THERAPY MANAGEMENT GUIDE

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

START

WITH RECOMMENDED DOSING & ADMINISTRATION

INDICATIONS: 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[1,2]
- advanced non-small cell lung cancer with a *BRAF*^{V600E} mutation[1,2]

This international material is intended for EU healthcare professionals (outside the UK and ROI) and was developed in compliance with the EFPIA Code and EU SmPCs. Registration conditions and prescribing information may vary per country. Therefore, before prescribing any product, healthcare professionals must refer to their country's prescribing information.

LABORATOIRES Pierre Fabre

START WITH RECOMMENDED DOSING AND ADMINISTRATION

A guide to optimise your patients' treatment initiation with

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

For complete information, please refer to the BRAFTOVI® *Summary of Product Characteristics* and MEKTOVI® *Summary of Product Characteristics*.

LABORATOIRES Pierre Fabre

BRAFTOVI® + MEKTOVI® RECOMMENDED DOSING[1,2]

Confirm patient eligibility before treatment.[a]

- 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[b]

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

6x 75 mg

+

MEKTOVI® 45 mg — 1st DOSE

3x 15 mg ~ 12 HOURS APART 3x 15 mg

OR

1x 45 mg ~ 12 HOURS APART 1x 45 mg

MEKTOVI® 45 mg — 2nd DOSE

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 human milk. A risk to the newborns/infants cannot be excluded.

[a] Before taking BRAFTOVI® + MEKTOVI®, patients must have confirmation of *BRAF*V600 mutation for unresectable or metastatic melanoma, or *BRAF*V600E mutation for advanced NSCLC, assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

[b] 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]

NSCLC, non-small cell lung cancer. 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)

Tables adapted from Pinter M, et al. *ESMO Open* 2016:1(2)e000042.

[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.

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 products

DRUG-DRUG INTERACTIONS[1,2]

Effects of other medicinal products on BRAFTOVI® and MEKTOVI®

Effects of BRAFTOVI® and MEKTOVI® on other medicinal products

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

BRAFTOVI® is primarily metabolised by CYP3A4 and MEKTOVI® is primarily metabolised through UGT1A1 mediated glucuronidation.
CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; P-gp, permeability glycoprotein; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Please see the Summaries of Product Characteristics.

DRUG-DRUG INTERACTIONS[1,2]

Effects of other medicinal products on BRAFTOVI® and MEKTOVI®

Effects of BRAFTOVI® and MEKTOVI® on other medicinal products

	Effect on	Examples	Co-administration
BRAFTOVI®	CYP3A4 substrates	hormonal contraceptives	May result in loss of efficacy of CYP3A4 substrates If coadministration cannot be avoided, adjust the dose of these substrates in accordance with their approved SmPC.
BRAFTOVI®	UGT1A1 substrates	raltegravir, atorvastatin, dolutegravir	UGT1A1 substrates may have increased exposure Co-administer with caution
BRAFTOVI®	Transporter substrates (of renal transporters OAT1, OAT3, OCT2; hepatic transporters OATP1B1, OATP1B3, OCT1; BCRP and Pgp)	furosemide, penicillin, atorvastatin, bosentan, methotrexate, rosuvastatin, posaconazole	May result in increased exposure of these substrates Co-administer with caution
MEKTOVI®	CYP1A2 substrates	duloxetine, theophylline	MEKTOVI® is a potential inducer of CYP1A2 Co-administer sensitive substrates with caution
MEKTOVI®	OAT3 substrates	pravastatin, ciprofloxacin	MEKTOVI® is a weak inhibitor of OAT3 Co-administer sensitive substrates with caution

While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetinib exposure have been observed clinically when binimetinib was co-administered with encorafenib.

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 helps ensure optimal adverse reaction management.

- 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[1,2a]

	Very common	Common	Uncommon
Eye disorders	Visual impairment[b] RPED[b]	Uveitis[b]	
Cardiac disorders		LVD[c]	
Renal and urinary disorders		Renal failure[b]	
Vascular disorders	Haemorrhage[e] Hypertension[b]	VTE[f]	
Skin and subcutaneous disorders	Hyperkeratosis[b] Rash[b] Dry skin[b] Pruritus[b] Alopecia[b]	Dermatitis acneiform[b] PPES Erythema[b] Panniculitis[b] Photosensitivity[b]	
Neoplasms benign, malignant, & unspecified		cuSCC[d] Skin papilloma[b]	Basal cell carcinoma[b]
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.

Adverse reactions are listed by MedDRA body system organ class and the following frequency convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

[a] Included patients who received 450 mg BRAFTOVI® + 45 mg MEKTOVI®; 274 patients received the combination for melanoma and 98 for NSCLC.

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

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

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

[e] Includes haemorrhage at various sites including, but not limited to, cerebral haemorrhage, intracranial haemorrhage, vaginal haemorrhage, heavy menstrual bleeding, intermenstrual bleeding, haematochezia, haemoptysis, haemothorax, gastrointestinal haemorrhage and haematuria.

[f] Includes, but not limited to, pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial, thrombosis, phlebitis, superior vena cava syndrome, mesenteric vein thrombosis and vena cava thrombosis.

AR, adverse reaction; cuSCC, cutaneous squamous cell carcinoma; LVD, left ventricular dysfunction; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; PPES, palmoplantar erythrodysaesthesia syndrome; RPED, retinal pigment epithelial detachment; VTE, venous thromboembolism.

Please see the Summaries of Product Characteristics

NEXT PAGE

SAFETY PROFILE OF THE COMBINATION[1,2a]

Investigations

Very common	Common	Uncommon
Blood creatine phosphokinase increased γ-glutamyl transferase increased[b] Transaminase increased[b]	Blood alkaline phosphatase increased Blood creatinine increased[b] Amylase increased Lipase increased	×

Gastrointestinal disorders

Very common	Common	Uncommon
Nausea Vomiting[b] Constipation Abdominal pain[b] Diarrhoea[b]	Colitis[g]	Pancreatitis[b]

Musculoskeletal and connective tissue disorders

Very common	Common	Uncommon
Arthralgia[b] Myopathy/Muscular disorder[h] Pain in extremity Back pain[b]	×	Rhabdomyolysis

Immune system disorders

Very common	Common	Uncommon
×	Hypersensitivity[i]	×

Nervous system disorders

Very common	Common	Uncommon
Neuropathy peripheral[b] Dizziness[b] Headache[b]	Dysgeusia[b]	Facial paresis[j]

General disorders and administration site conditions

Very common	Common	Uncommon
Fatigue[b] Pyrexia[b] Peripheral oedema[k]	×	×

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.

Adverse reactions are listed by MedDRA body system organ class and the following frequency convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

[a] Included patients who received 450 mg BRAFTOVI® + 45 mg MEKTOVI®; 274 patients received the combination for melanoma and 98 for NSCLC.

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

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

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

[i] Includes, but not limited to, angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, and urticaria.

[j] Includes facial nerve disorder, facial paralysis, facial paresis, Bell's palsy.

[k] Includes, but not limited to, fluid retention, peripheral oedema, localised oedema, generalised oedema and swelling.

AR, adverse reaction; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer.

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 hard capsules

For Melanoma and NSCLC

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

For Melanoma only

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

MEKTOVI® (binimetinib) is supplied as 45 mg and 15 mg tablets

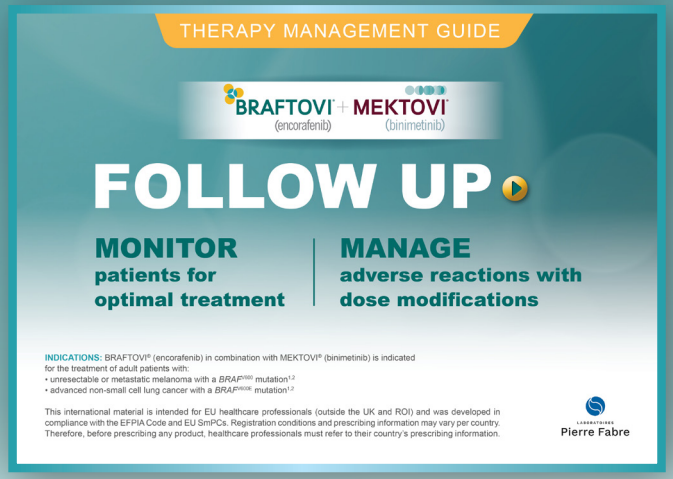
MEKTOVI® 15 mg is available in packs of 84 tablets (7 blisters of 12 tablets each) for patients treated with MEKTOVI® at any dose.

MEKTOVI® 45 mg is available in packs of 28 tablets (2 blisters of 14 tablets each) for patients treated with MEKTOVI® at the 45 mg dose.

All MEKTOVI® tablets contain lactose, regardless of dose. 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, 2024.
2. MEKTOVI® Summary of Product Characteristics. Pierre Fabre Médicament, 2024.
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 optimise your patients **treatment follow up** with BRAFTOVI® + MEKTOVI®

Contact your local Pierre Fabre representative for more information

LABORATOIRES Pierre Fabre

HQ–05-25-2500001 Elaboration date: May 2025