THERAPY MANAGEMENT GUIDE

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

START

WITH RECOMMENDED DOSING & ADMINISTRATION

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.

For complete information, please refer to the BRAFTOVI® + MEKTOVI® SmPCs

Pierre Fabre

START WITH RECOMMENDED DOSING AND ADMINISTRATION

A guide to optimize your patients treatment initiation with

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

Pierre Fabre

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

PATIENTS SHOULD NOT TAKE A MISSED DOSE OF:

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

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

BRAFTOVI 450 mg[a]

ONE DOSE PER DAY (in the morning OR at night)

6x 75 mg

+

MEKTOVI 45 mg — 1st DOSE — 3x 15 mg

~ 12 HOURS APART

MEKTOVI 45 mg — 2nd DOSE — 3x 15 mg

DURATION:

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

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.

[a] For patients with mild hepatic impairment, administration of BRAFTOVI should be undertaken with caution at a reduced dose of 300 mg once daily. 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

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 class	BRAFTOVI	MEKTOVI
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 class[3]

Variable	POINTS		
	1	2	3
Hepatic encephalopathy[a]	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

Prognostic subgroup[1-3]

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

[a] 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]

Please see the Summaries of Product Characteristics

DOSING IN SPECIFIC POPULATIONS[1,2]

HEPATIC IMPAIRMENT[1,2] | RENAL IMPAIRMENT[1,2] | ELDERLY PATIENTS[1,2]

Degree of renal impairment	BRAFTOVI	MEKTOVI
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**	

Blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation.[1]
Patients should ensure adequate fluid intake during treatment.

eGFR, estimated glomerular filtration rate

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DOSING IN SPECIFIC POPULATIONS[1,2]

HEPATIC IMPAIRMENT[1,2] | RENAL IMPAIRMENT[1,2] | ELDERLY PATIENTS[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

Effects of BRAFTOVI and MEKTOVI on other medicinal agents

DRUG-DRUG INTERACTIONS[1,2]

Effects of other medicinal products on BRAFTOVI and MEKTOVI

Effects of BRAFTOVI and MEKTOVI on other medicinal agents

Effect on		Co-administration	Examples
Strong **CYP3A4** inhibitors	BRAFTOVI	Increase BRAFTOVI exposure and potentially increase toxicity Concomitant administration should be avoided If unavoidable, carefully monitor safety	ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, grapefruit juice
Moderate **CYP3A4** inhibitors	BRAFTOVI	Increase BRAFTOVI exposure Co-administer with caution and carefully monitor safety	amiodarone, erythromycin, fluconazole, diltiazem, amprenavir, imatinib
CYP3A4 inducers	BRAFTOVI	May reduce BRAFTOVI exposure and 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
Pgp 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.

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DRUG-DRUG INTERACTIONS[1,2]

Effects of other medicinal products on BRAFTOVI and MEKTOVI

Effects of BRAFTOVI and MEKTOVI on other medicinal agents

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

Please see the Summaries of Product Characteristics

RECOMMENDATIONS ON MONITORING PATIENTS PRIOR TO TREATMENT[1,2]

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

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.

Please see the Summaries of Product Characteristics

SAFETY PROFILE OF THE COMBINATION[1,2]

Very common	Common	Uncommon
Eye disorders		
Visual impairment[a] RPED[a]	Uveitis[a]	×
Cardiac disorders		
×	LVD[b]	×
Renal and urinary disorders		
×	Renal failure[a]	×
Vascular disorders		
Haemorrhage[d] Hypertension[a]	VTE[e]	×

Very common	Common	Uncommon
Skin and subcutaneous disorders		
Hyperkeratosis[a] Rash[a] Dry skin[a] Pruritus[a] Alopecia[a]	Dermatitis acneiform[a] PPES Erythema[a] Panniculitis[a] Photosensitivity[a]	×
Neoplasms benign, malignant, & unspecified		
×	Basal cell carcinoma[a] Skin papilloma[a] cuSCC[c]	×
Blood and lymphatic system disorders		
Anaemia	×	×

The management of ARs may require dose reduction, temporary interruption, or treatment discontinuation.
For more information please refer to the SmPCs or the treatment follow-up guide.

[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 keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma, and squamous cell carcinoma of the skin.
[d] Includes haemorrhage at various sites including cerebral haemorrhage.
[e] 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.

Please see the Summaries of Product Characteristics

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SAFETY PROFILE OF THE COMBINATION[1,2]

Investigations

Very common	Common	Uncommon
Blood creatine phosphokinase increased γ-glutamyl transferase increased[a] Transaminase increased[a]	Blood alkalinephosphatase increased Blood creatinine increased[a] Amylase increased Lipase increased	×

Gastrointestinal disorders

Very common	Common	Uncommon
Nausea Vomiting[a] Constipation Abdominal pain[a] Diarrhoea[a]	Colitis[f]	Pancreatitis[a]

Musculoskeletal and connective tissue disorders

Very common	Common	Uncommon
Arthralgia[a] Pain in extremity Back pain Muscular disorders/myalgia[g]	×	Rhabdomyolysis

Immune system disorders

Very common	Common	Uncommon
×	Hypersensitivity[h]	×

Nervous system disorders

Very common	Common	Uncommon
Neuropathy peripheral[a] Dizziness[a] Headache[a]	Dysgeusia[a]	Facial paresis[i]

General disorders and administration site conditions

Very common	Common	Uncommon
Fatigue[a] Pyrexia[a] Peripheral oedema[j]	×	×

The management of ARs may require dose reduction, temporary interruption, or treatment discontinuation.
For more information please refer to the SmPCs or the treatment follow-up guide.

[a] Composite terms which included more than one preferred term.
[f] Includes colitis, ulcerative colitis, enterocolitis, and proctitis.
[g] Includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, and myositis.
[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.

Please see the Summaries of Product Characteristics

PREVIOUS PAGE

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.

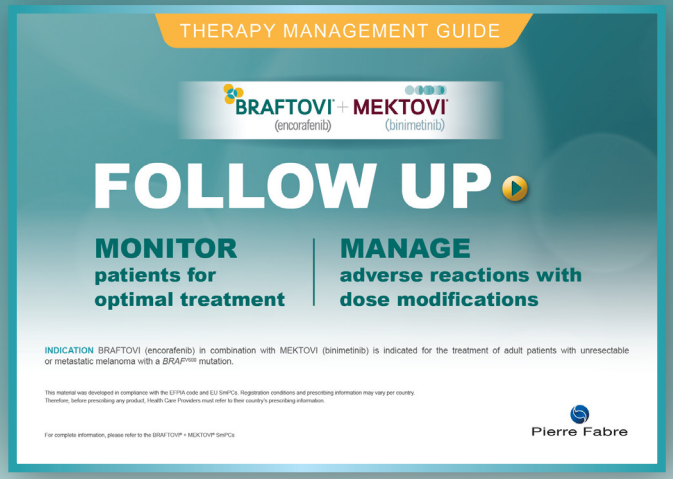
BRAFTOVI® 50 mg is available in packs of 28x1 capsules (7 peelable blisters of 4 capsules each) for patients undergoing dose reduction at 100 mg.

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®.

REFERENCES

1. BRAFTOVI Summary of Product Characteristics. Pierre Fabre Médicament, 2023.
2. MEKTOVI Summary of Product Characteristics. Pierre Fabre Médicament, 2023.
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.



Also available

A guide to optimize your patients **treatment follow up** with BRAFTOVI + MEKTOVI

Contact your local Pierre Fabre representative for more information

Pierre Fabre

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