



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #258
(Replaces Document #255)

RECOMMENDATION ON THE USE AND MANAGEMENT OF EMICIZUMAB-KXWH (HEMLIBRA®) FOR HEMOPHILIA A WITH AND WITHOUT INHIBITORS

The document was approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) on February 28, 2020, and adopted by the NHF Board of Directors on March 16, 2020.

A. Introduction

Emicizumab is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody that substitutes for part of the cofactor function of activated factor VIII (FVIIIa) by bridging activated factor IX(FIXa) and factor X(FX). It is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A with and without factor VIII inhibitors. The drug is given subcutaneously at a loading dose of 3 mg/kg weekly for 4 doses, followed by one of three subsequent maintenance dose regimens: either 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks. There is significant reduction in annualized bleeding rates at all doses for all age groups, with or without inhibitors.

Factor VIII and emicizumab are fundamentally different proteins and are regulated differently. Some of the differences are:

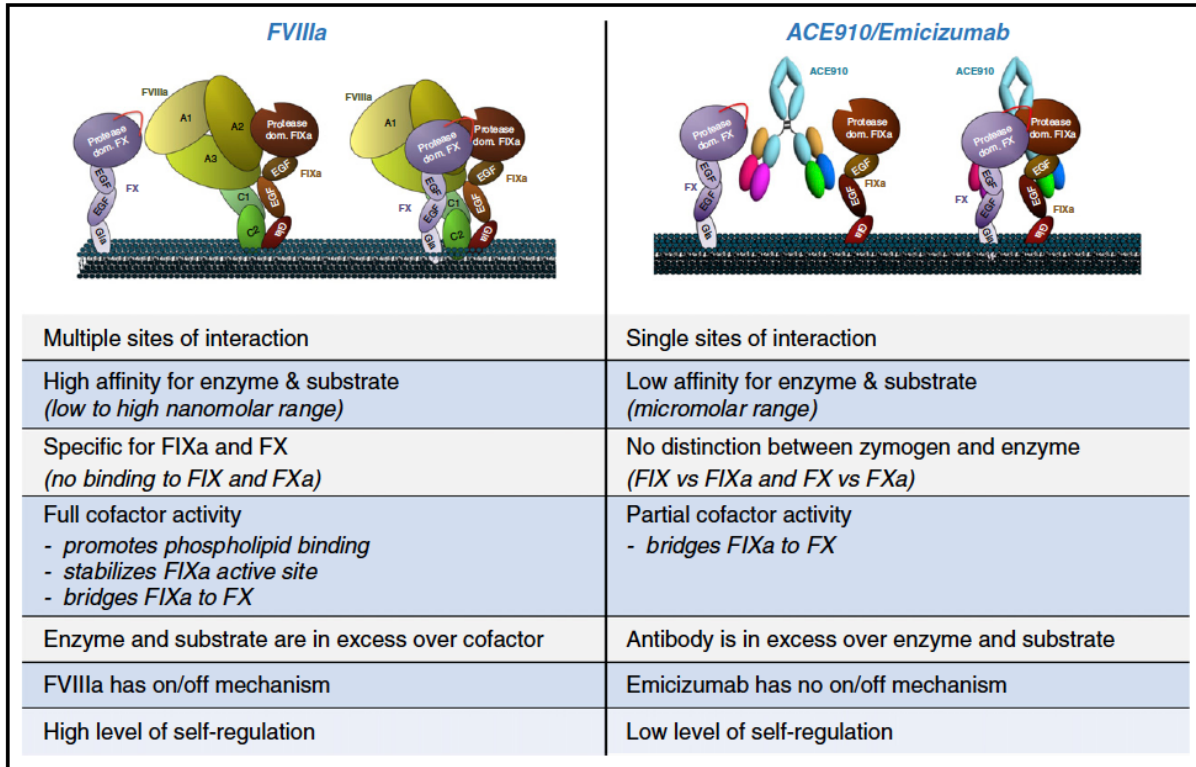


Figure 1. Schematic representation of how FVIIIa and ACE910/emicizumab promote FXa generation. Comparison of the various differences in the interactions with enzyme and substrate between FVIIIa and ACE910/emicizumab. In the left panel, FVIIIa is bound to the phospholipid surface only by its C2 domain.^{53,54} Other models predict that also the C1 domain may contribute directly to phospholipid binding (eg, see Meems et al⁵⁵).

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- FVIIIa has multiple sites of interaction with FIXa, FX and the phospholipid surface whereas emicizumab binds to single sites within FIX(a) and FX(a)
- FVIII needs to be activated (thrombin mediated), emicizumab does not
- FVIII binds to von Willebrand Factor (VWF), emicizumab does not
- FVIIIa binds to phospholipid surface, emicizumab does not -> FVIIIa binding limits movement of the FX-activating complex more than emicizumab
- FVIIIa binds to surface on activated platelet, emicizumab probably does not
- FVIIIa has a much higher binding affinity than emicizumab
- FVIIIa enhances FXa generation ~ 10-fold over emicizumab
- Emicizumab can bind both activated and non-activated forms of FIX and FX

B. Clinical Management Guidance

***Full prescribing information is available in the package insert. In addition, the prescribing information contains a boxed warning regarding the risk of thrombotic microangiopathy (TMA) and thromboembolism. These adverse events have occurred in association with the use of activated prothrombin complex concentrates (aPCC) to treat breakthrough bleeding in patients receiving emicizumab. Therefore, for patients with inhibitors and an acute bleed, recombinant factor VIIa (rFVIIa) is recommended over aPCC. A bleed management plan should be developed and managed in close coordination**

with appropriate staff of the patient's HTC, including physicians/advanced practice providers, nurse coordinators, and pharmacy staff. The following recommendations are intended to address clinical management issues that are not addressed fully within the package insert.

1. Who is appropriate to be considered for treatment with emicizumab?

Physicians/advanced practice providers caring for persons with hemophilia A (PwHA), of any age or severity, with or without inhibitors should discuss this new therapeutic option with them, including an assessment of the risks and benefits of emicizumab compared to their existing therapy.

Based on the clinical trial data, any PwHA with an inhibitor who has spontaneous or traumatic bleeding episodes, whether treated with episodic or prophylactic BPA, will likely derive significant benefit from emicizumab prophylaxis and should be considered first-line of therapy. Those on BPA prophylaxis with few bleeding episodes could consider switching from BPA prophylaxis to emicizumab prophylaxis based on overall cost-effectiveness and simpler administration. In addition, infants should be considered for prophylaxis with emicizumab at any time after birth given the increased risk of intracranial hemorrhage prior to initiation of FVIII prophylaxis. Note, there are limited clinical trial data on the use of emicizumab in infants under 6 months of age and the pharmacokinetic exposure is likely to be less than in older infants and children. However, published experience supports the prophylactic efficacy of emicizumab in infants. We strongly encourage prospective data collection concurrent with its use in this age group through sponsored clinical trials, American Thrombosis and Hemostasis Network (ATHN) studies and the CDC Registry for Bleeding Disorders Surveillance.

2. Recommendations for initiation of emicizumab

a. PwHA and inhibitors

Administration of aPCCs should be discontinued at least 24 hours prior to initiation of emicizumab.

b. PwHA and no inhibitors

FVIII prophylaxis continuation during the week after initiation of emicizumab is a common and reasonable approach. However, given that steady-state levels of emicizumab are not achieved until after four weekly doses of 3 mg/kg, it may be reasonable to continue FVIII prophylaxis in select individuals based on their bleeding history and physical activity level, until they are ready to start maintenance dosing.

c. Standard patient education should include:

- i. Giving the loading dose(s) under medical supervision, in order to review and observe self-administration technique, and determination of what dose will be used after the 4-week loading period is complete. If the loading dose (in mg) is different than the maintenance, then patients should be educated about the dose and how to prepare it.
- ii. Visually inspecting emicizumab for particulate matter and discoloration before administration. Emicizumab for subcutaneous administration is a

- colorless to slightly yellow solution. Do not use if particulate matter is visible or product is discolored and contact the hemophilia treatment center and manufacturer so the vial can be returned.
- iii. Discussion of the appropriate clotting factor product (factor VIII concentrate or BPA) and dose to use for a breakthrough bleed, review of the signs and symptoms of a bleed, and stressing the need to contact the Hemophilia Treatment Center (HTC) to report all bleed events, especially if bleeding is not responsive to treatment.
 - iv. For patients with inhibitors, warning against concomitant use of aPCCs and associated risks, including what a thrombosis is, the associated symptoms, and to seek medical help should it occur
 - v. Reminding when emicizumab is re-ordered, patients must provide their current weight to assure proper dosing and proper vial combinations to achieve the calculated dose. Patient should develop a plan to ensure adequate supply of emicizumab to avoid missing doses of prophylaxis. Instructing patients to give missed dose as soon as they remember and not to give two doses on the same day.
 - vi. Patients must contact the HTC in the event of surgery, whether elective or emergent, to assure a plan for treatment is developed, including if any clotting factor product will be used, and, if so, at what dose and frequency, and if antifibrinolytic agents are advised.
 - vii. Patients should be warned that if they stop emicizumab, residual plasma levels may persist for as long as 6 months, and thus, risk mitigation regarding the use of aPCCs should be used during that 6-month period to avoid the risk for thrombotic and TMA complications
 - viii. Regular clinical review of the efficacy for bleed prevention should be conducted once the patient has reached the maintenance dosing and at 3 months, 6 months and 12 months after initiation of therapy, and thereafter at 6-month intervals at the discretion of their provider.
 - ix. Loss of efficacy should prompt evaluation for anti-drug antibodies (see below).
 - x. Patients should be counseled to travel with an emergency dose(s) of factor concentrate to allow prompt management of any *significant and serious or life-threatening bleeding* (MASAC Document #257).

3. **Recommendations on Acute Bleed Management – PwHA and Inhibitors**

Despite the high efficacy in the prevention of bleeding events, clinicians and patients should still expect breakthrough bleeding events in patients on emicizumab prophylaxis, which in PwHA with inhibitors will likely mean the need for concomitant use of alternative hemostatic therapies. Due to the serious adverse events observed in the clinical trial program, we recommend the following guidance on management of breakthrough bleeding, prevention of and surveillance for thromboembolic and thrombotic microangiopathy (TMA) events, and appropriate use of laboratory assays. TMA and serious thrombotic events can be avoided by adherence to these management principles as has been observed after implementation within the global clinical trial program or since commercial availability within the US in pediatric and adult patients.

- a. General approach to breakthrough bleeding: Emicizumab is likely to transform the bleeding phenotype of patients to a milder phenotype with a significant reduction in bleeding events requiring treatment. *Significant and serious or life-threatening bleeding should continue to be treated promptly.*
- b. Caution with dose and duration of BPA:
 - i. Acute bleeding events should be managed with rFVIIa, at a dose of 90-120 mcg/kg as an initial dose. The vast majority of bleeds should be able to be managed with 1-3 doses administered at no more frequency than q2h intervals.
 - ii. Use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat bleeds as the use in combination with emicizumab does not alter the rFVIIa safety profile. If aPCC is used, it should be limited to no more than 50 IU/kg administered as an initial dose and not exceed 100 IU/kg/day. Duration of aPCC therapy should also be minimized, as prolonged use for ≥ 24 hours with doses above 100 IU/kg/day may be associated with thrombosis and TMA.
 - iii. Repeated dosing of any BPA beyond the above recommendations should be performed under medical supervision with consideration for verifying severity of bleeds prior to continuing to repeat dosing.
 - iv. For significant bleeding that is not responding to BPA, consider using porcine FVIII or human FVIII if partially tolerized. Use of these agents would also allow therapeutic monitoring with the bovine chromogenic assay.
 - v. Clinical and laboratory monitoring: All patients on emicizumab prophylaxis who have received aPCC for breakthrough bleeding for more than 24 hrs should do so in close contact with their treatment team for the duration of the aPCC course. They should be evaluated for any clinical symptoms that could be consistent with a thromboembolic event (with a high level of suspicion for atypical sites, e.g. cerebral sinus venous thrombosis), and have clinical evaluation for hypertension and proteinuria to look for evidence for TMA. Laboratory monitoring should include complete blood count, peripheral blood smear analysis to look for schistocytes, D-dimer, prothrombin fragment F1+2 (if available), haptoglobin, bilirubin, serum creatinine, LDH and troponin. For patients who require aPCC beyond the recommended dose and duration guidelines, consider daily laboratory monitoring.
 - vi. Management of TMA: Use of aPCC should cease immediately. The half-life of emicizumab is >28 days and it will remain in the patient's system for months after discontinuation of emicizumab. Each of the reported cases of emicizumab+aPCC TMA resolved quickly after discontinuation of aPCC with supportive care alone or in conjunction with plasmapheresis. In the 2 cases treated with plasmapheresis,

emicizumab was not completely removed and in spite of discontinuation of emicizumab one of these patients had measurable emicizumab laboratory effects for several months. Emicizumab has been restarted successfully in patients without recurrence of TMA.

4. Recommendations on Acute Bleed Management – PwHA without inhibitors

Despite the high efficacy in the prevention of bleeding events, clinicians and patients should still expect breakthrough bleeding events in patients on emicizumab prophylaxis, which in PwHA without inhibitors will likely mean the need for concomitant use of FVIII replacement therapy. No serious adverse events have been observed related to concomitant use of FVIII concentrates in patients on emicizumab prophylaxis. Specifically, no thrombotic or TMA events have been observed. Below are some specific guidelines for consideration in this patient group.

- a. General approach to breakthrough bleeding: Emicizumab is likely to transform the bleeding phenotype of PwHA without inhibitors to a milder phenotype with a significant reduction in bleeding events requiring treatment. *Significant and serious or life-threatening bleeding should continue to be treated promptly.*
- b. All FVIII concentrates (standard half-life and extended half-life) may be used for breakthrough bleeding events. Dosing should follow the same recommendations as when the patient was on FVIII replacement therapy (MASAC document #257).

5. Recommendations on laboratory assays while on emicizumab

Although emicizumab mimics the function of FVIIIa, it is biologically different from FVIIIa, having much lower affinity for factor IXa and X, not requiring activation, and not deactivated by the protein C/S pathway. These fundamental differences affect our interpretation of clotting assays.

- a. Laboratory monitoring of emicizumab is not required while on routine prophylactic dosing
- b. aPTT-based assays, including clot-based FVIII activity assays, should not be performed while on emicizumab, as they will yield misleading results (ie. artefactually shortened aPTT and elevated FVIII activity).
- c. Chromogenic FVIII activity assays will only provide an assessment of emicizumab activity if the assay includes all human reagents but these are not widely available. A chromogenic FVIII assay that uses bovine reagents may be used to assay the FVIII activity of any additional FVIII concentrate administered or endogenous FVIII.
- d. The clot-based Bethesda assay cannot be utilized to assess FVIII inhibitor levels. However, a bovine-reagent chromogenic-based inhibitor assay can report out FVIII inhibitor levels. If samples are submitted to the Centers for Disease Control and Prevention (CDC) for central laboratory testing, they must be clearly identified that the patient is on emicizumab.
- e. Exploratory laboratory assays:
 - i. Thromboelastography/thrombelastometry/thrombin generation
 - ii. Clot waveform analysis

These and other assays under continued investigation are likely to allow for

quantitation of emicizumab concentration from plasma. However, due to the intrinsic differences between emicizumab and FVIII, this complicates assignment and interpretation of FVIII-equivalent activity. Caution should remain in extrapolating clinical correlates using 'FVIII-equivalence' from such assays until further clinical data is available.

Summary of Assay Principles with Emicizumab

• Results affected by emicizumab

- Activated partial thromboplastin time (aPTT)
- Bethesda assays (clotting-based) for FVIII inhibitors
- One-stage, aPTT-based single factor assays (eg. FVIII activity)
- aPTT-based activated protein C resistance
- Activated clotting time (ACT)

• Result unaffected by emicizumab

- Bethesda assays using bovine chromogenic reagents for FVIII inhibitors
- Thrombin time (TT)
- One-stage, prothrombin time (PT)-based single factor assays (eg. FX activity)
- Immuno-based assays (ie. ELISA, turbidometric methods) – eg. VWF antigen
- Genetic tests of coagulation factors (eg. Factor V Leiden, prothrombin 20210 mutation)

f. Anti-drug antibodies:

- i. The prescribing information for emicizumab includes important safety information on the risk for anti-drug antibodies (ADAs). Use of any therapeutic protein carries the potential for the development of ADAs. These were observed within the global clinical trial program with emicizumab and are described within the US and European Union (EU) emicizumab product labels. The immunogenicity of emicizumab was evaluated using an enzyme-linked immunosorbent assay or an electrochemiluminescence assay. In the dose-finding trial (n = 18), four patients tested positive for ADAs. In the pooled HAVEN clinical trials, 3.5% of patients (14/398) tested positive for anti-emicizumab antibodies and <1% (3/398) developed ADAs with neutralizing potential (based on declining pharmacokinetics). One patient from HAVEN 2, who developed an ADA, experienced loss of efficacy after 5 weeks of treatment. There was no clinically apparent impact of the presence of ADAs on safety. Two of 88 children in HAVEN 2 developed ADAs with one patient having loss of emicizumab efficacy. As of December 2019 (<https://www.emicizumabinfo.com/>), more than 6,100 persons with hemophilia, with and without inhibitors to FVIII have been treated with emicizumab worldwide.
- ii. The development of an anti-drug antibody to emicizumab is distinct from the development of an inhibitor to FVIII. Notably, anti-drug antibodies directed against emicizumab may affect how it works in the patient but will not affect

the person's underlying hemophilia or inhibitor status, nor the ability to manage bleeding events with their conventional therapies, including bypassing agents.

- iii. Continued diligence in evaluation of clinical efficacy of emicizumab as would be expected for any hemophilia therapeutic. Loss of efficacy of emicizumab may be manifest by an increase in breakthrough bleeding events. Patients concerned about a loss of efficacy should seek prompt evaluation by their provider.
- iv. We have provided information on assays that may be utilized for evaluation of the activity of emicizumab, utilizing a chromogenic FVIII activity assay with human reagents that are recognized by emicizumab. However, the widely available conventional aPTT and clot-based FVIII activity assays can be used in evaluating a case of loss of efficacy. The aPTT should be within the normal range in all persons with hemophilia when obtained during ongoing treatment with emicizumab; similarly, clot-based FVIII activity assays will be well above the normal range. In the course of evaluating a reported loss of efficacy, a prolonged conventional aPTT assay and/or a low FVIII activity (by clot-based assay or chromogenic assay using human reagents) in a person treated with emicizumab should be a useful initial evaluation for the presence of a neutralizing anti-drug antibody directed against emicizumab. Additional information regarding laboratory assays may be found within the prescribing information.
- v. There are no commercially available assays in the US for determination of anti-drug antibodies directed against emicizumab. Should a patient and provider have suspicion of an anti-drug antibody outside of the ongoing clinical trial program, they should contact the manufacturer (<https://www.gene.com/contact-us/submit-medical-inquiry>) for guidance on subsequent evaluation.
- vi. Recommend that patients and providers continue diligence in reporting any unanticipated adverse events. Available reporting mechanisms can be reviewed here (<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm>)

6. Recommendations on surgical management with emicizumab

Emicizumab is approved for prophylaxis but how this extends to surgical prophylaxis remains to be fully understood. While it improves hemostasis, it does not normalize hemostasis. This is especially important when planning hemostatic control in the surgical setting. Within the clinical trials, some patients had adequate hemostatic control with emicizumab alone for minor surgical procedures while others did not. This is similar to what has historically been seen in patients with mild hemophilia.

- a. Surgeries should be conducted at centers with appropriate experience and access to necessary laboratory monitoring assays for concomitant use of hemostatic agents

b. Elective surgeries should be conducted after patients have completed the loading dose phase and are at steady state maintenance dosing.

c. Emicizumab alone should not be presumed to be adequate for major procedures where current standards of care are to maintain factor levels within the normal range for a period of days.

d. Close monitoring of bleeding control as well as access to appropriate laboratory assays to monitor therapy (eg. chromogenic FVIII assay with FVIII replacement) is very important when determining treatment plans for patients on emicizumab needing surgical procedures.

e. For major surgeries and procedures where bleeding could result in serious complications, patients should be provided rFVIIa or FVIII replacement pre- and post-operatively to maintain adequate hemostasis at the discretion of the treating physician. Further research/experience is needed to form better defined treatment plans for different surgical procedures.

f. Providers are cautioned to consider that bleeding complications from surgeries in patients with hemophilia still greatly outweigh thrombotic complications in frequency and morbidity/mortality.

7. Recommendations on concomitant use of emicizumab during immune tolerance induction.

There is limited data on the concomitant use of emicizumab prophylaxis during immune tolerance induction (ITI). Batsuli et al. described a case series of children with hemophilia A and inhibitor who underwent ITI in combination with emicizumab prophylaxis (Atlanta Protocol), and a larger clinical trial of this protocol is underway. MASAC recommends that the pros and cons of the various approaches for PwHA and inhibitors be part of a patient/clinician shared decision-making and ITI should remain an option for their care. We also recommend that long term follow up and interventional trials that include the concomitant use of emicizumab with ITI should be encouraged. If ITI with concomitant emicizumab prophylaxis will be pursued we provide the following recommendations:

a. No more than 50-100 IU/kg per dose be administered unless observation will occur within a clinical trial. This relates to the uncertainty as to any potential incremental risk of an elevated FVIII level, even transiently, in patients on emicizumab who may need treatment with a BPA for breakthrough bleeding during ITI.

b. Data on the use of emicizumab prophylaxis with ITI should be conducted under a clinical trial or as part of existing databases collecting data on the natural history of emicizumab use within the US.

8. Other unresolved issues and potential new avenues of research

a. MASAC recognizes the potential utility of emicizumab prophylaxis in patients with severe Type 3 VWD with inhibitors to von Willebrand factor.

- b. ATHN 7 is a prospective observational study which includes data collection on the use of emicizumab within the US patient population and we strongly encourage that the availability of this study be discussed with patients who are prescribed emicizumab.
- c. ATHN 8 is a longitudinal, observational study aimed at determining the percentage of PUPs with confirmed inhibitors within the first 50 exposure days and will include subjects who are on emicizumab prophylaxis.
- d. We encourage additional investigations to determine potential safe and efficacious dosing of aPCCs with concurrent emicizumab.
- e. We encourage the continued accumulation of management of surgical experiences in patients prescribed emicizumab.
- f. Important clinical trial data will be collected in mild and moderate hemophilia A without inhibitors. HAVEN 6 is a study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of emicizumab in participants with mild or moderate hemophilia A without FVIII inhibitors (NCT04158648).
- g. There are insufficient data on the level of protection provided by emicizumab prophylaxis to patients who participate in high impact activities/organized sports and MASAC encourages additional research to study this.
- h. The use of emicizumab prophylaxis in ITI will be explored in the MOTIVATE study (NCT 04023019). The purpose of the study is to capture different approaches in the management of persons with hemophilia A and FVIII inhibitors, document current immune tolerance induction approaches, and evaluate the efficacy and safety of immune tolerance induction, including the combination of FVIII and emicizumab.
- i. The INHIBIT trial is a study that will investigate hemophilia prevention and eradication and includes evaluation of the role of emicizumab

9. Additional patient education recommendations

- a. Revised ED and travel letters that include:
 - i. information that the patient is on emicizumab prophylaxis
 - ii. the potential impact on laboratory assays and acute bleed management
 - iii. Contact information for the HTC
- b. Instructions on Travel
 - i. Revised travel letter as detailed above
 - ii. Need to travel with appropriate dose of FVIII concentrate or BPA to manage breakthrough bleeding
- c. Provision of dosing cards that detail the dose and frequency of FVIII concentrate or BPA for management of breakthrough bleeding
- d. Instructions on when to call the HTC:
 - i. When uncertain about whether or not symptoms are consistent with bleeding and should be treated
 - ii. For breakthrough bleeding events requiring treatment
 - iii. For significant trauma including, but not limited to, head trauma
 - iv. For emergent or scheduled surgery, including invasive dental work

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