ໄພເອັນເທຣ 100
PHOENTRE 100

ສ່ວນປະກອບ:

ໃນ 1 ເມັດ ປະກອບດ້ວຍ Entrectinib 100 mg

ສັບພະຄຸນ:

ສຳລັບຢິ່ນປ໋ວ:

-ມະເຮັ້ງປອດ ຊະນິດທີ່ບໍ່ແມ່ນເຊວຂະໜາດນ້ອຍ (NSCLC) ໄລຍະແຜ່ລາມ ໃນຜູ້ປ່ວຍຜູ້ໃຫຍ່ ທີ່ມີ ROS1-positive.

-ຮັກສາຜູ້ປ່ວຍທີ່ເປັນເນື້ອງອກກະດັນ NTRK Gene Fusion-Positive Solid Tumors ໃນຜູ້ໃຫຍ່ ແລະ ເດັກນ້ອຍອາຍຸ 12 ປີຂຶ້ນໄປ.

ຂະໜາດ, ວິທີໃຊ້ ແລະ ຄຳເຕືອນ:

-ປະລິມານທີ່ແນະນຳສຳຫຼັບ ມະເຮັ້ງປອດ ຊະນິດທີ່ບໍ່ແມ່ນເຊວຂະໜາດນ້ອຍ (NSCLC) ທີ່ມີ ROS1-positive: ແມ່ນຮັບປະທານ 600 mg / ຄັ້ງ / ວັນ ຮ່ວມກັບ ຫຼື ບໍ່ຮ່ວມກັບອາຫານ ຈົນກ່ວາຈະມີການແຜ່ລາມຂອງພະຍາດ ຫຼື ຄວາມເປັນຜິດທີ່ບໍ່ສາມາດຍອມຮັບໄດ້.

-ປະລິມານທີ່ແນະນຳສຳຫຼັບ ເນື້ອງອກກະດັນ NTRK Gene Fusion-Positive Solid Tumors:

●ສຳຫຼັບຜູ້ໃຫຍ່ ແມ່ນຮັບປະທານ 600 mg / ຄັ້ງ / ວັນ ຮ່ວມກັບ ຫຼື ບໍ່ຮ່ວມກັບອາຫານ ຈົນກ່ວາຈະມີການແຜ່ລາມຂອງພະຍາດ ຫຼື ຄວາມເປັນຜິດທີ່ບໍ່ສາມາດຍອມຮັບໄດ້;

●ສຳຫຼັບເດັກນ້ອຍອາຍຸ 12 ປີຂຶ້ນໄປ ແມ່ນຄິດໄລ່ຕາມພື້ນທີ່ໜ້າຕັດຂອງຮ່າງກາຍ (BSA) ທີ່ສະແດງໃນຕາຕະລາງລຸ່ມນີ້:

ຕາຕະລາງ 1: ປະລິມານທີ່ແນະນຳ ສຳຫຼັບເດັກນ້ອຍອາຍຸ 12 ປີຂຶ້ນໄປ

ພື້ນທີ່ໜ້າຕັດຂອງຮ່າງກາຍ (BSA)	ປະລິມານທີ່ແນະນຳ (ຮັບລະຄັ້ງ)
ຫຼາຍກວ່າ 1.50 m2	600 mg
1.11 to 1.50 m2	500 mg
0.91 to 1.10 m2	400 mg

ໃຊ້ຢາບໍ່ຈົນກ່ວາຈະມີການແຜ່ລາມຂອງພະຍາດ ຫຼື ຄວາມເປັນຜິດທີ່ບໍ່ສາມາດຍອມຮັບໄດ້

ຜົນຂ້າງຄຽງເມື່ອໃຊ້ຢາ:

ໃນເວລາໃຊ້ຢາ ຈະພົບເຫັນອາການດັ່ງລຸ່ມນີ້:

-ການຮັບຄົວຊຸດຜິດປົກກະຕິ;

-ມີອາການເມື່ອຍລ້າ, ອ່ອນເພຍ, ມຶນງົງ, ມືຕີນຊາ;

-ຖ່າຍຍາກ, ປວດຮາກ ຫລື ຖອກທ້ອງ;

-ນ້ຳໜັກເພີ່ມຂຶ້ນ;

-ຄ່າໝາກໄຂ່ຫຼັງສູງຂຶ້ນ, ຄ່າ AST ໃນເລືອດເພີ່ມຂຶ້ນ;

-ປວດຕາມຂ່າງກາຍ ແລະ ຂໍ້, ແຂບຂາບວມ.

ຂະໜາດການບັນຈຸ:

ບັນຈຸໃນຂວດພລາສຕິກ ຈຳນວນ 60 ເມັດ, ໃສ່ໃນກັບເຈ້ຍ ກັບລະ 1 ຂວດ.

ການເກັບຮັກສາ:

ເກັບມ້ຽນບ່ອນແຫ້ງບໍ່ມີແສງແດດສ່ອງເຖິງ ແລະ ໃນອຸນຫະພູມ 15-30 ອົງສາ, ເກັບໄວ້ໃນທີ່ຫ່າງໄກຈາກມືເດັກນ້ອຍ.

ຜະລິດ ແລະ ຈຳໜ່າຍໂດຍ:

ໂຮງງານຜະລິດຢາເລກ 2 ວຽງຈັນ

ຕູ້ ປ.ນ 2580, ຖະໜົນລາວໄທ, ໂສກປ່າໝາວ, 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

1.1*ROS1*-Positive Non-Small Cell Lung Cancer

PHOENTRE is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive.

1.2*NTRK* Gene Fusion-Positive Solid Tumors

PHOENTRE is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have either progressed following treatment or have no satisfactory alternative therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1Patient Selection

Select patients for the treatment of metastatic NSCLC with PHOENTRE based on the presence of *ROS1* rearrangement(s) in tumor specimens. An FDA-approved test for detection of *ROS1* rearrangement(s) in NSCLC for selecting patients for treatment with PHOENTRE is not available.

Select patients for treatment of locally advanced or metastatic solid tumors with PHOENTRE based on the presence of a *NTRK* gene fusion. An FDA-approved test for the detection of *NTRK* gene fusion in solid tumors is not available.

2.2Recommended Dosage for *ROS1*-Positive Non-Small Cell Lung Cancer

The recommended dosage of PHOENTRE is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity.

2.3Recommended Dosage for *NTRK* Gene Fusion-Positive Solid Tumors

Adults

The recommended dosage of PHOENTRE in adults is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity.

Pediatric Patients 12 Years and Older (Adolescents)

The recommended dosage of PHOENTRE is based on body surface area (BSA) as shown in Table 1 below. Take PHOENTRE orally once daily with or without food until disease progression or unacceptable toxicity.

Table 1: Dosing in Pediatric Patients 12 Years and Older (Adolescents)

Body Surface Area (BSA)	Recommended Dosage (Orally once daily)
Greater than 1.50 m^2	600 mg
1.11 to 1.50 m^2	500 mg
0.91 to 1.10 m^2	400 mg

2.4Dosage Modifications for Adverse Reactions

The recommended dosage reductions for adverse reactions are provided in Table 2.

Table 2: Recommended Dose Reductions for PHOENTRE Adverse Reactions

Action	Adults and Pediatric Patients 12 Years and Older with BSA Greater than 1.50 m^2 (Orally once daily)	Pediatric Patients 12 Years and Older with BSA of 1.11 to 1.50 m^2 (Orally once daily)	Pediatric Patients 12 Years and Older with BSA of 0.91 to 1.10 m^2 (Orally once daily)
First dose reduction	400 mg	400 mg	300 mg
Second dose reduction*	200 mg	200 mg	200 mg

*For a subsequent modification, permanently discontinue PHOENTRE in patients who are unable to tolerate PHOENTRE after two dose reductions.

2.5Dosage Modifications for Drug Interactions

Moderate and Strong CYP3A Inhibitors

Adults and Pediatric Patients 12 Years and Older with BSA Greater than 1.50 m^2

Avoid coadministration of PHOENTRE with moderate or strong CYP3A inhibitors.

If coadministration cannot be avoided, reduce the PHOENTRE dose as follows:

- *Moderate CYP3A Inhibitors:* 200 mg orally once daily
- *Strong CYP3A Inhibitors:* 100 mg orally once daily

After discontinuation of a strong or moderate CYP3A inhibitor for 3 to 5 elimination half-lives, resume the PHOENTRE dose that was taken prior to initiating the CYP3A inhibitor.

2.6Administration

Swallow capsules whole. Do not open, crush, chew, or dissolve the contents of the capsule.

If a patient misses a dose, instruct patients to make up that dose unless the next dose is due within 12 hours. If a patient vomits immediately after taking a dose, instruct patients to repeat that dose.

3 DOSAGE FORMS AND STRENGTHS

Capsules :100 mg

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1Congestive Heart Failure

Among the 355 patients who received PHOENTRE across clinical trials, congestive heart failure (CHF) occurred in 3.4% of patients, including Grade 3 (2.3%). In clinical trials, baseline cardiac function and routine cardiac monitoring other than electrocardiograms (ECGs) were not conducted and eligibility criteria excluded patients with symptomatic CHF, myocardial infarction, unstable angina, and coronary artery bypass graft within 3 months of study entry. Among the 12 patients with CHF, the median time to onset was 2 months (range: 11 days to 12 months). PHOENTRE was interrupted in 6 of these patients (50%) and discontinued in 2 of these patients (17%). CHF resolved in 6 patients (50%) following interruption or discontinuation of PHOENTRE and institution of appropriate medical management. In addition, myocarditis in the absence of CHF was documented in 0.3% of patients.

Assess left ventricular ejection fraction (LVEF) prior to initiation of PHOENTRE in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of CHF, including shortness of breath and edema. For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For patients with new onset or worsening CHF, withhold PHOENTRE, institute appropriate medical management, and reassess LVEF. Based on the severity of CHF or worsening LVEF, resume PHOENTRE at a reduced dose upon recovery to baseline or permanently discontinue.

5.2Central Nervous System Effects

A broad spectrum of central nervous system (CNS) adverse reactions occurred in patients receiving PHOENTRE, including cognitive impairment, mood disorders, dizziness, and sleep disturbances.

Among the 355 patients who received PHOENTRE across clinical trials, 96 (27%) experienced cognitive impairment; symptoms occurred within 3 months of starting PHOENTRE in 74 (77%). Cognitive impairment included cognitive disorders (8%), confusional state (7%), disturbance in attention (4.8%), memory impairment (3.7%), amnesia (2.5%), aphasia (2.3%), mental status changes (2%), hallucinations (1.1%), and delirium (0.8%). Grade 3 cognitive adverse reactions occurred in 4.5% of patients. Among the 96 patients with cognitive impairment, 13% required a dose reduction, 18% required dose interruption and 1% discontinued PHOENTRE due to cognitive adverse reactions.

Among the 355 patients who received PHOENTRE across clinical trials, 36 (10%) experienced mood disorders. The median time to onset of mood disorders was 1 month (range: 1 day to 9 months). Mood disorders occurring in ≥□1% of patients included anxiety (4.8%), depression (2.8%) and agitation (2%). Grade 3 mood disorders occurred in 0.6% of patients. One completed suicide was reported 11 days after treatment had ended. Among the 36 patients who experienced mood disorders, 6% required a dose reduction, 6% required dose interruption and no patients discontinued PHOENTRE due to mood disorders.

Dizziness occurred in 136 (38%) of the 355 patients. Among the 136 patients who experienced dizziness, Grade 3 dizziness occurred in 2.2% of patients. Ten percent of patients required a dose reduction, 7% required dose interruption and 0.7% discontinued PHOENTRE due to dizziness.

Among the 355 patients who received PHOENTRE across clinical trials, 51 (14%) experienced sleep disturbances. Sleep disturbances included insomnia (7%), somnolence (7%), hypersomnia (1.1%), and sleep disorder (0.3%). Grade 3 sleep disturbances occurred in 0.6% of patients. Among the 51 patients who experienced sleep disturbances, 6% required a dose reduction and no patients discontinued PHOENTRE due to sleep disturbances.

The incidence of CNS adverse reactions was similar in patients with and without CNS metastases; however, the incidence of dizziness (38% vs 31%), headache (21% vs 13%), paresthesia (20% vs 6%), balance disorder (13% vs 4%), and confusional state (11% vs 2%) appeared to be increased in patients with CNS metastases who had received prior CNS irradiation (N = 90) compared to those who did not (N = 48).
Advise patients and caregivers of these risks with PHOENTRE. Advise patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue PHOENTRE based on severity.

5.3Skeletal Fractures

PHOENTRE increases the risk of fractures. In an expanded safety population that included 338 adult patients and 30 pediatric patients who received PHOENTRE across clinical trials, 5% of adult patients and 23% of pediatric patients experienced fractures . In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients all fractures occurred in patients with minimal or no trauma. In general, there was inadequate assessment for tumor involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumor involvement were reported in some patients. In both adult and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In a limited number of patients, bilateral femoral neck fractures occurred. The median time to fracture was 3.8 months (range 0.3 to 18.5 months) in adults and 4.0 months (range: 1.8 months to 7.4 months) in pediatric patients. PHOENTRE was interrupted in 41% of adults and 43% of pediatric patients due to fractures. No patients discontinued PHOENTRE due to fractures.
Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. There are no data on the effects of PHOENTRE on healing of known fractures and risk of future fractures.

5.4Hepatotoxicity

Among the 355 patients who received PHOENTRE, increased AST of any grade occurred in 42% of patients and increased ALT of any grade occurred in 36%. Grade 3 – 4 increased AST or ALT occurred in 2.5% and 2.8% of patients, respectively; the incidence may be underestimated as 4.5% of patients had no post-treatment liver function tests. The median time to onset of increased AST was 2 weeks (range: 1 day to 29.5 months). The median time to onset of increased ALT was 2 weeks (range: 1 day to 9.2 months). Increased AST or ALT leading to dose interruptions or reductions occurred in 0.8% and 0.8% of patients, respectively. PHOENTRE was discontinued due to increased AST or ALT in 0.8% patients.
Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue PHOENTRE based on the severity. If withheld, resume PHOENTRE at the same or reduced dose.

5.5Hyperuricemia

Among 355 patients who received PHOENTRE across clinical trials, 32 patients (9%) experienced hyperuricemia reported as adverse reactions with symptoms, as well as elevated uric acid levels. Grade 4 hyperuricemia occurred in 1.7% of patients, including one patient who died due to tumor lysis syndrome.Among the 32 patients with hyperuricemic adverse reactions, 34% required urate-lowering medication to reduce uric acid levels, 6% required dose reduction and 6% required dose interruption.
Hyperuricemia resolved in 73% of patients following initiation of urate-lowering medication without interruption or dose reduction of PHOENTRE. No patients discontinued PHOENTRE due to hyperuricemia.
Assess serum uric acid levels prior to initiating PHOENTRE and periodically during treatment. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold PHOENTRE for signs and symptoms of hyperuricemia. Resume PHOENTRE at same or reduced dose upon improvement of signs or symptoms based on severity.

5.6QT Interval Prolongation

Among the 355 patients who received PHOENTRE across the clinical trials, 3.1% of patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of > 60 ms after starting PHOENTRE and 0.6% had a QTcF interval > 500 ms.
Monitor patients who already have or who are at significant risk of developing QTc interval prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment, adjusting frequency based upon risk factors such as congestive heart failure, electrolyte abnormalities, or concomitant medications known to prolong the QTc interval. Based on the severity of QTc interval prolongation, withhold PHOENTRE and then resume at same or reduced dose, or permanently discontinue .

5.7Vision Disorders

Among the 355 patients who received PHOENTRE across clinical trials, vision changes occurred in 21% of patients, including Grade 1 (82%), Grade 2 (14%) and Grade 3 (0,8%). Vision disorders occurring in >1% included blurred vision (8.7%), photophobia (5.1%), diplopia (3.1%), visual impairment (2%), photopsia (1.3%), cataract (1.1%), and vitreous floaters (1.1%).
For patients with new visual changes or changes that interfere with activities of daily living, withhold PHOENTRE until improvement or stabilization and conduct an ophthalmological evaluation as clinically appropriate. Upon improvement or stabilization, resume PHOENTRE at same or reduced dose.

5.8Embryo-Fetal Toxicity

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, PHOENTRE can cause fetal harm when administered to a pregnant woman. Administration of entrectinib to pregnant rats resulted in malformations at exposures approximately 2.7 times the human exposure at the 600 mg dose based on area under the curve (AUC).
Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PHOENTRE and for 5 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PHOENTRE and for 3 months after the final dose.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Congestive Heart Failure
- Central Nervous System Effects
- Skeletal Fractures
- Hepatotoxicity
- Hyperuricemia
- QT Interval Prolongation
- Vision Disorders

7 DRUG INTERACTIONS

7.1Effect of Other Drugs on PHOENTRE

Moderate and Strong CYP3A Inhibitors

Adults and Pediatric Patients 12 Years and Older with BSA Greater than 1.50 m^2

Coadministration of PHOENTRE with a strong or moderate CYP3A inhibitor increases entrectinib plasma concentrations, which could increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with PHOENTRE. If coadministration is unavoidable, reduce the PHOENTRE dose.

Pediatric Patients 12 Years and Older with BSA Less Than or Equal to 1.50 m^2

Avoid coadministration of PHOENTRE with moderate or strong CYP3A inhibitors.
Avoid grapefruit products during treatment with PHOENTRE, as they contain inhibitors of CYP3A.

Moderate and Strong CYP3A Inducers

Coadministration of PHOENTRE with a strong or moderate CYP3A inducer decreases entrectinib plasma concentrations, which may reduce PHOENTRE efficacy. Avoid coadministration of strong and moderate CYP3A inducers with PHOENTRE.

7.2Drugs That Prolong QT Interval

QTc interval prolongation can occur with PHOENTRE. Avoid coadministration of PHOENTRE with other products with a known potential to prolong QT/QTc interval.

8 USE IN SPECIFIC POPULATIONS

8.1Pregnancy

Risk Summary

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, PHOENTRE can cause fetal harm when administered to a pregnant woman. There are no available data on PHOENTRE use in pregnant women. Administration of entrectinib to pregnant rats during the period of organogenesis resulted in malformations at maternal exposures approximately 2.7 times the human exposure at the 600 mg dose. 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% to 4% and 15% to 20%, respectively.

8.2Lactation

Risk Summary

There are no data on the presence of entrectinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential adverse reactions in breastfed children from PHOENTRE, advise a lactating woman to discontinue breastfeeding during treatment with PHOENTRE and for 7 days 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 PHOENTRE .

Contraception

PHOENTRE can cause embryo-fetal harm when administered to a pregnant woman.

Females

Advise female patients of reproductive potential to use effective contraception during treatment with PHOENTRE and for at least 5 weeks following the final dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PHOENTRE and for 3 months following the final dose.

8.4Pediatric Use

The safety and effectiveness of PHOENTRE in pediatric patients aged 12 years and older with solid tumors that have an NTRK gene fusion have been established. The effectiveness of PHOENTRE in adolescent patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumors harboring an NTRK gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacokinetic data in adolescents enrolled in STARTRK-NG. PHOENTRE doses based on body surface area in pediatric patients 12 years and older resulted in similar systemic exposure compared to that in adults who received a PHOENTRE dose of 600 mg.
There is limited clinical experience with PHOENTRE in pediatric patients. The safety of PHOENTRE in pediatric patients 12 years of age and older was established based on extrapolation of data in adults and data from 30 pediatric patients enrolled in STARTRK-NG. Of these 30 patients, 7% were < 2 years (n = 2), 17% were 2 to < 12 years (n = 23), 17% were 12 to < 18 years (n = 5); 57% had metastatic disease (n = 17) and 44% had locally advanced disease (n = 13); and all patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%). The median duration of exposure for all pediatric patients was 4.2 months (range: 0.2 to 22.7 months).
Due to the small number of pediatric and adult patients, the single arm design of clinical studies of PHOENTRE, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to PHOENTRE are related to patient age or other factors. In an expanded safety database that included 338 adult patients and 30 pediatric patients who received PHOENTRE across clinical trials, the Grade 3 or 4 adverse reactions and laboratory abnormalities that occurred more frequently (≥ 5%) in pediatric patients (n = 30) compared with adults (n = 338) were neutropenia (27% vs 2%), bone fractures (23% vs 5%), increased weight (20% vs 7%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma glutamyl transferase (7% vs 0%), and device-related infection (7% vs 0.3%). Three pediatric patients discontinued PHOENTRE due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis).
The safety and effectiveness of PHOENTRE in pediatric patients less than 12 years of age with solid tumors who have an NTRK gene fusion have not been established.
The safety and effectiveness of PHOENTRE in pediatric patients with ROS1-positive NSCLC have not been established.

Juvenile Animal Toxicity Data

In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Entrectinib resulted in:
- decreased body weight gain and delayed sexual maturation at doses ≥ 4 mg/kg/day (approximately 0.06 times the human exposure (AUC) at the 600 mg dose),
- deficits in neurobehavioral assessments including functional observational battery and learning and memory (at doses ≥ 8 mg/kg/day, approximately 0.14 times the human exposure at the 600 mg dose), and
- decreased femur length at doses ≥ 16 mg/kg/day (approximately 0.18 times the human exposure at the 600 mg dose).

8.5Geriatric Use

Of the 355 patients who received PHOENTRE across clinical trials, 25% were 65 years or older, and 5% were 75 years of age or older. Clinical studies of PHOENTRE did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients.

8.6Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr 30 to < 90 mL/min calculated by Cockcroft-Gault equation). PHOENTRE has not been studied in patients with severe renal impairment (CLcr < 30 mL/min).

8.7Hepatic Impairment

No dose adjustment is recommended for patients with mild (total bilirubin ≤ 1.5 times ULN) hepatic impairment. PHOENTRE has not been studied in patients with moderate (total bilirubin >1.5 to 3 times ULN) and severe (total bilirubin > 3 times ULN) hepatic impairment.

9 HOW SUPPLIED/STORAGE AND HANDLING

- 100 mg capsules: available in: HDPE bottles of 60 capsules.

Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F)

10 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information). Congestive Heart Failure
- Inform patients of the risks of CHF and advise patients to contact their healthcare provider immediately for any new or worsening signs or symptoms of CHF.

Central Nervous System Effects
- Advise patients to inform their healthcare provider if they experience new or worsening central nervous system symptoms. Instruct patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions.

Skeletal Fractures
- Inform patients that bone fractures have been reported in patients taking PHOENTRE. Advise patients to report symptoms such as pain, changes in mobility, or deformity to their healthcare provider.

Hepatotoxicity
- Advise patients that they will need to undergo laboratory tests to monitor liver function and to immediately report symptoms of hepatotoxicity .

Hyperuricemia
- Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia .

QT Interval Prolongation
- Inform patients of the risks of QT interval prolongation and to advise patients to contact their healthcare provider immediately for any symptoms of QT interval prolongation .

Vision Disorders
- Advise patients to inform their healthcare provider if they experience visual changes .

Embryo-Fetal Toxicity
- Advise pregnant women and 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 PHOENTRE and for 5 weeks after the final dose.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose.

Lactation
- Advise females not to breastfeed during treatment with PHOENTRE and for 1 week after the final dose.

Drug Interactions
- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit juice while taking PHOENTRE.

Administration
- Advise patients to swallow PHOENTRE capsules whole.
- Instruct patients if they miss a dose to make up that dose unless the next dose is due within 12 hours.
- Instruct patients if they vomit immediately after taking a dose of PHOENTRE to take a dose as soon as possible.