Nye metoder: Innspill til metoder, oppdrag og beslutninger

Bruk dette skjemaet for å gi innspill til metoder i Nye metoder uansett hvor de befinner seg i prosessen. Skjemaet skal for eksempel brukes hvis du har innspill til en metode i en anmodning eller et forslag som skal behandles i Bestillerforum for nye metoder. Det skal også brukes for innspill til oppdrag som er gitt av Bestillerforum, og for innspill til beslutninger som er tatt.

Det er generelt ønskelig at innspill kommer inn så tidlig som mulig i prosessen, gjerne før metoden behandles i Bestillerforum.

Utfylt skjema sendes til Sekretariatet for Nye metoder; nyemetoder@helse-sorost.no. Merk e-posten med "innspill" og ID-nummer.

Merk: **Punkt 1-3 og 11 skal fylles ut av alle.** Øvrige punkter fylles ut avhengig av hva innspillet gjelder.

Jeg er klar over at skjemaet kan bli publisert i sin helhet på nyemetoder.no (kryss av): ☒
Har du informasjon du mener ikke kan offentliggjøres, ta kontakt med sekretariatet før innsending.

Jeg har fylt ut punkt 11 «Interesser og eventuelle interessekonflikter» (kryss av): ☒

1.Hvilken metode gjelder innspillet?	
ID-nummer*:	ID2021_135
Metodens navn:	Kabozantinib (Cabometyx) til behandling av voksne og unge ≥ 12 år med lokalavansert eller metastatisk, differensiert skjoldbruskkjertelkreft (DTC), som er refraktær eller ikke kvalifisert for radioaktivt jod (RAI) og har progrediert under eller etter VEGFR-rettet behandling

*ID-nummer finner du på metodesiden på nyemetoder.no og har formen ID2024_XXX.

2. Opplysninger om den som gir innspill	
Navn	Sonja Tähti
Eventuell organisasjonstilhørighet/arbeidsplass/firma	Ipsen AB
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3. Innspill til metode, oppdrag, eller beslutning (besvares av alle) *Skriv kort og oppsummer gjerne hovedpoenget.*
Ipsen refers to the ongoing assessment (ID 2021_135) regarding cabozantinib (Cabometyx®) in differentiated thyroid cancer (DTC). The request for assessment was submitted by Elin Hallan Naderi, who is responsible for the thyroid oncological treatment at Oslo University Hospital.

On February 7th, 2025, Ipsen had a meeting with representatives from DMP regarding the submission and the type of assessment required. Given the limited number of DTC patients, IPSEN is unable to provide a full health economic evaluation due to resource implications. According to Dr. Naderi, there could be up to 10 patients eligible for treatment with Cabometyx® in Norway. However, Ipsen believes it is important for these few patients to have access to treatment with cabozantinib (Cabometyx®) and, therefore submits this proposal. Ipsen kindly requests Nye Metoder change the method to a simplified assessment, excluding the cost effectiveness evaluation (Metodevurdering uten en helseøkonomisk analyse).

To support this, TLV (the Dental and Pharmaceutical benefit agency) in Sweden has already accepted the use of cabozantinib (Cabometyx®) for treating patients with DTC without requiring a health economic evaluation, highlighting the value of the treatment for these patients. During the meeting with DMP, it was conveyed that the representatives strongly encouraged Ipsen to submit an "innspill" regarding the ongoing assessment. The interaction suggested openness to considering input without a full health economic evaluation from Ipsen as part of the evaluation process.

Medical summary

Differentiated thyroid cancer is the most common form of thyroid cancer, accounting for about 90%-95% of all cases. However, only 5% to 15% of patients experience a significant impact on health-related quality of life (HRQoL), a poor prognosis, and a life expectancy of only 3-5 years. There is a significant unmet medical need for efficacious and tolerable second-line treatments in RAI-refractory DTC.

Cabozantinib is a multiple receptor tyrosine kinase (RTK) inhibitor that targets MET, RET, AXL, and vascular endothelial growth factor receptor 2 (VEGFR2), and the first drug with robust data in second-line RAI-refractory DTC. Cabozantinib tablets (Cabometyx®) have been approved in the EU, Canada, and US for use in the second-line treatment of RAI-refractory DTC. Cabometyx® could become the standard of care for the second-line treatment of patients with RAI-refractory DTC and has the potential to address this unmet need.

The efficacy and safety of cabozantinib in treating patients with DTC was evaluated in Phase III COSMIC-311 trial. COSMIC-311 was specially designed to target second-line RAI-refractory DTC and assessed cabozantinib (Cabometyx®) 60 mg tablets once daily versus matching placebo tablets. All patients in the trial received best supportive care (BSC) in addition to their randomised treatment. Patients were eligible for enrolment in COSMIC-311 if they had locally advanced or metastatic RAI-refractory DTC which had progressed during or after prior systemic therapy. Patients must have received previous treatment with lenvatinib or sorafenib, and up to two previous VEGFR-targeting TKIs were allowed. Patients that were randomised to placebo were allowed to cross over to receive cabozantinib upon experiencing progressive disease. Progression-free survival (PFS) and objective response rate (ORR) were multiple primary endpoints of the trial. Data are available at two data cuts: Clinical Cutoff 1 (CCO1) on August 19th, 2020, and Clinical Cutoff 2 (CCO2) on February 8th, 2021.

Table 1. Patient characteristics from the latest data cutoff CCO2 for full ITT

CC02: Patient characteristics ITT population median follow- up 10.1 months			
% (unless otherwise specified)		Cabozantinib (Cabometyx) (n=170)	Placebo (n=88)
Median age, years (IQR)		65 (31–85)	66 (37-83)
Male		83 (49)	39 (44)
Region	Europe	82 (48)	39 (44)
	Asia	24 (14)	19 (22)
	USA and Canada	15 (9)	12 (14)
	Rest of the world	49 (29)	18 (20)
ECOG PS	0	74 (44)	43 (49)
	1	95 (56)	45 (51)
Histological subtype‡	Papillary	96 (56)	54 (61)
	Follicular	78 (46)	35 (40)
Number of prior VEGFR TKIs	1	126 (74)	65 (74)
	2	43 (25)	23 (26)
Prior sorafenib/ lenvatinib	Sorafenib only	101 (59)	54 (61)
	Lenvatinib only	108 64)	55 (63)
	Both	39 (23)	21 (24)

Clinical value

Cabozantinib significantly reduces the risk of PFS compared with placebo (from CCO1: HR=0.22, 96% CI: 0.13, 0.36; p-value <0.0001), whilst demonstrating numerically higher response rates and showing a trend for longer OS, in adults with locally advanced or metastatic RAI-refractory DTC who have progressed during or after prior systemic therapy.

At CCO1, a numerical benefit in ORR (multiple primary endpoint) was demonstrated for cabozantinib versus placebo in the overall response rate intention-to-treat (OITT) population; 15% (99% CI: 5.8, 29.3) versus 0% (99% CI: 0.0, 14.8), p-value=0.021.

Supportive analyses at CCO2 showed that this numerical benefit was maintained in the Full intention-to-treat (ITT) population, with an ORR of 11% (95% CI 6.9, 16.9) in the cabozantinib arm and 0% (95% CI 0.0, 4.1) in the placebo arm.

At CCO1, cabozantinib demonstrated a statistically significant improvement in PFS (multiple primary endpoint), reducing by 78% the risk of progression or death compared with placebo (HR=0.22, 96% CI 0.13, 0.36; stratified log-rank p-value <0.0001) in the ITT population. Supporting analyses at CCO2 showed that cabozantinib maintained the same statistically significant benefit (HR=0.22, 96% CI 0.15, 0.32; stratified log-rank p-value <0.0001) in the Full ITT population. Median PFS at CCO2 was 11.0 months (96% CI: 7.4, 13.8) for the cabozantinib arm versus 1.9 months (96% CI: 1.9, 3.7) for the placebo arm.

In addition to the multiple primary endpoints, several additional endpoints were explored in the COSMIC-311 trial. The analysis of OS was descriptive and log-rank p-values were calculated for descriptive purposes; formal inferences were not drawn.

At CCO1, the analysis demonstrated a trend for longer OS for patients in the cabozantinib arm compared with the placebo arm in the ITT population (HR=0.54, 95% CI: 0.27, 1.11). Median OS at CCO1 was not estimable in both treatment arms. At CCO2, the analysis showed a trend in benefit for cabozantinib versus placebo despite a crossover of 45% of placebo patients in the Full ITT

population (HR=0.76, 95% CI: 0.45, 1.31). Median OS at CCO2 in the Full ITT population was 19.4 months (95% CI: 15.9, NE) for the cabozantinib arm and not estimable for the placebo arm.
The HRQoL of patients in the COSMIC-311 trial was assessed using the EQ-5D-5L instrument. Cabozantinib did not deteriorate patients' HRQoL with no minimal important differences versus placebo or versus baseline in EQ-Index or EQ-VAS at CCO1 in the ITT population.

Table 2. Results from the latest data cutoff CCO2 (Full ITT) from COSMIC -331

CCO2: Median follow-up of 10.1 months (ITT)			
% (unless otherwise specified)		Cabozantinib (Cabometyx) (n=170)	Placebo (n=88)
ORR, % (99% CI)		11 (6.9–16.9)	0 (0–4.1)
		p=0.0003*	
BOR, %	CR	1	0
	PR	11	0
	SD	69	39
	PD	6	48
	Unable to evaluate	13	13
SD ≥16 weeks		42	19
DCR (ORR + SD ≥16 weeks)		53	19
Median DoR, months (95% CI)		10.2 (9.3-NE)	NA
Median TTR, months (IQR)		3.6 (1.7–7.5)	NA

*Unstratified Fisher exact test.
BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ITT, intention-to-treat; NA, not applicable; NE, not estimable; NR, not reached; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease, TTR, time to response.

Safety

The safety profile of cabozantinib in COSMIC-311 was consistent with its known safety profile, with no new safety signals. The most frequently reported grade three or four treatment-related adverse events (TRAEs) were palmar-plantar erythrodysesthesia, hypertension, diarrhea, fatigue and hypocalcemia. As of CCO2 there was a low rate of treatment discontinuation due to TRAEs; 5.9% in the cabozantinib arm and 0% in the placebo arm.

Dosing and cost of cabozantinib

Recommended dose of cabozantinib (Cabometyx) for patients with DTC is 60 mg per day. Treatment should continue until the patient no longer experiences clinical benefit from the treatment or until unacceptable toxicity occurs. The list price of cabozantinib is 72 522,60 NOK for package of 60 mg tablets per 30-day supply. However, this price will not be relevant in regard to this application. Since Ipsen has a national tender on cabozantinib, the net price will apply.

Table 3. Drug costs of cabozantinib- based on list price

Strength	Package, Product number	List price (NOK)	Drug costs per day per patient (NOK)	Drug costs per month per patient (NOK)	Drug costs per year per patient (NOK)
20 mg	30 stk. (boks) 118175	72 522,60	2482,66	75 522,60	906 271,20
40 mg	30 stk. (boks) 126777	72 522,60	2482,66	75 522,60	906 271,20
60 mg	30 stk. (boks) 111502	72 522,60	2482,66	75 522,60	906 271,20

In summary, there is a significant unmet medical need for efficacious second-line treatments for patients with RAI-refractory DTC. Positive results from the Phase III COSMIC-311 trial demonstrated that Cabometyx® offers a clinical benefit associated with manageable tolerability. These positive results led to the approval and recommendation of Cabometyx® in second-line RAI-refractory DTC, which could address this unmet medical need.

Mer detaljert informasjon og innspill til PICO*

*PICO er et verktøy for å formulere presise problemstillinger i metodevurderingsarbeid. PICO er en forkortelse for Population/Problem – Intervention – Comparison – Outcome. PICO brukes til å presisere hvilken populasjon/problem som skal studeres, hvilke(t) tiltak (metode/behandling) som skal vurderes, hvilket tiltak det er naturlig å sammenligne med, og hvilke utfall/endepunkter det å er relevant å måle/vurdere. PICO er viktig for planlegging og gjennomføring av en metodevurdering.

4. Kjenner du til om metoden er i bruk i Norge i dag?

Er metoden i bruk utenom kliniske studier i dag (kryss av hvis ja): ☐
Fra hvilket tidspunkt har den vært i bruk: Klikk eller trykk her for å skrive inn tekst.
Hvor er eventuelt metoden i bruk: Klikk eller trykk her for å skrive inn tekst.

5. Hvilken pasientgruppe i den norske spesialisthelsetjenesten er metoden aktuell for? (PICO)
Beskriv kortfattet: Klikk eller trykk her for å skrive inn tekst.

6. Er du kjent med behandlingsalternativer til denne metoden og hvordan disse fungerer for pasientgruppen i dag? (PICO)
Beskriv kortfattet: Klikk eller trykk her for å skrive inn tekst.

7. Har du innspill til hva som vil være viktig for pasienter som er aktuelle for behandling med metoden? (PICO)
Hva kan oppfattes som en fordel for pasienter og brukere med denne metoden sammenlignet med aktuelle alternativer? Hvilke endepunkter/resultater av behandlingen er det aktuelt å måle? Beskriv kortfattet: Klikk eller trykk her for å skrive inn tekst.

8. Spesielt for medisinsk utstyr (besvares av leverandør): CE-merking
Foreligger det CE-merking for bruksområdet som beskrives i metoden? I så fall angi type og tidspunkt:Klikk eller trykk her for å skrive inn tekst.

9. Spesielt for legemidler (besvares av leverandør): Markedsføringstillatelse (MT)
Har legemiddelet MT for indikasjonen som omfattes av metoden? Angi i så fall tidspunkt eller ventet tidspunkt for MT: EMA approved on April 29th 2022 extension of indication for Cabometyx® (cabozantinib) in the indication covered by the method.

10. Andre kommentarer
Klikk eller trykk her for å skrive inn tekst.

11. Interesser og eventuelle interessekonflikter Beskriv dine relasjoner eller aktiviteter som kan påvirke, påvirkes av eller oppfattes av andre å ha betydning for den videre håndteringen av metoden som det gis innspill på (for eksempel: økonomiske interesser i saken, oppdrag eller andre bindinger).
Beskriv kortfattet: Ipsen Pharma is the holder of the marketing authorization for Cabometyx® (kabozantinib) for the indication covered by the method.