Zongertinib

Indication

Zongertinib is a kinase inhibitor indicated for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain, activating mutations who have received prior systemic therapy.

Regimen details

Zongertinib is to be taken orally once daily with or without food until disease progression or unacceptable toxicity.
The recommended dose of Zongertinib is based on weight,

< 90 kg: 120 mg
≥ 90 kg: 180 mg

Cycle frequency

Every 28 days

Number of cycles

continue treatment until disease progression or unacceptable toxicity

Administration

Swallow Zongertinib tablets whole with water. Do not split, crush, or chew tablets.

Inform patients that if they miss a dose of Zongertinib within 12 hours, they should take it as soon as they remember. If the next dose is missed by more than 12 hours, the patient should skip the missed dose and wait until the next scheduled dose [see Dosage and Administration.

If a dose is vomited, do not take an additional dose. Take the next dose at the regularly scheduled time.

Pre-medication

Not required.

Emetogenicity

Minimal

Additional supportive medication

Provide emollient, steroid cream and loperamide

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Echocardiogram (LVEF)	6 months

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST)

Medical review every 4 weeks initially

Chest X-ray and CT scans as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Dose modifications

Current Zongertinib dose	First reduction	Second reduction
180mg	120mg	60mg
120mg	60mg	Permanently discontinue
Permanently discontinue Zongertinib in patients who are unable to tolerate 60mg once daily		

Adverse reactions	Severity	Dosage Modification
Hepatotoxicity	Grade 3 or 4 ALT and/or AST without increased total bilirubin	• Interrupt Zongertinib until recovered to ≤ Grade 1 or baseline • Resume Zongertinib at reduced dose level
	Grade 3 total bilirubin	• Interrupt Zongertinib until recovered to ≤ Grade 1 or baseline • Resume Zongertinib at reduced dose level
	Grade 4 total bilirubin	• Permanently discontinue Zongertinib
	ALT or AST ≥ 3x ULN with total bilirubin ≥ 2x ULN	• Permanently discontinue Zongertinib
Left Ventricular Dysfunction	LVEF 40 to 50% and decrease from baseline of 10 to 19%	• Interrupt Zongertinib until recovered to ≤ Grade 1 or within 10% from baseline. • If recovered to ≤ Grade 1 in ≤ 4 weeks, resume Zongertinib at the same dose level. • If not recovered to ≤ Grade 1 within 4 weeks, permanently discontinue Zongertinib.
	LVEF 20 to 39% or ≥ 20% decrease from baseline	• Interrupt Zongertinib until recovered to ≤ Grade 1 or within 10% from baseline. • If recovered to ≤ Grade 1 in ≤ 4 weeks, resume Zongertinib at the same dose level. • If not recovered to ≤ Grade 1 within 4 weeks, permanently discontinue Zongertinib.
	Symptomatic Congestive Heart Failure	• Permanently discontinue Zongertinib.
Interstitial lung disease / Pneumonitis	Grade 2	• Withhold Zongertinib until resolution. • Resume Zongertinib at reduced dose level. • Permanently discontinue Zongertinib for recurrent ILD/pneumonitis.
	Grade 3 or Grade 4	• Permanently discontinue Zongertinib.
Diarrhoea	Grade 2	• Maintain Zongertinib dose. • Initiate anti-diarrheal treatment.
	Grade 2 lasting ≥ 2 days despite anti-diarrheal treatment	• Interrupt Zongertinib until recovered to ≤ Grade 1. • Resume Zongertinib at reduced dose level.
	Grade 3 or Grade 4	• Interrupt Zongertinib until recovered to ≤ Grade 1. • Resume Zongertinib at reduced dose level. • Permanently discontinue Zongertinib if diarrhea does not

		resolve to ≤ Grade 1 within 14 days, despite optimal supportive care (including anti-diarrheal treatment) and treatment interruption.
Other adverse reactions	Grade 3	• Interrupt Zongertinib until recovered to ≤ Grade 1. • Resume Zongertinib at reduced dose level.
	Grade 4	• Permanently discontinue Zongertinib.

Strong CYP3A Inducers (e.g. rifampicin, carbamazepine, phenytoin, St. John's Wort)
Avoid concomitant use of strong CYP3A inducers with Zongertinib. If concomitant use cannot be avoided, increase the HERNEXEOS dose based on body weight:

< 90 kg: from 120 mg to 240 mg
≥ 90 kg: from 180 mg to 360 mg

After discontinuing a CYP3A inducer, resume the Zongertinib dose (7 to 14 days after discontinuing the CYP3A inducer) that was taken prior to initiating the CYP3A inducer.

Adverse effects - for full details consult product literature/ reference texts

Per experience in Beamion LUNG-1

- **Diarrhoea** (all grades 52%, grade 3 or above 1%)
- Nausea (all grades 24%, grade 3 or above 1%)
- Vomiting (all grades 15%, grade 3 or above 1.9%)
- Rash (all grades 32%, grade 3 or above 1%)
- Nail disorders (all grades 19%, grade 3 or above 0%)
- Fatigue (all grades 25%, grade 3 or above 0%)
- Cough (all grades 24%, grade 3 or above 0%)
- Dyspnoea (all grades 15%, grade 3 or above 16%)
- Thromobocytopenia (all grades 23%, grade 3 or above 1%)
- **ALT increase** (all grades 39%, grade 3 or above 7%)
- **Bilirubin increase** (all grades 26%, grade 3 or above 1%)
- **ILD/pneumonitis** 1.2%, median time to first onset was 19 weeks.
- **Left ventricular dysfunction** – LVEF decrease occurred in 6%, 1.9% grade 3. Median time to onset of decreased LVEF was 9 weeks.

Significant drug interactions – for full details consult product literature/ reference texts

- Avoid concomitant use of Zongertinib with strong CYP3A inducers.
- Avoid concomitant use of Zongertinib with certain BCRP substrates where minimal concentration changes may lead to serious adverse reactions. Common BCRP substrates include tyrosine kinase inhibitors (e.g., imatinib, gefitinib), statins (e.g., rosuvastatin, pitavastatin), antivirals (e.g., sofosbuvir), and chemotherapeutics (e.g., methotrexate, topotecan).

Additional comments

Nil

References

Prescribing information of HERNEXEOS (Zongertinib) 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219042s000lbl.pdf

Heymach JV, Ruiter G, Ahn MJ, et al. Zongertinib in Previously Treated HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. 2025 Jun 19;392(23):2321-2333. doi: 10.1056/NEJMoa2503704.

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAM, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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