For the Treatment of Adults With Unresectable or Metastatic Melanoma With a BRAF V600 Mutation[1,2]

BRAFTOVI + MEKTOVI:

STRIKING IMPACT IN FIRST LINE[3]

Major Efficacy Outcome Measure: Progression-Free Survival (PFS)[4]

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)		vemurafenib
14.9 MONTHS MEDIAN PFS	vs	**7.3** MONTHS MEDIAN PFS
(n=192) (95% CI: 11.0-18.5)		(n=191) (95% CI: 5.6-8.2)

Primary Analysis: (HR=0.54 [95% CI: 0.41-0.71], *P*<0.001)

In the metastatic setting, 30% of patients receiving BRAFTOVI + MEKTOVI in the COLUMBUS trial had prior treatment with immunotherapy.[4]

EDA Approval No.HF0098A9695/032024
EDA Invalidation Date:03/03/2027

PP-BMK-EGY-0003

BRAFTOVI® (encorafenib) 75 mg Hard Gelatin Capsules + MEKTOVI® (binimetinib) 15 mg Film Coated Tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600 mutation[1,2]

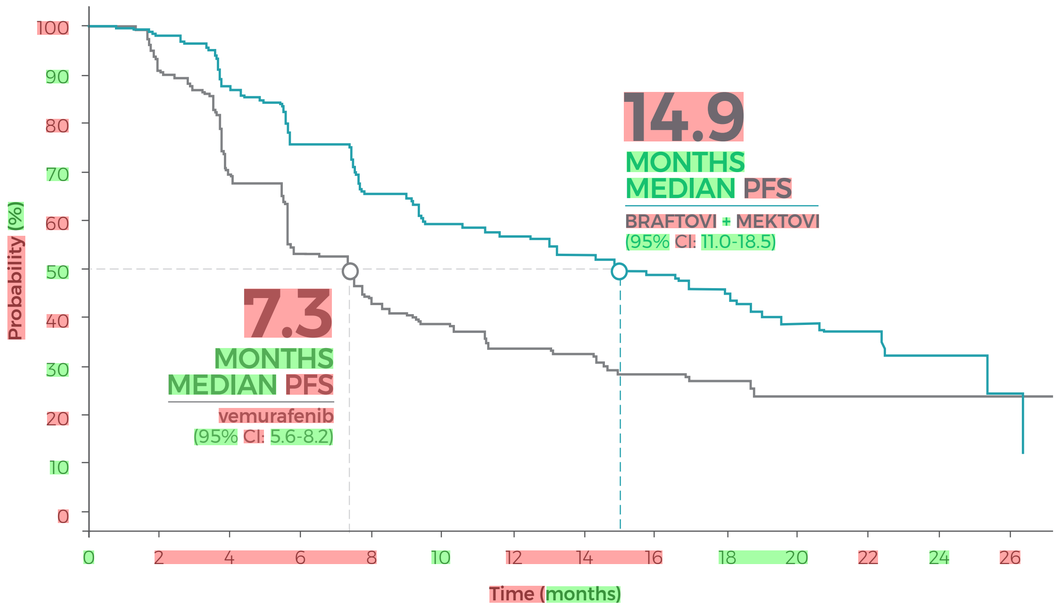
Primary and updated post hoc PFS results by BIRC[4]

The 5-year PFS update is a descriptive post hoc analysis and should be interpreted in the context of this limitation.[5]

Primary analysis: PFS[4]

Primary analysis: HR=0.54 (95% CI: 0.41-0.71)
Log-rank *P* value: <0.0001

Median follow-up of 16.7 months



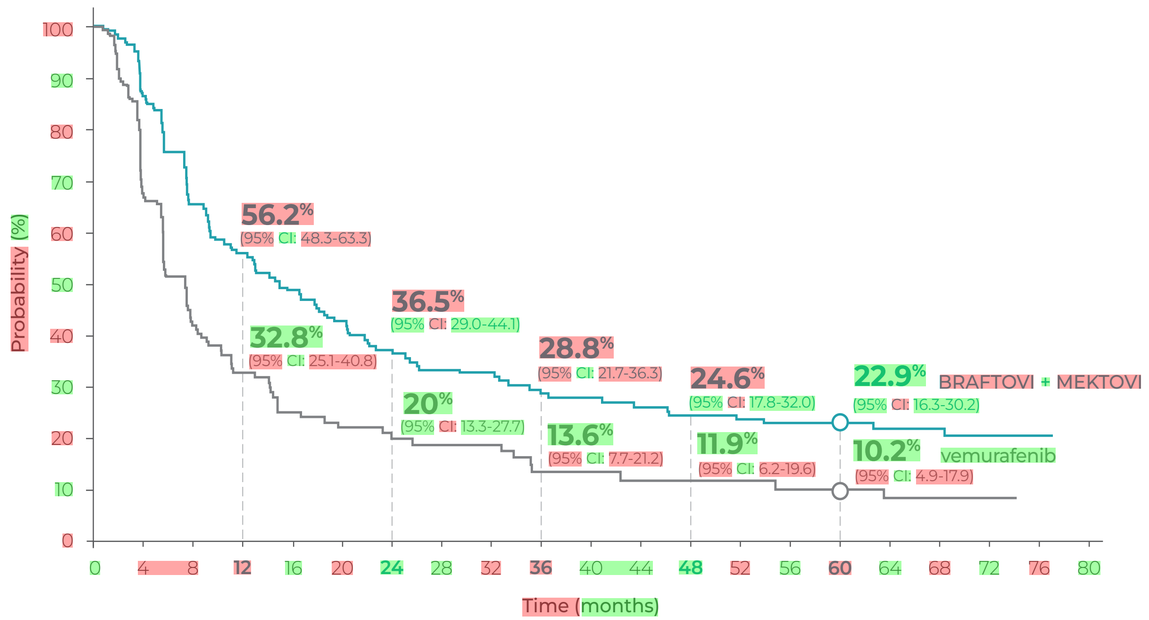
Patients at risk

BRAFTOVI + MEKTOVI	192	171	151	128	107	92	87	70	57	41	28	14	4	0
vemurafenib	191	149	101	75	56	45	36	32	23	18	13	10	4	3

Updated post hoc PFS analysis at 5 years[5]

Updated analysis: HR=0.51 (95% CI: 0.40-0.67)

Median follow-up of 40.8 months



Patients at risk

BRAFTOVI + MEKTOVI	192	151	108	87	73	63	50	45	43	35	33	31	29	28	27	26	23	19	9	2	0
vemurafenib	191	98	55	36	26	22	18	16	15	10	10	7	7	7	6	6	5	3	1	0	0

PFS, progression-free survival; BIRC, blinded independent review committee.

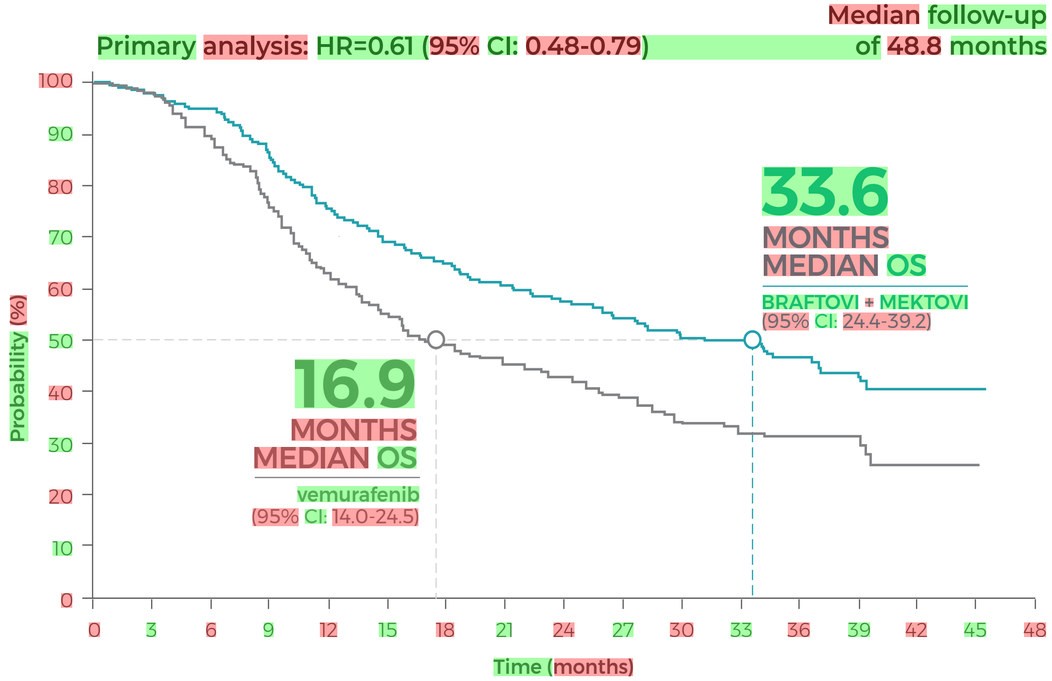
An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600 mutation[1,2]

Primary and updated post hoc OS results

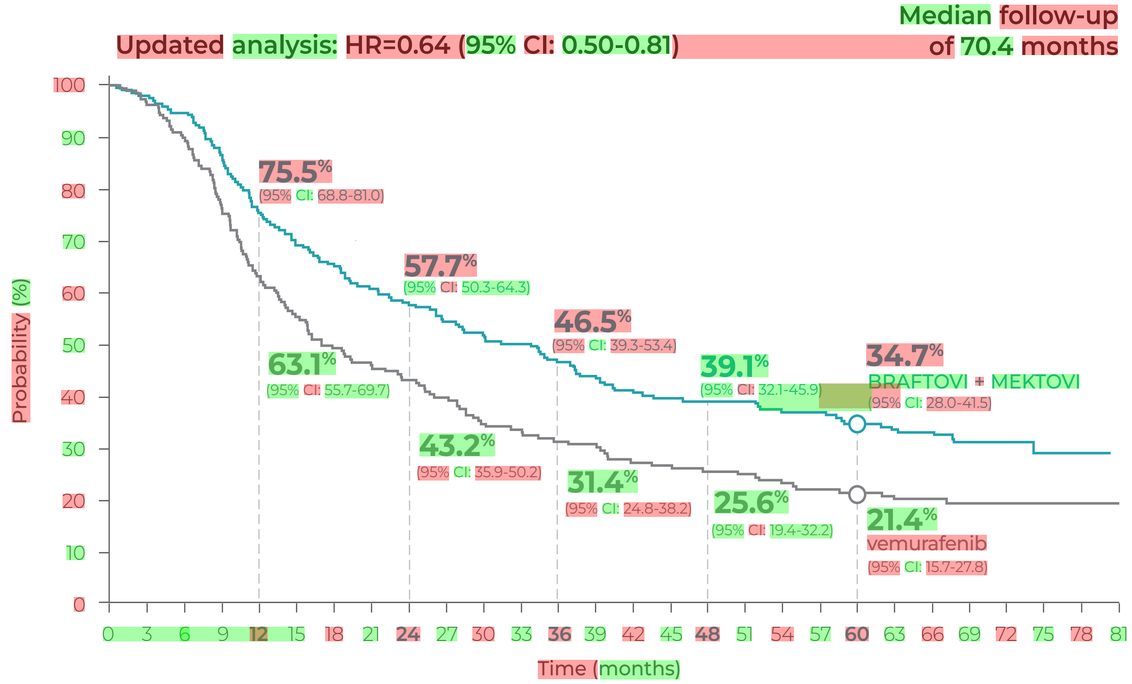
The hierarchical testing procedure prevented formal assessment of the statistical significance of OS; therefore, the OS results are descriptive in nature only.[5]

The 5-year OS update is a descriptive post hoc analysis and should be interpreted in the context of this limitation.[5]

Primary analysis: OS[6]



Updated post hoc OS analysis at 5 years[5]



OS, overall survival.

- In the **primary analysis** of OS (data cutoff: November 7, 2017), the number of events observed in each arm was 105/192 (54.7%) with BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) and 127/191 (66.5%) with vemurafenib[1]

- In this updated post hoc analysis, the median OS of BRAFTOVI + MEKTOVI was 33.6 months (95% CI: 24.4-39.2) and 16.9 months (95% CI: 14.0-24.5) with vemurafenib[5]
- In this updated post hoc analysis of OS (minimum follow-up of 65 months; data cutoff: September 15, 2020), the number of events observed in each arm was 131/192 (68.2%) with BRAFTOVI + MEKTOVI and 145/191 (75.9%) with vemurafenib[5]

Primary analysis of ORR and median duration of response (mDoR) by BIRC[4*†]

	ORR	mDoR
BRAFTOVI + MEKTOVI (n=192)	**63%** (95% CI: 56-70; CR: 8%; PR: 55%)	**16.6 months** (95% CI: 12.2-20.4)
vemurafenib (n=191)	**40%** (95% CI: 33-48; CR: 6%; PR: 35%)	**12.3 months** (95% CI: 6.9-16.9)

*ORRs and DoRs were assessed at the time of the primary PFS analysis (data cutoff: May 19, 2016).[4]

†ORR and DoR were both prespecified analyses assessed by BIRC using RECIST v1.1, but did not evaluate statistical significance; therefore, the ORR and DoR results are descriptive in nature only.[4]

CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; OS, overall survival; PFS, progression-free survival; BIRC, blinded independent review committee; ORR, objective response rate; mDoR, median duration of response

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Dosing and administration

Confirm the presence of *BRAF* V600 mutation by an FDA-approved test before treatment.[1,2]

Recommended dose

Treatment with BRAFTOVI + MEKTOVI should be continued until disease progression or unacceptable toxicity[1,2]

- Instruct patients not to take a missed dose of:
  - BRAFTOVI within **12 hours** of the next dose[1]
  - MEKTOVI within **6 hours** of the next dose[2]
- In case of vomiting, do not take an additional dose of BRAFTOVI + MEKTOVI; resume dosing with the next scheduled dose[1,2]
- No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A). As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients[2]

Selected BRAFTOVI drug interactions[1]

Effects of other medicinal products on encorafenib: Encorafenib is primarily metabolised by CYP3A4.

- CYP3A4 inhibitors: concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity). Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety. Moderate CYP3A4 inhibitors should be co-administered with caution. Examples of moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, diltiazem, amprenavir and imatinib. When encorafenib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.[1]

- CYP3A4 inducers: Co-administration of encorafenib with a CYP3A4 inducer was not assessed in a clinical study; however, a reduction in encorafenib exposure is likely and may result in compromised efficacy. Examples of moderate or strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no or minimal CYP3A induction potential should be considered.[1]

- Effects of encorafenib on other medicinal products:[1]

CYP substrates: Encorafenib is both an inhibitor and inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents. Agents that are CYP3A4 substrates should be co-administered with caution. Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g.raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution. Effect of encorafenib on binimetinib: 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. Transporter substrates: In vivo, encorafenib is an inhibitor of OATP1B1, OATP1B3 and/or BCRP. Coadministration of encorafenib with OATP1B1, OATP1B3 or BCRP substrates (such as rosuvastatin, atorvastatin, methotrexate) can result in increased. In vitro, encorafenib potentially inhibits a number of other transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OCT1 (such as, bosentan) or substrates of P-gp (e.g. posaconazole) may also have increased exposure. Therefore, these agents, substrates of transporters should be co-administered with caution.

The BRAF inhibitor + MEK inhibitor combination with continuous dosing and no fasting or refrigeration requirements[1,2]

Continuous dosing schedule[1,2]

May be taken with or without food[1,2]

No refrigeration requirement

- BRAFTOVI + MEKTOVI should be stored at room temperature[1,2]

BCRP, breast cancer resistance protein; CYP3A4, cytochrome P450 3A4; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3.

For the Treatment of Adults With Unresectable or Metastatic Melanoma With a *BRAF* V600 Mutation[1,2]

BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib):

STRIKING IMPACT IN FIRST LINE[3]

NCCN

NCCN Category 1* Recommendation[3]

Encorafenib (BRAFTOVI) in combination with binimetinib (MEKTOVI) as a first-line systemic therapy option for patients with metastatic or unresectable cutaneous melanoma with a *BRAF* V600–activating mutation.

*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

PFS

14.9 months median PFS per primary analysis[4]

- BRAFTOVI + MEKTOVI (n=192) more than doubled median PFS vs vemurafenib (n=191): 14.9 months (95% CI: 11.0-18.5) vs 7.3 months (95% CI: 5.6-8.2) (HR=0.54 [95% CI: 0.41-0.71], *P*<0.0001) per primary analysis of major efficacy outcome measure

OS

OS per primary analysis[5]

†**The hierarchical testing procedure prevented formal assessment of the statistical significance of OS; therefore, the OS results are descriptive in nature only.**

- 33.6 months median OS observed with BRAFTOVI + MEKTOVI (95% CI: 24.4-39.2) (n=192) and 16.9 months with vemurafenib (95% CI: 14.0-24.5) (n=191) (HR=0.61 [95% CI: 0.47-0.79]) in the primary OS analysis

The **most common adverse reactions** (≥25%) with BRAFTOVI + MEKTOVI were fatigue (43.8%), nausea (41.6%), diarrhea (38%), vomiting (28.1%), abdominal pain (27.4%), and arthralgia[1,2]

NCCN, National Comprehensive Cancer Network® (NCCN®); OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

References

1. Braftovi 50, 75 mg .Egypt LPD. Revision Date July 2022 Egyptian Drug Authority Leaflet Approval Date: 12-02-2023

2. Mektovi 15mg .Egypt LPD. Revision Date September 2021 Egyptian Drug Authority Leaflet Approval Date: 12-03-2023

3. National Comprehensive Cancer Network (NCCN). Melanoma: Cutaneous. Available at https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492. Last accessed 16/11/2023.

4. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, Chiarion-Sileni V. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. The Lancet Oncology. 2018 May 1;19(5):603-15.

5. Dummer R, Flaherty KT, Robert C, Arance A, B de Groot JW, Garbe C, Gogas HJ, Gutzmer R, Krajsová I, Liszkay G, Loquai C. COLUMBUS 5-year update: a randomized, open-label, phase III trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF. Future Oncology. 2023 Jun(0).

6. Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R. Update on tolerability and overall survival in COLUMBUS: Landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600–mutant melanoma. European Journal of Cancer. 2020 Feb 1;126:33-44.

Braftovi® Abbreviated Prescribing Information / Summary of Product Information

TARGET AUDIENCE: For Healthcare Professionals
Braftovi® Abbreviated Prescribing Information / Summaty of Product Information
GENERIC NAME: Encorafenib
PRESENTATION: 50 mg and 75 mg Hard Capsule
NATURE AND CONTENT OF THE CONTAINER: No. of stripes, as applicable
Braftovi 50 mg: Pack of 28 Capsules, including 7 blisters, each of 4 hard capsules.
Braftovi 75 mg: Pack of 42 Capsules, including 7 blisters, each of 6 hard capsules.
INDICATION(s): Encorafenib is indicated:
in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.
DOSAGE AND ADMINISTRATION:
Melanoma The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib. Colorectal cancer The recommended dose of encorafenib is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab. Braftovi is for oral use. The capsules are to be swallowed whole with water. They may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided
MISSED DOSES:
If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose
SPECIAL POPULATION:
Elderly patients No dose adjustment is required for patients aged 65 years and older.
Hepatic impairment Patients with mild to severe hepatic impairment may have increased encorafenib exposure. Administration of encorafenib should be undeltaken with caution at a dose of 300 mg once daily in patients with mild hepatic impairment (Child-Pugh Class A). No dosing recommendation can be made in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.
Renal impairment No dose adjustment is required for patients with mild or moderate renal impairment based on a population phannacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be detennined. Encorafenib should be used with caution in patients with severe renal impairment.
Paediatric population The safety and efficacy of encorafenib have not yet been established in children and adolescents. No data are available.
Fertility, pregnancy and lactation
Women of childbearing potential /Contraception in females Women of childbearing potential must use effective contraception during treatment with encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the efficacy of hormonal Contraceptives. Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least I month following the last dose.
Pregnancy
There are no data from the use of encorafenib in pregnant women. Studies in animals have shown reproductive toxicity. Encorafenib is not recommended during pregnancy and in women of child bearing potential not using contraception. If encorafenib is used during pregnancy or if the patient becomes pregnant while taking encorafenib, the patient should be informed of the potential hazard to the foetus.
Breast-feeding
It is unknown whether encorafenib or its metabolites are excreted in human milk. A risk to the newboms/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue encorafenib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.
Fertility
There are no data on the effects of encorafenib on fertility in humans. Based on findings in animals, the use of encorafenib may impact fertility in males of reproductive potential. As the clinical relevance of this is unknown, male patients should be informed of the potential lisk for impaired spermatogenesis.
CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients
WARNING AND PRECAUTIONS:
Encorafenib is to be given in combination with binimetinib (for patients with BRAF V600 mutant unresectable or metastatic melanoma), or in combination with cetuximab (for patients with BRAF V600E mutant metastatic colorectal cancer). For additional infonnation on wamings and precautions associated with binimetinib

or cetuximab treatment, see section 4.4 of binimetinib SmPC or cetuximab SmPC.

BRAF mutation testing:

Before taking encorafenib, patients must have unresectable or metastatic melanoma with BRAF V600 mutation or metastatic colorectal cancer with BRAF V600E mutation confirmed by a validated test. The efficacy and safety of encorafenib have been established only in patients with melanoma tumours expressing BRAF V600E and V600K mutations or colorectal tumours expressing BRAF V600E mutation. Encorafenib should not be used in patients with wild type BRAF malignant melanoma or wild type BRAF colorectal cancer. Encorafenib in combination with binimetinib in patients who have progressed on a BRAF ilmibitor. There are limited data for the use of the combination of encorafenib with binimetinib in patients who have progressed on a prior BRAF inhibitor given for the treatment of umesectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients. Encorafenib in combination with binimetinib in patients with brain metastases There are limited efficacy data with the combination of encorafenib and binimetinib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain

Left ventricular dysfunction (LVD)

LVD defined as symptomatic or asymptomatic decreases in ejection fraction has been repolted when encorafenib is used in combination with binimetinib. It is recommended that left ventricular ejection fraction (LVEF) is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of encorafenib and binimetinib, one month after initiation, and then at approximately 3-month intenrals or more frequently as clinically indicated, while on treatment. If during treatment LVD occurs. The safety of encorafenib in combination with binimetinib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limits of normal. Therefore, in these patients, binimetinib should be used with caution and for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF decrease or for absolute decrease of LVEF from baseline of ≥ 10%, binimetinib and encorafenib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Haemorrhage

Haemorrhages, including major Hemorrhagic events, can occur with encorafenib. The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occunence of Grade ≥3 Hemorrhagic events should be managed with dose interruption or treatment discontinuation and as clinically indicated.

Ocular toxicities

Ocular toxicities including uveitis, iritis, and iridocyclitis can occur when encorafenib is administered. RPED has also been reported in patients treated with encorafenib in combination with binimetinib. Patients should be assessed at each visit for symptoms of new or worsening visual disturbance. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. If uveitis including iridocyclitis and ilitis occurs during treatment. If during treatment patient develops RPED or RVO.

QT prolongation

QT Prolongation has been observed in patients treated with BRAF-inhibitors. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted. Overall, results suggest that single agent encorafenib has the potential to cause mild increases in health rate. Across pooled combination studies of encorafenib and binimetinib at the recommended doses and a single-agent encorafenib study, results suggest that encorafenib has the potential to result in small increases in QTc intenral. There are insufficient data to exclude a clinically significant exposure dependent QT prolongation. Due to the potential risk for QT prolongation, it is recommended that serum electrolytes abnormalities, including magnesium and potassium, are conected and risk factors for QT prolongation controlled (e.g. congestive healt failure, bradyanhythmias) before treatment initiation and during treatment. It is recommended that an electrocardiogram (ECG) is assessed before initiation of encorafenib, one month after initiation, and then at approximately 3-month intelvals or more frequently as clinically indicated, while on treatment. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors.

New primary malignancies

New primary malignancies, cutaneous and non-cutaneous, have been obselved in patients treated with BRAF inhibitors and can occur when encorafenib is administered

Cutaneous malignancies

Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma have been observed in patients treated with BRAF-inhibitors including encorafenib. New primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib. dermatologic evaluations should be performed prior to initiation of therapy with encorafenib, every 2 months while on therapy and for up to 6 months following treatment discontinuation. Suspicious skin lesions should be managed with dermatologic excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib should be continued without any dose modification.

Non-cutaneous malignancies

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. It should be considered to permanently discontinue encorafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations have been obselved with encorafenib. Liver laboratory values should be monitored before initiation of encorafenib and monitored at least monthly during the 6 first months of treatment, then as clinically indicated. laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation.

Hepatic impairment:

As encorafenib is primarily metabolised and eliminated via the liver, patients with mild to severe hepatic impairment may have increased encorafenib exposure over the range of inter-subject variability exposure. In the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment. Administration of encorafenib should be undertaken with caution at a dose of 300 mg once daily in patients with mild hepatic impairment. 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.

Renal impairment

There are no data available in patients with severe renal impairment. Encorafenib should be used with caution in patients with severe renal impairment.Creatinine elevation has been commonly reported with encorafenib as single agent or in combination with binimetinib or cetuximab. Observed cases of renal failure including acute kidney injury and renal impairment were generally associated with vomiting and dehydration. Other contributing factors included diabetes and hypertension. Blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation. Patients should ensure adequate fluid intake during treatment

Effects of other medicinal products on encorafenib

concurrent use of strong CYP3A inhibitors during treatment with encorafenib should be avoided. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib. EXCIPIENTS: For the full list of excipients, see section 6.1.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES:

Encorafenib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with encorafenib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machines.

DRUG Interactions:

No drug drug interaction was evidenced between encorafenib and cetuximab.

Effect of CYP enzymes on encorafenib

Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. In vitro, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (—83.3%), followed by CYP2C19 and CYP2D6 (—16.0% and 0.71%, respectively). Effect of encorafenib on CYP substrates In vitro experiments indicate encorafenib is a relatively potent reversible inhibitor of UGTIAI, CYP2B6, CYP2C9 and CYP3A4/5, as well as a time-dependent of CYP3A4. Encorafenib induced CYPIA2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Simulations of 450 mg encorafenib coadministered with probe substrates for CYP2B6, CYPIA2, CYP2C9, CYP2C19 and CYP2D6 on Day 1 and Day 15 all indicated no clinically relevant interactions are expected. For co-administration with CYP3A4 and UGTIAI substrates that undergo gut extraction, a minor to moderate interaction is expected. While binimetinib is a UGTIAI substrate, it does not undergo gut extraction and therefore no DDI with encorafenib is expected. Additionally, no differences in exposure have been observed clinically when binimetinib is co-administered with encorafenib.

Effect of transporters on encorafenib

Encorafenib was found to be a substrate ofthe P-glycoprotein (P-gp) transporters. Inhibition of P-gp is unlikely to result in a clinically important increase in encorafenib concentrations as encorafenib exhibits high intrinsic permeability. The involvement of several uptake transporter families (OCT 1, OATPIBI, OATPIB3 and OATPBI) was

investigated in vitro using relevant transponer inhibitors. The data suggest that hepatic uptake transponers are not involved in encorafenib distribution into primary human hepatocytes.

Effect of encorafenib on transporters

Repeated administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a OATPIBI, OATPIB3 and BCRP substrate) increased rosuvastatin Cmax by 2.7-fold and AUC by 1.6-fold indicating a mild inhibition of OATPIBI, OATPIB3 and/or BCRP transporters. In vitro, encorafenib inhibited the hepatic transponer OCT 1, but is unlikely to be an effective inhibitor clinically. Based on in vitro studies, there is potential for encorafenib to inhibit renal transporters OCT 2, OAT 1, OAT 3. at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut at the expected clinical concentrations.

OVERDOSE: Symptoms

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatinaemia) was obselved in 3 out of 14 patients. The highest administered dose occuned as a dosing error in one patient who took encorafenib at a dose of 600 mg twice daily for 1 day (total dose 1200 mg). Adverse reactions repolted by this patient were Grade 1 events of nausea, vomiting and blurred vision; all subsequently resolved.

Management

There is no specific treatment for overdose. Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib. There is no known antidote for encorafenib. In the event of an overdose, encorafenib treatment should be interrupted and renal function must be monitored as well as adverse reactions. Symptomatic treatment and supportive care should be provided as needed.

ADVERSE REACTION:

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally fivice daily) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the pooled Combo 450 population), based on two Phase II studies (CMEK162X2110 and CLGX81SX2109) and one Phase 111 study (CMEK162B2301, Part 1). At the recommended dose (n = 274) in patients with unresectable or metastatic melanoma, the most commonadverse reactions (>25%) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, althralgia, blood CK increased and myalgia. The safety of encorafenib (300 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 257 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the Combo 300 population), based on the Phase III study (CMEK162B2301, Part 2). The most common adverse reactions (>25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea. The encorafenib single agent (300 mg orally once daily) safety profile is based on data from 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encomfenib 300 population). The most common adverse drug reactions (ADRs) (>25%) reported with encorafenib 300 were hyperkeratosis, alopecia, PPES, fatigue, rash, althralgia, dry skin, nausea, myalgia, headache, vomiting and pmritus. The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (dosed as per its SmPC) was evaluated in 216 patients with BRAF V600E- mutant metastatic colorectal cancer, based on the phase III study ARRAY-818-302. The most common ADRs (>25%) reported in this population were: fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, althralgia/musculoskeletal pain, decreased appetite, rash and vomiting. The rate of all study drug discontinuation due to any adverse reaction was 1.9 % in patients treated with encorafenib 300 mg in combination with cetuximab.

DOSE MODIFICATIONS (IF APPLICABLE):

Recommended dose modifications for encorafenib when used in combination with binimetinib in melanoma indication

Starting dose Six 75 mg (450 mg) capsules once daily 1st dose reduction Four 75 mg (300 mg) capsules once daily 2nd dose reduction Three 75 mg (225 mg) capsules once daily Subsequent modification, There are limited data for dose reduction to 100 mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100 mg (two 50 mg capsules) once daily.

Recommended dose modifications for encorafenib when used in combination with cetuximab in CRC indication

starting dose Four 75 mg (300 mg) capsules once daily 1st dose reduction Three 75 mg (225 mg) capsules once daily 2nd dose reduction Two 75 mg (150 mg) capsules once daily If encorafenib is permanently discontinued, cetuximab should be discontinued. If cetuximab is permanently discontinued, encorafenib should be discontinued.

PHARMACEUTICAL PRECAUTIONS Special precautions for disposal:

Keep out of the sight and reach of children. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PHARMACOKINETICS / PHARMACODYNAMICS (If required per local regulations)

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma harboufing a BRAF-V600E or K mutation, and in adult patients with metastatic colorectal cancer with a BRAF V600E mutation. The pharmacokinetics of encorafenib have been shown to be approximatively dose linear after single and multiples doses. After repeat once-daily dosing, steady-state conditions were reached within 15 days. The accumulation ratio of approximately 0.5 is likely due to auto-induction of CYP3A4. The inter- subject variability (CV%) of AUC is ranged from 12.3% to 68.9%. Absorption After oral administration, encorafenib is rapidly absorbed with a median Tmax of 1.5 to 2 hours. Following a single oral dose of 100 mg [14C]

encorafenib in healthy subjects, at least 86% of the encorafenib dose was absorbed. Administration of a single 100 mg dose of encorafenib with a highfat, high-calorie meal decreased the Cmax by 36%, while the AUC was unchanged. A drug interaction study in healthy subjects indicated the extent of encorafenib exposure was not altered in the presence of a gastlic pH-altering agent (rabeprazole). Distribution Encorafenib is moderately (86.1%) bound to human plasma proteins in vitro. Following a single oral dose of 100 mg [14C] encorafenib in healthy subjects, the mean (SD) blood-to-plasma concentration ratio is 0.58 (0.02) and the mean (CV%) apparent volume of distribution (Vz/F) of encorafenib is 226 L (32.7%).

SHELF LIFE:

Do not use Braftovi after the expiry date which is stated on the blister foil and canon after "EXP". The expiry date refers to the last day of that month.

STORAGE AND HANDLING:

Store below 300C. Store in the original package in order to protect from moisture.

Further details can be found in the full prescribing information. Full Prescribing Information is available upon request.

REFERENCE:

Braftovi 50 , 75 mg_Egypt LPD_(Revision Date July 2022). Egyptian Drug Leaflet Approval Date: 12-February-2023.

- Always read the full prescribing information.
- Healthcare professionals are asked to report any suspected adverse reactions to Egyptian pharmacovigilance center (EPVC) pv.report@edaegypt.gov.eg Pfizer Reporting email: EGY. AEReporting@pfizer.com
- Braftovi 50 , 75 mg Egyptian Drug Authority Leaflet Approval Date: 12-February-2023

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

TARGET AUDIENCE: For Healthcare Professionals
[Mektovi]® Abbreviated Prescribing Information / Summary of Product Information
GENERIC NAME: Binimetinib
PRESENTATION: 15 mg film-coated tablets
NATURE AND CONTENT OF THE CONTAINER:
Carton box containing 7 blisters, each of 12 tablets (Pack of 84 tablets).
INDICATION(s):
Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
DOSAGE AND ADMINISTRATION:
The recommended dose ofbinimetinib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg approximately 12 hours apart.
MISSED DOSES:
If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until the next dose is due.
SPECIAL POPULATION:
Elderly patients No dose adjustment is required for patients aged 65 years and older. Hepatic impairment No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A). As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe
hepatic impairment
(Child-Pugh C), administration of binimetinib is not recommended in these patients.
Renal impairment
No dose adjustment is recommended for patients with renal impairment.
Paediatric population The safety and efficacy of binimetinib in children and adolescents have not yet been established. No data are available
FERTILITY, PREGNANCY AND LACTATION:
Women of child bearing potential/Contraception in females: Women of childbearing potential must use effective contraception during treatment with binimetinib and for at least 1 month following the last dose.
Pregnancy
There are no data from the use of binimetinb in pregnant women. Studies in animals have shown reproductive toxicity. Binimetinib is not recommended during pregnancy and in women of child bearing potential not using contraception. If binimetinib is used during pregnancy, or if the patient becomes pregnant while taking binimetinib, the patient should be informed of the potential hazard to the foetus.
Breast-feeding
It is unknown whether binimetinib or its metabolite are excreted in human milk. A risk to the newboms/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Mektovi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.
Feltility
There are no data on the effect on feltility in humans for binimetinib.
CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.
WARNING AND PRECAUTIONS:
Binimetinib is to be given in combination with encorafenib. For additional information on warnings and precautions associated with encorafenib treatment, see section 4.4 of encorafenib SmPC.
BRAF mutation testing
Before taking binimetinib in combination with encorafenib, patients must have BRAF V600 mutation confirmed by validated test. The efficacy and safety of binimetinib in combination with encorafenib have been established only in patients with tumours expressing BRAF V600E and V600K mutations. Binimetinib in combination with encorafenib should not be used in patients with wild type BRAF malignant melanoma. Binimetinib in combination with encorafenib in patients who have progressed on a BRAF inhibitor There are limited data for use of the combination of binimetinib with encorafenib in patients who have progressed on a prior BRAF inhibitor given for the treatment of umesectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients. Binimetinib in combination with encorafenib in patients with brain metastases There are limited efficacy data with the combination of binimetinib and

encorafenib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain (see section 5.1).

Left ventricular dysfunction (LVD)

defined as symptomatic or asymptomatic decreases in ejection fraction can occur when binimetinib is administered. It is recommended that LVEF is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of binimetinib, 1 month after initiation, and then at approximately 3-month intercals or more frequently as clinically indicated, while on treatment. The occun•ence of LVEF decrease can be managed with treatment interruption, dose reduction or with treatment discontinuation (see section 4.2). The safety of binimetinib in combination with encorafenib has not been established in patients with a baseline LivTF that is either below 50 % or below the institutional LLN. Therefore, in these patients, binimetinib should be used with caution and for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF, or absolute decrease of LVEF from baseline of 10 %, binimetinib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Haemorrhages

including major hemorrhagic events, can occur when binimetinib is administered (see section 4.8). The risk of hemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occunence of Grade 3 hemorrhagic events should be managed with dose interruption, reduction or treatment discontinuation (see Table 2 in section 4.2) and as clinically indicated.

Ocular toxicities

Ocular toxicities including RPED and R VO can occur when binimetinib is administered. Uveitis including ilidocyclitis and iritis have been repolted in patients treated with binimetinib in combination with encorafenib (see section 4.8). Binimetinib is not recommended in patients with a history of R VO. The safety of binimetinib has not been established in patients with predisposing factors for R VO including uncontrolled glaucoma, ocular hypertension, uncontrolled diabetes mellitus or a history of hyperviscosity or hypercoagulability syndromes. Therefore, binimetinibshould be used with caution in these patients. Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. The occurrence of symptomatic RPED can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2). Binimetinib should be permanently discontinued with the occurrence of R VO (see Table 1 in section 4.2). If during treatment patient develops uveitis, see section 4.2 of encorafenib SmPC for guidance. CK elevation and rhabdomyolysis Asymptomatic CK elevations are seen in patients treated with binimetinib (see section 4.8), and, rhabdomyolysis was uncommonly repolted. Special attention should be paid to patients with neuromuscular conditions associated with CK elevation and rhabdomyolysis. CK and creatinine levels should be monitored monthly during the first 6 months of treatment and as clinically indicated. The patient should be advised to maintain an adequate fluid intake during treatment. Depending on the severity of symptoms, degree of CK elevation or creatinine elevation, dose reduction, dose interruption or pulmonary discontinuation of binimetinib may be required (see Table I in section 4.2).

Hypertension

Hypertension, or worsening of pre-existing hypertension, can occur with the use of binimetinib. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate. In case of severe hypertension, temporally interruption of binimetinib is recommended until hypertension is controlled (see Table 2 in section 4.2).

Venous thromboembolism (VTE)

VTE can occur when binimetinib is administered (see section 4.8). Binimetinib should be used with caution in patients who are at lisk for, or who have a history of VTE. If during treatment patient develops VTE or pulmonary embolism, it should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).

Pneumonitis/Interstitial lung disease

Pneumonitis/ILD can occur with binimetinib. Treatment with binimetinib should be withheld in patients with suspected pneumonitis or ILD, including patients presenting new or progressive pulmonary symptoms or findings such as cough, dyspnoea, hypoxia, reticular opacities or pulmonary infiltrates (see Table 1 in section 4.2). Binimetinib should be permanently discontinued in patients diagnosed with treatment related pneumonitis or ILD.

New primary malignancies New primary malignancies,

cutaneous and non-cutaneous, have been obselved in patients treated with BRAF ilmibitors and can occur when binimetinib is administered in combination with encorafenib(see section 4.8).

Cutaneous malignancies Cutaneous malignancies

such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma has been obselved in patients treated with binimetinib when used in combination with encorafenib. Dennatologic evaluations should be performed prior to initiation of therapy with binimetinib in combination with encorafenib, every 2 months

while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed with dermatologic excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Binimetinib and encorafenib should be continued without any dose modifications. Non-cutaneous malignancies Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving binimetinib in combination with encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. permanent discontinuation of binimetinib and encorafenib should be considered in patients who develops RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering binimetinib in combination with encorafenib to patients with a prior or concun·ent cancer associated with RAS mutation.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations can occur with binimetinib (see section 4.8). Liver laboratory values should be monitored before initiation of binimetinib and encorafenib and at least monthly during the 6 first months of treatment, and then as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).

Hepatic impairment

Liver metabolism mainly via glucuronidation is the primarily route of elimination of binimetinib (see section 5.2). As encorafenib is not recommended in patients with moderate (Child Pugh B) and severe hepatic impairment (Child Pugh C), administration of binimetinib is not recommended in these patients (see sections 4.2 and 5.2).

Lactose intolerance

Mektovi contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsolption should not take this medicinal product.

EXCIPIENTS: Excipient with known effect: Each film-coated tablet contains 133.5 mg of lactose monohydrate. For the full list of excipients, see section 6.1 in the LPD.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES:

Binimetinib has minor influence on the ability to drive or use machines. Visual disturbances have been repolted in patients treated with binimetinib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reaction that may affect their ability to drive and use machines

DRUG INTERACTIONS:

Effects of other medicinal products on binimetinib Binimetinib is primarily metabolised through UGTIAI mediated glucuronidation. The extent of drug interactions mediated by UGTIAI is unlikely to be clinically relevant; however, as this has not been evaluated in a formal clinical study, UGTIAI inducers (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co-administered with caution. While encorafenib is a relatively potent reversible inhibitor of UGTIAI, no differences in binilnetinib exposure have been observed clinically when binimetinib is co-administered with encorafenib. Inducers of CYPIA2 enzymes (such as carbamazepine and lifampicin) and inducers of Pgp transport (such as Saint John's wort or phenytoin) may decrease binimetinib exposure, which could result in a decrease of efficacy. Effects of binimetinib on other medicinal products Binimetinib is a potential inducer of CYPIA2, and caution should be taken when it is used with sensitive substrates (such as duloxetine or theophylline). Binimetinib is a weak inhibitor of OAT 3, and caution should be taken when it is used with sensitive substrates (such as pravastatin or ciprofloxacin). Effect ofUGTIAI inducers or inhibitors on binimetinib Binimetinib is primalily metabolised through UGTIAI mediated glucuronidation. In clinical study sub-analysis, however, there was no apparent relationship observed between binimetinib exposure and UGTIAI mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGTIAI inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib Cmax in the presence or absence of atazanavir. Therefore, the extent of drug interactions mediated by UGTIAI is minimal, and unlikely clinically relevant; however, as this has not been evaluated in a formal clinical study, UGTIAI inducers or inhibitors should be administered with caution.

Effect of CYP enzymes on binimetinib

In vitro, CYPIA2 and CYP2C19 catalyse the formation of the active metabolite, AR00426032 (M3) by oxidative N-desmethylation. Effect of binimetinib on CYP substrates Binimetinib is a weak reversible inhibitor of CYPIA2 and CYP2C9. Effect of transporters on binimetinib In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetinib concentrations as binimetinib exhibits moderate to high passive permeability. Effect of binimetinib on transporters Binimetinib is a weak inhibitor of OAT3. No clinicallly significant drug-drug interactions caused by binimetinib on other transporters is expected. Binimetinib is metabolised by UGTs and CYPIA2 and is a substrate for Pgp. Specific inducers of these enzymes have not been studied and may result in a loss of efficacy.

OVERDOSE:
The highest dose of binimetinib evaluated as single agent in clinical studies was 80 mg administered orally fivice daily and was associated with ocular (chorioretinopathy) and skin toxicities (dennatitis acneifonn). There is no specific treatment of overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Since binimetinib is highly bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with binimetinib.
ADVERSE REACTION

System Organ Class	Adverse reaction	Frequency (All grades)
Neoplasms benign, malignant and unspecified	Cutaneous squamous cell carcinoma[a]	Common
	Basal cell carcinoma*	Common
	Skin papilloma*	Common
Blood and lymphatic system disorders	Anaemia	Very common
Immune system disorders	Hypersensitivity[b]	Common
Nervous system disorders	Neuropathy peripheral*	Very common
	Dizziness*	Very common
	Headache*	Very common
	Dysgeusia	Common
	Facial paresis[c]	Uncommon
Eye disorders	Visual impairment*	Very common
	RPED*	Very common
	Uveitis*	Common
Cardiac disorders	Left ventricular dysfunction[d]	Common
Vascular disorders	Haemorrhage[e]	Very common
	Hypertension*	Very common
Gastrointestinal disorders	Abdominal pain*	Very common
	Diarrhoea*	Very common
	Vomiting*	Very common
	Nausea	Very common
	Constipation	Very common
	Colitis[g]	Common
	Pancreatitis*	Uncommon
Skin and subcutaneous tissue disorders	Hyperkeratosis *	Very common
	Rash *	Very common
	Dry skin*	Very common
	Pruritus*	Very common
	Alopecia*	Very common
	Photosensitivity*	Common
	Dermatitis acneiform*	Common
	Palmar-plantar erythrodysaesthesia syndrome (PPES)	Common

	Erythema*	Common
	Panniculitis*	Common
Musculoskeletal and connective tissue disorders	Arthralgia*	Very common
	Muscular disorders/Myalgia[h]	Very common
	Back pain	Very common
	Pain in extremity	Very common
	Rhabdomyolysis	Uncommon
Renal and urinary disorders	Renal failure*	Common
General disorders and administration site conditions	Pyrexia*	Very common
	Peripheral oedema[i]	Very common
	Fatigue*	Very common
Investigations	Blood creatine phosphokinase increased	Very Common
	Transaminase increased*	Very Common
	Gamma-glutamyl transferase increased*	Very Common
	Blood creatinine increased*	Common
	Blood alkaline phosphatase increased	Common
	Amylase increased	Common
	Lipase increased	Common

DOSE MODIFICATIONS:

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation. For patients receiving 45 mg binimetinib twice daily, the recommended reduced dose of binimetinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily. If the adverse reaction that resulted in a dose reduction is under effective management, dose re-escalation to 45 mg twice daily may be considered. Dose re-escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventlicular dysfunction (LVD) or any Grade 4 toxicity. If treatment-related toxicities occur when binimetinib is used in combination with encorafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose reductions are necessary for encorafenib only (adverse reactions plimarily related to encorafenib) are: palmar-plantar elythrodysaesthesia syndrome (PPES), uveitis including ilitis and ridocyclitis and QTc prolongation. If one of these toxicities occurs, see section 4.2. of encorafenib Summary of Product Charactelistics (SmPC) for dose modification instructions for encorafenib. If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued. If encorafenib is temporalily interrupted (see section 4.2 of encorafenib SmPC), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued. For information on the posology and recommended dose modifications of encorafenib, see section 4.2 of encorafenib SmPC.

PHARMACEUTICAL PRECAUTIONS Special precautions for disposal

Keep out of the sight and reach of children. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PHARMACOKINETICS / PHARMACODYNAMICS:

The mean (CV %) Cmax,ss was 654 ng mL (34.7 %) and mean AUCss was 2.35 ug.h/mL (28.0 %) in combination with encorafenib as estimated by population PK modelling. After oral administration, binimetinib is rapidly absorbed with a median Tmax of 1.5 hours Binimetinib phannacokinetics have been shown to be approximately dose-linear. The mean (CV %) apparent clearance (CL/F) of binimetinib was 28.2 Lih (17.5 %). The median (range) binimetinib tenninal half-life (T 1/2) was 8.66 h (8.10 to 13.6 h). SHELF LIFE: Do not use Mektovi after the expiry date which is stated on the blister foil and carton after "EXP". The expiry date refers to the last day of that month.

Mektovi® Abbreviated Prescribing Information / Summary of Product Information

STORAGE AND HANDLING:
Store below 300C.
Further details can be found in the full prescribing information. Full Prescribing Information is available upon request.
REFERENCE:
Mektovi_(15 mg)_Egypt LPD_(Revision Date September-2021). Egyptian Drug Authority Leaflet Approval Date: 22-March-2023

- Always read the full prescribing information.
- Healthcare professionals are asked to report any suspected adverse reactions to Egyptian pharmacovigilance center (EPVC) pv.report@edaegypt.gov.eg Pfizer Reporting email: EGY.AEReporting@pfizer.com
- (Mektovi 15 mg) Egyptian Drug Authority. EDA Leaflet Approval date: 22-March-2023.

Pfizer Oncology

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Further information is available upon request
Pfizer Service Company BV
Cairo, Egypt Scientific Office
5th settlement, Cairo Festival city, Taha Hussein
street, Podium Building number 4, 5th floor.
Postal code:11835, Cairo, Egypt

BRAFTOVI® + MEKTOVI®
(encorafenib) 75 mg Hard Gelatin Capsules
(binimetinib) 15 mg Film Coated Tablets

ADVERTISING/PROMOTIONAL MATERIAL APPROVAL FORM

[1] Product Names:		[2] Type of promotion:	
BRAFTOVI MEKTOVI		Digital Sales Presentation (DSP)	
[3] Identification No :	[5] Date of Piece	Date of Expiry	[6] Other Identifier:
PP-BMK-EGY-0003	12/12/2023	3/3/2026	

[7] Description:

Localized From Global Marterial "PP-BMK-SAU-0001"

Marketing Representative

[8] Approved by:

I have reviewed the attached promotional material or activity and certify that it meets the requirements set forth in the Global Policy on Interactions with Healthcare Professionals and the Policy on Preparing, Reviewing and Approving Promotional Activities and/or Materials.

In addition, for our Pfizer Country Office, we have reviewed the promotional material or activity and certify that it meets all local laws and regulations and complies with local ethical and medical standards.

Name	Date	Role
Name: Salma Farghaly (salma.farghaly@pfizer.com) on behalf of Mostafa Nada Title:	26-Mar-2024 14:02:19 GMT+0000	Operation Acceptance