THERAPY MANAGEMENT GUIDE

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

FOLLOW UP

MONITOR
patients for optimal treatment

MANAGE
adverse reactions with dose modifications

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

MANAGE & MONITOR

A therapy management guide to support your patients receiving

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

- MONITORING PATIENTS DURING TREATMENT
- SAFETY PROFILE OF THE COMBINATION
- RECOMMENDED DOSE ADJUSTMENTS
- MANAGING ADVERSE REACTION THROUGH DOSE MODIFICATION
- DOSAGE FORMS AND STRENGTHS
- REFERENCES

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

LABORATOIRES Pierre Fabre

RECOMMENDATIONS ON MONITORING PATIENTS DURING TREATMENT[1,2]

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

		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		

The occurrence of tumour lysis syndrome (TLS), which may be fatal, has been associated with the use of BRAFTOVI® + MEKTOVI®. Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

Specific monitoring might apply if clinically indicated.

*For more information about monitoring at treatment initiation please refer to the SmPCs or the start therapy management guide.

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

Please see the Summaries of Product Characteristics.

For Prior treatment:

Please refer to the start therapy management guide

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]	×

Very common	Common	Uncommon
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.

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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

RECOMMENDED DOSE ADJUSTMENTS[1,2]

Dose reduction melanoma | Dose reduction NSCLC | Dose interruption and discontinuation

BRAFTOVI® (encorafenib)

Starting dose	First reduction[a]	Second reduction	Subsequent modification[b]	
450 mg QD	300 mg QD	225 mg QD	100 mg QD	PERMANENTLY DISCONTINUE
6x 75 mg	4x 75 mg	3x 75 mg	2x 50 mg (limited data)	

MEKTOVI® (binimetinib)

Starting dose	First reduction[c]	
45 mg BID	30 mg BID	PERMANENTLY DISCONTINUE
3x 15 mg OR 1x 45 mg	2x 15 mg	

Dose modifications are recommended to manage certain adverse reactions.

Please see the following section: Managing ARs through dose modification

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

[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] [b]For melanoma, there are limited data for dose reduction to 100 mg QD. If unable to tolerate 100 mg QD, permanently discontinue BRAFTOVI®.[1] [c]If unable to tolerate 30 mg BID, permanently discontinue MEKTOVI®.[2]

AR, adverse reaction; BID, twice daily; QD, once daily.

Please see the Summaries of Product Characteristics.

RECOMMENDED DOSE ADJUSTMENTS[1,2]

Dose reduction NSCLC | Dose reduction melanoma | Dose interruption and discontinuation

BRAFTOVI (encorafenib)

Starting dose	First reduction[a]	Second reduction[b]	
450 mg QD	300 mg QD	225 mg QD	PERMANENTLY DISCONTINUE
6x 75 mg	4x 75 mg	3x 75 mg	

MEKTOVI (binimetinib)

Starting dose	First reduction[c]	
45 mg BID	30 mg BID	PERMANENTLY DISCONTINUE
3x 15 mg OR 1x 45 mg	2x 15 mg	

Dose modifications are recommended to manage certain adverse reactions.

Please see the following section — Managing ARs through dose modification

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

[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] [b]For NSCLC, BRAFTOVI® should be permanently discontinued if the patient is unable to tolerate 225 mg (three 75 mg capsules) QD.[1] [c]If unable to tolerate 30 mg BID, permanently discontinue MEKTOVI®.[2]

AR, adverse reaction; BID, twice daily; NSCLC, non-small cell lung cancer; QD, once daily.

Please see the Summaries of Product Characteristics.

RECOMMENDED DOSE ADJUSTMENTS[1,2]

Dose reduction melanoma | Dose reduction NSCLC | **Dose interruption and discontinuation**

BRAFTOVI®	MEKTOVI®
Temporarily interrupted →	Temporarily interrupt
Reduce BRAFTOVI® to 300 mg QD during the time MEKTOVI® is interrupted ←	Temporarily interrupted
Permanently discontinued ↔	Permanently discontinued

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

QD, once daily.

Please see the Summaries of Product Characteristics.

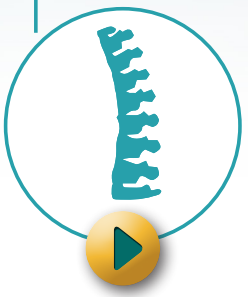
MANAGING ARs THROUGH DOSE MODIFICATION

Ocular events

Cardiac

Skin & subcutaneous

Musculoskeletal



Liver laboratory abnormalities & hepatotoxicity

Lung

Vascular

Other[a]

[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.®

AR, adverse reaction, QTc, QT interval corrected.

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Ocular events

RPED[1,2] | RVO[1,2] | Uveitis including iritis and iridocyclitis[1,2]

BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4 Symptomatic associated with reduced visual acuity (Grade 4)	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
GRADE 3 Symptomatic	If MEKTOVI® is withheld, the BRAFTOVI® 450 mg dose should be **reduced to 300 mg during the time of MEKTOVI® interruption.** If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.	**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.**
GRADE 2 Symptomatic		
GRADE 1		

AR, adverse reaction; 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.

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Ocular events

RPED[1,2] | **RVO[1,2]** | Uveitis including iritis and iridocyclitis[1,2]

BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
GRADE 3		
GRADE 2		
GRADE 1		

AR, adverse reaction; 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.

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Ocular events

RPED[1,2] | RVO[1,2] | **Uveitis including iritis and iridocyclitis[1,2]**

BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4	Permanently discontinue BRAFTOVI® and **follow up with ophthalmologic monitoring.**	Permanently discontinue MEKTOVI® and **follow up with ophthalmologic monitoring.**
GRADE 3 GRADE 2 GRADE 1	**Withhold for Grade 1/2 uveitis that doesn't respond to ocular therapy or for Grade 3 uveitis and monitor within 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. If BRAFTOVI® is permanently discontinued MEKTOVI® should be discontinued.

AR, adverse reaction; 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.

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Cardiac

LVEF[1,2] → QTc prolongation[1,2] → BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4[b]	Permanently discontinue BRAFTOVI®. LVEF should be **evaluated every 2 weeks** until recovery.	Permanently discontinue MEKTOVI®. LVEF should be **evaluated every 2 weeks** until recovery.
GRADE 3[b]		
GRADE 2[a]	If MEKTOVI® is withheld, the BRAFTOVI® 450 mg dose should be **reduced to 300 mg during the time of MEKTOVI® interruption.** If MEKTOVI® is permanently discontinued, BRAFTOVI® should be discontinued.	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 1	×	×

[a] Grade 2 LVEF decrease or asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is below LLN. [b] Grade 3 or 4 LVEF decrease or symptomatic LVD.

AR, adverse reaction; LLN, lower limit of normal; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; QTc, QT interval corrected.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Cardiac

LVEF[1,2] | QTc prolongation[1,2] | BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
QTcF >500 ms & increased by > 60 ms from pre-treatment value	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
QTcF >500 ms & 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. If BRAFTOVI® is permanently discontinued MEKTOVI® should be discontinued.

AR, adverse reaction; 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.
Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Skin and subcutaneous

Cutaneous reactions[1,2] → PPES[1,2] → BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
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.**	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 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 1	×	×

AR, adverse reaction; PPES, palmar-plantar erythrodysaesthesia syndrome.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Skin and subcutaneous

Cutaneous reactions[1,2] | PPES[1,2]

BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4	×	×
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.
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.**	
GRADE 1	×	×

AR, adverse reaction; PPES, palmar-plantar erythrodysaesthesia syndrome.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Musculoskeletal

Asymptomatic rhabdomyolysis or CK elevations[1,2] → **Symptomatic rhabdomyolysis or CK elevations**[1,2]

BACK TO AR LIST

		BRAFTOVI®	MEKTOVI®
GRADE 4	CK > 10 x ULN asymptomatic	If MEKTOVI® is withheld, the BRAFTOVI® 450 mg dose should be **reduced to 300 mg during the time of MEKTOVI® interruption.**	Withhold until improved to Grade 0 or 1 and **ensure patient is adequately hydrated.**
GRADE 3	CK > 5-10 x ULN asymptomatic	Maintain dose.	Maintain dose and **ensure patient is adequately hydrated.**
GRADE 2	×	×	×
GRADE 1	×	×	×

AR, adverse reaction; CK, creatine phosphokinase; ULN, upper limit of normal.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Musculoskeletal

Asymptomatic rhabdomyolysis or CK elevations[1,2]

Symptomatic rhabdomyolysis or CK elevations[1,2]

BACK TO AR LIST

		BRAFTOVI®	MEKTOVI®
GRADE 4	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 during the time of MEKTOVI® interruption.** If MEKTOVI® is permanently discontinued BRAFTOVI® should be discontinued.	Withhold until improved to Grade 0 or 1 If resolved in ≤ 4 weeks, resume at a reduced dose. OR permanently discontinue MEKTOVI®.
GRADE 3	Grade 3 (CK > 5 x ULN) with muscle symptoms OR with renal impairment		
GRADE 2	×	×	×
GRADE 1	×	×	×

AR, adverse reaction; CK, creatine phosphokinase; ULN, upper limit of normal.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Liver laboratory abnormalities and hepatotoxicity

AST or ALT elevations[1,2]

BACK TO AR LIST

		BRAFTOVI®	MEKTOVI®
GRADE 4	First occurrence or recurrent Grade 4 (AST or ALT > 20 x ULN)	Other[1,2]	Other[1,2]
GRADE 3	First occurrence or recurrent Grade 3 (AST or ALT > 5 x ULN and blood bilirubin > 2 x ULN)		
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].**
GRADE 1	×	×	×

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

ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; ULN, upper limit of normal.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Lung

ILD/pneumonitis[1,2]

BACK TO AR LIST

	BRAFTOVI®	MEKTOVI®
GRADE 4	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
GRADE 3		
GRADE 2	If MEKTOVI® is withheld, the BRAFTOVI® 450 mg dose should be **reduced to 300 mg during the time of MEKTOVI® interruption.** If MEKTOVI® is permanently discontinued, BRAFTOVI® should 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 1	×	×

AR, adverse reaction; ILD, interstitial lung disease.

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

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Vascular

VTE[1,2]

BACK TO AR LIST

		BRAFTOVI®	MEKTOVI®
GRADE 4	Grade 4 PE	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
GRADE 3	Uncomplicated DVT or PE ≤ Grade 3	If MEKTOVI® is withheld, the BRAFTOVI® 450 mg dose should be **reduced to 300 mg during the time of MEKTOVI® interruption.** If MEKTOVI® is permanently discontinued, BRAFTOVI® should be permanently discontinued.	**Withhold** - **If improved to Grade 0 or 1, resume at a reduced dose.** - **If not improved, permanently discontinue.**

AR, adverse reaction; 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.

Please see the Summaries of Product Characteristics.

MANAGING ARs THROUGH DOSE MODIFICATION

Dose modification | Other[a]

Other[a,1,2]

BACK TO AR LIST

		BRAFTOVI®	MEKTOVI®
GRADE 4	Recurrent Grade 4 ARs	Permanently discontinue BRAFTOVI®.	Permanently discontinue MEKTOVI®.
	First occurrence of any Grade 4 AR	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 BRAFTOVI®. OR permanently discontinue BRAFTOVI®.	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 MEKTOVI®. OR permanently discontinue MEKTOVI®.
GRADE 3	Recurrent Grade 3 ARs	Consider permanently discontinuing BRAFTOVI®.	Consider permanently discontinuing MEKTOVI®.
	First occurrence of any Grade 3 AR	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 BRAFTOVI®.	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 MEKTOVI®.
GRADE 2	Recurrent or intolerable Grade 2 ARs		
GRADE 1	×	×	×

[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.

Please see the Summaries of Product Characteristics.

AR, adverse reaction; PPES, palmoplantar erythrodysaesthesia syndrome; QTc, QT interval corrected.

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.

Also available

A guide to optimise your patients **treatment initiation** with BRAFTOVI® + MEKTOVI®

Contact your local Pierre Fabre representative for more information

LABORATOIRES Pierre Fabre

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