OPINION ON MEDICINAL PRODUCTS

cabozantinib

CABOMETYX 20 mg, 40 mg, and 60 mg,

film-coated tablets

New indication

Adopted by the Transparency Committee on 9 November 2022

SUMMARY

The legally binding text is the original French opinion version

- **Thyroid cancer**
- **Sectors: Community and Hospital**

Key points

Approval for reimbursement as monotherapy for the treatment of adult patients with progressive, radioactive iodine (RAI)-refractory or ineligible, locally advanced or metastatic differentiated thyroid carcinoma (DTC), during and after prior systemic treatment.

Therapeutic improvement?

Therapeutic improvement in the care of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), that is refractory to or ineligible for radioactive iodine (RAI) and progressive during and after prior systemic treatment.

Role in therapeutic strategy?

In cases of locally advanced or metastatic differentiated thyroid cancer, that are inoperable and not susceptible to radioactive iodine treatment, the indication of systemic treatment may be discussed in the presence of progressive disease with large metastases.

In 2014, NEXAVAR (sorafenib), was granted a European marketing authorisation for the treatment of adult patients with progressive locally advanced or metastatic differentiated thyroid carcinoma (papillary, follicular, Hürthle cell), refractory to radioactive iodine (RAI), followed one year later by LENVIMA (lenvatinib) for the same indication.

The latest NCCN guidelines from 2022 in the United States propose CABOMETYX (cabozantinib) after progression with LENVIMA (lenvatinib) and/or NEXAVAR (sorafenib) treatment for aggressive and/or symptomatic forms (category 1), and the ESMO European guidelines of 2022 similarly consider cabozantinib as a treatment option for patients for progressive and/or symptomatic radioactive iodine-refractory advanced/metastatic differentiated cancer, after prior Multi Kinase Inhibitor treatment with lenvatinib or sorafenib (category [I, A]).

Role of the medicinal product

CABOMETYX (cabozantinib) is a second-line and subsequent treatment for adult patients with progressive, radioactive iodine (RAI)-refractory or ineligible, locally advanced or metastatic differentiated thyroid carcinoma (DTC), during and after prior systemic treatment.

Special recommendation

The Committee highlights the need for validation of the prescription of CABOMETYX (cabozantinib) by centres of excellence or in multidisciplinary review meetings including an oncologist or a differentiated thyroid cancer care specialist (endocrinologist).

Committee's conclusions

Actual Clinical Benefit

- Progressive, radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid carcinoma is life-threatening.
- The proprietary medicinal product CABOMETYX (cabozantinib) is a curative medicinal product.
- The efficacy/adverse effect ratio of cabozantinib is significant among adult patients with progressive, radioactive iodine (RAI)-refractory or ineligible, locally advanced or metastatic differentiated thyroid carcinoma (DTC), during and after prior systemic treatment.
- At this stage of the disease, marketing authorisation-validated alternative medication is available – LENVIMA (lenvatinib) as a second-line treatment (also indicated as a first-line treatment); however, in view of the updated ESMO European guidelines, and the long-term clinical experience with this treatment, LENVIMA (lenvatinib) is now mostly used as a first-line treatment, i.e. after failure to respond to RAI therapy.
- It is a second-line treatment after failure to respond to systemic treatment among patients with progressive, radioactive iodine-refractory differentiated thyroid cancer.

Public health benefit

Considering:

- the severity, and also the rare nature, of radioactive iodine-refractory differentiated thyroid cancer failing to respond to prior treatment, the annual incidence of which in France is estimated at under 200 patients,
- the identified medical need after a first prior systemic treatment, for this type of cancer, among radioactive iodine-refractory or ineligible patients in particular,
- the data obtained from the COSMIC-311 study *versus* placebo providing evidence of an improvement in progression-free survival only (the gain in months is not quantifiable as the median survival was not reached for the cabozantinib group and it was 1.9 months $CI_{95\%}$ [1,8 ;3,6] for the placebo group), without providing evidence of a gain in overall survival or in quality of life among patients in this clinical scenario,
- the lack of data supporting an impact on the patient's care pathway,

CABOMETYX (cabozantinib) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems the actual clinical benefit of CABOMETYX (cabozantinib) to be significant for the marketing authorisation indication "as monotherapy for the treatment of adult patients with progressive, radioactive iodine (RAI)-refractory or ineligible, locally advanced or metastatic differentiated thyroid carcinoma (DTC), during and after prior systemic treatment".

The Committee approves continued inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use in the new marketing authorisation indication and at the dosages of the marketing authorisation.

Recommended reimbursement rate: 100%

Clinical Added Value

Considering:

- **the evidence in the COSMIC-311 phase III, randomised, double-blind study of the superiority of CABOMETYX (cabozantinib) versus placebo in terms of progression-free survival (PFS) where HR = 0.22 (96% CI [0.13; 0.36] ; p<0.0001),**
- **the acceptability of the comparator (placebo) due to the almost exclusive use in French clinical practice of LENVIMA (lenvatinib) as a first-line treatment (expert opinion),**

and despite:

- **the lack of evidence of superiority in terms of the response rate (second primary outcome measure of the study),**
- **the lack of evidence of a gain in overall survival (exploratory secondary outcome measure of the study),**
- **the lack of formal conclusions that can be drawn from the exploratory quality-of-life findings,**
- **a safety profile marked by the onset of serious adverse events in one-third of patients, and grade ≥ 3 adverse events in approximately one-half of patients,**

the Transparency Committee deems that CABOMETYX (cabozantinib) provides minor clinical added value (CAV IV), in terms of efficacy, for the treatment of progressive, radioactive iodine (RAI)-refractory or ineligible, locally advanced or metastatic differentiated thyroid carcinoma (DTC), during and after prior systemic treatment.