HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New medicinal product
July 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

EQWILATE (von Willebrand factor + human coagulation factor VIII)

High clinical benefit in von Willebrand's disease, but no demonstrated clinical benefit in the therapeutic strategy.

Insufficient clinical benefit to justify reimbursement for haemophilia A.

Main points

- EQWILATE has been granted marketing authorisation in the prophylaxis and treatment of bleeding episodes in patients with congenital haemophilia A, in the prophylaxis and treatment of surgical bleeding or bleeding in patients over the age of 6 years with von Willebrand's disease, and when desmopressin treatment alone is ineffective or contraindicated.
- In von Willebrand's disease, the haemostatic efficacy of EQWILATE was no different from that of VONCENTO, WILSTART or WILFACTIN. The available data do not allow these medicinal products to be compared.
- In haemophilia A, the benefit of combining von Willebrand factor with factor III has not been demonstrated; consequently, EQWILATE has no role over purified factor VIII concentrates in this indication.

Therapeutic strategy

von Willebrand's disease

- Bleeding episodes can be treated with von Willebrand factor (VWF) concentrates when desmopressin cannot be used, i.e. mainly in cases of type 2 and 3 disease and in a few type 1 patients. The administration of von Willebrand factor helps to normalise Factor VIII levels by chronometric assay (FVIII:C) a few hours after the initial injection. Administration of a concentrate combining VWF and FVIII immediately normalises FVIII:C levels. The choice between administering VWF concentrate alone and a concentrate combining VWF and factor VIII is governed by the clinical context and degree of urgency of haemostasis normalisation.
- Long-term prophylactic treatment with concentrates combining VWF and FVIII, or von Willebrand factor concentrate alone, may be considered in patients suffering from a severe form of von Willebrand's disease, including recurrent bleeding at critical sites (gastrointestinal bleeding, haemarthrosis, recurrent nosebleeds in children).

Haemophilia A

- The treatment of haemophilia A aims to achieve early control of and/or to prevent bleeding episodes and their short- and long-term complications. First-line treatment is replacement therapy based on the administration of coagulation factor VIII concentrates. These may be administered:
  - as "on demand" curative treatment, in the event of an haemorrhagic accident that cannot be controlled via local hemostatics, or unsuitable for treatment with desmopressin or tranexamic acid,
  - as preventive treatment:
    - as primary prophylaxis: this treatment concerns children under the age of 2 years with severe haemophilia as of the occurrence of the 2nd haemarthrosis,
    - as secondary prophylaxis (long-term or periodic) after occurrence of the 2nd haemarthrosis,
    - in the prevention of bleeding during surgery or invasive procedures (depending on severity and expected bleeding risk).

Role of the medicinal product in the therapeutic strategy

Von Willebrand's disease

EQWILATE, like VONCENTO and WILSTART, is a combination of VWF and FVIII, representing second-line treatment, exclusively in children over the age of 6 years, if desmopressin is contraindicated.

For long-term prophylaxis and by comparison to WILFACTIN (VWF alone), both EQWILATE and VONCENTO serve primarily to simplify patient management upon initiation of treatment for a bleeding episode or preoperatively in patients with spontaneously low FVIII levels (type 3 and many type 2), situations during which FVIII needs to be combined with WILFACTIN for the first injection.

Haemophilia A

EQWILATE plays no role in the management of haemophilia A, considering the lack of demonstrated benefit of combining VWF and FVIII, along with the existence of numerous high-purity FVIII concentrates. It's clinical benefit is not established in cases of uncertain diagnosis concerning factor VIII deficiency, when haemostatic treatment is necessary (urgent context, particularly surgical and/or difficult differential diagnosis between haemophilia A and von Willebrand's disease).

Clinical data

Von Willebrand's disease

- EQWILATE was evaluated in 5 prospective, non-comparative studies having included a total of 102 patients over the age of 6 years.
- The efficacy of EQWILATE in the prevention of bleeding in a surgical context has been established mainly by 1 study that included patients aged 12 years and over. Overall haemostatic efficacy was deemed a success in 96.7% of scheduled procedures evaluated (n=29/30). In children under the age of 12 years, surgical prophylactic efficacy was evaluated in an exploratory manner in another study, covering 10 minor procedures. Overall efficacy was deemed "excellent" in 9 cases and "good" in 1 case.
- As a treatment for bleeding and for long-term prophylaxis, the efficacy of EQWILATE was evaluated as secondary endpoint in four studies, in patients aged between 5 and 77 years. As an on-demand treatment, haemostatic efficacy was evaluated in 62 patients during 1,269 mainly minor to moderate bleeding episodes. According to the study, treatment with EQWILATE was considered a success in 85% (main study) to 100% of cases.
- As long-term prophylactic treatment for bleeding, the efficacy was evaluated *post-hoc* in 9 patients treated over short periods of time (25 to 51 days of cumulative exposure), according to an overall clinical score. The investigator deemed efficacy to be "excellent" for all patients.

Haemophilia A

- EQWILATE was evaluated in 5 prospective, non-comparative studies having included 81 patients with severe haemophilia, not previously treated.
- As an on-demand treatment for bleeding, the available data are derived essentially from one study, the only one to have used a predefined overall scoring scale. Overall haemostatic efficacy was deemed to be "excellent" in 52.7% of cases and "good" in 41.8% of cases (n=35 patients, 857 bleeding episodes). Clinical efficacy for long-term prophylaxis is poorly documented (n=4 patients).
- These non-comparative studies do not allow the benefits of this product to be assessed relative to factor VIII concentrates.

In both indications, the safety profile of EQWILATE is the same as that of the other factor VIII and/or VWF concentrates. The adverse events to monitor are the appearance of FVIII and/or VWF inhibitors, along with the occurrence of an anaphylactic reaction or thrombosis.

Special prescription requirements

Medicinal product subject to hospital prescription

Benefit of the medicinal product

Von Willebrand's disease

- The actual clinical benefit* of EQWILATE is high
- EQWILATE does not provide any clinical added value** (CAV V, non-existent) in the therapeutic strategy.
- Approval for hospital treatment

Haemophilia A

- The clinical benefit* of EQWILATE is insufficient to justify public funding cover
- Not approved for hospital treatment

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This document was drafted on the basis of the Transparency Committee opinion dated 11 July 2018 (CT-16745) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) is its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"