Epic®

kisunla™ (donanemab-azbt) | injection for IV infusion 350 mg/20 mL

OPTIONS FOR UPDATING THERAPY PLANS TO INCLUDE KISUNLA

INSTRUCTIONS FOR THE EPIC® ELECTRONIC HEALTH RECORD (EHR) SYSTEM

INDICATION AND USAGE

Kisunla is indicated for the treatment of Alzheimer's disease (AD). Treatment with Kisunla should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.

ApoE ε4 Homozygotes: Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes treated with this class of medications, including Kisunla, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.

Consider the benefit for the treatment of Alzheimer's disease and risk of ARIA when deciding to treat with Kisunla.

Please see Important Safety Information on **pages 14-17**, and full **Prescribing Information**, including Boxed Warning regarding ARIA, and **Medication Guide** for Kisunla.

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1. Overview and Limitations

Therapy Plans contain orders needed to plan the patient's care for the duration of their therapy, from pre-infusion orders, during infusion assistance orders, to post-infusion needs, such as maintenance medications and imaging.

After initial release, Therapy Plans may benefit from a clinical update. The optimization of these Therapy Plans in the Epic EHR system is a standard process and provides an opportunity to incorporate treatment updates. A customer may choose to update existing Therapy Plans with new treatments, such as Kisunla™ (donanemab-azbt).

This document is intended to provide health systems with instructions on how to update a Therapy Plan with Kisunla, within the approved indication and consistent with the full Prescribing Information. These instructions are specific to the Epic EHR system and the use of Kisunla in the treatment of early symptomatic Alzheimer's disease. They are not appropriate for other conditions, treatments, therapeutic areas, or other EHR systems. These instructions detail how to add dosing information and infusion instructions for Kisunla.

The process outlined on the following pages is variable, and all steps may not apply to every customer. Any steps or settings outlined in this document that are not part of a customer's standard process should be excluded or modified accordingly. Any questions should be directed to the appropriate service provider. The customer is solely responsible for implementing, testing, monitoring, and maintaining the ongoing operation of any EHR resources. The elements provided herein are only suggestions, and clinical and operational leadership determines that the final elements align with the expectations and goals of the organization. A Notes section (located on **page 18** of this guide) can be used to document any additions or changes that need to be made prior to implementation.

Typically, a health system will conduct a clinical review process to confirm and approve the suggested build and subsequent optimizations. Various stakeholders may participate in reviewing Therapy Plan requests prior to implementation.

This document is not intended to provide any clinical advice or clinical recommendations, which are solely the responsibility of the customer and its healthcare providers. Treatment selection is always a decision made by the healthcare provider, and Therapy Plans may be overridden to reflect this. An EHR newsletter or other communication medium may be considered to notify end users of the availability and contents of any updated Therapy Plans.

2. Indication and Usage

Kisunla is indicated for the treatment of Alzheimer's disease (AD). Treatment with Kisunla should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.

SELECT IMPORTANT SAFETY INFORMATION

- **Hypersensitivity: Kisunla is contraindicated** in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients. Reactions have included anaphylaxis.

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3. Dosing and Administration

The following is an overview and quick-reference guide for the dosing and administration details for Kisunla for its approved indication as per the full Prescribing Information. Step-by-step instructions for applying some of these medication details in the Therapy Plan update are shown in the following section of this guide.

Patient Selection

Confirm the presence of amyloid beta pathology prior to initiating treatment [see Clinical Pharmacology (12.1)]. Obtain a recent baseline brain magnetic resonance imaging (MRI) prior to initiating treatment with Kisunla.

Dosing Instructions

The recommended dosage of Kisunla is 700 mg every four weeks for three doses, then 1400 mg every four weeks (see Table 1 in the full Prescribing Information, reproduced below). Kisunla is administered every four weeks as an intravenous infusion over approximately 30 minutes. Kisunla must be diluted prior to administration (see Table 4 in the full Prescribing Information, reproduced on **page 7**).

Table 1 From Full Prescribing Information: Dosing Schedule

Intravenous Infusion (every 4 weeks)	Kisunla Dosage (administered over approximately 30 minutes)
Infusions 1, 2, and 3	700 mg
Infusion 4 and beyond	1400 mg

Consider stopping dosing with Kisunla based on reduction of amyloid plaques to minimal levels on amyloid PET imaging. In Study 1, dosing was stopped based on a reduction of amyloid levels below predefined thresholds on PET imaging *[see Clinical Studies (14)]*.

If an infusion is missed, resume administration every four weeks at the same dose as soon as possible.

SELECT IMPORTANT SAFETY INFORMATION

Amyloid-Related Imaging Abnormalities (ARIA)

Kisunla can cause ARIA-E, which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H generally occurs with ARIA-E. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages (ICH) >1 cm in diameter have occurred in patients treated with Kisunla.

Risk Factors for ARIA and Intracerebral Hemorrhages

- **ApoE ε4 Carrier Status**: The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes.
- The recommendations for management of ARIA do not differ between ApoE ε4 carriers and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

→ *See next page for additional content.*

Please see Important Safety Information on **pages 14-17**, and full **Prescribing Information**, including Boxed Warning regarding ARIA, and **Medication Guide** for Kisunla.

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3. Dosing and Administration (Cont'd)

Monitoring and Dosing Interruption for Amyloid-Related Imaging Abnormalities

Consider stopping dosing with Kisunla based on reduction of amyloid plaques to minimal levels on amyloid PET imaging. In Study 1, dosing was stopped based on a reduction of amyloid levels below predefined thresholds on PET imaging *[see Clinical Studies (14)]*.

Monitoring for ARIA

Obtain a recent baseline brain magnetic resonance imaging (MRI) prior to initiating treatment with Kisunla. Obtain an MRI prior to the 2nd, 3rd, 4th, and 7th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

Recommendations for Dosing Interruptions in Patients With ARIA

ARIA-E

The recommendations for dosing interruptions for patients with ARIA-E are provided in Table 2 of the full Prescribing Information, reproduced below:

Table 2 From Full Prescribing Information: Dosing Recommendations for Patients With ARIA-E[1]

	ARIA-E Severity on MRI		
Clinical Symptom Severity[a]	**Mild**	**Moderate**	**Severe**
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[b]	Suspend dosing[b]
Mild	May continue dosing based on clinical judgement	Suspend dosing[b]	
Moderate or Severe	Suspend dosing[b]		

[a]Mild: discomfort noticed, but no disruption of normal daily activity; Moderate: discomfort sufficient to reduce or affect normal daily activity; Severe: incapacitating, with inability to work or to perform normal daily activity.

[b]Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

ARIA-E=amyloid-related imaging abnormalities-edema; MRI=magnetic resonance imaging.

SELECT IMPORTANT SAFETY INFORMATION

Risk Factors for ARIA and Intracerebral Hemorrhages (ICH) (continued)

- **Radiographic Findings of Cerebral Amyloid Angiopathy (CAA)**: Neuroimaging findings that may indicate CAA include evidence of prior ICH, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for ICH. The presence of an ApoE ε4 allele is also associated with CAA.
- In Study 1, the baseline presence of at least 2 microhemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, were identified as risk factors for ARIA. Patients were excluded from enrollment for findings on neuroimaging of prior ICH >1 cm in diameter, >4 microhemorrhages, >1 area of superficial siderosis, severe white matter disease, and vasogenic edema.

→ *See next page for additional content.*

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3. Dosing and Administration (Cont'd)

Monitoring and Dosing Interruption for Amyloid-Related Imaging Abnormalities (Cont'd)

Recommendations for Dosing Interruptions in Patients With ARIA (Cont'd)

ARIA-H

The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 3 of the full Prescribing Information, reproduced below:

Table 3 From Full Prescribing Information: Dosing Recommendations for Patients With ARIA-H[1]

	ARIA-H Severity on MRI		
Clinical Symptom Severity	**Mild**	**Moderate**	**Severe**
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[a]	Suspend dosing[b]
Symptomatic	Suspend dosing[a]		

[a]Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.

[b]Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment when considering whether to continue treatment or permanently discontinue Kisunla.

ARIA-H=amyloid-related imaging abnormalities-hemosiderin deposition.

In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with Kisunla, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Resumption of dosing should be guided by clinical judgment.[1]

SELECT IMPORTANT SAFETY INFORMATION

Risk Factors for ARIA and Intracerebral Hemorrhages (ICH) (continued)

- **Concomitant Antithrombotic or Thrombolytic Medication**: In Study 1, the majority of exposures to antithrombotic medications were to aspirin. The number of events and the limited exposure to non-aspirin antithrombotic medications limit definitive conclusions about the risk of ARIA or ICH in patients taking antithrombotic medications.
- Additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (eg, tissue plasminogen activator) to a patient already being treated with Kisunla. One fatal ICH occurred in a patient taking Kisunla in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent.
- Consider whether ischemic stroke symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla, because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke.
- Caution should be exercised when considering the use of Kisunla in patients with factors that indicate an increased risk for ICH and in particular for patients who need to be on anticoagulant therapy or patients with findings on MRI that are suggestive of CAA.

→ *See next page for additional content.*

3. Dosing and Administration (Cont'd)

Dilution Instructions

- Prior to administration, Kisunla must be diluted with 0.9% sodium chloride injection, USP.
- Use aseptic technique when preparing the diluted Kisunla solution for intravenous infusion.
- Allow Kisunla to equilibrate to room temperature before preparation.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Kisunla solution is clear to opalescent, colorless to slightly yellow to slightly brown. Do not use if particulate matter or discolorations are present.
- Withdraw required volume of Kisunla and mix with 0.9% sodium chloride injection, to the recommended total volume for a final concentration of 4 mg/mL to 10 mg/mL (see Table 4 in the full Prescribing Information, reproduced below). Use only 0.9% sodium chloride injection for dilution.

Table 4 From Full Prescribing Information: Preparation and Reconstitution of Kisunla

Kisunla Dose (mg)	Kisunla Volume (mL)	Volume of 0.9% Sodium Chloride Injection Diluent (mL)	Final Volume of Diluted Solution to be Infused (mL)	Final Concentration of Diluted Solution (mg/mL)[a]
700 mg	40 mL[b]	30 mL to 135 mL	70 mL to 175 mL	700 mg/175 mL (4 mg/mL) to 700 mg/70 mL (10 mg/mL)
1400 mg	80 mL[c]	60 mL to 270 mL	140 mL to 350 mL	1400 mg/350 mL (4 mg/mL) to 1400 mg/140 mL (10 mg/mL)

[a]Final concentration of 4 mg/mL to 10 mg/mL.
[b]2 vials of Kisunla.
[c]4 vials of Kisunla.

SELECT IMPORTANT SAFETY INFORMATION

ARIA Monitoring and Dose Management Guidelines

- Baseline brain MRI and periodic monitoring with MRI are recommended prior to the 2nd, 3rd, 4th, and 7th infusions. Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with Kisunla. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.
- Recommendations for dosing in patients with ARIA-E and ARIA-H depend on clinical symptoms and radiographic severity. Depending on ARIA severity, use clinical judgment in considering whether to continue dosing, interrupt treatment, or permanently discontinue Kisunla. See Prescribing Information for additional dosing considerations.
- There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data for dosing patients who experienced recurrent episodes of ARIA-E.

→ *See next page for additional content.*

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3. Dosing and Administration (Cont'd)

Dilution Instructions (Cont'd)

- Each vial is for one-time use only. Discard any unused portion left in the vial.
- Gently invert the diluted Kisunla solution to mix completely. Do not shake.
- After dilution, immediate use is recommended (see Description [Section 11] in the full Prescribing Information). If the diluted Kisunla solution is not administered immediately, store refrigerated at 2 °C to 8 °C (36 °F to 46 °F) for up to 72 hours or at room temperature (20 °C to 25 °C [68 °F to 77 °F]) for up to 12 hours.
- Do not freeze the diluted Kisunla solution.
- Storage times include the duration of infusion.

Administration Instructions

- Visually inspect the diluted Kisunla solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque, or foreign particles are seen.
- Prior to infusion, if the diluted solution has been stored under refrigeration, allow the diluted Kisunla solution to warm to room temperature.
- Administer the entire diluted solution intravenously over approximately 30 minutes.
- Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction (see Warnings and Precautions [Section 5.2] in the full Prescribing Information).
- Flush the line only with 0.9% sodium chloride injection at the end of the infusion per access-specific line maintenance protocol.
- Observe the patient post-infusion for a minimum of 30 minutes to evaluate for infusion reactions and hypersensitivity reactions (see Warnings and Precautions [Section 5.2] in the full Prescribing Information).

SELECT IMPORTANT SAFETY INFORMATION

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients who were treated with Kisunla. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy.

Infusion-Related Reactions (IRR)

IRRs were observed with Kisunla: 9% (74/853); placebo: 0.5% (4/874); the majority (70%, 52/74) occurred within the first 4 infusions. IRRs typically occur during infusion or within 30 minutes post-infusion. IRRs were mostly mild (57%) or moderate (39%) in severity. Signs and symptoms of IRRs include chills, erythema, nausea/vomiting, difficulty breathing/dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure. In the event of an IRR, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated.

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4. Epic® Electronic Health Record Instructions

Confirm a diagnosis of early symptomatic Alzheimer's disease (mild cognitive impairment or mild dementia stage of disease) and also the presence of amyloid beta pathology prior to initiating treatment (See Patient Selection [section 2.1] In the full Prescribing Information).

Updating existing Order Groups and Therapy Plans requires minimal time but must be implemented at the system level per the preferences of the health system.

THINGS TO CONSIDER

What groups should each Order Group be placed in, for example:

- **Imaging Studies**
- **Provider**
- **Nursing Notes**
- **Nursing Interventions**
- **Supportive Care**
- **Appointment Requests**

4.1 Updating an Order Group

Selection mode:

- Basic – this will be used if this will always be part of a protocol.
- Single – clinicians can only select one order in the group.
- Multi-Select – clinicians can select multiple orders in the group.
- Select-All – this is if ALL orders in the group are required, BUT the order group itself may not be required.
- Default Category – this will be what describes the types of orders contained within the group.

1. Chart Search > **Order Group Builder**.
2. **Select existing Order Group** and name based on the organization's naming convention or if there is no appropriate Order Group for Kisunla, consider creating a new Order Group.*
3. **Select** desired options, such as single-select or multi-select, synonyms, comments, etc.
   a. Default category: For example, imaging or Nursing orders.
   b. In the toolbar, click **ADD ORDER**.
   c. Search for the desired order to add. For example, Brain MRI W W/O Contrast.

*If creating a new Order Group, the system should consider what other medications may also warrant inclusion.

SELECT IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reactions reported in ≥5% of patients treated with Kisunla (n=853) and ≥2% higher than placebo (n=874): ARIA-H microhemorrhage (25% vs 11%), ARIA-E (24% vs 2%), ARIA-H superficial siderosis (15% vs 3%), headache (13% vs 10%), and IRRs (9% vs 0.5%).

→ *See next page for additional content and steps.*

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4. Epic® Electronic Health Record Instructions (Cont'd)

4. Chart Search > **Order Group Builder**.
5. **Select** desired options such as single-select or multi-select, synonyms, comments, etc.
   a. Default category: For example, intra-procedures or medications
   b. In the toolbar, click **ADD ORDER**.
   c. Search for the desired order to add. For example, Kisunla 700-mg dosing.
   d. Enter dose admin details within the order.
      i. Route: Intravenous.
      ii. Frequency: Every 4 weeks for three doses.
      iii. Admin Duration: 30 min.
      iv. Add additional administration instructions: 700 mg every 4 weeks for the first 3 doses, properly diluted and administered as an intravenous infusion over approximately 30 minutes. Observe the patient post-infusion for a minimum of 30 minutes to evaluate for infusion reactions and hypersensitivity reactions.
   e. Release when completed.
6. Chart Search > **Order Group Builder**.
7. If there is no existing Order Group appropriate to include Kisunla, consider creating a new Order Group.*
8. **Select** desired options such as single-select or multi-select, synonyms, comments, etc.
   a. Default category: For example, intra-procedures or nursing orders.
   b. In the toolbar click **ADD ORDER**.

*If creating a new Order Group, consider what other medications may also warrant inclusion.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.

ApoE ε4 Homozygotes: Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes treated with this class of medications, including Kisunla, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.

Consider the benefit for the treatment of Alzheimer's disease and risk of ARIA when deciding to treat with Kisunla.

See next page for additional steps.

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4. Epic® Electronic Health Record Instructions (Cont'd)

c. Search for the desired order to add. For example, Kisunla 1400-mg dosing.

d. Enter dose admin details within the order.

   i. Route: Intravenous.

   ii. Frequency: Every four weeks for dose 4 and beyond.

   iii. Admin Duration: 30 min.

   iv. Add additional administration instructions: 1400 mg every 4 weeks for infusion 4 and beyond, properly diluted and administered as an intravenous infusion over approximately 30 minutes. Observe the patient post-infusion for a minimum of 30 minutes to evaluate for infusion reactions and hypersensitivity reactions.

e. Release when completed.

The process can be repeated for each Order Group as needed for remaining items, such as supportive care and nursing interventions.

4.2 Updating a Therapy Plan Protocol to Include Kisunla

1. Chart Search > **Therapy Protocol Builder**.
2. **Select new Therapy Plan** and name based on the organization's naming convention.
3. **Add** default information as needed, such as Description and Abbreviation.
4. Protocol Type – **Select the episode type** you wish to associate this new Protocol with (REQUIRED).
5. Scheduling window – **Select** how far in advance the schedulable orders will be released. Leave blank if episode default is sufficient.
6. **Add** any additional notes, such as the requirement for a provider to confirm diagnosis.
7. **Click ORDER GROUP** – search Order Groups updated in previous steps.
   a. For example, select the imaging studies for MRI that are required prior to infusions 2,3,4 and 7 and mark them as such in intervals.
   b. Category Imaging or most applicable.

SELECT IMPORTANT SAFETY INFORMATION

- **Hypersensitivity: Kisunla is contraindicated** in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients. Reactions have included anaphylaxis.

→ *See next page for additional content.*

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4. Epic® Electronic Health Record Instructions (Cont'd)

8. **Click ORDER GROUP** – search Order Groups updated in previous steps.
   a. For example, select the medications required every four weeks for dose 4 and beyond.
   b. Category – Intra-Procedure or most applicable.
   c. Interval – Daily, every four weeks for dose 4 and beyond.
   d. Duration – 3 treatments.
9. Save.

NOTE: If updating a Therapy Plan to include Kisunla, consider what other medications may also warrant creation of a Therapy Plan.

The process of adding all subsequent Order Groups will be repeated until complete.

SELECT IMPORTANT SAFETY INFORMATION

Amyloid-Related Imaging Abnormalities (ARIA)

Kisunla can cause ARIA-E, which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H generally occurs with ARIA-E. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages (ICH) >1 cm in diameter have occurred in patients treated with Kisunla.

Risk Factors for ARIA and Intracerebral Hemorrhages

- **ApoE ε4 Carrier Status**: The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes.
- The recommendations for management of ARIA do not differ between ApoE ε4 carriers and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

→ *See next page for additional steps.*

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5. Disclaimers

- The Customer (eg, the physician, medical group, integrated delivery network [IDN]) shall be solely responsible for the implementation, testing, and monitoring of the instructions to ensure proper orientation in each Customer's EHR system.
- Capabilities, functionality, and set-up (customization) for each EHR system may vary. Lilly shall not be responsible for revising the implementation instructions it provides to any Customer if the Customer modifies or changes its software, or the configuration of its EHR system, after such time as the implementation instructions have been initially provided by Lilly.
- While Lilly tests its implementation instructions on multiple EHR systems, the instructions are not guaranteed to work for all available EHR systems, and Lilly shall have no liability thereto.
- While EHRs may assist providers in identifying appropriate patients for consideration of assessment, treatment, and referral, the decision and action should ultimately be decided by a provider in consultation with the patient, after a review of the patient's records to determine eligibility, and Lilly shall have no liability related to a provider's decision and action (or inaction) regarding any patient identified or treated using this resource.
- The instructions have not been designed to and are not resources and/or solutions for meeting Advancing Care Information and/or any other quality/accreditation requirement.
- All product/company names mentioned herein are the trademarks of their respective owners, all rights reserved. Reference to these products is not intended to imply affiliation with or sponsorship of Lilly and/or its affiliates.

6. Important Safety Information With Boxed Warning

IMPORTANT SAFETY INFORMATION FOR Kisunla™ (donanemab-azbt)

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.

ApoE ε4 Homozygotes: Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including Kisunla, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with Kisunla; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of Kisunla for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with Kisunla.

Kisunla is **contraindicated** in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients. Reactions have included anaphylaxis.

Amyloid-Related Imaging Abnormalities (ARIA)

Kisunla can cause ARIA-E, which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease (AD), particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H generally occurs with ARIA-E.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages (ICH) >1 cm in diameter have occurred in patients treated with Kisunla.

Please see Important Safety Information on **pages 15-17**, and full **Prescribing Information**, including Boxed Warning regarding ARIA, and **Medication Guide** for Kisunla.

kisunla™ (donanemab-azbt) injection for IV infusion 350 mg/20 mL

6. Important Safety Information With Boxed Warning (Cont'd)

IMPORTANT SAFETY INFORMATION FOR Kisunla™ (donanemab-azbt) (Cont'd)

Amyloid-Related Imaging Abnormalities (ARIA) (Cont'd)

Incidence of ARIA

Symptomatic ARIA occurred in 6% (52/853) of patients treated with Kisunla. Clinical symptoms associated with ARIA resolved in approximately 85% (44/52) of patients.

Including asymptomatic radiographic events, ARIA was observed with Kisunla: 36% (307/853); placebo: 14% (122/874). ARIA-E was observed with Kisunla: 24% (201/853); placebo: 2% (17/874). ARIA-H was observed with Kisunla: 31% (263/853); placebo: 13% (111/874). There was no increase in isolated ARIA-H for Kisunla vs placebo.

Incidence of ICH

ICH >1 cm in diameter was reported in 0.5% (4/853) of patients after treatment with Kisunla vs 0.2% (2/874) on placebo. Fatal events of ICH have been observed.

Risk Factors for ARIA and ICH

ApoE ε4 Carrier Status

The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. 17% (143/850) of patients in the Kisunla arm were ApoE ε4 homozygotes, 53% (452/850) were heterozygotes, and 30% (255/850) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (Kisunla: 55%; placebo: 22%) than in heterozygotes (Kisunla: 36%; placebo: 13%) and noncarriers (Kisunla: 25%; placebo: 12%). Among patients treated with Kisunla, symptomatic ARIA-E occurred in 8% of ApoE ε4 homozygotes compared with 7% of heterozygotes and 4% of noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, 2% of heterozygotes, and 1% of noncarriers.

The recommendations for management of ARIA do not differ between ApoE ε4 carriers and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. An FDA-authorized test for detection of ApoE ε4 alleles is not currently available. Currently available tests may vary in accuracy and design.

Radiographic Findings of Cerebral Amyloid Angiopathy (CAA)

Neuroimaging findings that may indicate CAA include evidence of prior ICH, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for ICH. The presence of an ApoE ε4 allele is also associated with CAA.

The baseline presence of at least 2 microhemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, were identified as risk factors for ARIA. Patients were excluded from enrollment in Study 1 for findings on neuroimaging of prior ICH >1 cm in diameter, >4 microhemorrhages, >1 area of superficial siderosis, severe white matter disease, and vasogenic edema.

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6. Important Safety Information With Boxed Warning (Cont'd)

IMPORTANT SAFETY INFORMATION FOR Kisunla™ (donanemab-azbt) (Cont'd)

Amyloid-Related Imaging Abnormalities (ARIA) (Cont'd)

Concomitant Antithrombotic or Thrombolytic Medication

In Study 1, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed. The majority of exposures to antithrombotic medications were to aspirin. The incidence of ARIA-H was 30% (106/349) in patients taking Kisunla with a concomitant antithrombotic medication within 30 days vs 29% (148/504) in patients who did not receive an antithrombotic within 30 days of an ARIA-H event. The incidence of ICH >1 cm in diameter was 0.6% (2/349) in patients taking Kisunla with a concomitant antithrombotic medication vs 0.4% (2/504) in those who did not receive an antithrombotic. The number of events and the limited exposure to non-aspirin antithrombotic medications limit definitive conclusions about the risk of ARIA or ICH in patients taking antithrombotic medications.

One fatal ICH occurred in a patient taking Kisunla in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent. Additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (eg, tissue plasminogen activator) to a patient already being treated with Kisunla.

Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla. Advise patients to carry information that they are being treated with Kisunla.

Caution should be exercised when considering the use of Kisunla in patients with factors that indicate an increased risk for ICH and in particular for patients who need to be on anticoagulant therapy or patients with findings on MRI that are suggestive of CAA.

Radiographic Severity

The majority of ARIA-E radiographic events occurred early in treatment (within the first 24 weeks), although ARIA can occur at any time and patients can have more than one episode. The maximum radiographic severity of ARIA-E in patients treated with Kisunla was mild in 7% (59/853), moderate in 15% (128/853), and severe in 2% (14/853). Resolution on MRI after the first ARIA-E event occurred in 63% of patients treated with Kisunla by 12 weeks, 80% by 20 weeks, and 83% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with Kisunla was mild in 17% (143/853), moderate in 4% (34/853), and severe in 5% (40/853). The maximum radiographic severity of ARIA-H superficial siderosis in patients treated with Kisunla was mild in 6% (47/853), moderate in 4% (32/853), and severe in 5% (46/853). Among patients treated with Kisunla, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 3% (4/143) vs heterozygotes 2% (9/452) or noncarriers 0.4% (1/255). The rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 22% (31/143) vs heterozygotes 8% (38/452) or noncarriers 4% (9/255).

Monitoring and Dose Management Guidelines

Baseline brain MRI and periodic monitoring with MRI are recommended. Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with Kisunla. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

Please see Important Safety Information on page 17, and full Prescribing Information, including Boxed Warning regarding ARIA, and Medication Guide for Kisunla.

6. Important Safety Information With Boxed Warning (Cont'd)

IMPORTANT SAFETY INFORMATION FOR Kisunla™ (donanemab-azbt) (Cont'd)

Amyloid-Related Imaging Abnormalities (ARIA) (Cont'd)

Monitoring and Dose Management Guidelines (Cont'd)

Recommendations for dosing in patients with ARIA-E and ARIA-H depend on clinical symptoms and radiographic severity. Depending on ARIA severity, use clinical judgment in considering whether to continue dosing, interrupt treatment, or permanently discontinue Kisunla. See Prescribing Information for additional dosing considerations.

There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data for dosing patients who experienced recurrent episodes of ARIA-E.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients who were treated with Kisunla. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy.

Infusion-Related Reactions (IRR)

IRRs were observed with Kisunla: 9% (74/853); placebo: 0.5% (4/874); the majority (70%, 52/74) occurred within the first 4 infusions. IRRs typically occur during infusion or within 30 minutes post-infusion. IRRs were mostly mild (57%) or moderate (39%) in severity. IRRs resulted in discontinuations in 4% (31/853). Signs and symptoms of IRRs include chills, erythema, nausea/vomiting, difficulty breathing/dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure.

In the event of an IRR, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Pretreatment with antihistamines, acetaminophen, or corticosteroids prior to subsequent dosing may be considered.

Adverse Reactions: The most common adverse reactions reported in ≥5% of patients treated with Kisunla (n=853) and ≥2% higher than placebo (n=874): ARIA-H microhemorrhage (25% vs 11%), ARIA-E (24% vs 2%), ARIA-H superficial siderosis (15% vs 3%), headache (13% vs 10%), IRRs (9% vs 0.5%).

Please see full Prescribing Information, including Boxed Warning regarding ARIA, and Medication Guide for Kisunla.

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7. Notes

Please see Important Safety Information on **pages 14-17**, and full **Prescribing Information**, including Boxed Warning regarding ARIA, and **Medication Guide** for Kisunla.

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For more information about Kisunla, visit **https://kisunla.lilly.com/hcp**

Please see Important Safety Information on **pages 14-17**, and full **Prescribing Information**, including Boxed Warning regarding ARIA, and **Medication Guide** for Kisunla.

REFERENCE: 1. Kisunla (donanemab-azbt) Prescribing Information. Lilly USA, LLC.

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