EFANESOCTOCOG ALFANESOCTACOG ALFA

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The FVIII:C reported by clinical trials of efanesoctocog alfa were either one-stage (OSA) using Siemens Actin FSL or chromogenic substrate assay (CSA) using Hyphen Biomed (Lissitchkov Blood adv 2022;6;4;1089–94 and Konkle NEJM 2020;383;11;1018–27) or Coatest SP4 (Chhabra Blood 2020;135;17;1484–96). The prescribing information for ALTUVIIIO (below) recommends monitoring by a validated OSA. If this is not possible and Actin FS (the specific ellagic acid reagent alluded to below) or a chromogenic assay is used, then applying a correction factor of 2.5 will approximate the efanesoctocog alfa activity in plasma.

5.3 Monitoring Laboratory Tests

If assessment of plasma Factor VIII activity is needed, it is recommended to use a validated one-stage clotting assay *[see Dosage and Administration (2)]*. The ALTUVIIIO Factor VIII activity level is overestimated by the chromogenic assay and a specific ellagic acid based aPTT reagent in one-stage clotting assay by approximately 2.5-fold. If these assays are used, divide the result by 2.5 to approximate the patient's ALTUVIIIO Factor VIII activity level. Use of a reference laboratory is recommended when a qualified one-stage clotting assay or chromogenic assay is not available locally.

Monitor for the development of Factor VIII inhibitors. If bleeding is not controlled with ALTUVIIIO and the expected factor VIII activity plasma levels are not attained, perform an assay to determine if Factor VIII inhibitors are present (use Bethesda Units to titer inhibitors).

The results from a global laboratory field study were published in January 2024 (Pipe, Haemophilia;2024;30;1;214–23). Data was returned using OSA with14 different APTT reagents; the mostly common being Synthasil, Actin FS and Actin FSL, and 8 different CSAs. The range for accurate measurement was +/-25% of the expected target at each concentration studied. OSA using Actin FSL recovered within 25% of expected target. OSA using Actin FS overestimated by more than 200%, OSA with Synthasil underestimated by 30-40%. Other APTT reagents that may be acceptable for use were reported by 1–4 labs, so more data are required to confirm these findings. Unlike other EHL molecules including Elocta (Eloctate), overestimation of CSA activity was reported by all CSA kits. The degree of overestimation varied between kits; Trinichrom and Rossix demonstrated approximately 130–180% recovery whilst other CSAs recovered more than 200%. Again, the number of labs returning results using CSA was small and more data are required.

Laboratories should use either OSA using Actin FSL or locally evaluate whether APTT reagents such as Synthafax, PTT-A, Pathromtin SL and CK Prest recover efanesoctocog alfa as expected. In the UK, this will likely again require laboratories to validate new OSA since Synthasil and Actin FS are the most common APTT reagents; Actin FSL is rarely used. The provision of laboratory testing kits similar to those made available for emicizumab and Refixia (Rebinyn) would greatly aid laboratories in the local validation of their reagents.

I would avoid the use of CSA with correction factor for the monitoring of efanesoctocog alfa. For a correction factor to be robust, it requires extensive evaluation using different lots of CSA reagents, calibrators and different platforms. The field study data do not support the use of a correction factor of 2.5 for every CSA studied. There was wide variation between labs using the same CSA kit so the application of a single correction factor would not be valid. This is also true for Actin FS. The field study data showed a range of 250–350% overestimation between labs. This lack of consistency means that I would not use a correction factor with this reagent either.

A further aspect that will need guidance is the monitoring of efanesoctocog alfa in patients receiving prophylaxis with emicizumab. One-stage assays are grossly overestimated in the presence of emicizumab, and bovine FX-containing CSA are recommended for the accurate monitoring of additional recombinant FVIII therapy. This may not be possible for efanesoctocog alfa and I have not yet seen any real world data related to this.