# ໃບຄາໂບ 20
# PHOCABO 20

**ສ່ວນປະກອບ:**

ໃນ 1 ເມັດເຄືອບຊຸມ ປະກອບດ້ວຍ Cabozantinib (S) - Malate 25 mg (20 mg base).

**ສັບພະຄຸນ:**

-ສຳລັບປິ່ນປົວ ມະເຮັງໝາກໄຂ່ຫຼັງ (RCC) ໄລ່ຍະແຜ່ລາມ;

-ໃຊ້ປິ່ນປົວຜູ້ປ່ວຍມະເຮັງຕັບ (HCC) ທີ່ເຄີຍໄດ້ຮັບການປິ່ນປົວດ້ວຍຢາ Sorafenib ມາກ່ອນ.

**ຂະໜາດ, ວິທີໃຊ້ ແລະ ຄຳເຕືອນ:**

-ຮັບປະທານ ວັນລະ 1 ຄັ້ງ, ຄັ້ງລະ 3 ເມັດ. ຮັບປະທານພ້ອມອາຫານ;

-ຄວນກິນໃນເວລາດຽວກັນຂອງທຸກໆວັນ.

**ຜົນຂ້າງຄຽງເມື່ອໃຊ້ຢາ:**

ໃນເວລາໃຊ້ຢາ ຈະພົບເຫັນອາການດັ່ງລຸ່ມນີ້:

-ວິນຫົວ, ປວດຮາກ, ຖອກທ້ອງ;

-ອາດເກີດອາການປວດ ຫຼື ມີບາດແຜໃນຜົ້ງປາກ ແລະ ລຳຄໍ, ສຽງແຫບ;

-ອ່ອນເພຍ, ບໍ່ຢາກອາຫານ, ນ້ຳໜັກລຸດ;

-ອາດມີອາການຜິມລົ່ນຊື່ວຄາວ.

**ຂະໜາດການບັນຈຸ:**

ບັນຈຸໃນຂວດພລາສຕິກ ຈຳນວນ 90 ເມັດ, ໃສ່ໃນກັບເຈ້ຍກັບລະ 1 ຂວດ.

**ການເກັບຮັກສາ:**

ເກັບມ້ຽນບ່ອນແຫ້ງບໍ່ມີແສງແດດສ່ອງເຖິງ ແລະ ໃນອຸນຫະພູມ 15-30 ອົງສາ, ເກັບໄວ້ໃນທີ່ຫ່າງໄກຈາກມືເດັກນ້ອຍ.

**ຜະລິດ ແລະ ຈຳໜ່າຍໂດຍ:**

ໂຮງງານຜະລິດຢາເລກ 2 ວຽງຈັນ

ຕູ້ ປ.ນ 2580, ຖະໜົນລາວໄທ, ໂສກປ່າຫຼວງ, ນະຄອນຫຼວງວຽງຈັນ, ສປປ ລາວ.

ໂທ: (856-21) 315 293, 351 586, 030 526 4122.

ແຟກ: (856-21) 314 722, 263 246, 351 866.

## FULL PRESCRIBING INFORMATION

**1 INDICATIONS AND USAGE**

**1.1Renal Cell Carcinoma**

PHOCABO is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

**1.2Hepatocellular Carcinoma**

PHOCABO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

**2 DOSAGE AND ADMINISTRATION**

**2.1Important Dosage Information**

- Stop treatment with PHOCABO at least 3 weeks prior to scheduled surgery, including dental surgery.
- Do not substitute PHOCABO capsules with cabozantinib capsules.
- Do not administer PHOCABO with food. Administer at least 1 hour before or at least 2 hours after eating.
- Swallow PHOCABO capsules whole. Do not crush PHOCABO capsules.
- Do not take a missed dose within 12 hours of the next dose.
- Modify the dose for certain patients with hepatic impairment and for patients taking drugs known to strongly induce or inhibit CYP450.

**2.2Recommended Dosage for Renal Cell Carcinoma**

The recommended dosage of PHOCABO is 60 mg once daily without food until the patient no longer experiences clinical benefit or experiences unacceptable toxicity.

**2.3Recommended Dosage for Hepatocellular Carcinoma**

The recommended dosage of PHOCABO is 60 mg once daily without food until disease progression or unacceptable toxicity.

**2.4Dosage Modifications for Adverse Reactions**

Withhold PHOCABO for:

- Intolerable Grade 2 adverse reactions
- Grade 3 or 4 adverse reactions
- Osteonecrosis of the jaw

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

- If previously receiving 60 mg daily dose, resume treatment at 40 mg daily.
- If previously receiving 40 mg daily dose, resume treatment at 20 mg daily.
- If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue PHOCABO.

Permanently discontinue PHOCABO for any of the following:

- Severe hemorrhage
- Development of gastrointestinal (GI) perforation or Grade 4 fistula
- Acute myocardial infarction or arterial or venous thromboembolic events that require medical intervention
- Severe hypertension that cannot be controlled with anti-hypertensive therapy or hypertensive crisis
- Nephrotic syndrome
- Reversible posterior leukoencephalopathy syndrome

**2.5Dosage Modifications for Coadministration with Strong CYP3A4 Inhibitors**

Reduce the daily PHOCABO dose by 20 mg (for example, from 60 mg to 40 mg daily or from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

**2.6Dosage Modifications for Coadministration with Strong CYP3A4 Inducers**

Increase the daily PHOCABO dose by 20 mg (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily) as tolerated. Resume the dose that was used prior to initiating the strong CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. Do not exceed a daily dose of 80 mg.

**2.7Dosage Modifications for Patients with Moderate and Severe Hepatic Impairment**

Reduce the starting dose of PHOCABO to 40 mg once daily in patients with moderate hepatic impairment (Child-Pugh B). Avoid PHOCABO in patients with severe hepatic impairment (Child-Pugh C).

**3 DOSAGE FORMS AND STRENGTHS**

Capsules:

- 80 mg: Opaque capsules.
- 20 mg: Opaque capsules.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1Hemorrhage**

Severe and fatal hemorrhages occurred with PHOCABO. The incidence of Grade 3 to 5 hemorrhagic events was 5% in PHOCABO-treated patients in RCC and HCC studies.

Discontinue PHOCABO for Grade 3 or 4 hemorrhage. Do not administer PHOCABO to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

**5.2Perforations and Fistulas**

Fistulas, including fatal cases, occurred in 1% of PHOCABO-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of PHOCABO-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue PHOCABO in patients who experience a Grade 4 fistula or a GI perforation.

**5.3Thrombotic Events**

PHOCABO increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of PHOCABO-treated patients. Fatal thrombotic events occurred in PHOCABO-treated patients.

Discontinue PHOCABO in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

**5.4Hypertension and Hypertensive Crisis**

PHOCABO can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of PHOCABO- treated patients.

Do not initiate PHOCABO in patients with uncontrolled hypertension. Monitor blood pressure regularly during PHOCABO treatment. Withhold PHOCABO for hypertension that is not adequately controlled with medical management; when controlled, resume PHOCABO at a reduced dose. Discontinue PHOCABO for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

**5.5Diarrhea**

Diarrhea occurred in 63% of patients treated with PHOCABO. Grade 3 diarrhea occurred in 11% of patients treated with PHOCABO.

Withhold PHOCABO until improvement to Grade 1 and resume PHOCABO at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

**5.6Palmar-Plantar Erythrodysesthesia**

Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with PHOCABO. Grade 3 PPE occurred in 13% of patients treated with PHOCABO.

Withhold PHOCABO until improvement to Grade 1 and resume PHOCABO at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**5.7Proteinuria**

Proteinuria was observed in 7% of patients receiving PHOCABO. Monitor urine protein regularly during PHOCABO treatment. Discontinue PHOCABO in patients who develop nephrotic syndrome.

**5.8Osteonecrosis of the Jaw**
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with PHOCABO. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of PHOCABO and periodically during PHOCABO. Advise patients regarding good oral hygiene practices. Withhold PHOCABO for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold PHOCABO for development of ONJ until complete resolution.

**5.9Impaired Wound Healing**
Wound complications occurred with PHOCABO. Withhold PHOCABO for at least 3 weeks prior to elective surgery. Do not administer PHOCABO for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of PHOCABO after resolution of wound healing complications has not been established.

**5.10Reversible Posterior Leukoencephalopathy Syndrome**
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with PHOCABO. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue PHOCABO in patients who develop RPLS.

**5.11Embryo-Fetal Toxicity**
Based on data from animal studies and its mechanism of action, PHOCABO can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PHOCABO and for 4 months after the last dose.

## 6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling:
- Hemorrhage
- Perforations and Fistulas
- Thrombotic Events
- Hypertension and Hypertensive Crisis
- Diarrhea
- Palmar-plantar Erythrodysesthesia
- Proteinuria
- Osteonecrosis of the Jaw
- Impaired Wound Healing
- Reversible Posterior Leukoencephalopathy Syndrome

## 7 DRUG INTERACTIONS
**7.1Effects of Other Drugs on PHOCABO**
Strong CYP3A4 Inhibitors
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of PHOCABO with strong CYP3A4 inhibitors. Reduce the dosage of PHOCABO if coadministration with strong.
CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.
Strong CYP3A Inducers
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of PHOCABO with strong CYP3A4 inducers. Increase the dosage of PHOCABO if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

## 8 USE IN SPECIFIC POPULATIONS
**8.1Pregnancy**
Risk Summary
Based on findings from animal studies and its mechanism of action, PHOCABO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose (see Data). Advise pregnant women of the potential risk to a fetus.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Data
*Animal Data*
In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).
In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).
In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

**8.2Lactation**
Risk Summary
There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with PHOCABO and for 4 months after the final dose.

**8.3Females and Males of Reproductive Potential**
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating PHOCABO.
Contraception
PHOCABO can cause fetal harm when administered to a pregnant woman.
*Females*
Advise females of reproductive potential to use effective contraception during treatment with PHOCABO and for 4 months after the final dose.
Infertility
*Females and Males*
Based on findings in animals, PHOCABO may impair fertility in females and males of reproductive potential.

**8.4Pediatric Use**
The safety and effectiveness of PHOCABO in pediatric patients have not been established.
Juvenile Animal Toxicity Data
Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels.
Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

**8.5Geriatric Use**
In CABOSUN and METEOR, 41% of 409 patients treated with PHOCABO were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with PHOCABO were age 65 years and older, and 15% were 75 years and older.
No overall differences in safety or effectiveness were observed between these patients and younger patients.

**8.6Hepatic Impairment**
Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the PHOCABO dose in patients with moderate hepatic impairment. Avoid PHOCABO in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

**8.7Renal Impairment**
No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with PHOCABO in patients with severe renal impairment.

## 9 OVERDOSAGE
One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

## 10 HOW SUPPLIED/STORAGE AND HANDLING
PHOCABO capsules are supplied as follows:
80 mg capsules are available in bottles of 30 capsules
20 mg capsules are available in bottles of 90 capsules:
Not allthe packages on the market.
Store PHOCABO at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F)

## 11 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.
- Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during PHOCABO treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking PHOCABO.
- Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.
- Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.
- Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.
- Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.
- Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.
- Impaired wound healing: Advise patients that PHOCABO may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.
- Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.
- Embryo-fetal toxicity:
  - Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.
  - Advise females of reproductive potential to use effective contraception during treatment with PHOCABO and for 4 months after the final dose.
- Lactation: Advise women not to breastfeed during treatment with PHOCABO and for 4 months following the last dose.
- Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information
- Instruct patients to take PHOCABO at least 1 hour before or at least 2 hours after eating.