, urticaria
- *Hepatic disorders*: increased hepatic enzymes
- *Nervous system disorders*: agitation, anxiety, dystonia, extrapyramidal disorder, seizure
- *Psychiatric disorders*: confusional state, insomnia, somnolence
- *Vascular disorders*: hypotension

7 DRUG INTERACTIONS

7.1 Dopamine Agonists

Reciprocal antagonism of effects occurs between dopamine agonists (e.g., levodopa) and BARHEMSYS. Avoid using levodopa with BARHEMSYS.

7.2 Drugs Prolonging the QT Interval

BARHEMSYS causes dose- and concentration-dependent QT prolongation *[see Clinical Pharmacology (12.2)]*. To avoid potential additive effects, avoid use of BARHEMSYS in patients taking droperidol. ECG monitoring is recommended in patients taking other drugs known to prolong the QT interval (e.g., ondansetron) *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with amisulpride use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of amisulpride in rats and rabbits during the

period of organogenesis at exposures about 43 and 645 times, respectively, the exposure delivered by the highest recommended human dose *(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.

Data

Animal Data
Reproduction studies of amisulpride were conducted in pregnant rats administered oral doses up to 160 mg/kg/day (43 times the exposure based on area under the curve (AUC) at the highest recommended dose of 10 mg) throughout the period of organogenesis. No adverse embryo-fetal developmental effects were observed at any dose level. Maternal animals exhibited a dose-related decrease in overall mean body weight gain. In rabbits administered amisulpride throughout the period of organogenesis, oral doses up to 210 mg/kg/day (645 times the exposure based on AUC at the highest recommended dose of 10 mg) had no adverse developmental effects on the fetus. Maternal animals exhibited reduced mean body weight gain at doses of 100 and 210 mg/kg/day and reduced food intake was observed at 210 mg/kg/day.

The pre- and post-natal developmental effects of amisulpride were assessed in rats administered oral doses of 60, 100 or 160 mg/kg/day during the periods of organogenesis and lactation. At 160 mg/kg/day (43 times the exposure based on AUC at the highest recommended dose of 10 mg), maternal animals exhibited a reduction in mean body weight gain and decrease in food intake during lactation. Amisulpride had no effect on maternal pregnancy parameters, litter survival or pup growth, development or maturation at any dose tested.

8.2 Lactation

Risk Summary

Based on case reports in published literature, amisulpride is present in human milk at concentrations that are 11- to 20-fold higher than human plasma in patients taking multiple oral doses of amisulpride (200 to 400 mg/day). The estimated infant daily dose ranged from 5% to 11% of the maternal dose. There are ways to minimize drug exposure to a breastfed infant *(see Clinical Considerations).* There are no reports of adverse effects on the breastfed child and no information on the effects of amisulpride on milk production. The pharmacological action of amisulpride, a dopamine-2 (D_2) receptor antagonist, may result in an increase in serum prolactin levels, which may lead to a reversible increase in maternal milk production *[see Adverse Reactions (6.1)].* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BARHEMSYS and any potential adverse effects on the breastfed child from BARHEMSYS or from the underlying maternal condition.

Clinical Considerations

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 48 hours after BARHEMSYS administration to minimize drug exposure to a breastfed infant.

8.3 Females and Males of Reproductive Potential

Infertility

In animal fertility studies, administration of repeated doses of amisulpride over a 10-day period to female rats resulted in infertility that was reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients enrolled in controlled clinical trials who received BARHEMSYS 5 mg for prevention of PONV or 10 mg for treatment of PONV, 235 (17%) were 65 years of age and older, while 59 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amisulpride is known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Avoid BARHEMSYS in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). The pharmacokinetics of amisulpride in patients with severe renal impairment have not been adequately studied in clinical trials *[see Clinical Pharmacology (12.3)]*. Amisulpride is known to be substantially excreted by the kidneys and patients with severe renal impairment may have increased systemic exposure and an increased risk of adverse reactions.

No dosage adjustment is necessary in patients with mild to moderate renal impairment (eGFR 30 mL/min/1.73 m^2 and above).

10 OVERDOSAGE

Doses of oral amisulpride (BARHEMSYS is not approved for oral dosing) above 1200 mg/day have been associated with adverse reactions related to dopamine-2 (D_2) antagonism, in particular:

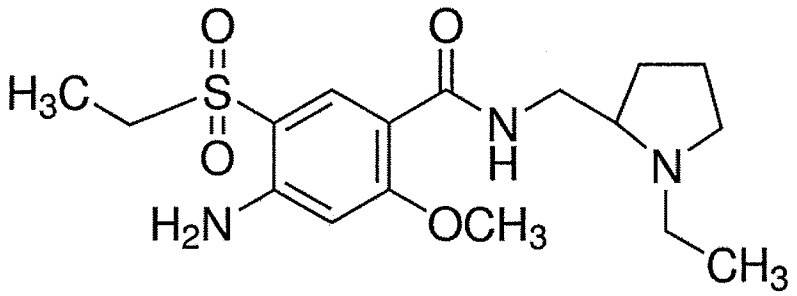
- cardiovascular adverse reactions (e.g., prolongation of the QT interval, torsades de pointes, bradycardia and hypotension) *[see Warnings and Precautions (5.1)]*.
- neuropsychiatric adverse reactions (e.g., sedation, coma, seizures, and dystonic and extrapyramidal reactions).

There is no specific antidote for amisulpride overdose. Management includes cardiac monitoring and treatment of severe extrapyramidal symptoms.

Since amisulpride is weakly dialyzed, hemodialysis should not be used to eliminate the drug.

11 DESCRIPTION

The active ingredient of BARHEMSYS is amisulpride, a dopamine-2 (D_2) receptor antagonist. Its chemical name is 4-Amino-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-*o*-anisamide. It has the following chemical structure:



(racemic)

The empirical formula is $C_{17}H_{27}N_3O_4S$ representing a molecular weight of 369.48.

Amisulpride is a white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in ethanol and freely soluble in methylene chloride, and has a melting point of around 126°C. The compound is racemic and shows no optical rotation and is not hygroscopic. No other polymorphs of amisulpride have been reported.

BARHEMSYS (amisulpride) injection is a clear, colorless, nonpyrogenic, sterile solution formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous infusion presented in a single-dose vial. It has a pH of approximately 5.0 and the osmolality of the product is between 250 and 330 mOsmol/kg.

Each 2 mL vial of BARHEMSYS contains 5 mg of amisulpride; 18.7 mg of citric acid monohydrate USP; 3.6 mg of sodium chloride USP; 32.64 mg of trisodium citrate dihydrate; hydrochloric acid NF and sodium hydroxide NF as needed to adjust the pH (4.75 to 5.25); and Water for Injection USP to make up to volume.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amisulpride is a selective dopamine-2 (D_2) and dopamine-3 (D_3) receptor antagonist. D_2 receptors are located in the chemoreceptor trigger zone (CTZ) and respond to the dopamine released from the nerve endings. Activation of CTZ relays stimuli to the vomiting center which is involved in emesis. Studies in multiple species indicate that D_3 receptors in the area postrema also play a role in emesis. Studies conducted in ferrets have shown that amisulpride inhibits emesis caused by apomorphine, with an estimated ED_{50} of less than 1 mcg/kg, subcutaneously; and inhibits cisplatin-induced emesis at 2 mg/kg and morphine-induced emesis at 3 to 6 mg/kg, when given intravenously.

Amisulpride has no appreciable affinity for any other receptor types apart from low affinities for 5-HT_{2B} and 5-HT_7 receptors.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In 40 healthy Caucasian and Japanese subjects, the maximum mean difference (95% upper confidence bound) in QTcF from placebo after baseline-correction (ΔΔQTcF) was 5.0 (7.1) milliseconds after a 2-minute intravenous infusion of 5 mg BARHEMSYS and 23.4 (25.5) milliseconds after an 8-minute intravenous infusion of 40 mg BARHEMSYS *[see Warnings and Precautions (5.1)]*.

A significant exposure-response relationship was identified between amisulpride concentration and ΔΔQTcF. Using this exposure-response relationship, 10 mg BARHEMSYS infused intravenously over 1 min has a maximal predicted (95% upper prediction interval) ΔΔQTcF of 13.4 (15.1) milliseconds.

The recommended infusion rate is 1 to 2 minutes for 5 mg or 10 mg of BARHEMSYS *[see Dosage and Administration (2.1)]*.

12.3 Pharmacokinetics

After an intravenous infusion, the peak plasma concentration of amisulpride is achieved at the end of the infusion period and the plasma concentration decreases to about 50% of the peak value within approximately 15 minutes. The $AUC_{(0-\infty)}$ increases dose-proportionally in the dose range from 5 mg to 40 mg (4-times the maximum recommended dose).

The following mean pharmacokinetic parameters of amisulpride were observed following a single 5 or 10 mg intravenous dose in adult healthy subjects and surgical patients.

Table 2. Summary of Key Pharmacokinetic Parameters of Amisulpride from Clinical Studies

	Single Dose	Infusion Duration (minutes)	Number of Subjects	Mean (SD)	
				Peak Plasma Concentration (ng/mL)	$AUC_{(0-\infty)}$ (ng·h/mL)
Healthy Subjects	5 mg	2	39	200 (139)	154 (30)
Healthy Subjects	10 mg	1	29	451 (230)	136 (28)[a]
Patients	5 mg	1 to 2	26[b]	161 (58)	260 (65)
			27[c]	127 (64)	204 (94)
Patients	10 mg	1 to 2	31[c]	285 (446)	401 (149)

[a] $AUC_{(0-2\ hr)}$
[b] Patients in a clinical trial for prophylaxis of PONV
[c] Patients in clinical trials for treatment of PONV

Distribution

Following intravenous infusion, the mean volume of distribution of amisulpride is estimated to be 127 to 144 L in surgical patients and 171 L in healthy subjects.

Amisulpride distributes into erythrocytes. Plasma protein binding is 25% to 30% in the concentration range from 37 to 1850 ng/mL.

Elimination

The mean elimination half-life is approximately 4 to 5 hours and similar between healthy subjects and surgical patients. Population pharmacokinetic analysis

estimated that the plasma clearance of amisulpride is 20.6 L/h in surgical patients and 24.1 L/h in healthy subjects.

Metabolism

In a mass balance study, no metabolites were detectable in plasma while four metabolites were identified in urine and feces. Each metabolite accounts for less than 7% of the dose. *In vitro* amisulpride is not metabolized by major cytochrome P450 enzymes.

Excretion

After intravenous administration of amisulpride, 74% and 23% of the administered dose was recovered in urine and feces, respectively. 58% and 20% of the dose was excreted as unchanged amisulpride in urine and feces, respectively.

Renal clearance was estimated to be 20.5 L/hr (342 mL/min) in healthy subjects suggesting that amisulpride undergoes active renal secretion.

Specific Populations

Age, Sex, and Racial Groups

No clinically significant effect on the pharmacokinetics of amisulpride was observed based on age (18 to 90 years), sex, or race.

Patients with Renal Impairment

In surgical patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), the C_{max} of amisulpride was not significantly different and the $AUC_{(0-\infty)}$ of amisulpride increased about 1.3-fold compared to patients with normal renal function. The pharmacokinetics of amisulpride in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) have not been adequately studied in clinical trials *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

No clinical drug interaction trials have been conducted with BARHEMSYS.

In Vitro Studies

Cytochrome P450-Related Metabolism

In vitro, amisulpride did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, or induce CYP1A2, CYP2C9, CYP2C19, or CYP3A4.

In vitro, amisulpride was not a substrate of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Transporters

Amisulpride inhibits MATE1 and MATE2-K transporters.

Amisulpride does not inhibit P-gp, BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3 at therapeutic concentrations.

Amisulpride is a substrate for P-gp, BCRP, OCT1, MATE1 and MATE2-K, but not a substrate for OATP1B1, OATP1B3, OAT1, OAT3 and OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to assess the carcinogenic potential of amisulpride have not been conducted. Amisulpride was not genotoxic in the bacterial reverse mutation assay, the *in vitro* human peripheral blood lymphocytes assay, and the *in vivo* rat bone marrow micronucleus assay.

The effect of amisulpride on fertility was studied in rats at oral doses up to 160 mg/kg/day (43 times the exposure based on AUC at the highest recommended dose of 10 mg). Most female animals (90% to 95%) at each dose level remained in diestrus and failed to mate. However, this effect on mating reversed following cessation of treatment. No treatment-related effects were observed on uterine/implantation parameters or sperm counts, sperm motility or sperm morphology.

14 CLINICAL STUDIES

14.1 Prevention of Postoperative Nausea and Vomiting

The efficacy of BARHEMSYS for the prevention of PONV was evaluated in two randomized, double-blind, placebo-controlled, multi-center trials in patients undergoing general anesthesia and elective surgery (Study 1 and Study 2). In Study 1 (NCT01991860), patients received monotherapy with BARHEMSYS; while in Study 2 (NCT02337062), patients received BARHEMSYS in combination with one other intravenously administered, non-dopaminergic antiemetic (ondansetron, dexamethasone or betamethasone). In both trials, patients were administered BARHEMSYS at the induction of anesthesia.

Study 1 was conducted in the United States in 342 patients. The mean age was 54 years (range 21 to 88 years); 65% female; 87% White/Caucasian, 12% Black, and 1% Asian race. The treatment groups were similarly matched in terms of risk for PONV with 30% of patients having two risk factors, 47% of patients having three risk factors and 23% of patients having four risk factors.

Study 2 was conducted in the United States and Europe in 1,147 patients. The mean age was 49 years (range 18 to 91 years); 97% female; 75% White/Caucasian, 9% Black, 1% Asian, and 14% of unreported race. The treatment groups were similarly matched in terms of risk for PONV with 56% of patients having three risk factors and 43% of patients having four risk factors.

The primary efficacy endpoint in both trials was Complete Response, defined as absence of any episode of emesis or use of rescue medication within the first 24 hours postoperatively. Results for both trials are shown in Table 3.

Table 3. Complete Response Rates in Adult Patients for the Prevention of PONV Within 24 Hours After End of Surgery in Studies 1 and 2

	Study 1		Study 2	
	BARHEMSYS 5 mg (n=176)	**Placebo (n=166)**	**BARHEMSYS 5 mg with Another Antiemetic (n=572)**	**Placebo with Another Antiemetic (n=575)**
Complete Response	78 (44%)	54 (33%)	330 (58%)	268 (47%)
Difference (95% CI)*	12% (2%, 22%)		11% (5%, 17%)	

*Unadjusted, nominal 95% confidence interval

14.2 Treatment of Postoperative Nausea and Vomiting

The efficacy of BARHEMSYS 10 mg as a single dose was evaluated in two randomized, double-blind, placebo-controlled, multi-center trials in patients experiencing PONV after general anesthesia and elective surgery (Study 3 and Study 4). Study 3 (NCT02449291) enrolled patients who had not received prior PONV prophylaxis, whereas Study 4 (NCT02646566) included patients who had received and failed PONV prophylaxis with an antiemetic of another class. Patients were excluded if they had received a D_2 receptor antagonist antiemetic.

Study 3 was conducted in 369 patients (mean age 47 years, range 19 to 82 years; 76% female; 82% White/Caucasian, 8% Black, 2% Asian, and 8% of unreported race). Most of the patients had either two risk factors (36%) or three risk factors (53%) for PONV and these percentages were similar between treatment groups.

Study 4 was conducted in 465 patients (mean age 46 years, range 18 to 85 years; 90% female; 82% White/Caucasian, 9% Black, 3% Asian, and 6% of unreported race). Patients had received prior PONV prophylaxis with one or more non-dopaminergic antiemetics: a 5-HT_3-antagonist in 77%, dexamethasone in 65% and another antiemetic class in 10%. Most of the patients had either three risk factors (43%) or four risk factors (51%) for PONV and these percentages were similar between treatment groups.

For both trials, the primary efficacy endpoint was Complete Response defined as absence of any episode of emesis or use of rescue medication within the first 24 hours after treatment (excluding emesis within the first 30 minutes).

BARHEMSYS Complete Response in both studies is shown in Table 4.

Table 4. Complete Response Rates in Adult Patients for the Treatment of PONV Within 24 Hours After Treatment[a] in Studies 3 and 4

	Study 3 (no prophylaxis)		Study 4 (prior prophylaxis)[b]	
	BARHEMSYS 10 mg (n=188)	**Placebo (n=181)**	**BARHEMSYS 10 mg (n=230)**	**Placebo (n=235)**
Complete Response	59 (31%)	39 (22%)	96 (42%)	67 (29%)
Difference (95% CI)[c]	10% (1%, 19%)		13% (5%, 22%)	

[a] Excluding emesis within the first 30 minutes

[b] Received prior PONV prophylaxis with one or more non-dopaminergic antiemetics: a 5-HT_3-antagonist in 77%, dexamethasone in 65% and another antiemetic class in 10%

[c] Unadjusted, nominal 95% confidence interval

16 HOW SUPPLIED/STORAGE AND HANDLING

BARHEMSYS (amisulpride) injection is supplied as follows:

NDC 71390-125-20: Package of 10 cartons. Each carton (NDC 71390-125-21) contains one single-dose vial of clear, colorless, sterile solution of BARHEMSYS (amisulpride) injection, 5 mg in 2 mL (2.5 mg/mL).

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

Protect from light. Administer BARHEMSYS within 12 hours after the vial is removed from the protective carton *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

QT Prolongation

Instruct patients to contact their healthcare provider immediately if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode *[see Warnings and Precautions (5.1)]*.

Drug Interactions

Advise patients to report to their healthcare provider if they are taking drugs which prolong the QT interval *[see Warnings and Precautions (5.1)]*.

Lactation

Women may consider reducing infant exposure through pumping and discarding breastmilk for 48 hours after BARHEMSYS administration *[see Use in Specific Populations (8.2)]*.

Distributed by Acacia Pharma Inc.

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Indianapolis, IN 46250 USA

BAR-0001-USPI-02/2020

Attachment E

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

ANGIOMAX RTU (bivalirudin) injection, for intravenous use
Initial U.S. Approval: 2000

----------INDICATIONS AND USAGE ----------
ANGIOMAX RTU is a direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI), including patients with heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- The recommended dosage is a 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure. Five minutes after the bolus dose, assess activated clotting time (ACT) to determine if an additional bolus of 0.3 mg/kg is needed. (2.1)
- Consider extending duration of infusion post-procedure up to 4 hours in patients with ST segment elevation MI. (2.1)

----------DOSAGE FORMS AND STRENGTHS ----------
Injection: 250 mg/50 mL (5 mg/mL) in a single- dose vial. Ready-to-use. (3)

---------- CONTRAINDICATIONS ----------
- Significant active bleeding (4)
- Hypersensitivity to bivalirudin or its components (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Bleeding events: bivalirudin increases the risk of bleeding. Its anticoagulant effect subsides approximately one hour after discontinuation. (5.1, 6.1, 12.2)
- Thrombotic risk with coronary artery brachytherapy: An increased risk of thrombus formation, including fatal outcomes, in gamma brachytherapy. (5.2, 6.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reaction was bleeding (3.7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MAIA Pharmaceuticals, Inc. at 1-888-877-9064 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
Heparin, warfarin, thrombolytics, or GPIs: Increased major bleeding risk with concomitant use. (7)

---------- USE IN SPECIFIC POPULATIONS ----------
Geriatric patients: Increased bleeding risk possible. (8.5)
Renal impairment: Reduce infusion dose and monitor ACT. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ANGIOMAX RTU is indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI), including patients with heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ANGIOMAX RTU is an intravenous bolus dose of 0.75 mg/kg, followed immediately by a maintenance infusion of 1.75 mg/kg/h for the duration of the procedure. Five minutes after the bolus dose has been administered, assess activated clotting time (ACT) to determine if an additional bolus of 0.3 mg/kg is needed.

Consider extending duration of infusion following PCI at 1.75 mg/kg/h for up to 4 hours post-procedure in patients with ST segment elevation MI (STEMI).

2.2 Dose Adjustment in Renal Impairment

Bolus Dose:

No reduction in the bolus dose is needed for any degree of renal impairment.

Maintenance Infusion:

In patients with creatinine clearance less than 30 mL/min (by Cockcroft Gault equation), reduce the infusion rate to 1 mg/kg/h.

In patients on hemodialysis, reduce the infusion rate to 0.25 mg/kg/h *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.3 Instructions for Administration

Inspection of Container

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

Once removed from refrigerator, use immediately *[see How Supplied Storage and Handling (16.2)]*. Discard any unused portion.

Drug Compatibilities

No incompatibilities have been observed with administration sets.

Do not administer the drugs listed in **Table 1** in the same intravenous line with ANGIOMAX RTU.

Table 1. Drugs Not for Administration in the Same Intravenous Line with ANGIOMAX RTU

Alteplase
Amiodarone HCl
Amphotericin B
Chlorpromazine HCl
Diazepam
Dobutamine
Prochlorperazine Edisylate

Reteplase
Streptokinase
Vancomycin HCl

3 DOSAGE FORMS AND STRENGTHS

Injection, clear to slightly opalescent, colorless to yellow sterile solution:

- 250 mg of bivalirudin per 50 mL (5 mg/mL) in a single-dose vial. Ready-to-use. Each vial contains 250 mg of bivalirudin equivalent to an average of 275 mg bivalirudin trifluoroacetate*.

**The range of bivalirudin trifluoroacetate is 270 to 280 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.*

4 CONTRAINDICATIONS

ANGIOMAX RTU is contraindicated in patients with:

- Significant active bleeding;
- Hypersensitivity to ANGIOMAX RTU or its components *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bleeding Events

Bivalirudin increases the risk of bleeding *[see Adverse Reactions (6.1)]*. Bivalirudin's anticoagulant effect subsides approximately one hour after discontinuation *[see Clinical Pharmacology (12.2)]*.

5.2 Thrombotic Risk with Coronary Artery Brachytherapy

An increased risk of thrombus formation, including fatal outcomes, has been associated with the use of bivalirudin in gamma brachytherapy *[see Adverse Reactions (6.2)]*.

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.

In the BAT trials, 79 of the 2161 (3.7%) of subjects undergoing PCI for treatment of unstable angina and randomized to bivalirudin experienced intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin greater than 3 g/dL or leading to a transfusion of greater than 2 units of blood.

Immunogenicity/Re-Exposure

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bivalirudin in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In *in vitro* studies, bivalirudin exhibited no platelet aggregation response against sera from patients with a history of HIT/HITTS.

Among 494 subjects who received bivalirudin in clinical trials and were tested for antibodies, 2 subjects had treatment-emergent positive bivalirudin antibody tests. Neither subject demonstrated clinical evidence of allergic or anaphylactic reactions and repeat testing was not performed. Nine additional patients who had initial positive tests were negative on repeat testing.

6.2 Postmarketing Experience

Because postmarketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of bivalirudin: fatal bleeding; hypersensitivity and allergic reactions including reports of anaphylaxis; lack of anticoagulant effect; thrombus formation during PCI with and without intracoronary brachytherapy, including reports of fatal outcomes; pulmonary hemorrhage; cardiac tamponade; and INR increased.

7 DRUG INTERACTIONS

In clinical trials in patients undergoing PCI, co-administration of bivalirudin with heparin, warfarin, thrombolytics, or GPIs was associated with increased risks of major bleeding events compared to patients not receiving these concomitant medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of bivalirudin in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Reproduction studies in rats and rabbits administered subcutaneously (SC) doses up to 1.6 times and 3.2 times the maximum recommended human dose (MRHD) based on body surface area (BSA), respectively, revealed no evidence of fetal harm.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

Data

Animal Data

Reproductive studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no harm to the fetus attributable to bivalirudin.

At 500 mg/kg/day subcutaneously, litter sizes and live fetuses in rats were reduced. Fetal skeletal variations were also noted. Some of these changes could be attributed to maternal toxicity observed at high doses.

8.2 Lactation

Risk Summary

It is not known whether bivalirudin is present in human milk. No data are available on the effects of bivalirudin on the breastfed child or on milk production.

8.4 Pediatric Use

The safety and effectiveness of bivalirudin in pediatric patients have not been established.

8.5 Geriatric Use

In studies of patients undergoing PCI, 44% were ≥65 years of age and 12% of patients were ≥75 years old. Elderly patients experienced more bleeding events than younger patients.

8.6 Renal Impairment

The disposition of bivalirudin was studied in PTCA patients with mild, moderate and severe renal impairment. The clearance of bivalirudin was reduced approximately 21% in patients with moderate and severe renal impairment and was reduced approximately 70% in dialysis- dependent patients *[see Clinical Pharmacology (12.3)]*. The infusion dose of ANGIOMAX RTU may need to be reduced, and anticoagulant status monitored in patients with renal impairment *[see Dosage and Administration (2.2)]*.

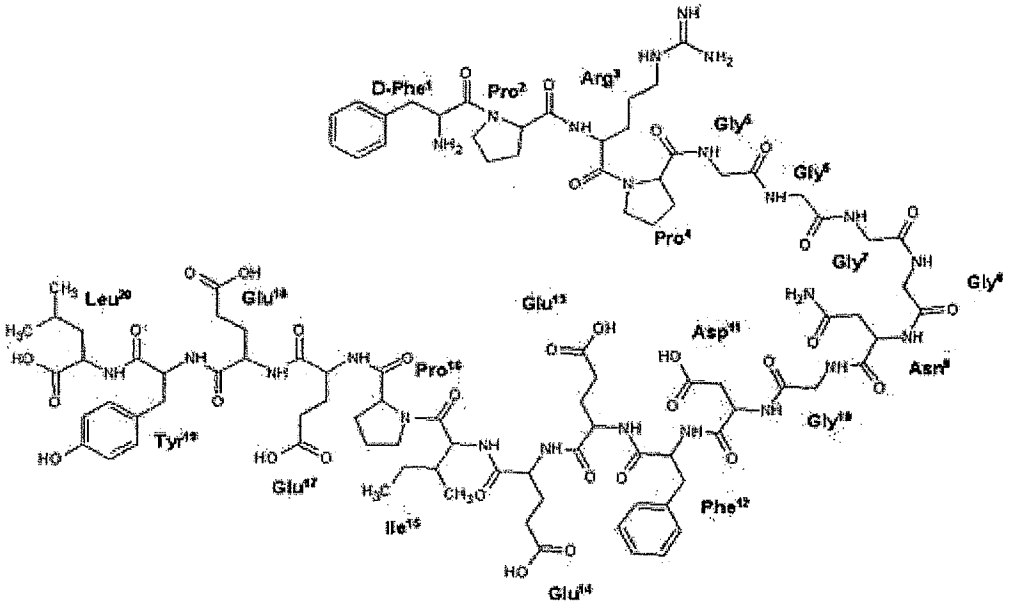
10 OVERDOSAGE

Cases of overdose of up to 10 times the recommended bolus or continuous infusion dose of bivalirudin have been reported in clinical trials and in postmarketing reports. A number of the reported overdoses were due to failure to adjust the infusion dose of bivalirudin in persons with renal dysfunction including persons on hemodialysis *[see Dosage and Administration (2.2)]*. Bleeding, as well as deaths due to hemorrhage, have been observed in some reports of overdose. In cases of suspected overdosage, discontinue bivalirudin immediately and monitor the patient closely for signs of bleeding. There is no known antidote to bivalirudin. Bivalirudin is hemodialyzable *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

ANGIOMAX RTU contains bivalirudin trifluoroacetate, which is a specific and reversible direct thrombin inhibitor. Bivalirudin trifluoroacetate is a synthetic, 20 amino acid peptide salt, with the chemical name of D-phenylalanyl-L-prolyl-L-arginyl-L-prolylglycylglycylglycylglycyl-L-asparagylglycyl-L-α-aspartyl-L-phenylalanyl-L-α-glutamyl-L-α-glutamyl-L-isoleucyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-tyrosyl-L-leucine trifluoroacetate. Each molecule of bivalirudin trifluoroacetate contains 1.7 to 2.6 equivalents of trifluoroacetic acid. The molecular formula of bivalirudin free base is $C_{98}H_{138}N_{24}O_{33}$ and its molecular weight is 2180.32 Daltons (anhydrous free base peptide). The structural formula of bivalirudin free base is

Figure 1: Structural Formula of Bivalirudin



ANGIOMAX RTU is supplied as a refrigerated, ready-to-use, sterile solution packaged in a 50 mL single-dose vial. Each milliliter of ANGIOMAX RTU contains 5 mg bivalirudin (as trifluoroacetate salt)*, 0.8 mg sodium acetate trihydrate, 100 mg polyethylene glycol 400, and Water for Injection.

The pH of ANGIOMAX RTU may have been adjusted with sodium hydroxide and/or glacial acetic acid to 5.0 to 5.5. The solution is intended for intravenous administration at room temperature (20°C to 25°C/68°F to 77°F).

**The range of bivalirudin trifluoroacetate is 5.4 to 5.6 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bivalirudin directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Thrombin is a serine proteinase that plays a central role in the thrombotic process, acting to cleave fibrinogen into fibrin monomers and to activate Factor XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework which stabilizes the thrombus; thrombin also activates Factors V and VIII, promoting further thrombin generation, and activates platelets, stimulating aggregation and granule release. The binding of bivalirudin to thrombin is reversible as thrombin slowly cleaves the bivalirudin-Arg3-Pro4 bond, resulting in recovery of thrombin active site functions.

12.2 Pharmacodynamics

In healthy volunteers and patients (with ≥70% vessel occlusion undergoing routine PTCA), bivalirudin exhibited dose- and concentration-dependent anticoagulant activity as evidenced by prolongation of the ACT, aPTT, PT, and TT. Intravenous administration of bivalirudin produces an immediate anticoagulant effect. Coagulation times return to baseline approximately 1 hour following cessation of bivalirudin administration. Bivalirudin also increases INR.

In 291 patients with ≥70% vessel occlusion undergoing routine PTCA, a positive correlation was observed between the dose of bivalirudin and the proportion of patients achieving ACT values of 300 sec or 350 sec. At a bivalirudin dose of 1 mg/kg intravenous bolus plus 2.5 mg/kg/h intravenous infusion (1.4

times higher than the approved dose of 1.75 mg/kg/h) for 4 hours, followed by 0.2 mg/kg/h, all patients reached maximal ACT values greater than 300 sec.

12.3 Pharmacokinetics

Bivalirudin exhibits linear pharmacokinetics following intravenous administration to patients undergoing PTCA. In these patients, a mean steady state bivalirudin concentration of 12.3 ± 1.7 mcg/mL is achieved following an intravenous bolus of 1 mg/kg and a 4-hour 2.5 mg/kg/h intravenous infusion.

Distribution

Bivalirudin does not bind to plasma proteins (except thrombin) or to red blood cells.

Elimination

Bivalirudin has a half-life of 25 minutes in PTCA patients with normal renal function. The total body clearance of bivalirudin in PTCA patients with normal renal function is 3.4 mL/min/kg.

Metabolism

Bivalirudin is metabolized by proteolytic cleavage.

Excretion

Bivalirudin undergoes glomerular filtration. Tubular secretion and tubular reabsorption are also implicated in the excretion of bivalirudin, although the extent is unknown.

Specific Populations

Patients with Renal Impairment

Total body clearance was similar for PTCA patients with normal renal function and with mild renal impairment. Clearance was reduced by 21% in patients with moderate and severe renal impairment with a half-life of 34 and 57 minutes, respectively. In dialysis patients, clearance was reduced by 70%, with a half-life of 3.5 hours. Approximately 25% bivalirudin is cleared by hemodialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of bivalirudin. Bivalirudin displayed no genotoxic potential in the *in vitro* bacterial cell reverse mutation assay (Ames test), the *in vitro* Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the *in vitro* human lymphocyte chromosomal aberration assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, and the *in vitro* rat micronucleus assay. Fertility and general reproductive performance in rats were unaffected by subcutaneous doses of bivalirudin up to 150 mg/kg/day, about 1.6 times the dose on a body surface area basis (mg/m^2) of a 50 kg person given the maximum recommended dose of 15 mg/kg/day.

14 CLINICAL STUDIES

Bivalirudin Angioplasty Trial (BAT)

In the BAT studies, patients with unstable angina undergoing PCI were randomized 1:1 to a 1 mg/kg bolus of bivalirudin and then 2.5 mg/kg/h for four hours and then 0.2 mg/kg/h for 14 to 20 hours or to 175 IU/kg bolus of heparin followed by an 18- to 24-hour infusion of 15 IU/kg/h infusion. Additional heparin but not bivalirudin could be administered for ACT less than 350 seconds. The studies were designed to demonstrate the superiority of bivalirudin to heparin on the occurrence of any of the following during hospitalization up to seven days of death, MI, abrupt closure of the dilated vessel, or clinical deterioration requiring revascularization or placement of an aortic balloon pump.

The 4312 subjects ranged in age from 29 to 90 (median 63) years. 68% were male, and 91% were

Caucasian. Median weight was 80 kg (39 to 120 kg). 741 (17%) subjects had post-MI angina. Twenty-three percent of patients were treated with heparin within one hour prior to randomization.

The studies did not demonstrate that bivalirudin was statistically superior to heparin for reducing the risk of death, MI, abrupt closure of the dilated vessel, or clinical deterioration requiring revascularization or placement of an aortic balloon pump, but the occurrence of these events was similar in both treatment groups. Study outcomes are shown in **Table 2.**

Table 2: Incidences of In-hospital Endpoints in BAT Trial

Endpoint	Bivalirudin (n=2161)	HEPARIN (n=2151)
Primary endpoint†	7.9%	9.3%
Death, MI, revascularization	6.2%	7.9%
Death	0.2%	0.2%
MI	3.3%	4.2%

† A composite of death or MI or clinical deterioration of cardiac origin requiring revascularization or placement of an aortic balloon pump or angiographic evidence of abrupt vessel closure

AT-BAT Trial (NCT# 00043940)

This was a single-arm open-label study in which 51 subjects with heparin-induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. The majority of patients achieved adequate ACT at the time of device activation and no major bleeding was reported. Two patients developed thrombocytopenia.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ANGIOMAX RTU is supplied as a refrigerated, ready-to-use, clear to slightly opalescent, colorless to yellow, sterile solution in 250 mg/50 mL (5 mg/mL) single-dose, glass vials. The single-dose vials are available as follows:

- NDC 70511-141-50: Carton containing 1 ANGIOMAX RTU single-dose vial
- NDC 70511-141-84: Carton containing 10 ANGIOMAX RTU single-dose vials

Each vial contains 250 mg of bivalirudin (equivalent to an average of 275 mg bivalirudin trifluoroacetate*).

**The range of bivalirudin trifluoroacetate is 270 to 280 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.*

16.2 Storage

Store ANGIOMAX RTU vials in the refrigerator between 2° to 8°C (36°to 46°F). Excursions are permitted to 20° to 25°C (68 to 77°F) *[see Dosage and Administration (2.3)]*. Avoid excess heat.

17 PATIENT COUNSELING INFORMATION

Advise patients to watch carefully for any signs of bleeding or bruising and to report these to their healthcare provider when they occur.

Manufactured for
MAIA Pharmaceuticals, Inc.

Princeton, NJ 08540
Distributed by
Sandoz Inc.
Princeton, NJ 08540

Attachment F

Drugs@FDA: FDA-Approved Drugs

Home (index.cfm) | Previous Page

New Drug Application (NDA): 019593
Company: TELIGENT

Products on NDA 019593

CSV | Excel | Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code
ZANTAC IN PLASTIC CONTAINER	RANITIDINE HYDROCHLORIDE	EQ 50MG BASE/100ML	INJECTABLE;INJECTION	Discontinued	None
ZANTAC IN PLASTIC CONTAINER	RANITIDINE HYDROCHLORIDE	EQ 1MG BASE/ML	INJECTABLE;INJECTION	Discontinued	None

Showing 1 to 2 of 2 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 019593