Binixen

Binimetinib INN

Everest

COMPOSITION

BINIXEN tablet: Each film-coated tablet contains Binimetinib INN 15 mg.

PHARMACOLOGY

Binimetinib is a reversible inhibitor of MEK1 and MEK2, key regulators in the RAS/RAF/MEK/ERK signaling pathway. It blocks ERK phosphorylation and inhibits growth of BRAF-mutant melanoma cells in vitro and in vivo. Combined with Encorafenib, which targets a different kinase in the same pathway, Binimetinib shows enhanced anti-tumor activity and delays resistance in BRAF V600E mutant models compared to either drug alone.

INDICATION

Binimetinib is indicated for the treatment of patients with:

- Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation in combination with Encorafenib.
- Metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation in combination with Encorafenib.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Melanoma: The recommended dose is 45 mg orally twice daily, with or without food, in combination with Encorafenib. For patients with moderate or severe hepatic impairment the recommended dose is 30 mg orally twice daily.

NSCLC: The recommended dose is 45 mg orally twice daily, with or without food, in combination with Encorafenib.

DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS:

If Encorafenib is permanently discontinued, discontinue Binimetinib.

Dose reductions for adverse reactions associated with Binimetinib are presented in Table 1.

Table 1: Recommended Dose Reductions for Binimetinib for Adverse Reactions

Action	Recommended Dose
First Dose Reduction	30 mg orally twice daily
Subsequent Modification	Permanently discontinue if unable to tolerate Binimetinib 30 mg orally twice daily

Dosage modifications for adverse reactions associated with Binimetinib are presented in Table 2.

Table 2: Recommended Dosage Modifications for Binimetinib for Adverse Reactions

Severity of Adverse Reaction*	Dose Modification for Binimetinib
Cardiomyopathy	
• Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is also below lower limit of normal (LLN)	Withhold Binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume Binimetinib at a reduced dose if the following are present: • LVEF is at or above the lower limit of normal and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If the LVEF does not recover within 4 weeks permanently discontinue Binimetinib.
• Symptomatic congestive heart failure or absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Permanently discontinue Binimetinib.
Venous Thromboembolism	
• Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)	Withhold Binimetinib. • If improves to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue Binimetinib.
Life threatening PE	Permanently discontinue Binimetinib.
Serous Retinopathy	
• Symptomatic serous retinopathy/Retinal pigment epithelial detachments	Withhold Binimetinib for up to 10 days. •If improves and becomes asymptomatic, resume at same dose. •If not improved, resume at a lower dose level or permanently discontinue Binimetinib.
Retinal Vein Occlusion (RVO)	
• Any Grade	Permanently discontinue Binimetinib.
Uveitis	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold Binimetinib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue Binimetinib.
• Grade 4	Permanently discontinue Binimetinib.
Interstitial Lung Disease	
• Grade 2	Withhold Binimetinib for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue Binimetinib.
• Grade 3 or Grade 4	Permanently discontinue Binimetinib.
Hepatotoxicity	
• Grade 2 AST or ALT increased	Maintain Binimetinib dose. • If no improvement within 2 weeks, withhold Binimetinib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
• Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
• Grade 4 asymptomatic CPK elevation or • Any Grade CPK elevation with symptoms or with renal impairment	Withhold Binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue Binimetinib.
Dermatologic (other than palmar plantar erythrodysesthesia syndrome (PPES))	
• Grade 2	If no improvement within 2 weeks, withhold Binimetinib until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 3	Withhold Binimetinib until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue Binimetinib.
Other Adverse Reactions (including Hemorrhage) †	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold Binimetinib for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue Binimetinib.
• First occurrence of any Grade 4	Permanently discontinue Binimetinib, or Withhold Binimetinib for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue Binimetinib.
• Recurrent Grade 3	Consider permanently discontinuing Binimetinib.
• Recurrent Grade 4	Permanently discontinue Binimetinib.

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Dose modification of Binimetinib when administered with Encorafenib is not recommended for the following adverse reactions: palmar-plantar erythrodysesthesia syndrome (PPES), non-cutaneous RAS mutation-positive malignancies, and QTc prolongation.

Refer to the Encorafenib prescribing information for dose modifications for adverse reactions associated with Encorafenib.

Dosage Modifications for Moderate or Severe Hepatic Impairment
For patients with moderate (total bilirubin greater than 1.5 and less than or equal to 3 × ULN and any AST) or severe (total bilirubin levels greater than 3 × ULN and any AST) hepatic impairment, the recommended dosage is 30 mg orally taken twice daily.

CONTRAINDICATION
None.

ADVERSE REACTION
Melanoma: Most common adverse reactions (≥25%) for Binimetinib, in combination with encorafenib, are fatigue, nausea, diarrhea, vomiting, and abdominal pain.

NSCLC: Most common adverse reactions (≥25%) for Binimetinib, in combination with encorafenib, are fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, constipation, dyspnea, rash, and cough.

WARNINGS AND PRECAUTION

New Primary Malignancies
Cutaneous and non-cutaneous malignancies have occurred with combination use. In PHAROS, cutaneous squamous cell carcinoma and skin papilloma were reported in 2% of patients. Monitor for new malignancies before, during, and after treatment.

Cardiomyopathy
Left ventricular dysfunction has been reported. In COLUMBUS and PHAROS, cardiomyopathy occurred in 7% and 11% of patients, respectively. Most cases resolved. Assess LVEF prior to treatment, at 1 month, then every 2–3 months. Monitor closely in patients with cardiovascular risks.

Venous Thromboembolism (VTE)
VTE occurred in up to 7% of patients in trials, including pulmonary embolism. Manage based on severity.

Ocular Toxicities
Serous retinopathy, retinal vein occlusion (RVO), and uveitis have occurred. Retinopathy was seen in up to 20% of patients; RVO in 0.1%. Conduct baseline and periodic ophthalmic exams, and evaluate urgently for vision loss. Discontinue in cases of RVO.

Interstitial Lung Disease (ILD)
ILD, including pneumonitis, has been reported rarely. Evaluate unexplained respiratory symptoms promptly.

Hepatotoxicity
Elevated liver enzymes occurred in up to 10% of patients. Monitor liver function tests before and during treatment.

Rhabdomyolysis
Elevations in CPK occurred in up to 58% of patients; rare cases of rhabdomyolysis reported. Monitor CPK and renal function regularly.

Hemorrhage
Hemorrhagic events occurred in up to 19% of patients, including fatal intracranial hemorrhage. Monitor for signs of bleeding.

Embryo-Fetal Toxicity
Binimetinib may cause fetal harm. Advise effective contraception during treatment and for 30 days after the last dose.

Combination Treatment Risks
Binimetinib must be used with Encorafenib. Refer to Encorafenib's prescribing information for additional safety details.

USE IN SPECIFIC POPULATIONS

Pregnancy
Binimetinib may cause fetal harm based on animal studies and its mechanism of action. No clinical data are available for use during pregnancy. In animals, Binimetinib caused embryo toxicity, malformations, and pregnancy loss at exposures similar to or above those seen in humans. Advise pregnant women and females of reproductive potential about the potential risk to the fetus.

Effective contraception is recommended during treatment and for 30 days after the last dose.

Lactation
Advise women not to breastfeed during treatment with Binimetinib and for 3 days after the last dose.

Females and Males of Reproductive Potential
Based on animal data, Binimetinib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating Binimetinib.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with Binimetinib and for 30 days after the last dose

Pediatric Use
The safety and efficacy of Binimetinib in pediatric patients younger have not been established.

Hepatic Impairment
Binimetinib concentrations may increase in patients with moderate or severe hepatic impairment. Dose adjustment for Binimetinib is not recommended in patients with mild hepatic impairment (total bilirubin >1 and ≤1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN). Reduce the dose of Binimetinib for patients with moderate (total bilirubin >1.5 and ≤3 × ULN and any AST) or severe (total bilirubin levels >3 × ULN and any AST) hepatic impairment.

OVERDOSE
Since Binimetinib is 97% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with Binimetinib.

DRUG INTERACTIONS
No clinically important drug interactions have been observed with Binimetinib.

PHARMACEUTICAL INFORMATION
Storage
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied
BINIXEN tablet: Each HDPE container contains 90 tablets (each film-coated tablet contains Binimetinib INN 15 mg), a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
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