A THERAPY MANAGEMENT GUIDE TO HELP SUPPORT YOUR PATIENTS RECEIVING

START

with recommended dosing and administration for BRAFTOVI + MEKTOVI

MONITOR

patients for optimal treatment

MANAGE

adverse reactions with dose modifications

INDICATION

BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib) is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation.

This material is based on EU Product Information and does not replace the Summaries of Product Characteristics (SmPC). Before prescribing, always refer to the SmPC approved in your country.

▼ These medicinal products are subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects via your national reporting system and/or to the Pharmacovigilance department of Pierre Fabre laboratories (https://www.pierre-fabre.com/en/pharmacovigilance).

Pierre Fabre

BRAFTOVI + MEKTOVI recommended dosing

Dosing in specific populations

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Dosage forms and strengths

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A THERAPY MANAGEMENT GUIDE TO HELP SUPPORT YOUR PATIENTS RECEIVING

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

INDICATION BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib) is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation.

BRAFTOVI + MEKTOVI recommended dosing[1,2]

Confirm the presence of *BRAF*^{V600} mutation before treatment.

- **May be taken with or without food, except grapefruit juice**
- **Swallow doses whole with water**
- **No refrigeration requirement; store BRAFTOVI® below 30°C**
- **Uninterrupted dosing schedule**

ONE DOSE PER DAY

(in the morning OR at night)

BRAFTOVI

450 mg[a]

6x 75 mg

Your patients should adopt a routine for taking BRAFTOVI® + MEKTOVI® that fits their lifestyle

MEKTOVI

45 mg

3x 15 mg

1st DOSE

12 HOURS APART

MEKTOVI

45 mg

3x 15 mg

2nd DOSE

Treatment with BRAFTOVI® + MEKTOVI® should be continued until the patient no longer derives benefit or the development of unacceptable toxicity.

Patients should not take a missed dose of:

- MEKTOVI® within **6 hours** of the next dose
- BRAFTOVI® within **12 hours** of the next dose

In case of vomiting after administration of BRAFTOVI® + MEKTOVI®, the patient should not take an additional dose and should take the next scheduled dose. BRAFTOVI® + MEKTOVI® are not recommended during pregnancy, breast-feeding and in women of childbearing potential not using contraception; it is unknown whether BRAFTOVI® or MEKTOVI® or their metabolites are excreted in humans. A risk to the newborns/infants cannot be excluded.

▼These medicinal products are subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects via your national reporting system and/or to the Pharmacovigilance department of Pierre Fabre laboratories (https://www.pierre-fabre.com/en/pharmacovigilance).

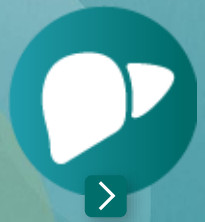
[a] For patients with mild hepatic impairment, administration of BRAFTOVI® should be undertaken with caution at a reduced dose. In the absence of clinical data, BRAFTOVI® is not recommended in patients with moderate to severe hepatic impairment.[1]

Please see the Summaries of Product Characteristics.

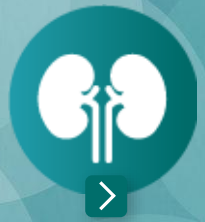
BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

Dosing in specific populations[1,2]

Hepatic impairment[1,2]



Renal impairment[1,2]



Elderly patients[1,2]

Dosing in specific populations[1,2]

Hepatic impairment[1,2]

Degree of hepatic impairment	Child-Pugh grade score	BRAFTOVI dosing	MEKTOVI dosing
Mild	A	Use with caution at a reduced dose of 300 mg once daily	No dose adjustment required
Moderate	B	Not recommended	Not recommended
Severe	C		

Closer monitoring of encorafenib related toxicities in patients with mild hepatic impairment is recommended, including clinical examination and liver function tests, with assessment of ECGs as clinically appropriate during treatment.

Child–Pugh score[3]

Variable	Points		
	1	2	3
Hepatic encephalopathy[b]	None	Stage I-II	Stage III-IV
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (seconds)	<4	4-6	>6

b Stage I may involve a trivial lack of awareness, euphoria or anxiety, a shortened attention span, impairment of the ability to perform addition or subtraction, or an altered sleep rhythm. Stage II may involve lethargy or apathy, time disorientation, obvious personality changes, inappropriate behaviour, dyspraxia, or asterixis. Stage III may involve a range of somnolence to a semi-stupor, responsiveness to stimuli, confusion, gross disorientation, or bizarre behaviour. Stage IV entails a coma.[4]

Prognostic subgroup[1-3]

Sum of points	5–6	7–9	10–15
Class	A (mild)	B (moderate)	C (severe)

Please see the Summaries of Product Characteristics.

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

Dosing in specific populations[1,2]

Renal impairment[1,2]

Degree of renal impairment	BRAFTOVI dosing	MEKTOVI dosing
Mild (eGFR 60-90 mL/min/1.73 m^2)	No dose adjustment required	No dose adjustment required
Moderate (eGFR 30-59 mL/min/1.73 m^2)		
Severe (eGFR ≤29 mL/min/1.73 m^2)	No clinical data Use with caution	

eGFR, estimated glomerular filtration rate.

Blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation.

Dosing in specific populations[1,2]

Elderly patients[1,2]

No dose adjustment is required for patients aged 65 years and older.

Drug-drug interactions[1,2]

Effects of other medicinal products on BRAFTOVI and MEKTOVI

	Effect on	Co-administration	Examples
Strong CYP3A4 inhibitors	**BRAFTOVI**	Increases BRAFTOVI® exposure and potentially increases toxicity Concomitant administration should be avoided If unavoidable, carefully monitor safety	ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, grapefruit juice
Moderate CYP3A4 inhibitors	**BRAFTOVI**	Increases BRAFTOVI® exposure Co-administer with caution and carefully monitor safety	amiodarone, erythromycin, fluconazole, diltiazem, amprenavir, imatinib
CYP3A4 inducers	**BRAFTOVI**	May result in compromised efficacy Alternative agents with no or minimal CYP3A induction potential should be considered	carbamazepine, rifampicin, phenytoin, St. John's wort
UGT1A1 inducers	**MEKTOVI**	Co-administer with caution	rifampicin, phenobarbital
UGT1A1 inhibitors	**MEKTOVI**	Co-administer with caution	indinavir, atazanavir, sorafenib
CYP1A2 inducers	**MEKTOVI**	May decrease MEKTOVI® exposure and could result in decreased efficacy	carbamazepine, rifampicin
P-gp transport inducers	**MEKTOVI**	May decrease MEKTOVI® exposure and could result in decreased efficacy	St. John's wort, phenytoin

CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; P-gp, permeability glycoprotein; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Drug-drug interactions[1,2]

Effect of BRAFTOVI and MEKTOVI on other medicinal agents

	Effect on	Co-administration	Examples
BRAFTOVI	CYP3A4 inhibitors and inducers	May result in increased toxicity or loss of efficacy of CYP3A4 substrates Co-administer with caution	hormonal contraceptives
	UGT1A1 inhibitors	UGT1A1 substrates may have increased exposure Co-administer with caution	raltegravir, atorvastatin, dolutegravir
	Transporter protein (renal transporters OAT1, OAT3, OCT2; hepatic transporters OATP1B1, OATP1B3, OCT1; BCRP) inhibitors, substrates of P-gp	May have increased exposure Co-administer with caution	furosemide, penicillin, atorvastatin, bosentan, methotrexate, rosuvastatin, posaconazole
MEKTOVI	CYP1A2 inducers	Co-administer sensitive substrates with caution	duloxetine, theophylline
	OAT3 weak inhibitors	Co-administer sensitive substrates with caution	pravastatin, ciprofloxacin

BCRP, breast cancer resistance protein; CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3; OCT1, organic cation transporter 1; OCT2, organic cation transporter 2; P-gp, permeability glycoprotein; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Recommendations on monitoring patients during treatment[1,2]

Monitoring at treatment initiation and during treatment helps ensure optimal adverse reaction management and treatment.

Prior to treatment

- Blood tests including complete blood cell counts
- Liver laboratory tests
- Blood pressure
- Dermatologic evaluations
- Head and neck examination
- Chest/abdomen CT scan
- Anal and pelvic examinations (for women)
- Echocardiogram/MUGA scan (LVEF)
- Ophthalmologic evaluation
- ECG (QT prolongation)

CT, computerised tomography; ECG, electrocardiogram; MUGA, multiple-gated acquisition; LVEF, Left Ventricular Ejection Fraction.

Recommendations on monitoring patients during treatment[1,2]

Recommended assessments

		During treatment	After treatment
Blood tests	Liver laboratory values	Should be monitored at least monthly during the first 6 months of treatment and then as clinically indicated	
	CK and creatinine levels		
	Serum electrolytes abnormalities (including magnesium and potassium)	Should be corrected during treatment	
Cardiac monitoring	Blood pressure measurements	Should be monitored with control of hypertension by standard therapy as clinically appropriate	
	Echocardiogram/MUGA scan (LVEF)	1 month after initiation and approximately every 3 months thereafter or more frequently if clinically indicated	
	ECG (QT prolongation)		
Ophthalmologic evaluation		Assess at each visit and refer for ophthalmologic exam if new or worsening symptoms are found	
Cutaneous Malignancies assessments	Dermatologic evaluation	Every 2 months	For up to 6 months after treatment discontinuation
Noncutaneous malignancy assessments	Head and neck examination	As clinically appropriate	As clinically appropriate
	Chest/abdomen CT scan		
	Anal and pelvic examinations (for women)		
	Complete blood cell counts		

- Specific monitoring might apply if clinically indicated

CK, creatine kinase; MUGA, multiple-gated acquisition; ECG, electrocardiogram; CT, computerised tomography; LVEF, Left Ventricular Ejection Fraction.

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

Please see the Summaries of Product Characteristics.

AR profile of the combination[1,2]

Median relative dose intensity[1,2]

100% BRAFTOVI + **99.6%** MEKTOVI

Eye disorders

Very common
- Visual impairment[a]
- RPED[a]

common
- Uveitis[a]

Cardiac disorders

Common
- LVD[b]

Renal and urinary disorders

Common
- Renal failure[a]

Gastrointestinal disorders

Very common
- Nausea
- Vomiting[a]
- Constipation
- Abdominal pain[a]
- Diarrhoea[a]

Common
- Colitis[c]

Uncommon
- Pancreatitis[a]

Musculoskeletal and connective tissue disorders

Very common
- Arthralgia[a]
- Muscular disorders/ myalgia[d]
- Pain in extremity
- Back pain

Uncommon
- Rhabdomyolysis

Skin and subcutaneous disorders

Very common
- Hyperkeratosis[a]
- Rash[a]
- Dry skin[a]
- Pruritus[a]
- Alopecia[a]

Common
- Dermatitis acneiform[a]
- PPES
- Erythema[a]
- Panniculitis[a]
- Photosensitivity[a]

Neoplasms benign, malignant, and unspecified

Common
- Basal cell carcinoma[a]
- Skin papilloma[a]
- cuSCC[e]

Vascular disorders

Very common
- Haemorrhage[f]
- Hypertension[a]

Common
- VTE[g]

Blood and lymphatic system disorders

Very common
- Anaemia

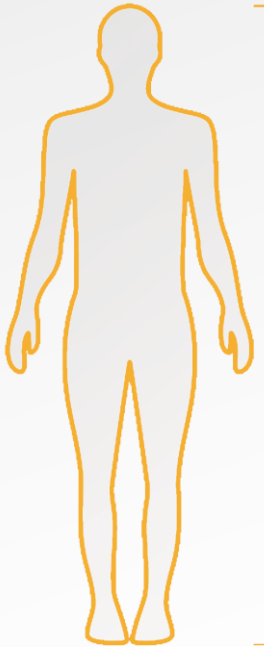
Please see the Summaries of Product Characteristics.

BRAFTOVI (encorafenib) + MEKTOVI (binimetinib)

AR profile of the combination[1,2]

Median relative dose intensity[1,2]

100% BRAFTOVI + **99.6%** MEKTOVI



Immune system disorders

Common
- Hypersensitivity[h]

Nervous system disorders

Very common
- Neuropathy peripheral[a]
- Dizziness[a]
- Headache[a]

Common
- Dysgeusia[a]

Uncommon
- Facial paresis[i]

General disorders and administration site conditions

Very common
- Fatigue[a]
- Pyrexia[a]
- Peripheral oedema[j]

Investigations

Very common
- Blood creatine phosphokinase increased
- γ-glutamyl transferase increased[a]
- Transaminase increased[a]

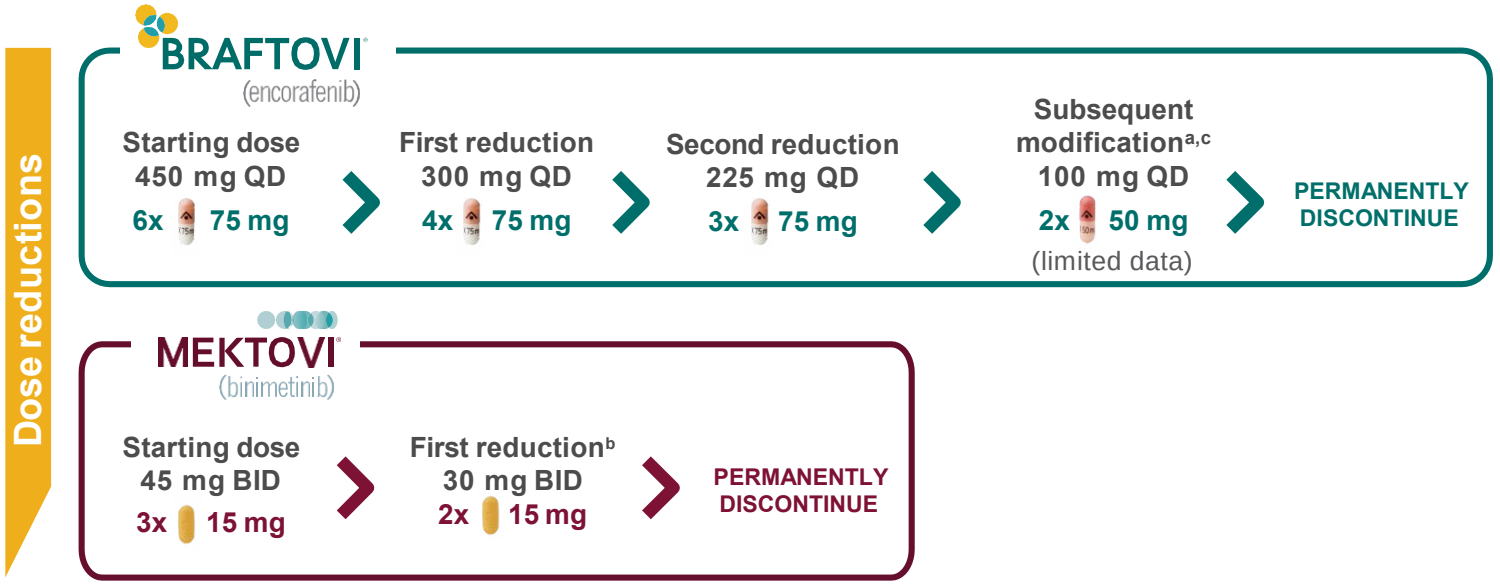
Common
- Blood alkaline phosphatase increased
- Blood creatinine increased[a]
- Amylase increased
- Lipase increased

Please see the Summaries of Product Characteristics.

BRAFTOVI (encorafenib) + MEKTOVI (binimetinib)

Recommended dose adjustments[1,2]

BRAFTOVI® + MEKTOVI® are indicated to be taken in combination.
The management of ARs may require dose reduction, temporary interruption, or treatment discontinuation.



Dose modifications are recommended to manage certain adverse reactions.
Please see the following section "managing ARs through dose modification"

[a] There are limited data for dose reduction to 100 mg QD. If unable to tolerate 100 mg QD, permanently discontinue BRAFTOVI®[1]
[b] If unable to tolerate 30 mg BID, permanently discontinue MEKTOVI®[2]
[C] For patients with mild hepatic impairment, administration of BRAFTOVI® should be undertaken with caution at a reduced dose. In the absence of clinical data, BRAFTOVI® is not recommended in patients with moderate to severe hepatic impairment.
BID, twice daily; QD, once daily.

Please see the Summaries of Product Characteristics.

BRAFTOVI (encorafenib) + MEKTOVI (binimetinib)

Recommended dose adjustments[1,2]

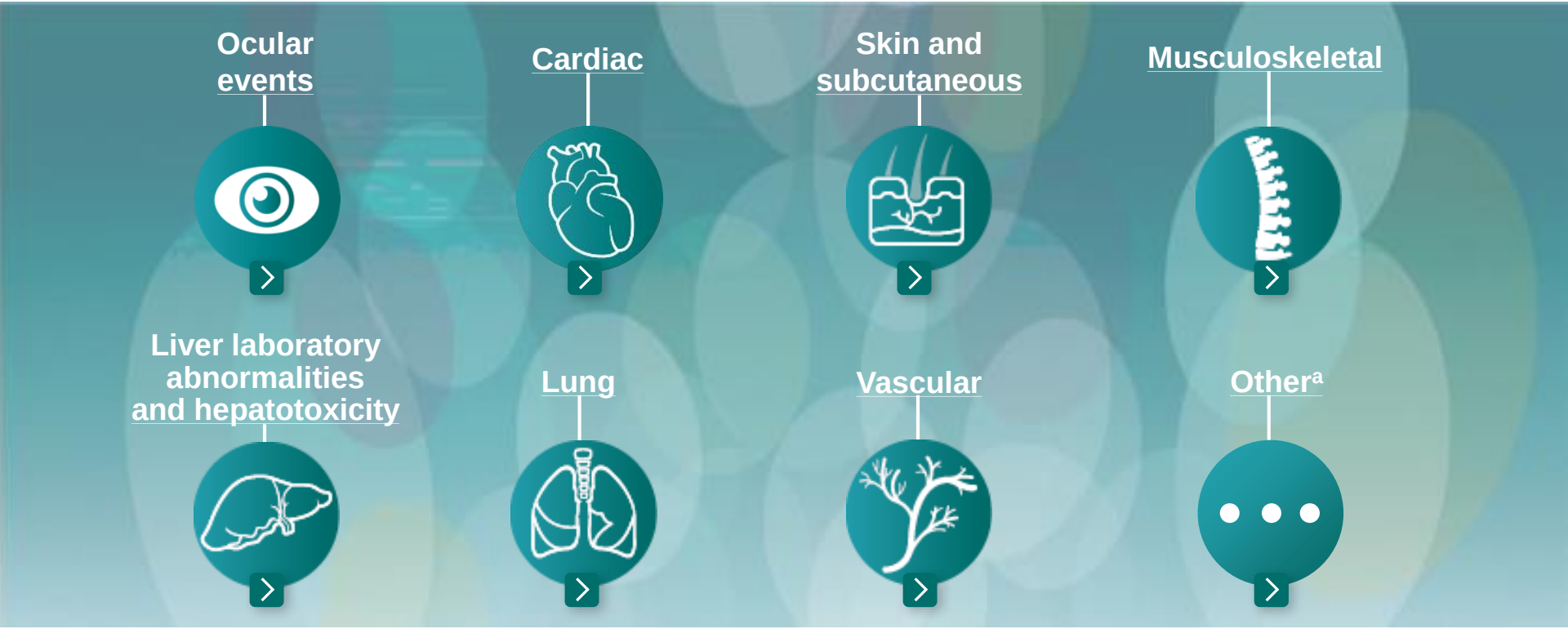
Dose interruption and discontinuation

If either BRAFTOVI® or MEKTOVI® is permanently discontinued, then discontinue both treatments

Please see the Summaries of Product Characteristics.

BRAFTOVI (encorafenib) + MEKTOVI (binimetinib)

Managing ARs through dose modification[1,2]



Please see the Summaries of Product Characteristics.

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

Managing ARs through dose modification[1,2]

Ocular events

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
RPED	Symptomatic (Grade 2 or 3)	If MEKTOVI® is withheld, the BRAFTOVI® 450-mg dose should be reduced to 300 mg.	Withhold for up to 2 weeks and repeat ophthalmologic monitoring including visual acuity assessment • If improved to Grade 0 or 1, resume at same dose • If improved to Grade 2, resume at a lower dose • If not improved to Grade 2, permanently discontinue
	Symptomatic (Grade 4) associated with reduced visual acuity (Grade 4)	Permanently discontinue both drugs.	
RVO	Any occurrence	Permanently discontinue both drugs.	
Uveitis including iritis and iridocyclitis	Grade 1-3	Withhold for Grade 1/2 uveitis that doesn't respond to ocular therapy or for Grade 3 uveitis and monitor every 2 weeks • If Grade 1 uveitis improves to Grade 0, then resume at the same dose • If Grade 2 or 3 uveitis improves to Grade 0 or 1, then resume at a reduced dose If not improved within 6 weeks, permanently discontinue and follow up with ophthalmologic monitoring.	If BRAFTOVI® is withheld, MEKTOVI® should be withheld.
	Grade 4	Permanently discontinue both drugs and follow up with ophthalmologic monitoring.	

RPED, retinal pigment epithelial detachment; RVO, retinal vein occlusion.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

Managing ARs through dose modification[1,2]

Cardiac

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
LVEF	Grade 2 LVEF decrease or asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is below lower limit of normal (LLN)	If MEKTOVI® is withheld, the BRAFTOVI® 450-mg dose should be reduced to 300 mg.	Withhold and evaluate LVEF every 2 weeks. Resume at a reduced dose if both of the following are present within 4 weeks: • LVEF is ≥ LLN • Absolute decrease from baseline is ≤10% If LVEF does not recover within 4 weeks, permanently discontinue.
	Grade 3 or 4 LVEF decrease or symptomatic LVD	Permanently discontinue both drugs. LVEF should be evaluated every 2 weeks until recovery.	
QTc prolongation	QTcF >500 ms and change ≤60 ms from pre-treatment value	Withhold and monitor risk factors • When QTcF returns to ≤500 ms, resume at a reduced dose • If more than 1 recurrence, discontinue	If BRAFTOVI® is withheld, MEKTOVI® should be withheld.
	QTcF >500 ms and increased by >60 ms from pre-treatment value	Permanently discontinue both drugs.	

LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; QTc, QT interval corrected; QTcF, QT interval corrected by Fridericia's formula.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

Managing ARs through dose modification[1,2]

Skin and subcutaneous

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
Cutaneous reactions	Grade 2	Maintain dose • If rash worsens or does not improve within 2 weeks with treatment, withhold until Grade 0 or 1 and then resume at same dose	Maintain dose • If rash worsens or does not improve within 2 weeks with treatment, withhold until Grade 0 or 1 and then resume at same dose if first occurrence or reduced dose if recurrent Grade 2
	Grade 3	Withhold both drugs until improved to Grade 0 or 1 • If first occurrence, resume at same dose • If recurrent Grade 3, resume at a reduced dose	
	Grade 4	Permanently discontinue both drugs.	
PPES	Grade 2	Maintain dose and institute supportive measures such as topical therapy • If not improved within 2 weeks, withhold until improved to Grade 0 or 1, then resume at same dose or a reduced dose	If BRAFTOVI® is withheld, MEKTOVI® should be withheld.
	Grade 3	Withhold, institute supportive measures such as topical therapy, and reassess weekly • When improved to Grade 0 or 1, resume at same dose level or a reduced dose	If BRAFTOVI® is withheld, MEKTOVI® should be withheld.

PPES, palmoplantar erythrodysaesthesia syndrome.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

Managing ARs through dose modification[1,2]

Musculoskeletal

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
Rhabdomyolysis or CK elevations	Grade 3 (CK > 5-10 x ULN) asymptomatic	Maintain dose.	Maintain dose and ensure patient is adequately hydrated.
	Grade 4 (CK > 10 x ULN) asymptomatic	If MEKTOVI® is withheld, the BRAFTOVI® 450-mg dose should be reduced to 300 mg.	Withhold until improved to Grade 0 or 1 and ensure patient is adequately hydrated.
	Grade 3 or Grade 4 (CK > 5 x ULN) with muscle symptoms OR with renal impairment	If MEKTOVI® is withheld, the BRAFTOVI® 450-mg dose should be reduced to 300 mg.	Withhold until improved to Grade 0 or 1 • If resolved in ≤ 4 weeks, resume at a reduced dose OR permanently discontinue both drugs

ULN, upper limit of normal.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

Managing ARs through dose modification[1,2]

Liver laboratory abnormalities and hepatotoxicity

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
AST or ALT	Grade 2 (AST or ALT > 3 x - ≤ 5 x ULN)	Maintain dose. If no improvement within 4 weeks, withhold until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resume at the same dose.[a]	Maintain dose If no improvement within 2 weeks, withhold until improved to Grade 0 or 1 or to pre-treatment baseline levels and then resume at the same dose.[a]
	First occurrence or recurrent Grade 3 (AST or ALT > 5 x ULN and blood bilirubin > 2 x ULN) OR first occurrence or recurrent Grade 4 (AST or ALT > 20 x ULN)		

ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

[a] When MEKTOVI® is withheld, the 450-mg BRAFTOVI® dose should be reduced to 300 mg.[1,2]

Managing ARs through dose modification[1,2]

Lung

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
ILD/pneumonitis	Grade 2	If MEKTOVI® is withheld, the BRAFTOVI® 450-mg dose should be reduced to 300 mg. If MEKTOVI® is permanently discontinued, BRAFTOVI® must be permanently discontinued.	Withhold for up to 4 weeks • If improved to Grade 0 or 1, resume at reduced dose • If not resolved within 4 weeks, permanently discontinue.
	Grade 3 or 4	Permanently discontinue both drugs.	

ILD, interstitial lung disease.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

Managing ARs through dose modification[1,2]

Vascular

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
VTE	Uncomplicated DVT or PE ≤ Grade 3	If MEKTOVI® is withheld, the BRAFTOVI® 450-mg dose should be reduced to 300 mg.	Withhold • If improved to Grade 0 or 1, resume at a reduced dose • If not improved, permanently discontinue.
	Grade 4 PE	Permanently discontinue both drugs.	

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

Managing ARs through dose modification[1,2]

Other[a]

Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI	Dose modification for MEKTOVI
Other	Recurrent or intolerable Grade 2 adverse reactions OR first occurrence of any Grade 3 adverse reaction	Withhold both drugs for up to 4 weeks • If improved to Grade 0 or 1 or to pre-treatment/baseline levels, resume at a reduced dose • If not improved, permanently discontinue both drugs	
	First occurrence of any Grade 4 adverse reaction	Withhold both drugs for up to 4 weeks • If improved to Grade 0 or 1 or to pre-treatment/baseline levels, then resume at a reduced dose • If no improvement, permanently discontinue both drugs OR permanently discontinue both drugs	
	Recurrent Grade 3 adverse reactions	Consider permanently discontinuing both drugs.	
	Recurrent Grade 4 adverse reactions	Permanently discontinue both drugs.	

[a] Exceptions where dose modifications are necessary for BRAFTOVI® only (adverse reactions primarily related to BRAFTOVI®) are: PPES, uveitis including iritis and iridocyclitis, and QTc prolongation. If one of these toxicities occurs, see section 4.2 of the BRAFTOVI® Summary of Product Characteristics for dose modification instructions for BRAFTOVI®. Exceptions where dose modifications are necessary for MEKTOVI® only (adverse reactions primarily related to MEKTOVI®) are: retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO), interstitial lung disease (ILD)/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous thromboembolism (VTE). If one of these toxicities occurs, see section 4.2 of the MEKTOVI® Summary of Product Characteristics for dose modification instructions for MEKTOVI®.

If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.
If BRAFTOVI® is permanently discontinued, MEKTOVI® should be discontinued.

BRAFTOVI + MEKTOVI is available in several dosage forms and strengths[1,2]

BRAFTOVI (encorafenib) is supplied as 75-mg and 50-mg capsules

BRAFTOVI® 75 mg is available in packs of 42x1 capsules (7 peelable blisters of 6 capsules each) for patients treated at full dose or undergoing dose reduction at 300 mg and 225 mg.

BRAFTOVI® 50 mg is available in packs of 28x1 capsules (7 peelable blisters of 4 capsules each). for patients undergoing dose reduction at 100 mg.

MEKTOVI (binimetinib) is supplied as 15-mg tablets

MEKTOVI® is available in packs of 84 tablets (7 blisters of 12 tablets each) for patients treated with MEKTOVI® at any dose. MEKTOVI® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take MEKTOVI®.

Please see the Summaries of Product Characteristics.

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

SUPPORTING YOUR PATIENTS THROUGH THEIR TREATMENTS WITH BRAFTOVI + MEKTOVI

with recommended dosing and administration BRAFTOVI® 450 mg QD + MEKTOVI® 45 mg BID[1,2]

- May be taken with or without food, except grapefruit juice
- No refrigeration requirement; store BRAFTOVI® below 30°C

for optimal treatment[1,2]

- Monitoring patients through certain tests and clinical evaluations is recommended prior to and during treatment with BRAFTOVI® + MEKTOVI®

through dose modifications

- Dose modifications are recommended to manage certain adverse reactions[1,2]

Please refer your patients to the patient information leaflet in their medication packaging for further information and guidance.

References

1. Braftovi Summary of Product Characteristics. Pierre Fabre Médicament, 2022.

2. Mektovi Summary of Product Characteristics. Pierre Fabre Médicament, 2022.

3. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open.* 2016:1(2)e000042. eCollection 2016.

4. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715-735.

Pierre Fabre

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

POP-UP

ARs are listed by MedDRA body system organ class and the following frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

[a] Composite terms which included more than one preferred term.

[b] Includes left ventricular dysfunction, ejection fraction decreased, cardiac failure, and ejection fraction abnormal.

[c] Includes colitis, ulcerative colitis, enterocolitis, and proctitis.

[d] Includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, and myositis.

[e] Includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma, and squamous cell carcinoma of the skin.

[f] Includes haemorrhage at various sites including cerebral haemorrhage.

[g] Includes pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, superficial thrombophlebitis, and thrombosis.

AR, adverse reaction; cuSCC, cutaneous squamous cell carcinoma; LVD, left ventricular dysfunction; PPES, palmoplantar erythrodysaesthesia syndrome; RPED, retinal pigment epithelial detachment; VTE, venous thromboembolism.

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[a] Composite terms which included more than one preferred term.

[h] Includes angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, and urticaria.

[i] Includes facial nerve disorder, facial paralysis, and facial paresis.

[j] Includes fluid retention, peripheral oedema, and localised oedema.

AR, adverse reaction.