8CHECK

F8 gene mutation analysis service

Informing your treatment decisions in hemophilia A to reduce inhibitor risk.

This service is sponsored by

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F8 gene mutations and inhibitor development

One of the most serious complications in hemophilia A management is the development of inhibitors to therapeutic factor VIII (FVIII)[1]

35% Inhibitors develop in up to 35% of Previously Untreated Patients (PUPs)[1-3]

In PUPs, inhibitors usually develop within the first 20 exposure days (EDs)[1,4]

70% Up to 70% of inhibitors in PUPs are high-titer (≥5 Bethesda units [BU]/mL)[2,3]

Inhibitor development in Previously Treated Patients (PTPs) is less common, but is a concern during intensive treatment such as that required for surgical procedures[5]

Hemophilia A is caused by mutations of the *F8* gene.

The type of *F8* mutation can affect the risk of inhibitor development.

F8 gene mutations can be classified as[6,7]

- **Non-null mutations:** still capable of producing FVIII, but quality and/or quantity is defective
- **Null mutations:** not capable of producing any FVIII protein

Null mutations are associated with a more severe disease phenotype and with a higher risk of inhibitor development.[6]

Although the genetic mutation is not modifiable, can we still intervene on the risk of inhibitor development?[7–9]

- *F8* mutation is a nonmodifiable risk factor for inhibitor development. Other nonmodifiable risk factors include age, disease severity, or having had inhibitors previously[10]
- Modifiable risk factors for inhibitor development include treatment intensity, type of treatment (prophylaxis or on-demand) and the type of FVIII product (plasma-, hamster- or human-derived)[10]

The impact of FVIII product type on inhibitor development risk also varies—depending on the type of *F8* mutation

For individuals with low risk *F8* (non-null) mutations:

- In the **SIPPET study**, no patients with a *non-null mutation* treated with a plasma-derived factor VIII (pdFVIII/VWF) developed inhibitors, compared with **30%** (cumulative incidence, log rank test: p=0.009) of those treated with hamster cell line-derived recombinant factor VIII (rFVIII)[3,9]
- In the **NuProtect study**, **no patients** with a *non-null mutation* treated with **NUWIQ®** (human cell line-derived rFVIII) developed inhibitors[8-11]

For individuals with intermediate or high risk *F8* (null) mutations:

- In the **SIPPET study**, **31%** of patients with a *null mutation* treated with pdFVIII/VWF developed inhibitors, compared with **47%** of those treated with hamster cell line-derived rFVIII[9]
- In the **NuProtect study**, **30%** (cumulative incidence) of patients with *null mutations* treated with **NUWIQ®** developed inhibitors[8-11]

Note: Information from the *NuProtect* study is presented in parallel to the SIPPET study for context, but please note that these trials were performed under different conditions and with different populations. The observed incidence of inhibitor formation may be influenced by a number of factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Knowledge of the underlying mutation may help to inform treatment decisions in order to reduce the risk of inhibitor development.

Please see Indications and Important Safety Information on back page.

INTRODUCING 8CHECK

F8 gene mutation analysis service

A free *F8* gene mutation analysis service offered by Octapharma

The analysis is carried out at **Bloodworks Hemostasis Genomics at Eastlake (BHGE), Seattle, WA**

The 8CHECK process

Six easy steps to using the service:

1. Discuss and agree with the patients with hemophilia A or their legal guardian and proceed with request and filling in the specific 8CHECK forms
2. Collect 4 - 5.0 mL whole blood (EDTA) sample
3. Tubes must be labeled with:
   Patient Name
   Date of Birth (DOB)
   Date of Sample
4. Place sample on cool pack
5. Send the sample via 8CHECK selected courier together with completed 'Molecular Diagnostic Order' and 'Permission for Genetic Testing' forms
6. Receive your results within 2 to 4 weeks from BHGE

For detailed information about sample collection and shipment, as well as services request forms, send an email to **eightcheckUSA@octapharma.com**

Results from the 8CHECK service could help to predict whether an individual with hemophilia A in your care is at high or low risk of developing inhibitors. This information may enable you to choose a FVIII treatment that is best suited to your patients.

Disclaimer: Octapharma will not receive any sample or patient data.

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F8 gene mutation analysis service

Helping you to choose an appropriate treatment for each individual with hemophilia A, while reducing the risk of inhibitor development in those starting prophylaxis, switching treatment or undergoing a surgical procedure.

Indications and Use

NUWIQ® is a recombinant antihemophilic factor [coagulation factor VIII (Factor VIII)] indicated in adults and children with Hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes. NUWIQ is not indicated for the treatment of von Willebrand Disease.

Contraindications

NUWIQ is contraindicated in patients who have manifested life-threatening hypersensitivity reactions, including anaphylaxis, to the product or its components.

Warnings and Precautions

Hypersensitivity reactions, including anaphylaxis, are possible with NUWIQ. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, or pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

The formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following the administration of NUWIQ. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the plasma Factor VIII level fails to increase as expected, or if bleeding is not controlled after NUWIQ administration, suspect the presence of an inhibitor (neutralizing antibody).

Adverse Reactions

The most frequently occurring adverse reactions (>0.5%) in clinical trials were paresthesia, headache, injection site inflammation, injection site pain, non-neutralizing anti-Factor VIII antibody formation, back pain, vertigo, and dry mouth.

Please see accompanying full Prescribing Information.

Abbreviations:
BU: Bethesda unit; **FVIII:** factor VIII; **PUP:** previously untreated patient; **pdFVIII:** plasma-derived FVIII; **PTP:** previously treated patient; **rFVIII:** recombinant FVIII.

References:
1. Vezina C, et al. Haemophilia. 2014;20:771–6. **2.** Gouw SC, et al. N Engl J Med. 2013;368:231–9. **3.** Peyvandi F, et al. N Engl J Med. 2016;374:2054–64. **4.** Kreuz W, Ettingshausen CE. Thromb Res. 2014;134 Suppl 1:S22-6. **5.** Hay CR, et al. Blood. 2011;117:6367–70. **6.** Oldenburg J & Pavlova A. Haemophilia. 2006;12:15–22. **7.** Carcao M, et al. Blood. 2013;121:3946–52. **8.** Liesner RJ, et al. Haemophilia. 2018;24:211–20. **9.** Rosendaal F, et al. Blood. 2017;130:1757–9. **10.** Astermark J, et al. Haemophilia. 2010;16:747–66. **11.** Data on file. Paramus, NJ: Octapharma USA, Inc.

www.octapharmausa.com

For healthcare professionals only.

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