PDL NEW DRUG REVIEW

Proprietary Name: Cometriq®
Common Name: cabozantinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Caprelsa	Recommended

Summary

Indications and Usage: Treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). This is a pregnancy category D medication. Additionally, effective contraception should be used during treatment and for up to 4 months after completion of treatment in females and males of reproductive potential. The safety and efficacy of use in children under 18 years of age has not been established.

Drug Interactions: The concomitant use of a strong CYP3A4 inhibitor (ie ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) or a strong CYP3A4 inducer (eg dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) should be avoided when taking Cometriq®.

Dosage Forms: Capsules: 20mg, 80mg

Recommended Dosage: Take 140mg (one 80mg and three 20mg capsules) daily on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking capsules. Treatment should be continued until disease progression or unacceptable toxicity occurs. Foods (eg grapefruit) or nutritional supplements known to inhibit CYP P450 should not be ingested during treatment. If NCI CTCAE Grade 4 hematologic adverse reactions (ARs), Grade 3 or greater non-hematologic ARs, or intolerable Grade 2 ARs occur, Cometriq® should be withheld. Please refer to the prescribing information for specific dose reduction instructions if resolution/improvement of the ARs. Please also refer to the Drug Interactions section for additional information regarding when dosage reductions are required.

Cometriq® should be permanently discontinued for any of the following: development of visceral perforation or fistula formation; severe hemorrhage; serious arterial thromboembolic events (eg MI, cerebral infarction); nephrotic syndrome; malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management; osteonecrosis of the jaw; or reversible posterior leukoencephalopathy syndrome.

Cometriq® use is not recommended in those with moderate and severe hepatic impairment, as safety and efficacy have not been established. Dosage adjustment is not required in those with mild or moderate renal impairment; however, there is no experience of use in those with severe renal impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse event reported with Cometriq® includes diarrhea (30%), stomatitis (45%), nausea (22%), oral pain (30%), constipation (21%), abdominal pain (14%), vomiting (22%), dysphagia (7%), dyspepsia (11%), hemorrhoids (6%), fatigue (13%), asthenia (6%), decreased

weight (38%), decreased appetite (30%), dehydration (5%), arthralgia (7%), muscle spasms (7%), musculoskeletal chest pain (5%), dysgeusia (28%), headache (10%), dizziness (7%), paresthesia (5%), peripheral sensory neuropathy (7%), anxiety (7%), dysphonia (11%), Palmar-plantar erythrodysesthesia syndrome (PPES;48%), hair color changes (33%), rash (9%), dry skin (16%), alopecia (14%), erythema (9%), hyperkeratosis (7%), hypertension (29%), and hypotension (7%).

Laboratory abnormalities reported include increased AST (51%), increased ALT (45%), increased ALP (17%), hypocalcemia (27%), hypophosphatemia (18%), hyperbilirubinemia (11%), hypomagnesemia (15%), hypokalemia (9%), hyponatremia (5%), lymphopenia (2%), neutropenia (20%), and thrombocytopenia (31%).

Almost all treated with Cometriq® had elevated BP (96% vs 84% placebo), and more had overt hypertension vs placebo (61% vs 30%).

Cometriq® has a boxed warning regarding the risk of perforations and fistulas with use. GI perforations were reported in 3% of those taking Cometriq® and fistula formations were reported in 1% of those taking Cometriq®. All were serious, and one GI fistula was fatal. Patients should be monitored for symptoms of perforations and fistulas, and treatment should be discontinued if one develops.

The boxed warning also includes the risk of hemorrhage with use, including serious and sometimes fatal hemorrhage. Grade >3 hemorrhagic events were reported more in those treated with Cometriq® vs placebo (3% vs 1%). Cometriq® should not be given to those with a recent history of hemorrhage or hemoptysis.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Exelixis, Inc

Analysis: Cabozantinib, the active ingredient of Comtriq®, is a kinase inhibitor. In vitro studies have shown that it inhibits the tyrosine kinase activity of RET, MET, VEGFR-1, -2, and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. These kinases are part of both normal cellular function and pathologic processes, such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor.

One multicenter, randomized, double-blind, placebo-controlled study was performed to assess the safety and efficacy of Cometriq®. Patients (N=330) with metastatic medullary thyroid carcinoma (MTC) with actively progressive disease within 14 months prior to study entry were randomized to treatment. The primary outcomes were progression-free survival (PFS), objective response (OR), and response duration. Results suggested that there was a statistically significant prolongation in PFS in those treated with Cometriq® vs placebo (hazard ratio [HR] 0.28; $p<0.0001$). The median PFS times were 11.2 months with Cometriq® vs 4 months with placebo. Partial responses were only seen in those treated with Cometriq® (27% vs 0% placebo; $p<0.0001$). The median duration of OR was 14.7 months for those treated Cometriq®. Statistically significant differences in overall survival were not seen between treatment arms.

It is recommended that Cometriq® be placed as non-recommended on the Recommended Drug List as more cost effective alternatives are available.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Cometriq [package insert]. So. San Francisco, CA: Exelixis, Inc; 2012.