HAUTE AUTORITÉ DE SANTÉ

# TRANSPARENCY COMMITTEE
## SUMMARY
## 30 MARCH 2022

*The legally binding text is the original French opinion version*

***roxadustat***
**EVRENZO 20 mg, 50 mg, 70 mg, 100 mg and 150 mg film-coated tablets**
**First assessment**

### Key points

Favourable opinion for maintenance of reimbursement in the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) only in adult patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months.

Unfavourable opinion for reimbursement in the other MA populations, i.e.:
- all patients already receiving ESA treatment, regardless of whether they are on dialysis or not,
- patients on dialysis for at least 4 months not previously treated with an ESA.

### What therapeutic improvement?

No therapeutic improvement compared to erythropoiesis-stimulating agents (ESA).

## ◗ Role in the care pathway?

Chronic kidney disease (CKD) causes anaemia, the prevalence and seriousness of which increases with the severity of the CKD.
Correcting haemoglobin levels should avoid the need for blood transfusions, limit the cardiovascular complications of anaemia, improve quality of life and prolong survival.
In any patients with chronic kidney disease and haemoglobin levels ≤ 10 g/dL on two assays performed five days apart, it is recommended to:
- Investigate for an extra-renal cause of anaemia, with the main cause being iron deficiency;
- Treat the iron deficiency, if present;

Treatment with an erythropoiesis-stimulating agent (ESA: epoietin alfa, beta or delta, or darbepoeitin alfa) should only be proposed:
- after verifying the absence of a curable cause for anaemia other than kidney disease and, if applicable, only if iron supplementation therapy is inadequately effective
- and only if the anaemia is symptomatic (asthenia, dyspnoea, angina). Reduced haemoglobin levels alone are not sufficient.

The administered dose should be individually tailored in order to maintain haemoglobin levels within the target range of 10 to 12 g/dL in adults and 9.5 to 11 g/dL in children (European SPC for erythropoietins).

Increasing haemoglobin levels to above 12 g/dL should be avoided. That is because haemoglobin levels > 13 g/dL under ESA are associated with increased risks of myocardial infarction, hospitalisation for heart failure, stroke and thrombosis of the arteriovenous dialysis fistula, without providing any additional symptomatic benefit.

Transfusions should be avoided as far as possible in patients with chronic kidney disease and, in particular, patients awaiting transplantation (risk of allo-immunisation).

Resistance to erythropoietin may be suspected if the target haemoglobin level is not achieved despite a dose of > 300 IU/kg of epoietin per week or > 1.5 µg/kg of darbepoeitin per week, or if these doses are continuously necessary to maintain the target level.

**Role of the medicinal product in the care pathway**

- Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) only in adult patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months

EVRENZO (roxadustat) is a first-line treatment, in the same way as ESA, for symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months.

Given uncertainties concerning the existence of an additional risk of cardiovascular events and mortality in non-dialysed patients in comparison with placebo, the decision to treat these patients with roxadustat should be based on similar criteria to those that would be applied before ESA therapy.

It is necessary to investigate for any other causes of anaemia and verify that iron reserves are sufficient before initiating treatment with roxadustat.

- Other clinical situations

EVRENZO (roxadustat) has no role in the care pathway for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in:
- all patients already receiving ESA treatment, regardless of whether they are on dialysis or not,
- patients on dialysis for at least 4 months not previously treated with an ESA.

## COMMITTEE'S CONCLUSIONS

**Considering all of this information and further to debate and voting, the Committee considers:**

## Clinical benefit

◗ Chronic kidney disease (CKD) is defined by a permanent reduction, present for at least 3 months, in glomerular filtration rate, which reflects the kidneys' filtration capacity. Chronic kidney disease causes anaemia, the degree of which increases with the severity of the kidney disease. Anaemia is associated with an increased risk of mortality, morbidity and hospitalisation and impairs patients' quality of life. In patients with end-stage CKD, i.e. with a filtration rate of less than 15 mL/min/1.73 m2, dialysis or transplantation should be considered.

◗ EVRENZO (roxadustat) is a curative medicinal product.

◗ The efficacy/adverse effects ratio is:
- high only in adult patients not on dialysis or on dialysis for less than 4 months, and not already treated with an erythropoiesis-stimulating agent (ESA)
- inadequately established in the other MA populations, considering:
    - the statistically significant increase in mortality observed in patients on dialysis for more than 4 months converted from an ESA to roxadustat, compared to maintenance of ESA, in a context in which only the non-inferiority of efficacy was demonstrated on the correction and/or maintenance of haemoglobin levels in the short term,
    - the absence of sufficient clinical data to be able to assess the risk of cardiovascular events and mortality in patients not on dialysis or on dialysis for less than 4 months converted from an ESA to roxadustat and in patients on dialysis for at least 4 months not already treated with an ESA.

◗ There are medicinal and non-medicinal alternatives (ESA and transfusions).

◗ EVRENZO (roxadustat) is a first-line treatment in adult patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months.
This treatment has no role in the other MA populations (see section 08 of the opinion).

**Public health impact:**
Considering:
- the seriousness of the disease and its prevalence,
- the partially met medical need,
- the lack of additional response to the identified need considering:
    - the absence of a demonstrated additional impact compared to ESA on the correction and control of haemoglobin levels and an additional mortality compared to ESA observed in patients on dialysis converted from ESA therapy, with high levels of uncertainty with respect to an additional risk of major cardiovascular events,
    - the lack of a demonstrated additional impact on quality of life,
- and despite the expected additional impact on the care pathway given the oral administration and reduced need for IV iron demonstrated in non-dialysed patients and in stable dialysed patients,

EVRENZO (roxadustat) is unlikely to have an additional impact on public health.

**Considering all these elements, the Committee deems that the clinical benefit of EVRENZO (roxadustat) in the treatment of adult patients with symptomatic anaemia associated with CKD is:**
- **SUBSTANTIAL only in patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months,**
- **INSUFFICIENT in the other populations of the MA to justify public funding cover, i.e. in:**

- **all patients already receiving ESA treatment, regardless of whether they are on dialysis or not,**
- **patients on dialysis for at least 4 months not previously treated with an ESA.**

**The Committee issues the following opinions:**

- **<u>favourable</u> for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of adult patients with symptomatic anaemia associated with CKD <u>only</u> in patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months,**
- **<u>unfavourable</u> for inclusion in the other MA populations.**

## Clinical Added Value

**<u>Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) only in adult patients not already treated with an erythropoiesis-stimulating agent (ESA), not on dialysis or on dialysis for less than 4 months</u>**

Considering:

- demonstration of an efficacy not inferior to that of ESA on the correction and control of haemoglobin,
- the partially met medical need,
- the reduced need for IV iron demonstrated in non-dialysed patients in comparison with ESA and its oral administration, which should improve the care pathway of patients,

But in view of:

- a higher risk of serious adverse events than under ESA, in particular thrombosis of the arteriovenous dialysis fistula, which is particularly harmful in dialysed patients,
- treatment discontinuations that are more frequent overall, in particular due to an adverse event,
- uncertainties relative to the existence of an additional risk of major cardiovascular events versus placebo in non-dialysed patients not receiving treatment with ESA at inclusion, with a statistically significant increase in MACE and all-cause mortality found in one of the three studies versus placebo, and an increase in MACE found in one of the two grouped analyses performed versus placebo
- the absence of demonstration of an improvement in quality of life,

the Transparency Committee considers that EVRENZO (roxadustat) provides no clinical added value (CAV V) in comparison with erythropoiesis-stimulating agents (ESA) in the treatment of symptomatic anaemia associated with CKD in adult patients not on dialysis or on dialysis for less than 4 months, not already treated with an erythropoiesis-stimulating agent (ESA).