タフィンラーカプセル 50mg,75mg に関する資料

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開発の経緯図を除く当該内容については，「2.5 臨床に関する概括評価」に記載した。

1 開発の経緯図

開発の経緯図を Figure1-1 に示す。

Figure 1-1 開発の経緯図

試験項目 ＼ 年		
薬理	効力を裏付ける試験	海外/効力を裏付ける試験
毒性	生殖発生毒性試験	海外/生殖発生毒性試験
生物薬剤学	比較BA試験及び生物学的同等性（BE）試験	海外/G2101試験：DRB436のHPMCカプセルと経口懸濁液の相対的バイオアベイラビリティ試験
		海外/MEK115892試験：TMT212の錠剤と小児液剤の相対的バイオアベイラビリティ試験
	生物学的及び理化学的分析法検討	海外/生物学的及び理化学的分析法検討
臨床	非対照試験	国際共同/X2201試験: BRAF遺伝子変異を有する腫瘍に対するオープンラベル試験
	非対照試験	海外/A2102試験: BRAF V 600変異陽性の腫瘍を有する小児患者を対象としたオープンラベル試験
	非対照試験	海外/X2101試験: 固形腫瘍又は蔓状神経線維腫を有する小児患者を対象としたオープンラベル試験
治験相談		医薬品申請前相談（オーファン以外），#P5250
		医薬品追加相談（オーファン以外），#P6524
		医薬品申請電子データ提出免除相談（オーファン以外），#電741

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1 外国における使用状況等

ダブラフェニブ及びトラメチニブは，BRAF V600 遺伝子変異を有する悪性黒色種の単剤療法における治療薬として 2013 年 5 月に米国で最初の承認を取得し，欧州でも 2013 年 8 月及び 2014 年 6 月に承認を取得した。その後，ダブラフェニブ及びトラメチニブは併用療法として，米国を中心に悪性黒色腫，非小細胞肺癌，甲状腺未分化癌及び固形腫瘍の効能効果に関する承認を取得してきた。現時点で両剤は，70 ヵ国以上で承認されている。

主要国での承認状況を Table 1-1 に示す。

Table 1-1 主要国の承認状況

効能効果		承認状況		
		米国	欧州	日本
BRAF 遺伝子変異を有する根治切除不能な悪性黒色腫 a)	ダブラフェニブ単剤	2013 年 5 月	2013 年 8 月	2016 年 3 月
	トラメチニブ単剤	2013 年 5 月	2014 年 6 月	―
	ダブラフェニブ／トラメチニブ併用	2014 年 1 月	2015 年 8 月	2016 年 3 月
BRAF 遺伝子変異を有する悪性黒色腫（術後補助療法の効能追加）	ダブラフェニブ／トラメチニブ併用	2018 年 4 月	2018 年 8 月	2018 年 7 月
BRAF 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌 b)	ダブラフェニブ／トラメチニブ併用	2017 年 6 月	2017 年 3 月	2018 年 3 月
BRAF V600E 遺伝子変異陽性の局所進行又は転移性の甲状腺未分化癌（ATC）	ダブラフェニブ／トラメチニブ併用	2018 年 5 月	―	―
BRAF V600E 遺伝子変異陽性の切除不能又は転移性の固形腫瘍	ダブラフェニブ／トラメチニブ併用	2022 年 6 月	―	―

a）日本の効能効果を記載した。

米国：BRAF V600E 遺伝子変異を有する切除不能又は転移性の悪性黒色腫（ダブラフェニブ単剤）
BRAF V600E/K 遺伝子変異を有する切除不能又は転移性の悪性黒色腫（トラメチニブ単剤，ダブラフェニブ／トラメチニブ併用）

欧州：BRAF V600 遺伝子変異を有する切除不能又は転移性の悪性黒色腫

b）日本の効能効果を記載した。

米国：BRAF V600E 遺伝子変異陽性の非小細胞肺癌

欧州：BRAF V600 遺伝子変異陽性の非小細胞肺癌

2 外国の添付文書等の概要

スイス・ノバルティスファーマ社の企業中核データシート（CCDS）を提出する。また現時点で最新の米国，EU の添付文書を提出する。

[redacted]

TAFINLAR® (dabrafenib)
50 mg and 75 mg Hard capsules
10 mg Dispersible tablets

Core Data Sheet (CDS)

[redacted]

P2-61は非公表とするため削除

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAFINLAR safely and effectively. See full prescribing information for TAFINLAR.

TAFINLAR® (dabrafenib) capsules, for oral use
TAFINLAR® (dabrafenib) tablets for oral suspension
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage, BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors (1.6)	8/2023
Indications and Usage, BRAF V600E Mutation-Positive Low-Grade Glioma (1.7)	3/2023
Dosage and Administration, Patient Selection (2.1)	3/2023
Dosage and Administration, Recommended Dosage (2.2)	3/2023
Dosage and Administration, Administration (2.3)	3/2023
Dosage and Administration, Dosage Modifications for Adverse Reactions (2.4)	3/2023
Warnings and Precautions, New Primary Malignancies (5.1)	3/2023
Warnings and Precautions, Hemorrhage (5.3)	3/2023
Warnings and Precautions, Cardiomyopathy (5.4)	3/2023
Warnings and Precautions, Uveitis (5.5)	3/2023
Warnings and Precautions, Serious Febrile Reactions (5.6)	3/2023
Warnings and Precautions, Serious Skin Toxicities (5.7)	3/2023
Warnings and Precautions, Hyperglycemia (5.8)	3/2023
Warnings and Precautions, Hemophagocytic Lymphohistiocytosis (5.11)	5/2023

----------INDICATIONS AND USAGE----------

TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1, 2.1)

TAFINLAR is indicated, in combination with trametinib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2, 2.1)
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. (1.3, 2.1)
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. (1.4, 2.1)
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options. (1.5, 2.1)
- the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.6, 2.1)
- the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. (1.7, 2.1)

Limitations of Use: TAFINLAR is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. (1.8, 12.1). TAFINLAR is not indicated for treatment of patients with wild-type BRAF solid tumors. (5.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of TAFINLAR in adult patients is 150 mg (two 75 mg capsules) orally twice daily. The recommended dosage for TAFINLAR in pediatric patients is based on body weight. Take TAFINLAR at least 1 hour before or at least 2 hours after a meal. (2)

----------DOSAGE FORMS AND STRENGTHS----------

TAFINLAR Capsules: 50 mg, 75 mg (3)
TAFINLAR Tablets for Oral Suspension: 10 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- New Primary Malignancies, Cutaneous and Non-Cutaneous: Can occur when TAFINLAR is administered as a single agent or with trametinib. Monitor patients for new malignancies prior to, or while on therapy, and following discontinuation of treatment. (5.1, 2.4)
- Tumor Promotion in BRAF Wild-type Tumors: Increased cell proliferation can occur with BRAF inhibitors. (5.2, 2.1)
- Hemorrhage: Major hemorrhagic events can occur in patients receiving TAFINLAR with trametinib. Monitor for signs and symptoms of bleeding. (5.3)
- Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) before treatment with TAFINLAR and trametinib, after one month of treatment, then every 2 to 3 months thereafter. (5.4, 2.4)
- Uveitis: Perform ophthalmological evaluation for any visual disturbances. (5.5, 2.4)
- Serious Febrile Reactions: Incidence and severity of pyrexia are increased with TAFINLAR and trametinib. (5.6, 2.4)
- Serious Skin Toxicities: Monitor for skin toxicities. Discontinue for intolerable Grade 2 or for Grade 3 or 4 rash not improving within 3 weeks despite interruption of TAFINLAR. Permanently discontinue for severe cutaneous adverse reactions (SCARs). (5.7, 2.4)
- Hyperglycemia: Monitor serum glucose levels in patients with preexisting diabetes or hyperglycemia. (5.8)
- Glucose-6-phosphate Dehydrogenase Deficiency (G6PD): Closely monitor for hemolytic anemia. (5.9)
- Hemophagocytic Lymphohistiocytosis (HLH): Interrupt treatment for suspected HLH. Discontinue treatment if HLH is confirmed. (5.11)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use an effective non-hormonal method of contraception. (5.12, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 20%) for TAFINLAR as a single agent are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. (6.1)

Most common adverse reactions (≥ 20%) for TAFINLAR in combination with trametinib include:

- Unresectable or metastatic melanoma: pyrexia, rash, chills, headache, arthralgia, and cough. (6.1)
- Adjuvant treatment of melanoma: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia. (6.1)
- NSCLC: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea. (6.1)
- Adult patients with solid tumors: pyrexia, fatigue, nausea, rash, chills, headache, hemorrhage, cough, vomiting, constipation, diarrhea, myalgia, arthralgia, and edema. (6.1)
- Pediatric patients with solid tumors: pyrexia, rash, vomiting, fatigue, dry skin, cough, diarrhea, dermatitis acneiform, headache, abdominal pain, nausea, hemorrhage, constipation, and paronychia. (6.1)
- Pediatric patients with LGG: pyrexia, rash, headache, vomiting, musculoskeletal pain, fatigue, diarrhea, dry skin, nausea, hemorrhage, abdominal pain, and dermatitis acneiform. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Avoid concurrent administration of strong inhibitors of CYP3A4 or CYP2C8. (7.1)
- Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Do not breastfeed. (8.2)
- Females and Males of Reproductive Potential: May impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2023

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma

TAFINLAR® is indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

TAFINLAR is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection *[see Dosage and Administration (2.1)]*.

1.4 BRAF V600E Mutation-Positive Metastatic NSCLC

TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer

TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options *[see Dosage and Administration (2.1)]*.

1.6 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

TAFINLAR is indicated, in combination with trametinib, for the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR) *[see Clinical Studies (14.6)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.7 BRAF V600E Mutation-Positive Low-Grade Glioma

TAFINLAR is indicated, in combination with trametinib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy *[see Dosage and Administration (2.1)]*.

1.8 Limitations of Use

- TAFINLAR is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition *[see Indications and Usage (1.6), Clinical Pharmacology (12.1)]*.
- TAFINLAR is not indicated for treatment of patients with wild-type BRAF solid tumors *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Melanoma

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent *[see Warnings and Precautions (5.2), Clinical Studies (14.1)]*.

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Warnings and Precautions (5.2), Clinical Studies (14.2, 14.3)]*.
- Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CcompanionDiagnostics.

NSCLC

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Clinical Studies (14.4)]*.
- Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CcompanionDiagnostics.

ATC

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Clinical Studies (14.5)]*. An FDA-approved test for the detection of BRAF V600E mutation in ATC is not currently available.

Solid Tumors

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Clinical Studies (14.6)]*. An FDA-approved test for the detection of BRAF V600E mutation in solid tumors other than melanoma and NSCLC is not currently available.

Low-Grade Glioma

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Clinical Studies (14.7)]*. An FDA-approved test for the detection of BRAF V600E mutation in LGG is not currently available.

2.2 Recommended Dosage

TAFINLAR Capsules

Adult Patients

The recommended dosage for TAFINLAR capsules in adult patients is 150 mg taken orally twice daily *[see Dosage and Administration (2.3)]*.

Pediatric Patients

The recommended dosage for TAFINLAR capsules in pediatric patients who weigh at least 26 kg is based on body weight (Table 1) *[see Dosage and Administration (2.3)]*. A recommended dosage of TAFINLAR capsules has not been established in patients who weigh less than 26 kg.

Table 1. Recommended Dosage for TAFINLAR Capsules in Pediatric Patients (Weight-based)

Body Weight	Recommended Dosage
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg orally twice daily
51 kg or greater	150 mg orally twice daily

TAFINLAR Tablets for Oral Suspension

The recommended dosage for TAFINLAR tablets for oral suspension is based on body weight (Table 2) *[see Dosage and Administration (2.3)]*.

Table 2. Recommended Dosage for TAFINLAR Tablets for Oral Suspension (Weight-based)

Body Weight	Recommended Dosage
8 to 9 kg	20 mg twice daily
10 to 13 kg	30 mg twice daily
14 to 17 kg	40 mg twice daily
18 to 21 kg	50 mg twice daily
22 to 25 kg	60 mg twice daily
26 to 29 kg	70 mg twice daily
30 to 33 kg	80 mg twice daily
34 to 37 kg	90 mg twice daily
38 to 41 kg	100 mg twice daily
42 to 45 kg	110 mg twice daily
46 to 50 kg	130 mg twice daily
≥ 51 kg	150 mg twice daily

- The recommended duration of treatment for patients with unresectable or metastatic melanoma or solid tumors, metastatic NSCLC, or locally advanced or metastatic anaplastic thyroid cancer is until disease progression or unacceptable toxicity.
- The recommended duration of treatment in the adjuvant melanoma setting is until disease recurrence or unacceptable toxicity for up to 1 year.
- The recommended duration of treatment for pediatric patients with LGG is until disease progression or until unacceptable toxicity.

Refer to the trametinib prescribing information for recommended trametinib dosing information.

2.3 Administration

- Take TAFINLAR at the same time each day, approximately 12 hours apart.
- Take TAFINLAR at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.
- Do not take a missed dose of TAFINLAR within 6 hours of the next dose of TAFINLAR.
- If vomiting occurs after TAFINLAR administration, do not take an additional dose. Take the next dose at its scheduled time.

TAFINLAR Capsules

- Do not open, crush, or break TAFINLAR capsules.

TAFINLAR Tablets for Oral Suspension

- Prior to use of the oral suspension, instruct caregivers (and if appropriate, patients) on proper dosing and administration of TAFINLAR tablets for oral suspension.
- Do not swallow whole, chew or crush TAFINLAR tablets for oral suspension.

Preparation and Administration

- Prepare suspension with approximately 5 mL of water for 1 to 4 tablets, and approximately 10 mL of water for 5 to 15 tablets in the provided cup.
- Gently stir the water and prescribed number of tablets with the handle of a teaspoon until the tablets are fully dissolved. It may take at least 3 minutes to fully dissolve the tablets. Once the tablets for oral suspension are dissolved, the suspension will be cloudy white.

- Administer suspension immediately after preparation from cup, oral dosing syringe or feeding tube.
- Discard suspension if not administered within 30 minutes after preparation.

2.4 Dosage Modifications for Adverse Reactions

Dose reductions for adverse reactions associated with TAFINLAR are presented in Tables 3 and 4.

Table 3. Recommended Dosage Reductions for TAFINLAR Capsules for Adverse Reactions

Recommended Dosage	**75 mg orally twice daily**	**100 mg orally twice daily**	**150 mg orally twice daily**
First dose reduction	50 mg orally twice daily	75 mg orally twice daily	100 mg orally twice daily
Second dose reduction	N/A	50 mg orally twice daily	75 mg orally twice daily
Third dose reduction	N/A	N/A	50 mg orally twice daily
Subsequent modification	Permanently discontinue if unable to tolerate TAFINLAR capsules 50 mg orally twice daily.		

Table 4. Recommended Dosage Reductions for TAFINLAR Tablets for Oral Suspension for Adverse Reactions

Body Weight (Recommended dosage)	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
	Tablets for oral suspension twice daily		
8 to 9 kg (20 mg twice daily)	10 mg twice daily	N/A	N/A
10 to 13 kg (30 mg twice daily)	20 mg twice daily	10 mg twice daily	N/A
14 to 17 kg (40 mg twice daily)	30 mg twice daily	20 mg twice daily	10 mg twice daily
18 to 21 kg (50 mg twice daily)	30 mg twice daily	20 mg twice daily	10 mg twice daily
22 to 25 kg (60 mg twice daily)	40 mg twice daily	30 mg twice daily	20 mg twice daily
26 to 29 kg (70 mg twice daily)	50 mg twice daily	40 mg twice daily	20 mg twice daily
30 to 33 kg (80 mg twice daily)	50 mg twice daily	40 mg twice daily	30 mg twice daily
34 to 37 kg (90 mg twice daily)	60 mg twice daily	50 mg twice daily	30 mg twice daily
38 to 41 kg (100 mg twice daily)	70 mg twice daily	50 mg twice daily	30 mg twice daily
42 to 45 kg (110 mg twice daily)	70 mg twice daily	60 mg twice daily	40 mg twice daily
46 to 50 kg (130 mg twice daily)	90 mg twice daily	70 mg twice daily	40 mg twice daily
≥ 51 kg (150 mg twice daily)	100 mg twice daily	80 mg twice daily	50 mg twice daily

Dosage modifications for adverse reactions associated with TAFINLAR are presented in Table 5.

Table 5. Recommended Dosage Modifications for TAFINLAR for Adverse Reactions

Severity of Adverse Reaction[a]	Dosage Modification for TAFINLAR[b]
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue TAFINLAR.
Cardiomyopathy [see Warnings and Precautions (5.4)]	
• Symptomatic congestive heart failure • Absolute decrease in left ventricular ejection fraction (LVEF) of greater than 20% from baseline that is below lower limit of normal (LLN)	Withhold TAFINLAR until LVEF improves to at least the institutional LLN and absolute decrease to less than or equal to 10% compared to baseline, then resume at same dose.
Uveitis [see Warnings and Precautions (5.5)]	
• Uveitis, including iritis and iridocyclitis	For mild or moderate uveitis does not respond to ocular therapy, or for severe uveitis, withhold TAFINLAR for up to 6 weeks. • If improved to Grade 0-1, then resume TAFINLAR at same or lower dose. • If not improved, permanently discontinue TAFINLAR.
Febrile Reactions [see Warnings and Precautions (5.6)]	
• Fever of 100.4°F to 104°F (or first symptoms in case of recurrence)	Withhold TAFINLAR until fever resolves, then resume TAFINLAR at same or lower dose.
• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	• Withhold TAFINLAR until febrile reactions resolve for at least 24 hours, then resume TAFINLAR at lower dose. Or • Permanently discontinue TAFINLAR.
Skin Toxicities [see Warnings and Precautions (5.7)]	
• Intolerable Grade 2 • Grade 3 or 4	Withhold TAFINLAR for up to 3 weeks. • If improved, resume TAFINLAR at lower dose. • If not improved, permanently discontinue TAFINLAR.
• Severe cutaneous adverse reactions (SCARs)	Permanently discontinue TAFINLAR.
Other Adverse Reactions[c], including Hemorrhage [see Warnings and Precautions (5.3)]	
• Intolerable Grade 2 • Any Grade 3	Withhold TAFINLAR. • If improved to Grade 0-1, resume TAFINLAR at lower dose. • If not improved, permanently discontinue TAFINLAR.
• First occurrence of any Grade 4	• Withhold TAFINLAR until improves to Grade 0-1, then resume at lower dose. Or • Permanently discontinue TAFINLAR.
• Recurrent Grade 4	Permanently discontinue TAFINLAR.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
[b] See Tables 3 and 4 for recommended dose reductions of TAFINLAR.
[c] Dose modifications are not recommended for TAFINLAR when administered with trametinib for the following adverse reactions of trametinib: retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), interstitial lung disease/pneumonitis, and uncomplicated venous thromboembolism. Dose modification of TAFINLAR is not required for new primary cutaneous malignancies.

Refer to the trametinib prescribing information for dose modifications for adverse reactions associated with trametinib.

3 DOSAGE FORMS AND STRENGTHS

TAFINLAR Capsules:

- 50 mg: Dark red capsule imprinted with 'GS TEW' and '50 mg'.
- 75 mg: Dark pink capsule imprinted with 'GS LHF' and '75 mg'.

TAFINLAR Tablets for Oral Suspension:

- 10 mg: White to slightly yellow, round, biconvex 6 mm tablet debossed with "D" on one side and "NVR" on the other, contains berry flavor.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

Cutaneous Malignancies

TAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)],* cutaneous squamous cell carcinomas (cuSCC), and keratoacanthomas occurred in 11% and 4% of patients, respectively. Basal cell carcinoma and new primary melanoma occurred in 4% and 1% of patients, respectively.

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, the incidence of cuSCC (including keratoacanthomas) occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and < 1% of patients, respectively.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, new primary melanoma occurred in < 1% of patients.

Perform dermatologic evaluations prior to initiation of TAFINLAR, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR.

Non-Cutaneous Malignancies

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*.

In the pooled adult safety populations of TAFINLAR monotherapy and TAFINLAR administered with trametinib *[see Adverse Reactions (6.1)]*, non-cutaneous malignancies occurred in 1% of patients.

Monitor patients receiving TAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.4)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of TAFINLAR as a single agent or in combination with trametinib *[see Indications and Usage (1.6), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur when TAFINLAR is administered with trametinib. Fatal cases have been reported.

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, hemorrhagic events occurred in 17% of patients; gastrointestinal hemorrhage occurred in 3% of patients;

intracranial hemorrhage occurred in 0.6% of patients; fatal hemorrhage occurred in 0.5% of patients. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, hemorrhagic events occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%) uterine hemorrhage (0.6%), post-procedural hemorrhage (0.6%), and epistaxis (0.6%).

Permanently discontinue TAFINLAR for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold TAFINLAR for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

5.4 Cardiomyopathy

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of TAFINLAR in 3% and < 1% of patients, respectively. Cardiomyopathy resolved in 45 of 50 patients who received TAFINLAR administered with trametinib.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, cardiomyopathy, defined as a decrease in LVEF ≥ 10% from baseline and below the institutional LLN, occurred in 9% of patients.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of TAFINLAR in combination with trametinib, one month after initiation, and then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic LV dysfunction of > 20% from baseline that is below institutional LLN. Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤ 10% compared to baseline *[see Dosage and Administration (2.4)]*.

5.5 Uveitis

TAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, uveitis occurred in 1% of patients.

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)],* uveitis occurred in 2% of patients.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, uveitis occurred in 1.2% of patients.

Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, eye pain). If iritis is diagnosed, administer ocular therapy and continue TAFINLAR without dose modification. If severe uveitis (i.e., iridocyclitis) or if mild or moderate uveitis does not respond to ocular therapy, withhold TAFINLAR and treat as clinically indicated. Resume TAFINLAR at the same or lower dose if improves to Grade 0 or 1. Permanently discontinue TAFINLAR for persistent Grade 2 or greater uveitis of > 6 weeks *[see Dosage and Administration (2.4)]*.

5.6 Serious Febrile Reactions

Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur with TAFINLAR.

The incidence and severity of pyrexia are increased when TAFINLAR is administered with trametinib compared with TAFINLAR as a single agent *[see Adverse Reactions (6.1)]*.

TAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, fever (serious and non-serious) occurred in 30% of patients. Approximately 13% of these patients experienced 3 or more

discrete episodes. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills occurred in 6% of patients.

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, fever occurred in 58% of patients. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration or renal failure occurred in 5% of patients. Fever was complicated by hypotension in 4%, dehydration in 3%, syncope in 2%, renal failure in 1%, and severe chills/rigors in < 1% of patients.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population *[see Adverse Reactions (6.1)],* pyrexia occurred in 66% of patients.

Withhold TAFINLAR when used as monotherapy, and both TAFINLAR and trametinib when used in combination, if the patient's temperature is ≥ 100.4°F. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia *[see Adverse Reactions (6.1)]*. Fever may be complicated by hypotension, rigors or chills, dehydration, or renal failure. Evaluate for signs and symptoms of infection and monitor serum creatinine and other evidence of renal function during and following severe pyrexia. If appropriate, TAFINLAR, or both TAFINLAR and trametinib when used in combination, may be restarted if the patient has recovered from the febrile reaction for at least 24 hours, either at the same or lower dose *[see Dosage and Administration (2.4)]*. Administer antipyretics as secondary prophylaxis when resuming TAFINLAR if patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (e.g., prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications, such as dehydration, hypotension, renal failure, or severe chills/rigors, and there is no evidence of active infection.

5.7 Serious Skin Toxicities

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with TAFINLAR administered with trametinib *[see Adverse Reactions (6.2)]*.

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, other serious skin toxicity occurred in < 1% of patients.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, serious adverse events of skin and subcutaneous tissue disorders occurred in 1.8% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue TAFINLAR for SCARs *[see Dosage and Administration (2.4)]*. For other skin toxicities, withhold TAFINLAR for intolerable or severe skin toxicity. Resume TAFINLAR at a lower dose in patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue TAFINLAR if skin toxicity has not improved within 3 weeks *[see Dosage and Administration (2.4)]*.

5.8 Hyperglycemia

TAFINLAR Monotherapy (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, 14% of patients with a history of diabetes that received TAFINLAR required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia occurred in 3% of patients.

TAFINLAR Administered with Trametinib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, 15% of patients with a history of diabetes who had received TAFINLAR with trametinib required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia occurred in 2% of patients.

TAFINLAR Administered with Trametinib (Pediatric): In the pooled safety population, Grade 3 and Grade 4 hyperglycemia events occurred in < 1% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate when TAFINLAR is administered in patients with preexisting diabetes or hyperglycemia. Initiate or optimize anti-hyperglycemic medications as clinically indicated.

5.9 Glucose-6-Phosphate Dehydrogenase Deficiency

TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR.

5.10 Risks Associated with Combination Treatment

TAFINLAR is indicated for use in combination with trametinib. Review the prescribing information for trametinib for information on the serious risks of trametinib prior to initiation of TAFINLAR with trametinib.

5.11 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) has been observed in the post-marketing setting when TAFINLAR was administered with trametinib. If HLH is suspected, interrupt treatment. If HLH is confirmed, discontinue treatment and initiate appropriate management of HLH.

5.12 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended adult clinical dose. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective non-hormonal contraception, since TAFINLAR can render hormonal contraceptives ineffective, during treatment with TAFINLAR and for 2 weeks after the last dose *[see Drug Interactions (7.2), Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Tumors *[see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Cardiomyopathy *[see Warnings and Precautions (5.4)]*
- Uveitis *[see Warnings and Precautions (5.5)]*
- Serious Febrile Reactions *[see Warnings and Precautions (5.6)]*
- Serious Skin Toxicities *[see Warnings and Precautions (5.7)]*
- Hyperglycemia *[see Warnings and Precautions (5.8)]*
- Glucose-6-Phosphate Dehydrogenase Deficiency *[see Warnings and Precautions (5.9)]*
- Hemophagocytic Lymphohistiocytosis *[see Warnings and Precautions (5.11)]*

There are additional adverse reactions associated with trametinib. Refer to the trametinib prescribing information for additional information.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Safety Pools

The TAFINLAR monotherapy pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to TAFINLAR 150 mg orally, taken twice daily as a single agent in 586 patients with various

solid tumors, including BRAF V600 mutation-positive unresectable or metastatic melanoma, enrolled in BREAK-2, BREAK-3, BREAK-MB, BRF113220, and BRF112680. Among these 586 patients who received TAFINLAR as a single agent, 46% were exposed for 6 months or longer and 15% were exposed for greater than one year.

The pooled safety population for TAFINLAR administered with trametinib (Adult) described in the WARNINGS AND PRECAUTIONS reflects exposure to TAFINLAR 150 mg orally, twice daily administered in combination with trametinib 2 mg orally, once daily, in 1087 patients enrolled in METRIC, MEK113583, MEK111504, COMBI-d, COMBI-v, COMBI-AD, and BRF113928 with unresectable or metastatic melanoma, adjuvant melanoma or NSCLC. Among these 1087 patients who received TAFINLAR administered with trametinib, 70% were exposed for 6 months or longer and 21% were exposed for greater than one year.

Pediatric Safety Pool

The pediatric pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to weight-based TAFINLAR orally, twice daily administered in combination with trametinib in 166 pediatric patients across two trials: a multi-center, open-label, multi-cohort study in pediatric patients with BRAF V600E mutation-positive glioma requiring systemic therapy (Study G2201; n = 123) and a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors with MAPK pathway activation (Study X2101; n = 43) *[see Clinical Studies (14.6, 14.7)]*. Among 166 patients who received TAFINLAR administered with trametinib, 84% were exposed for 6 months or longer and 70% were exposed for greater than one year. The most common (> 20%) adverse reactions were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%), and dermatitis acneiform (23%). The most common (> 2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and increased aspartate aminotransferase (3.1%).

Unresectable or Metastatic BRAF V600E or V600K Mutation-Positive Melanoma

TAFINLAR as a Single Agent

The safety of TAFINLAR was evaluated in BREAK-3, a multi-center, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n = 63) *[see Clinical Studies (14.1)]*. The trial excluded patients with abnormal LVEF or cardiac valve morphology (≥ Grade 2), corrected QT interval ≥ 480 milliseconds on electrocardiogram, or a known history of G6PD deficiency. The median duration on treatment was 4.9 months for patients treated with TAFINLAR and 2.8 months for dacarbazine-treated patients. The population exposed to TAFINLAR was 60% male, 99% White, and had a median age of 53 years.

The most common adverse reactions (≥ 20%) in patients treated with TAFINLAR were, in order of decreasing frequency: hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES).

The incidence of adverse events resulting in permanent discontinuation of study medication in the BREAK-3 study was 3% for patients treated with TAFINLAR and 3% for patients treated with dacarbazine. The most frequent (≥ 2%) adverse reactions leading to dose reduction of TAFINLAR were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%). Table 6 and Table 7 present adverse reactions and laboratory abnormalities, respectively, of TAFINLAR as a single agent in the BREAK-3 study.

Table 6. Select Adverse Reactions Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3 or 4) of Patients Treated with TAFINLAR in the BREAK-3 Study[a]

Adverse Reactions	TAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tissue				
Hyperkeratosis	37	1	0	0
Alopecia	22	NA	2	NA
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system				
Headache	32	0	8	0
General				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasms				
Papilloma[c]	27	0	2	0
cuSCC[d]	7	4	0	0
Respiratory system				
Cough	12	0	5	0
Gastrointestinal				
Constipation	11	2	14	0
Infections and infestations				
Nasopharyngitis	10	0	3	0

Abbreviations: cuSCC, cutaneous squamous cell carcinoma, includes squamous cell carcinoma of the skin and keratoacanthoma; NA, not applicable.

[a] Adverse reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.

[b] Grade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).

[c] Includes skin papilloma and papilloma.

[d] Cases of cuSCC were required to be reported as Grade 3 per protocol.

Table 7. Laboratory Abnormalities Worsening from Baseline Occurring at a Higher Incidence in Patients Treated with TAFINLAR in the BREAK-3 Study [Between-Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3 or 4)][a]

Laboratory Abnormality	TAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6[b]	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

[a] Adverse reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.

[b] Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions observed in less than 10% of patients (N = 586) treated with TAFINLAR were:

Gastrointestinal: Pancreatitis

Immune System: Hypersensitivity manifesting as bullous rash

Renal and Urinary: Interstitial nephritis

TAFINLAR with Trametinib

The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma who received TAFINLAR in two trials, the COMBI-d study (n = 209), a multi-center, double-blind, randomized (1:1), active-controlled trial and the COMBI-v study (n = 350), a multi-center, open-label, randomized (1:1), active-controlled trial. In both trials, patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. Both trials excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED), QTcB interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD deficiency *[see Clinical Studies (14.2)]*.

Among these 559 patients, 199 (36%) were exposed to TAFINLAR for > 6 months to 12 months while 185 (33%) were exposed to TAFINLAR for ≥ 1 year. The median age was 55 years (range: 18 to 91), 57% were male, 98% were White, 72% had baseline ECOG performance status 0 and 28% had ECOG performance status 1, 64% had M1c stage disease, 35% had elevated lactate dehydrogenase (LDH) at baseline, and 0.5% had a history of brain metastases.

The most common adverse reactions (≥ 20%) for TAFINLAR in patients who received TAFINLAR plus trametinib in the COMBI-d and COMBI-v studies were: pyrexia, rash, chills, headache, arthralgia, and cough.

The demographics and baseline tumor characteristics of patients enrolled in the COMBI-d study are summarized in Clinical Studies *[see Clinical Studies (14.2)]*. Patients who received TAFINLAR plus trametinib had a median duration of exposure of 11 months (range: 3 days to 30 months) to TAFINLAR. Among the 209 patients who received TAFINLAR plus trametinib, 26% were exposed to TAFINLAR for > 6 months to 12 months while 46% were exposed to TAFINLAR for > 1 year.

In the COMBI-d study, adverse reactions leading to discontinuation of TAFINLAR occurred in 11% of patients who received TAFINLAR plus trametinib; the most frequent was pyrexia (1.9%). Adverse reactions leading to dose reductions of TAFINLAR occurred in 26% of patients who received TAFINLAR plus trametinib; the most frequent were pyrexia (14%), neutropenia (1.9%), rash (1.9%), and chills (1.9%). Adverse reactions leading to dose interruptions of TAFINLAR occurred in 56% of patients who received TAFINLAR plus trametinib; the most frequent were pyrexia (35%), chills (11%), vomiting (7%), nausea (5%), and decreased ejection fraction (5%).

Table 8 and Table 9 present adverse reactions and laboratory abnormalities, respectively, observed in the COMBI-d study.

Table 8. Select Adverse Reactions Occurring in ≥ 10% (All Grades) of Patients Treated with TAFINLAR Administered with Trametinib in the COMBI-d Study[a]

Adverse Reactions	Pooled TAFINLAR plus Trametinib N = 559		COMBI-d Study			
			TAFINLAR plus Trametinib N = 209		TAFINLAR N = 211	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Skin and subcutaneous tissue						
Rash[c]	32	1.1	42	0	27	1.4
Dry skin	10	0	12	0	16	0
Nervous system						
Headache	30	0.9	33	0.5	30	1.4
Dizziness	11	0.2	14	0	7	0
Musculoskeletal and connective tissue						
Arthralgia	25	0.9	26	0.9	31	0
Myalgia	15	0.2	13	0.5	13	0
Respiratory system						
Cough	20	0	21	0	21	0
Gastrointestinal						
Constipation	13	0.2	13	0.5	10	0
Infections and infestations						
Nasopharyngitis	12	0	12	0	10	0

[a] NCI CTCAE version 4.0.

[b] Grade 4 adverse reactions limited to headache (n = 1).

[c] Includes rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, rash maculo-papular, and rash folliculitis.

Other clinically important adverse reactions for TAFINLAR across the COMBI-d and COMBI-v studies (N = 559) observed in less than 10% of patients who received TAFINLAR administered with trametinib were:

Gastrointestinal: Colitis, gastrointestinal perforation, pancreatitis

Immunologic: Sarcoidosis

Skin and subcutaneous tissue: Panniculitis

Table 9. Select Laboratory Abnormalities Worsening from Baseline Occurring at ≥ 10% (All Grades) of Patients Who Received TAFINLAR with Trametinib in the COMBI-d Study

Laboratory Abnormalities	Pooled TAFINLAR plus Trametinib N = 559[a]		COMBI-d Study			
			TAFINLAR plus Trametinib N = 209[b]		TAFINLAR N = 211[b]	
	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypophosphatemia	38	6	38	3.8	35	7
Hyponatremia	25	8	24	6	14	2.9
Hepatic						
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5

[a] For these laboratory tests, the denominator is 556.

[b] For these laboratory tests, the denominator is 208 for the combination arm, 208-209 for the TAFINLAR arm.

[c] Grade 4 adverse reactions limited to hyperglycemia (n = 4), hyponatremia and hypophosphatemia (each n = 1) in the pooled combination arm; hyperglycemia (n = 1) in the COMBI-d study combination arm; hypophosphatemia (n = 1) in the TAFINLAR arm.

Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The safety of TAFINLAR when administered with trametinib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study *[see Clinical Studies (14.3)]*. Patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily for 12 months. The trial excluded patients with abnormal LVEF; history of acute coronary syndromes, coronary angioplasty, or stenting within 6 months; Class II or greater congestive heart failure (New York Heart Association); QTc interval ≥ 480 msec; treatment refractory hypertension; uncontrolled arrhythmias; or history of RVO.

Patients who received TAFINLAR in combination with trametinib had a median duration of exposure of 11 months (range: 0 to 12) to TAFINLAR. Among the 435 patients receiving TAFINLAR in combination with trametinib, 71% were exposed to TAFINLAR for > 6 months. The median age of patients who received TAFINLAR administered with trametinib was 50 years (range: 18 to 89), 56% were male, 99% were White, 92% had baseline ECOG performance status 0, and 8% had baseline ECOG performance status of 1.

The most common adverse reactions (≥ 20%) in patients who received TAFINLAR administered with trametinib were: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia.

Adverse reactions resulting in discontinuation, dose reduction, or dose interruption of TAFINLAR occurred in 25%, 35%, and 66% of patients, respectively; the most frequent for each were pyrexia and chills.

Table 10 summarizes the adverse reactions that occurred in at least 20% of patients who received TAFINLAR administered with trametinib.

Table 10. Adverse Reactions Occurring in ≥ 20% of Patients in the COMBI-AD Study[a]

Adverse Reactions	TAFINLAR plus Trametinib N = 435		Placebo N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General				
Pyrexia[b]	63	5	11	< 1
Fatigue[c]	59	5	37	< 1
Chills	37	1	4	0
Gastrointestinal				
Nausea	40	< 1	20	0
Diarrhea	33	< 1	15	< 1
Vomiting	28	< 1	10	0
Nervous system				
Headache[d]	39	1	24	0
Skin and subcutaneous tissue				
Rash[e]	37	< 1	16	< 1
Musculoskeletal and connective tissue				
Arthralgia	28	< 1	14	0
Myalgia[f]	20	< 1	14	0

[a] NCI CTCAE version 4.0.
[b] Includes pyrexia and hyperpyrexia.
[c] Includes fatigue, asthenia, and malaise.
[d] Includes headache and tension headache.
[e] Includes rash, rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.
[f] Includes myalgia, musculoskeletal pain, and musculoskeletal chest pain.

Other clinically important adverse reactions observed in less than 20% of patients in the COMBI-AD study who received TAFINLAR administered with trametinib were: blurred vision (6%), ejection fraction decreased (5%), rhabdomyolysis (< 1%), and sarcoidosis (< 1%).

The laboratory abnormalities are summarized in Table 11.

Table 11. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the COMBI-AD Study

Laboratory Abnormality	TAFINLAR plus Trametinib[a] N = 435		Placebo[a] N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Chemistry				
Hyperglycemia	63	3	47	2
Hypophosphatemia	42	7	10	< 1
Hypoalbuminemia	25	< 1	< 1	0
Hepatic				
Increased AST	57	6	11	< 1
Increased ALT	48	5	18	< 1
Increased blood alkaline phosphatase	38	1	6	< 1
Hematology				
Neutropenia	47	6	12	< 1
Lymphopenia	26	5	6	< 1
Anemia	25	< 1	6	< 1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The incidence is based on the number of patients who had both a baseline and at least one on-study laboratory measurement: TAFINLAR plus Trametinib (range: 429 to 431) and placebo arm (range: 426 to 428).

Trial COMBI-APlus (Pyrexia Management Study)

COMBI-APlus evaluated the impact of pyrexia-related outcomes of a revised pyrexia management algorithm in patients who received dabrafenib administered with trametinib in the adjuvant treatment of BRAF V600 mutation-positive melanoma after complete resection. The pyrexia management algorithm interrupted both dabrafenib and trametinib when patient's temperature is ≥ 100.4°F.

Grade 3-4 pyrexia occurred in 4.3% of patients, hospitalizations due to pyrexia occurred in 5.1% of patients, pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) occurred in 2.2% of patients, and treatment discontinuation due to pyrexia occurred in 2.5% of patients.

Metastatic, BRAF V600E Mutation-Positive Non-Small Cell Lung Cancer

The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multi-center, multi-cohort, non-randomized, open-label trial (Study BRF113928). Patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. The trial excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), QTc interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, history of interstitial lung disease or pneumonitis, or history or current RVO *[see Clinical Studies (14.4)]*.

Among these 93 patients, 53 (57%) were exposed to TAFINLAR and trametinib for > 6 months and 27 (29%) were exposed to TAFINLAR and trametinib for ≥ 1 year. The median age was 65 years (range: 41 to 91); 46% were male; 85% were White; 32% had baseline ECOG performance status 0 and 61% had ECOG performance

status 1; 98% had non-squamous histology; and 12% were current smokers, 60% were former smokers, and 28% had never smoked.

The most common adverse reactions (≥ 20%) in these 93 patients were: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Adverse reactions leading to discontinuation of TAFINLAR occurred in 18% of patients; the most frequent were pyrexia (2.2%), decreased ejection fraction (2.2%), and respiratory distress (2.2%). Adverse reactions leading to dose reductions of TAFINLAR occurred in 35% of patients; the most frequent were pyrexia (10%), diarrhea (4.3%), nausea (4.3%), vomiting (4.3%), and neutropenia (3.2%). Adverse reactions leading to dose interruptions of TAFINLAR occurred in 62% of patients; the most frequent were pyrexia (27%), vomiting (11%), neutropenia (8%), and chills (6%).

Table 12 and Table 13 present adverse reactions and laboratory abnormalities, respectively, of TAFINLAR administered with trametinib in Study BRF113928.

Table 12. Adverse Reactions Occurring in ≥ 20% (All Grades) of Patients Treated with TAFINLAR Administered with Trametinib in Study BRF113928[a]

Adverse Reactions	TAFINLAR plus Trametinib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
General		
Pyrexia	55	5
Fatigue[b]	51	5
Edema[c]	28	0
Chills	23	1.1
Gastrointestinal		
Nausea	45	0
Vomiting	33	3.2
Diarrhea	32	2.2
Decreased appetite	29	0
Skin and subcutaneous tissue		
Dry skin	31	1.1
Rash[d]	28	3.2
Vascular		
Hemorrhage[e]	23	3.2
Respiratory system		
Cough	22	0
Dyspnea	20	5

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, malaise, and asthenia.
[c] Includes peripheral edema, edema, and generalized edema.
[d] Includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.
[e] Includes hemoptysis, hematoma, epistaxis, purpura, hematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, hematochezia, injection site hemorrhage, pulmonary hemorrhage, and retroperitoneal hemorrhage.

Other clinically important adverse reactions for TAFINLAR observed in less than 10% of patients with NSCLC receiving TAFINLAR administered with trametinib were:

Gastrointestinal: Pancreatitis

Renal and Urinary: Tubulointerstitial nephritis

Table 13. Treatment-Emergent Laboratory Abnormalities Occurring in ≥ 20% (All Grades) of Patients Who Received TAFINLAR with Trametinib in Study BRF113928

Laboratory Abnormality	TAFINLAR plus Trametinib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
Chemistry[a]		
Hyperglycemia	71	9
Hyponatremia	57	17
Hypophosphatemia	36	7
Increased creatinine	21	1.1
Hepatic[a]		
Increased blood alkaline phosphatase	64	0
Increased AST	61	4.4
Increased ALT	32	6
Hematology[b]		
Leukopenia	48	8
Anemia	46	10
Neutropenia	44	8
Lymphopenia	42	14

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] For these laboratory tests, the denominator is 90.
[b] For these laboratory tests, the denominator is 91.

Advanced BRAF V600E Mutation-Positive Tumors

Study BRF117019

The safety of TAFINLAR when administered with trametinib was evaluated in a multi-cohort, multi-center, non-randomized, open-label study in adult patients with cancers with the BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumor cohorts, and 65 in other malignancies *[see Clinical Studies (14.5, 14.6)]*. Patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity.

Among these 206 patients, 103 (50%) were exposed to TAFINLAR for ≥ 1 year and 101 (49%) were exposed to trametinib for ≥ 1 year. The median age was 60 years (range: 18 to 89); 56% were male; 79% were White; and 34% had baseline ECOG performance status 0 and 60% had ECOG performance status 1.

Serious adverse reactions occurred in 45% of patients who received TAFINLAR in combination with trametinib. Serious adverse reactions in > 5% of patients included pyrexia (11%) and pneumonia (6%). Fatal adverse reactions occurred in 3.9% of patients who received TAFINLAR in combination with trametinib. Fatal adverse reactions that occurred in > 1% of patients included sepsis (1.9%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 1% of patients included nausea (1.5%).

Dosage interruptions due to an adverse reaction occurred in 55% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (22%), chills (9%), fatigue (6%), neutropenia (6%), and nausea (5%).

Dose reductions due to an adverse reaction occurred in 44% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (18%), chills (8%), and fatigue (6%).

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, are listed in Table 14 and Table 15.

Table 14 summarizes the adverse reactions in Study BRF117019.

Table 14. Adverse Reactions (≥ 20%) in Adult Patients Treated with TAFINLAR Plus Trametinib in Study BRF117019

Adverse Reactions	TAFINLAR plus Trametinib[a] (N = 206)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	55	4.9
Fatigue[b]	50	5
Chills	30	0.5
Peripheral edema[c]	22	0
Gastrointestinal		
Nausea	40	1.5
Constipation	27	0
Vomiting	27	1.5
Diarrhea	26	2.9
Skin and subcutaneous tissue		
Rash[d]	40	2.4
Nervous system		
Headache	30	1.5
Vascular		
Hemorrhage[e]	29	4.4
Respiratory system		
Cough[f]	29	0
Musculoskeletal and connective tissue		
Myalgia[g]	24	0.5
Arthralgia	23	0.5

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia, and malaise.
[c] Includes peripheral edema and peripheral swelling.
[d] Includes rash, rash maculo-papular, rash erythematous, rash pustular, and rash papular.
[e] Includes epistaxis, hematuria, contusion, hematoma, hemoptysis, conjunctival hemorrhage, hematochezia, rectal hemorrhage, hemorrhoidal hemorrhage, melena, purpura, eye contusion, eye hemorrhage, gastric hemorrhage, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhagic stroke, hemothorax, increased tendency to bruise, large intestinal hemorrhage, mouth hemorrhage, petechiae, pharyngeal hemorrhage, prothrombin time prolonged, pulmonary hematoma, retinal hemorrhage, vaginal hemorrhage, and vitreous hemorrhage.
[f] Includes cough and productive cough.
[g] Includes myalgia, musculoskeletal chest pain, and musculoskeletal pain.

Clinically relevant adverse reactions in < 20% of adult patients who received TAFINLAR in combination with trametinib included ejection fraction decreased (8%), uveitis (1.9%) and hypersensitivity (1.9%).

Table 15 summarizes the laboratory abnormalities in Study BRF117019.

Table 15. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Adult Patients Treated with TAFINLAR Plus Trametinib in Study BRF117019

Laboratory Abnormality	TAFINLAR plus Trametinib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	61	8
Decreased sodium	35	10
Decreased magnesium	24	0
Increased creatinine	21	1.5
Hepatic		
Increased alkaline phosphatase	51	5
Increased AST	51	4.6
Increased ALT	39	3
Hematology		
Decreased hemoglobin	44	9

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The denominator used to calculate the rate varied from 199 to 202 based on the number of patients with a baseline value and at least one post-treatment value.

BRAF V600E Mutation-Positive Solid Tumors in Pediatric Patients

Study CTMT212X2101 (X2101)

The safety of TAFINLAR when administered with trametinib was evaluated in Study X2101, a multi-center, open-label, multi-cohort study in pediatric patients (n = 48) with refractory or recurrent solid tumors *[see Clinical Studies (14.6)]*. The median duration of exposure to TAFINLAR in Parts C (dose escalation) and D (cohort expansion) was 20.8 and 24.9 months, respectively. The median duration of exposure to trametinib in Parts C and D was 20.8 and 24.4 months, respectively. The median age of pediatric patients who received TAFINLAR with trametinib was 9 years (range: 1 to 17).

Serious adverse reactions occurred in 46% of patients who received TAFINLAR in combination with trametinib. Serious adverse reactions in > 5% of patients included pyrexia (25%) and ejection fraction decreased (6%). Permanent treatment discontinuation due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 3% of patients included ALT increased (6%), AST increased (4.2%) and ejection fraction decreased (4.2%). Dosage interruptions due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (56%), vomiting (19%), neutropenia (13%), rash (13%), ejection fraction decreased (6%), and uveitis (6%). Dose reductions due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (13%).

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, are listed in Table 16 and Table 17.

Table 16 summarizes the adverse reactions in Study X2101.

Table 16. Adverse Reactions (≥ 20%) in Pediatric Patients Treated with TAFINLAR Plus Trametinib in Study X2101[a]

Adverse Reactions	TAFINLAR plus Trametinib[a] (N = 48)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	75	17
Fatigue[b]	48	0
Skin and subcutaneous tissue		
Rash[c]	73	2.1
Dry skin	48	0
Dermatitis acneiform[d]	40	0
Gastrointestinal		
Vomiting	52	4.2
Diarrhea	42	2.1
Abdominal pain[e]	33	4.2
Nausea	33	2.1
Constipation	23	0
Respiratory system		
Cough	44	0
Nervous system		
Headache	35	0
Vascular		
Hemorrhage[f]	33	0
Infections and infestations		
Paronychia	23	0

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia, and malaise.
[c] Includes rash, rash maculo-papular, rash erythematous, rash papular, rash pustular, and rash macular.
[d] Includes dermatitis acneiform and acne.
[e] Includes abdominal pain and abdominal pain upper.
[f] Includes epistaxis, hematuria, contusion, hematoma, petechiae, rectal hemorrhage, and red blood cell count decreased.

Table 17 summarizes the laboratory abnormalities in Study X2101.

Table 17. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Pediatric Patients Treated with TAFINLAR Plus Trametinib in Study X2101

Laboratory Abnormality	TAFINLAR plus Trametinib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	65	2.2
Hypoalbuminemia	48	2.1
Hypocalcemia	40	2.1
Decreased phosphate	38	0
Decreased magnesium	33	2.1
Hypernatremia	27	0
Hypokalemia	21	2.1
Hepatic		
Increased AST	55	4.2
Increased ALT	40	6
Increased alkaline phosphatase	28	6
Increased total bilirubin	21	2.1
Hematology		
Decreased hemoglobin	60	6
Decreased neutrophils	49	28

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] The denominator used to calculate the rate varied from 39 to 48 based on the number of patients with a baseline value and at least one post-treatment value.

BRAF V600E Mutation-Positive Low-Grade Glioma in Pediatric Patients

Study CDRB436G2201 (G2201)

The safety of TAFINLAR in combination with trametinib was evaluated in pediatric patients 1 to < 18 years of age in Study G2201. Patients with low-grade glioma (LGG) who required first systemic therapy were randomized (2:1) to TAFINLAR plus trametinib (n = 73) or carboplatin plus vincristine (n = 33). Nine patients crossed over from the carboplatin plus vincristine arm to the TAFINLAR and trametinib arm. Pediatric patients received weight-based TAFINLAR orally twice daily administered in combination with trametinib until disease progression or intolerable toxicity. Patients in the control arm received carboplatin and vincristine at doses of 175 mg/m^2 and 1.5 mg/m^2, respectively in 10-week induction course followed by eight 6-week cycles of maintenance therapy or until disease progression or intolerable toxicity. Among patients with low-grade glioma who were randomized to TAFINLAR plus trametinib (n = 73), 95% were exposed for 6 months or longer and 71% were exposed for greater than one year.

The median age of these patients was 10 years (range: 1 to 17); 60% female; 75% White, 7% Asian, 2.7% Black or African American, 4% other race and 11% where race was unknown or not reported.

Serious adverse reactions occurred in 40% of these patients. Serious adverse reactions in > 3% of patients included pyrexia (14%) and vomiting (4%).

Permanent discontinuation of TAFINLAR due to an adverse reaction occurred in 4% of patients. Adverse reactions which resulted in permanent discontinuation of TAFINLAR included chills, fatigue, pyrexia, weight increased, and headache.

Dosage interruptions of TAFINLAR due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (53%).

Dose reductions of TAFINLAR due to an adverse reaction occurred in 48% of patients. Adverse reactions which required dose reductions in > 2% of patients included rash (2.7%). The most common (≥ 15%) adverse reactions were pyrexia (68%), rash (51%), headache (47%), vomiting (34%), musculoskeletal pain (34%), fatigue (33%), diarrhea (29%), dry skin (26%), nausea (25%), hemorrhage (25%), abdominal pain (25%), dermatitis acneiform (22%), dizziness (15%), upper respiratory tract infection (15%), and weight increased (15%).

The most common (≥ 20%) laboratory abnormalities that worsened from baseline were leukopenia (59%), increased alkaline phosphatase (55%), anemia (46%), decreased neutrophils (44%), increased AST (37%), decreased magnesium (34%), increased magnesium (32%), decreased platelets (30%), increased ALT (29%), and increased lymphocytes (24%).

Table 18 summarizes the adverse reactions in Study G2201.

Table 18. Adverse Reactions (≥ 15%) in Pediatric LGG Patients Who Received TAFINLAR in Combination with Trametinib in Study G2201[a]

Adverse Reactions	**TAFINLAR plus Trametinib N = 73**		**Carboplatin plus Vincristine N = 33**	
	All Grades (%)	**Grade ≥ 3 (%)**	**All Grades (%)**	**Grade ≥ 3 (%)**
Gastrointestinal				
Vomiting	34	1	48	3
Diarrhea[b]	29	0	18	6
Nausea	25	0	45	0
Abdominal pain[c]	25	0	24	0
Constipation	12	0	36	0
Stomatitis[d]	10	0	18	0

General				
Pyrexia[e]	68	8	18	3
Fatigue[f]	33	0	39	0
Nervous system				
Headache[g]	47	1	33	3
Dizziness[h]	15	0	9	3
Peripheral neuropathy[i]	7	0	45	6
Vascular				
Hemorrhage[j]	25	0	12	0
Skin and subcutaneous tissue				
Rash[k]	51	2.7	18	3
Dry skin	26	0	3	0
Dermatitis acneiform[l]	22	0	0	0
Alopecia	3	0	24	0
Musculoskeletal and connective tissue				
Musculoskeletal pain[m]	34	0	30	0
Pain in jaw	1.4	0	18	0
Metabolism and nutrition				
Decreased appetite	5	0	24	0
Respiratory, thoracic and mediastinal				
Oropharyngeal pain	11	0	18	0
Psychiatric				
Anxiety	1.4	0	15	3
Immune system				
Hypersensitivity	0	0	15	3
Infections and infestations				
Upper respiratory tract infection	15	0	6	0
Injury, poisoning and procedural complications				
Infusion related reaction	0	0	15	3
Investigations				
Weight increased	15	7	0	0

[a] NCI CTCAE version 4.03.
[b] Includes diarrhea, colitis, enterocolitis, and enteritis.
[c] Includes abdominal pain and upper abdominal pain.
[d] Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, and glossitis.
[e] Includes pyrexia and body temperature increased.
[f] Includes fatigue and asthenia.
[g] Includes headache and migraine with aura.
[h] Includes dizziness and vertigo.
[i] Includes peripheral neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, neuralgia, hypoaesthesia, and peripheral sensory neuropathy.
[j] Includes epistaxis, post-procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, and hemorrhage intracranial.
[k] Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysaesthesia syndrome, and dermatitis bullous.
[l] Includes dermatitis acneiform, acne, and acne pustular.
[m] Includes back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain, and musculoskeletal stiffness.

Table 19 summarizes the laboratory abnormalities in Study G2201.

Table 19. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Pediatric LGG Patients Who Received TAFINLAR in Combination with Trametinib in Study G2201[a]

Laboratory Abnormality	TAFINLAR plus Trametinib N = 73		Carboplatin plus Vincristine N = 33	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hepatic				
Increased alkaline phosphatase	55	0	13	0
Increased AST	37	1.4	55	0
Increased ALT	29	3	61	9
Chemistry				
Decreased magnesium	34	4.1	76	6
Increased magnesium	32	0	24	3
Increased potassium	15	4.2	21	6
Decreased calcium	14	4.1	22	9
Decreased potassium	8	1.4	70	0
Decreased phosphate	7	2.7	33	3
Decreased sodium	5	1.4	27	6
Increased serum fasting glucose	0	0	44	0
Hematology				
Decreased leukocytes	59	0	91	18
Decreased hemoglobin	46	0	94	36
Decreased neutrophils	44	17	84	75
Decreased platelets	30	0	73	18
Increased lymphocytes	24	0	13	3.1
Decreased lymphocytes	16	1.4	56	6

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The denominator used to calculate the rate varied from 70 to 73 in D + T arm and 9 to 33 in C + V arm based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TAFINLAR in combination with trametinib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic: SCAR (including DRESS and SJS) *[see Warnings and Precautions (5.7)]*

Immune System: Hemophagocytic lymphohistiocytosis (HLH) *[see Warnings and Precautions (5.11)]*

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on TAFINLAR

Strong inhibitors of CYP3A4 or CYP2C8 may increase the concentration of dabrafenib *[see Clinical Pharmacology (12.3)]*. Substitution of strong inhibitors of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors.

7.2 Effects of TAFINLAR on Other Drugs

Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate) *[see Clinical Pharmacology (12.3)]*. Monitor international normalized ratio (INR) levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of TAFINLAR with other substrates of these enzymes, including dexamethasone or hormonal contraceptives, can result in decreased concentrations and loss of

efficacy *[see Use in Specific Populations (8.1, 8.3)]*. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, TAFINLAR can cause fetal harm when administered to a pregnant woman. There is insufficient data in pregnant women exposed to TAFINLAR to assess the risks. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended adult clinical dose of 150 mg twice daily *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a combined female fertility and embryo-fetal development study in rats conducted during the period of organogenesis, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day [approximately three times the human exposure at the recommended adult dose based on area under the curve (AUC)]. At doses of 20 mg/kg/day or greater (equivalent to the human exposure at the recommended adult dose based on AUC), rats demonstrated delays in skeletal development and reduced fetal body weight.

8.2 Lactation

Risk Summary

There are no data on the presence of dabrafenib in human milk, or the effects of dabrafenib on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with TAFINLAR and for 2 weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TAFINLAR.

Contraception

Based on data from animal studies and its mechanism of action, TAFINLAR can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Females

Advise female patients of reproductive potential to use effective contraception during treatment with TAFINLAR and for 2 weeks after the last dose. Counsel patients to use a non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

To avoid potential drug exposure to pregnant partners and female partners of reproductive potential, advise male patients (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with TAFINLAR and for 2 weeks after the last dose.

Infertility

Females

Advise female patients of reproductive potential that TAFINLAR may impair fertility. A reduction in fertility was observed in female rats at dose exposures equivalent to the human exposure at the recommended adult dose. A reduction in the number of corpora lutea was noted in pregnant rats at dose exposures approximately three times the human exposure at the recommended adult dose *[see Nonclinical Toxicology (13.1)]*.

Males

Advise male patients of the potential risk for impaired spermatogenesis which may be irreversible. Effects on spermatogenesis have been observed in animals treated with dabrafenib at dose exposures up to three times the human exposure at the recommended adult dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors and LGG

The safety and effectiveness of TAFINLAR in combination with trametinib have been established in pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; or with LGG with BRAF V600E mutation who require systemic therapy. Use of TAFINLAR in combination with trametinib for these indications is supported by evidence from studies X2101 and G2201 that enrolled 171 patients (1 to < 18 years) with BRAF V600 mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (23%) patients were 2 to < 6 years of age, 54 (32%) patients were 6 to < 12 years of age, and 74 (43%) patients were 12 to < 18 years of age *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.6, 14.7)]*.

The safety and effectiveness of TAFINLAR in combination with trametinib have not been established for these indications in pediatric patients less than 1 year old.

The safety and effectiveness of TAFINLAR as a single agent in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a repeat-dose toxicity study in juvenile rats, an increased incidence of kidney cysts and tubular deposits were noted at doses as low as 0.2 times the human exposure at the recommended adult dose based on AUC. Additionally, forestomach hyperplasia, decreased bone length, and early vaginal opening were noted at doses as low as 0.8 times the human exposure at the recommended adult dose based on AUC.

8.5 Geriatric Use

Of the 586 patients with various solid tumors who received single agent TAFINLAR, 22% were aged 65 years and older. Of the 187 patients with melanoma who received single-agent TAFINLAR in the BREAK-3 study, 21% were aged 65 years or older *[see Clinical Studies (14.1)]*. No overall differences in the effectiveness or safety of TAFINLAR were observed between geriatric patients as compared to younger adults in the BREAK-3 study.

Of the 994 patients with melanoma who received TAFINLAR plus trametinib in the COMBI-d, COMBI-v, and COMBI-AD studies *[see Clinical Studies (14.2, 14.3)]*, 21% were aged 65 years and older and 5% were aged 75 years and older. No overall differences in the effectiveness of TAFINLAR plus trametinib were observed in geriatric patients as compared to younger adults across these melanoma studies. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs. 9%) were increased in geriatric patients as compared to younger adults in these studies.

Of the 171 patients with NSCLC who received TAFINLAR in Study BRF113928, there were insufficient numbers of geriatric patients to determine whether they respond differently from younger adults *[see Clinical Studies (14.4)]*.

Of the 26 patients with ATC who received TAFINLAR in Study BRF117019, 77% were aged 65 years and older, and 31% were aged 75 years and older *[see Clinical Studies (14.5)]*. This study in ATC did not include sufficient numbers of younger adults to determine whether they respond differently compared to geriatric patients.

8.6 Hepatic Impairment

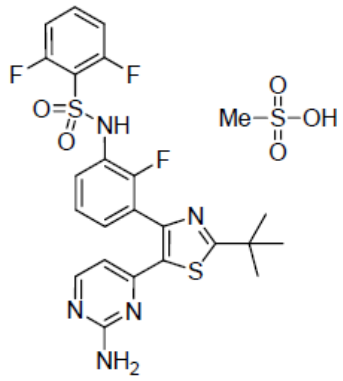
Dose adjustment is not recommended for patients with mild (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or bilirubin > 1x to 1.5x ULN and any AST) hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) to severe (bilirubin > 3x to 10x ULN and any AST) hepatic impairment may have increased exposure. An appropriate dosage has not been established for patients with moderate to severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdosage of TAFINLAR. Since dabrafenib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with TAFINLAR.

11 DESCRIPTION

Dabrafenib mesylate is a kinase inhibitor. The chemical name for dabrafenib mesylate is N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt. It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$ and a molecular weight of 615.68 g/mol. Dabrafenib mesylate has the following chemical structure:



Dabrafenib mesylate is a white to slightly colored solid with three pK_as: 6.6, 2.2, and -1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

TAFINLAR (dabrafenib) capsules for oral use are supplied as 50 mg and 75 mg capsules for oral administration. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75 mg capsule contains 88.88 mg dabrafenib mesylate equivalent to 75 mg of dabrafenib free base. The inactive ingredients of TAFINLAR capsules are colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171).

TAFINLAR (dabrafenib) tablets for oral suspension are supplied as 10 mg tablets for oral administration. Each 10 mg tablet contains 11.85 mg dabrafenib mesylate equivalent to 10 mg of dabrafenib base. The inactive ingredients of TAFINLAR tablets are, acesulfame potassium, artificial berry flavor, colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits

wild-type BRAF and CRAF kinases with IC_{50} values of 3.2 and 5.0 nM, respectively, and other kinases, such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth *[see Indications and Usage (1)]*. Dabrafenib inhibits cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo.

Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation-positive tumor xenografts compared with either drug alone.

In the setting of BRAF-mutant colorectal cancer, induction of EGFR-mediated MAPK pathway re-activation has been identified as a mechanism of intrinsic resistance to BRAF inhibitors *[see Indications and Usage (1.8)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The potential effect of TAFINLAR on QT interval was assessed in a dedicated multiple-dose study in 32 patients with BRAF V600 mutation-positive tumors. No large changes in the mean QT interval (i.e., > 20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage).

In clinical trials, QTc (heart rate-corrected QT) prolongation to ≥ 500 ms occurred in 0.8% of 264 patients who received TAFINLAR with trametinib and in 1.5% of patients who received TAFINLAR as a single agent. The QTc was increased > 60 ms from baseline in 3.8% of patients who received TAFINLAR with trametinib and 3% of patients treated with TAFINLAR as a single agent.

12.3 Pharmacokinetics

Following administration of TAFINLAR capsules, dabrafenib C_{max} and AUC increased in a dose-proportional manner across the dose range of 12 mg (0.08 times the approved recommended adult dose) to 300 mg (2 times the approved recommended adult dose), but the increase was less than dose-proportional after steady state twice-daily dosing. After twice-daily dosing, the mean accumulation ratio was 0.7, and the inter-subject variability (CV%) of AUC at steady-state was 38%.

Absorption

The median time to achieve peak plasma concentration (T_{max}) is 2 hours. Mean absolute bioavailability of TAFINLAR capsules is 95% and TAFINLAR tablets for oral suspension is 76%.

Effect of Food

Following administration of TAFINLAR capsules, a high-fat meal (approximately 1000 calories, 58-75 grams fat, 58 grams carbohydrates, and 33 grams protein) decreased C_{max} by 51%, decreased AUC by 31%, and delayed median T_{max} by 3.6 hours as compared with the fasted state.

Distribution

Dabrafenib is 99.7% bound to human plasma proteins. The apparent volume of distribution (V_c/F) is 70.3 L.

Elimination

The mean terminal half-life is 8 hours. Hydroxy-dabrafenib terminal half-life (10 hours) parallels that of dabrafenib while the carboxy- and desmethyl-dabrafenib metabolites exhibit longer half-lives (21 to 22 hours). The apparent clearance of dabrafenib is 17 L/h after a single dose and 34 L/h after twice-daily dosing for 2 weeks.

Metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib. Hydroxy-dabrafenib is further oxidized via CYP3A4 to form carboxy-dabrafenib and subsequently excreted in bile and urine. Carboxy-dabrafenib is decarboxylated to form desmethyl-dabrafenib; desmethyl-dabrafenib may

be reabsorbed from the gut. Desmethyl-dabrafenib is further metabolized by CYP3A4 to oxidative metabolites. Mean metabolite-to-parent AUC ratios following repeat-dose administration are 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on systemic exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib.

Excretion

Fecal excretion is the major route of elimination accounting for 71% of radioactive dose while urinary excretion accounted for 23% of total radioactivity as metabolites only.

Specific Populations

Age (18 to 93 years), sex, weight (36 to 170 kg), and renal impairment (eGFR 15 to 89 mL/min/1.73 m^2) have no clinically relevant effect on the pharmacokinetics of dabrafenib.

Pediatric Patients

The pharmacokinetics of dabrafenib in glioma and other solid tumors were evaluated in 243 patients aged 1 to < 18 years following a single dose or multiple doses. Pharmacokinetic parameters in patients aged 1 to < 18 years are within range of values previously observed in adults give the same dose based on weight. Weight (6 to 156 kg) had a statistically significant effect on dabrafenib oral clearance in this population.

Patients with Hepatic Impairment

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1x to 1.5x ULN and any AST) has no effect on systemic exposure to dabrafenib and its metabolites. No data are available in patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) or severe (bilirubin > 3x to 10x ULN and any AST) hepatic impairment.

Drug Interaction Studies

Effect of Trametinib on Dabrafenib: Coadministration of TAFINLAR 75 mg twice daily with trametinib 2 mg daily resulted in a 23% increase in AUC of dabrafenib, a 33% increase in AUC of desmethyl-dabrafenib, and no change in AUC of hydroxy-dabrafenib as compared with administration of dabrafenib.

Effect of Strong Inhibitors of CYP3A4 or CYP2C8 on Dabrafenib: Coadministration of TAFINLAR 75 mg twice daily and ketoconazole (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%.

Coadministration of TAFINLAR 75 mg twice daily and gemfibrozil (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites.

Effect of Strong Inducers of CYP3A4 or Moderate Inducers of CYP2C8 on Dabrafenib: Coadministration of TAFINLAR 150 mg twice daily and rifampin (a strong CYP3A4 and moderate CYP2C8 inducer) for 10 days decreased dabrafenib AUC by 34% and desmethyl-dabrafenib AUC by 30%, and had no effect on hydroxy-dabrafenib AUC.

Effect of Acid Reducing Agents on Dabrafenib: Coadministration of TAFINLAR 150 mg twice daily and rabeprazole for 4 days did not result in clinically relevant changes in exposures to dabrafenib and its metabolites.

Effect of Dabrafenib on CYP Substrates: Coadministration of TAFINLAR 150 mg twice daily for 15 days and a single dose of midazolam (a CYP3A4 substrate) decreased midazolam AUC by 65%. Coadministration of TAFINLAR 150 mg twice daily for 15 days and a single dose of warfarin decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (CYP3A4/CYP1A2 substrate) by 33%.

In vitro data demonstrate that dabrafenib is an inducer of CYP3A4 and CYP2B6 via activation of the pregnane X receptor (PXR) and constitutive androstane receptor (CAR) nuclear receptors. Dabrafenib may also induce CYP2C enzymes via the same mechanism.

Effect of Transporters on Dabrafenib: Dabrafenib and its metabolites, hydroxyl-dabrafenib and desmethyl-dabrafenib, are substrates of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but are not substrates of organic cation transporter (OCT1) or organic anion transporting polypeptide (OATP1A2, OATP1B1, OATP1B3, OATP2B1) in vitro.

Effect of Dabrafenib on Transporters: Coadministration of TAFINLAR 150 mg twice daily with a single dose of rosuvastatin (a sensitive OATP1B1 and OATP1B3 substrate) increased rosuvastatin C_{max} by 2.6-fold but did not change its AUC.

Dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, are inhibitors of organic anion transporter (OAT1 and OAT3) in vitro. Dabrafenib and desmethyl-dabrafenib are inhibitors of OCT2 and BCRP in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. TAFINLAR increased the risk of cuSCCs in patients in clinical trials.

Dabrafenib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay and was not clastogenic in an in vivo rat bone marrow micronucleus test.

In a combined female fertility and embryo-fetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended adult dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day (which is approximately three times the human exposure at the recommended adult dose based on AUC).

Male fertility studies with dabrafenib have not been conducted; however, in repeat-dose studies, testicular degeneration/depletion was seen in rats and dogs at doses equivalent to and three times the human exposure at the recommended adult dose based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

Adverse cardiovascular effects were noted in dogs at dabrafenib doses of 50 mg/kg/day (approximately five times the human exposure at the recommended adult dose based on AUC) or greater, when administered for up to 4 weeks. Adverse effects consisted of coronary arterial degeneration/necrosis and hemorrhage, as well as cardiac atrioventricular valve hypertrophy/hemorrhage.

14 CLINICAL STUDIES

14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR As a Single Agent

BREAK-3 Study

The safety and efficacy of TAFINLAR as a single agent were evaluated in an international, multi-center, randomized (3:1), open-label, active-controlled trial (the BREAK-3 study; NCT01227889) conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. Patients were randomized to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n = 63). Randomization was stratified by disease stage at baseline [unresectable Stage III (regional nodal or in-transit metastases), M1a (distant skin, subcutaneous, or nodal metastases), or M1b (lung metastases) versus M1c melanoma (all other visceral metastases or elevated serum LDH)]. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. In addition, an independent radiology review committee (IRRC) assessed the following efficacy outcome measures in pre-specified supportive analyses: PFS, confirmed overall response rate (ORR), and duration of response (DoR).

The median age of patients in the BREAK-3 study was 52 years. The majority of the trial population was male (60%), White (99%), had an ECOG performance status of 0 (67%), M1c disease (66%), and normal LDH (62%). All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF assay.

The median durations of follow-up prior to initiation of alternative treatment in patients randomized to receive TAFINLAR was 5.1 months and in the dacarbazine arm was 3.5 months. Twenty-eight (44%) patients crossed over from the dacarbazine arm at the time of disease progression to receive TAFINLAR.

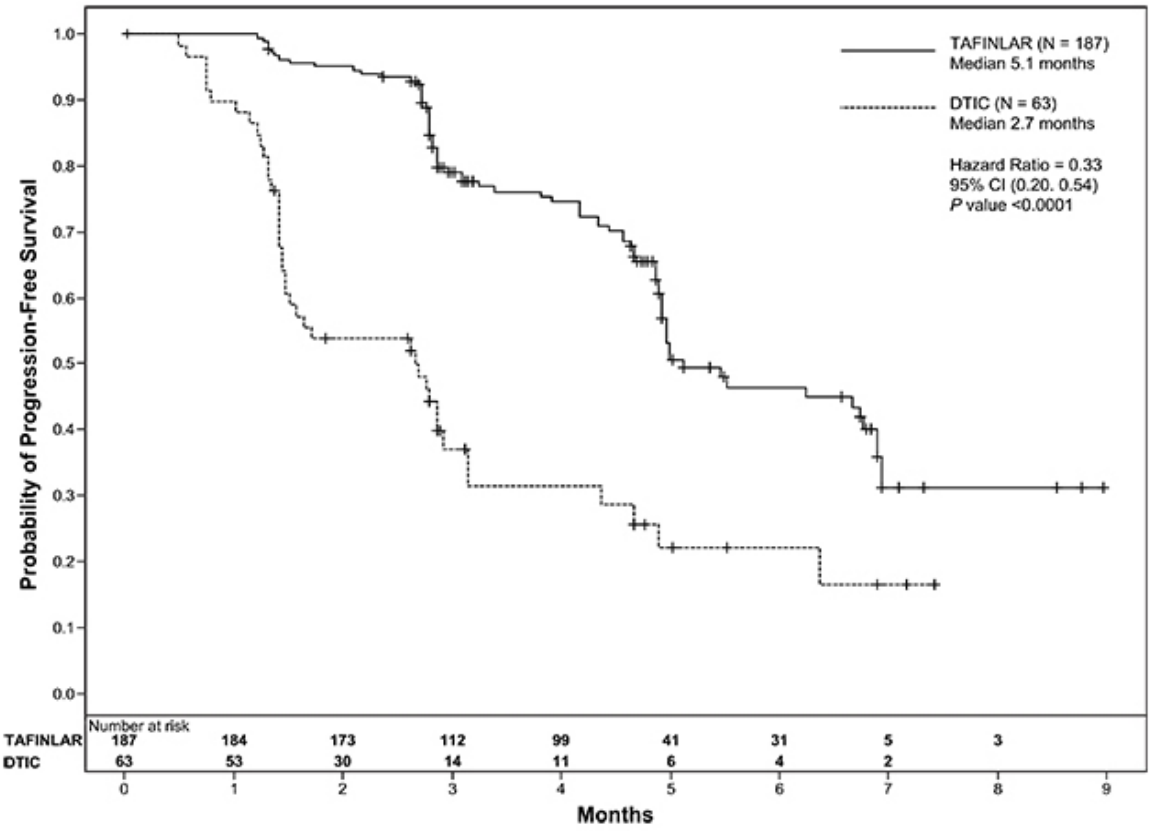
The BREAK-3 study demonstrated a statistically significant increase in progression-free survival in the patients treated with TAFINLAR. Table 20 and Figure 1 summarize the PFS results.

Table 20. Investigator-Assessed Progression-Free Survival and Confirmed Overall Response Results in the BREAK-3 Study

Investigator-Assessed Endpoints	**TAFINLAR N = 187**	**Dacarbazine N = 63**
Progression-Free Survival		
Number of events (%)	78 (42%)	41 (65%)
Progressive disease	76	41
Death	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR[a] (95% CI)	0.33 (0.20, 0.54)	
P value[b]	< 0.0001	
Confirmed Tumor Responses		
Overall response rate (95% CI)	52% (44%, 59%)	17% (9%, 29%)
Complete response, n (%)	6 (3%)	0
Partial response, n (%)	91 (48%)	11 (17%)
Duration of response		
Median DoR, months (95% CI)	5.6 (5.4, NR)	NR (5.0, NR)

Abbreviations: DoR, duration of response; CI, confidence interval; HR, hazard ratio; NR, not reached.
[a] Pike estimator, stratified by disease state.
[b] Stratified log-rank test.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival in the BREAK-3 Study



In supportive analyses based on IRRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis.

BREAK-MB Study

The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multi-center trial (the BREAK-MB study; NCT01266967). All patients received TAFINLAR 150 mg twice daily. Patients in Cohort A (n = 74) had received no prior local therapy for brain metastases, while patients in Cohort B (n = 65) had received at least one local therapy for brain metastases, including, but not limited to, surgical resection, whole brain radiotherapy, or stereotactic radiosurgery, such as gamma knife, linear-accelerated-based radiosurgery, or charged particles. In addition, patients in Cohort B were required to have evidence of disease progression in a previously treated lesion or an untreated lesion. Additional eligibility criteria were at least one measurable lesion of 0.5 cm or greater in largest diameter on contrast-enhanced MRI, stable or decreasing corticosteroid dose, and no more than two prior systemic regimens for treatment of metastatic disease. The major efficacy outcome measure was estimation of the overall intracranial response rate (OIRR) in each cohort.

The median age of patients in Cohort A was 50 years, 72% were male, 100% were White, 59% had a pre-treatment ECOG performance status of 0, and 57% had an elevated LDH value at baseline. The median age of patients in Cohort B was 51 years, 63% were male, 98% were White, 66% had a pre-treatment ECOG performance status of 0, and 54% had an elevated LDH value at baseline. The intracranial response rate as determined by an independent radiology review committee, masked to investigator response assessments, was 18% (95% CI: 10%, 28%) in Cohort A and 18% (95% CI: 10%, 30%) in Cohort B. The median duration of intracranial response was 4.6 months in both cohorts.

14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR With Trametinib

COMBI-d Study and COMBI-v Study

The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908).

The COMBI-d study compared TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or TAFINLAR 150 mg twice daily plus matching placebo. Randomization was stratified by LDH level (> ULN vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

The COMBI-v study compared TAFINLAR and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (> ULN vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1.

In the COMBI-d study, 423 patients were randomized to TAFINLAR plus trametinib (n = 211) or TAFINLAR plus placebo (n = 212). The median age was 56 years (range: 22 to 89), 53% were male, > 99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIC, 66% had M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing with the FDA-approved companion diagnostic test; 85% with BRAF V600E mutations and 15% with BRAF V600K mutations.

In the COMBI-v study, 704 patients were randomized to TAFINLAR plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91), 96% were White, and 55% were male, 6% percent of patients had Stage IIIC, 61% had M1c disease, 67% had a normal LDH, 70% had ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases.

The COMBI-d and COMBI-v studies demonstrated statistically significant improvements in OS and PFS. Table 21 and Figures 2 and 3 summarize the efficacy results.

Table 21. Efficacy Results in Patients with BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma[a]

Endpoint	COMBI-d Study		COMBI-v Study	
	TAFINLAR plus Trametinib N = 211	TAFINLAR plus Placebo N = 212	TAFINLAR plus Trametinib N = 352	Vemurafenib N = 352
Overall Survival				
Number of deaths (%)	99 (47%)	123 (58%)	100 (28%)	122 (35%)
Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.1)	NR (18.3, NR)	17.2 (16.4, NR)
HR (95% CI)	0.71 (0.55, 0.92)		0.69 (0.53, 0.89)	
P value (log-rank test)	0.01		0.005[a]	
Progression-Free Survival[b]				
Number of events (%)	102 (48%)	109 (51%)	166 (47%)	217 (62%)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
HR (95% CI)	0.75 (0.57, 0.99)		0.56 (0.46, 0.69)	
P value (log-rank test)	0.035		< 0.001	
Overall Response Rate[b]				
ORR (95% CI)	66% (60%, 73%)	51% (44%, 58%)	64% (59%, 69%)	51% (46%, 56%)
P value	< 0.001		< 0.001	
Complete response	10%	8%	13%	8%
Partial response	56%	42%	51%	43%
Median DoR, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

Abbreviations: DoR, duration of response; ORR, overall response rate; CI, confidence interval; HR, hazard ratio; NR, not reached.
[a] P-value is comparing with the allocated alpha of 0.021 for the interim analysis based on 77% information.
[b] PFS and ORR were assessed by investigator.

Figure 2. Kaplan-Meier Curves for Overall Survival in the COMBI-d Study

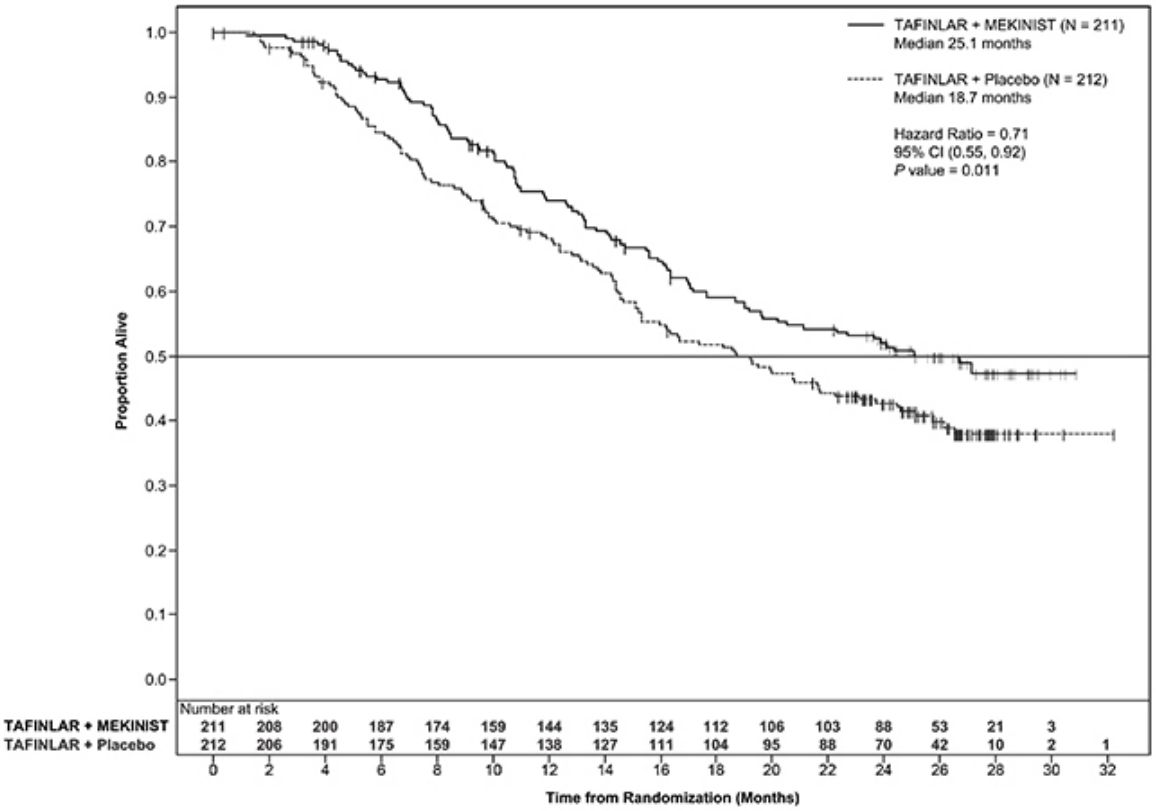
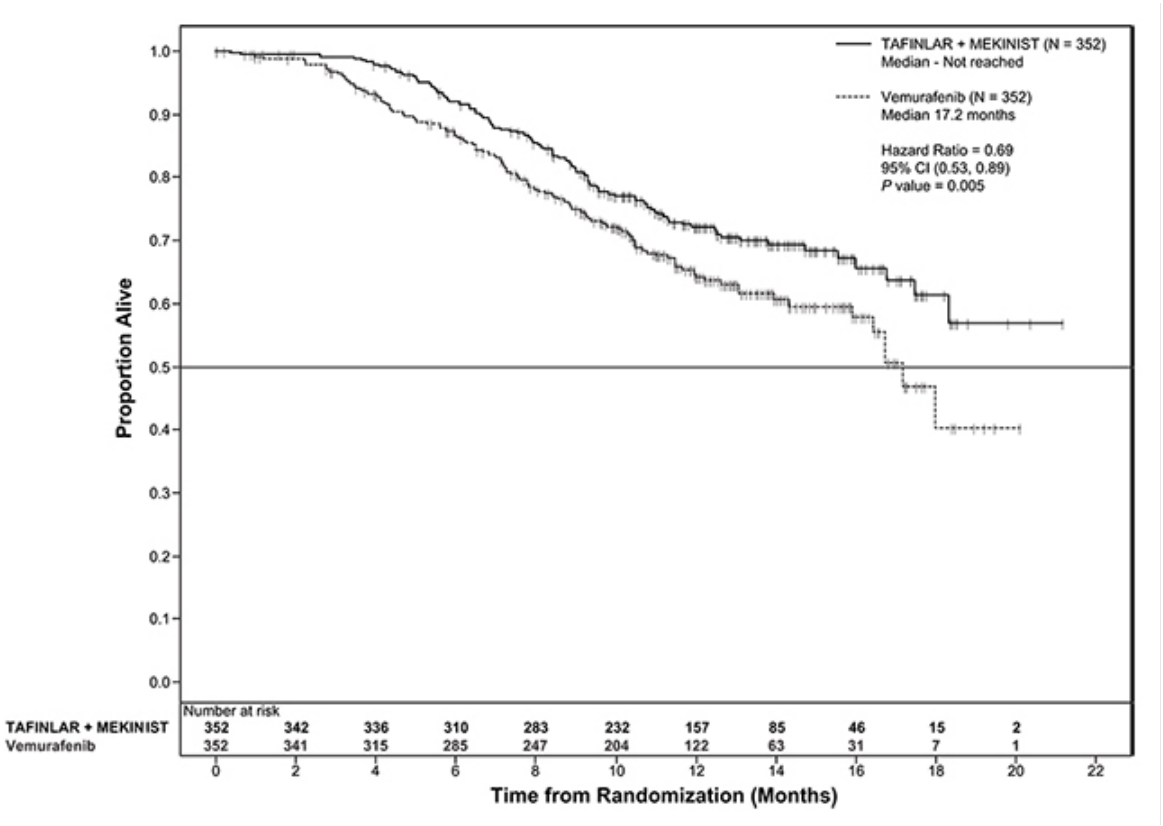


Figure 3. Kaplan-Meier Curves for Overall Survival in the COMBI-v Study



COMBI-MB Study

The activity of TAFINLAR with trametinib for the treatment of BRAF V600E or V600K mutation-positive melanoma, metastatic to the brain, was evaluated in a non-randomized, open-label, multi-center, multi-cohort trial (the COMBI-MB study; NCT02039947). Eligible patients were required to have at least one measurable intracranial lesion and to have no leptomeningeal disease, parenchymal brain metastasis greater than 4 cm in diameter, ocular melanoma, or primary mucosal melanoma. Patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was intracranial response rate, defined as the percentage of patients with a confirmed intracranial response per RECIST v1.1, modified to allow up to five intracranial target lesions at least 5 mm in diameter, as assessed by independent review.

The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84), 58% were male, 100% were White, 8% were from the United States, 65% had a normal LDH value at baseline, and 97% had an ECOG performance status of 0 or 1. Intracranial metastases were asymptomatic in 87% and symptomatic in 13% of patients, 22% received prior local therapy for brain metastases, and 87% also had extracranial metastases.

The intracranial response rate was 50% (95% CI: 41, 60), with a complete response rate of 4.1% and a partial response rate of 46%. The median duration of intracranial response was 6.4 months (range: 1 to 31). Of the patients with an intracranial response, 9% had stable or progressive disease as their best overall response.

14.3 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

COMBI-AD (NCT 01682083) was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations as detected by the THxID™-BRAF assay and pathologic involvement of regional lymph node(s). Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or two placebos for up to 1 year. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable in-transit metastases, distant metastatic disease, or prior systemic anti-cancer treatment, including radiotherapy. Randomization was stratified by BRAF mutation status (V600E or V600K) and American Joint Committee on Cancer (AJCC; 7th Edition) stage (IIIa, IIIb, or IIIc). The major efficacy outcome measure was relapse-free survival (RFS), defined as the time from randomization to disease recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first as assessed by the investigator. Patients underwent imaging for tumor recurrence every 3 months for the first two years and every 6 months thereafter.

In COMBI-AD, a total of 870 patients were randomized: 438 to TAFINLAR administered with trametinib and 432 to placebo. Median age was 51 years (range: 18 to 89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%). The median duration of follow-up (time from randomization to last contact or death) was 2.8 years.

COMBI-AD showed a statistically significant improvement in RFS in patients randomized to TAFINLAR administered with trametinib compared to those randomized to placebo. Efficacy results are presented in Table 22 and Figure 4.

Table 22. Efficacy Results in COMBI-AD in the Adjuvant Treatment of Melanoma

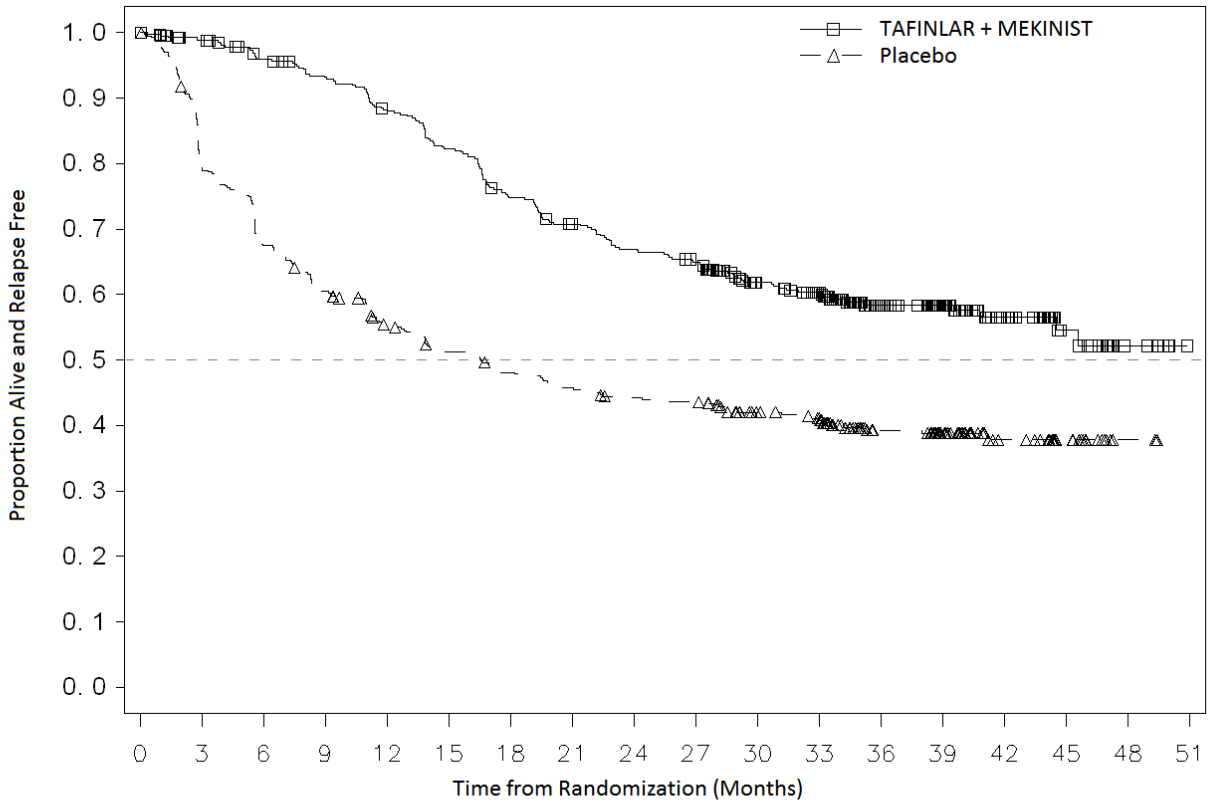
Endpoint	**TAFINLAR plus Trametinib N = 438**	**Placebo N = 432**
Relapse-Free Survival		
Number of events (%)	166 (38)	248 (57)
Median, months (95% CI)	NE (44.5, NE)	16.6 (12.7, 22.1)
HR (95% CI)[a]	0.47 (0.39, 0.58)	
P value[b]	< 0.0001	

Abbreviations: HR, hazard ratio; CI, confidence interval; NE, not estimable.

[a] Pike estimator obtained from the stratified log-rank test estimator.

[b] Log-rank test stratified by disease stage (IIIA vs. IIIB vs. IIIC) and BRAF V600 mutation type (V600E vs. V600K).

Figure 4. Kaplan-Meier Curves for Relapse-Free Survival in COMBI-AD in the Adjuvant Treatment of Melanoma



Subjects at Risk

TAFINLAR + MEKINIST	438	411	392	377	355	330	299	279	263	253	202	187	116	83	52	23	7	0
Placebo	432	335	280	250	219	199	185	176	168	166	141	132	87	62	33	16	3	0

14.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety and efficacy of TAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial (Study BRF113928, NCT01336634). Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK-inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). Patients enrolled in Cohorts A and B were required to have received at least one previous platinum-based chemotherapy regimen for NSCLC with demonstrated disease progression but no more than three prior systemic regimens. Patients enrolled in Cohort C could not have received prior systemic therapy for metastatic NSCLC. Patients in Cohort A received TAFINLAR 150 mg twice daily. Patients in Cohorts B and C received TAFINLAR 150 mg twice daily and trametinib 2 mg once daily. The major efficacy outcome measure was overall response rate (ORR) per RECIST v1.1 as assessed by independent review committee (IRC) and DoR.

There were a total of 171 patients enrolled which included 78 patients enrolled in Cohort A, 57 patients enrolled in Cohort B, and 36 patients enrolled in Cohort C. The characteristics of the study population were: a median age of 66 years, 48% male; 81% White, 14% Asian, 3% Black, and 2% Hispanic; 60% former smokers, 32% never smokers, and 8% current smokers; 27% had ECOG performance status (PS) 0, 63% had ECOG PS 1, and 11% had ECOG PS of 2; 99% had metastatic disease of which 6% had brain metastasis at baseline and 14% had liver metastasis at baseline; 11% had systemic anti-cancer therapy in the adjuvant setting and 58% of the 135 previously treated patients had only one line of prior systemic therapy for metastatic disease; and 98% had non-squamous histology.

Efficacy results are summarized in Table 23.

Table 23. Efficacy Results Based on Independent Review in Study BRF113928

Treatment	TAFINLAR	TAFINLAR + Trametinib	
Population	**Previously Treated N = 78**	**Previously Treated N = 57**	**Treatment Naïve N = 36**
Overall Response Rate[a]			
ORR (95% CI)	27% (18%, 38%)	61% (48%, 74%)	61% (44%, 77%)
Complete response	1%	5%	8%
Partial response	26%	56%	53%
Duration of Response[a]	n = 21	n = 35	n = 22
Median DoR, months (95% CI)	18.0 (4.2, 40.1)	9.0 (5.8, 26.2)	15.2 (7.8, 23.5)

Abbreviations: CI, confidence interval; DoR, duration of response; ORR, overall response rate.
[a] Represents final analysis results (cutoff date of 24 Feb 2021) for the primary analysis responder cohorts.

In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 22.

14.5 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer

The safety and efficacy of TAFINLAR administered with trametinib was evaluated in an activity estimating, nine-cohort, multi-center, non-randomized, open-label trial (Study BRF117019; NCT02034110) in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic ATC with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication; who received prior treatment with BRAF or MEK inhibitors; with symptomatic or untreated CNS metastases; or who had airway obstruction. Patients received TAFINLAR 150 mg twice daily and trametinib 2 mg once daily. The major efficacy outcome measure was overall response rate (ORR) per RECIST v1.1 as assessed by independent review committee (IRC) and DoR.

Thirty-six patients were enrolled and were evaluable for response in the ATC cohort. The median age was 71 years (range: 47 to 85); 44% were male, 50% White, 44% Asian; and 94% had ECOG performance status of 0 or 1. Prior anti-cancer treatments included surgery and external beam radiotherapy (83% each), and systemic therapy (67%).

Efficacy results are summarized in Table 24.

Table 24. Efficacy Results in the ATC Cohort Based on Independent Review of Study BRF117019

ATC Cohort Population	N = 36
Overall Response Rate	
ORR (95% CI)	53% (35.5%, 69.6%)
Complete response	6%
Partial response	47%
Duration of Response	n = 19
Median DoR, months (95% CI)	13.6 (3.8, NE)
% with DoR ≥ 6 months	68%
% with DoR ≥ 12 months	53%

Abbreviations: ATC, anaplastic thyroid cancer; DoR, duration of response; CI, confidence interval; NE, not estimable; ORR, overall response rate.

14.6 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and efficacy of TAFINLAR in combination with trametinib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT212X2101, and supported by results in COMBI-d, COMBI-v *[see Clinical Studies (14.2)]*, and BRF113928 *[see Clinical Studies (14.4)]*. In adult studies, patients received TAFINLAR 150 mg twice daily

and trametinib 2 mg once daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR).

BRF117019 Study and NCI-MATCH Study

Study BRF117019 (NCT02034110) *[see Clinical Studies (14.5)]* is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with the BRAF V600E mutation, including high grade glioma (HGG) (n = 45), biliary tract cancer (BTC) (n = 43), low grade glioma (LGG) (n = 13), adenocarcinoma of small intestine (ASI) (n = 3), gastrointestinal stromal tumor (GIST) (n = 1), and anaplastic thyroid cancer *[see Clinical Studies (14.5)]*. Patients were enrolled based on local assessments of BRAF V600E mutation status; a central laboratory confirmed the BRAF mutation in 93 of 105 patients.

Arm H (EAY131-H) of the NCI-MATCH study (NCT02465060) is a single-arm, open-label study that enrolled patients with a BRAF V600E mutation. Patients with melanoma, thyroid cancer, or CRC were excluded. BRAF V600E mutation status for enrollment was determined either by central or local laboratory test. The study included adult patients with solid tumors including gastrointestinal tumors (n = 14), lung tumors (n = 7), gynecologic or peritoneal tumors (n = 6), CNS tumors (n = 4), and ameloblastoma of mandible (n = 1).

Among the 131 patients enrolled in BRF117019 and NCI-MATCH with the tumor types shown in Table 21, the baseline characteristics were: median age of 51 years with 20% age 65 or older; 56% female; 85% White, 9% Asian, 3% Black, 3% Other; and 37% ECOG 0, 56% ECOG 1, and 6% ECOG 2. Of the 131 patients, 90% received prior systemic therapy.

Efficacy results in patients with solid tumors are summarized in Table 25.

Table 25. Efficacy Results Based on Independent Review in Studies BRF117019 and NCI-MATCH Arm H

Tumor Type[a]	N	Objective Response Rate		Duration of Response
		%	95% CI	Range (months)
Biliary tract cancer[b]	48	46	(31, 61)	1.8[d], 40[d]
High grade glioma[c]	48	33	(20, 48)	3.9, 44
Glioblastoma	32	25	(12, 43)	3.9, 27
Anaplastic pleomorphic xanthoastrocytoma	6	67	(22, 96)	6, 43
Anaplastic astrocytoma	5	20	(0.5, 72)	15
Astroblastoma	2	100	(16, 100)	15, 23[d]
Undifferentiated	1	PR	(2.5, 100)	6
Anaplastic ganglioglioma	1	0	NA	NA
Anaplastic oligodendroglioma	1	0	NA	NA
Low grade glioma	14	50	(23, 77)	6, 29[d]
Astrocytoma	4	50	(7, 93)	7, 23
Ganglioglioma	4	50	(7, 93)	6, 13
Pleomorphic xanthoastrocytoma	2	50	(1.3, 99)	6
Pilocytic astrocytoma	2	0	NA	NA
Choroid plexus papilloma	1	PR	(2.5, 100)	29[d]
Gangliocytoma/ganglioglioma	1	PR	(2.5, 100)	18[d]
Low grade serous ovarian carcinoma	5	80	(28, 100)	12, 42[d]
Adenocarcinoma small intestine	4	50	(7, 93)	7, 8
Adenocarcinoma pancreas	3	0	NA	NA

Mixed ductal/adenoneuroendocrine carcinoma	2	0	NA	NA
Neuroendocrine carcinoma of colon	2	0	NA	NA
Ameloblastoma of mandible	1	PR	(2.5, 100)	30
Combined small cell-squamous carcinoma of lung	1	PR	(2.5, 100)	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1	PR	(2.5, 100)	8
Adenocarcinoma of anus	1	0	NA	NA
Gastrointestinal stromal tumor	1	0	NA	NA

Abbreviations: PR, partial response.
[a] Excludes NSCLC (n = 6) and ATC (n = 36) (previously approved tumor types for TAFINLAR in combination with trametinib).
[b] Median DoR 9.8 months (95% CI: 5.3, 20.4).
[c] Median DoR 13.6 months (95% CI: 5.5, 26.7).
[d] Denotes a right-censored DoR.

CTMT212X2101 (X2101) Study

Study X2101 (NCT02124772) was a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors. Part C was a dose escalation of TAFINLAR in combination with trametinib in patients with a BRAF V600E mutation. Part D was a cohort expansion phase of TAFINLAR in combination with trametinib in patients with LGG with a BRAF V600E mutation. The major efficacy outcome measure was ORR as assessed by independent review committee per RANO criteria.

The efficacy of TAFINLAR in combination with trametinib was evaluated in 48 pediatric patients, including 34 patients with LGG and 2 patients with HGG.

For patients with BRAF V600E mutant LGG and HGG in Parts C and D, the median age was 10 years (range: 1 to 17); 50% were male, 75% White, 8% Asian, 3% Black; and 58% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (83%), external beam radiotherapy (2.8%), and systemic therapy (92%). The ORR was 25% (95% CI: 12%, 42%). For the 9 patients who responded, DoR was ≥ 6 months for 78% of patients and ≥ 24 months for 44% of patients.

CDRB436G2201 (G2201) Study – High-Grade Glioma Cohort

Study G2201 (NCT02684058) was a multi-center, randomized, open-label, Phase II study of dabrafenib and trametinib in chemotherapy naïve pediatric patients with BRAF V600E mutant low-grade glioma (LGG) and patients with relapsed or progressive BRAF V600E mutant HGG. Patients with HGG were enrolled in a single-arm cohort. The major efficacy outcome measure for the HGG cohort was ORR as assessed by independent review committee per RANO 2010 criteria.

The efficacy of TAFINLAR in combination with trametinib was evaluated in 41 pediatric patients with relapsed or progressive HGG.

For patients with BRAF V600E mutant HGG enrolled in the HGG cohort, the median age was 13 years (range: 2 to 17); 56% were female, 61% White, 27% Asian, 2.4% Black and 37% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (98%), radiotherapy (90%), and chemotherapy (81%). The ORR was 56% (95% CI: 40, 72). The median DoR was not reached (95% CI: 9.2, NE). For the 23 patients who responded in the HGG cohort, DoR was ≥ 6 months for 78% of patients, ≥ 12 months for 48% of patients, and ≥ 24 months for 22% of patients.

14.7 BRAF V600E Mutation-Positive Low-Grade Glioma

CDRB436G2201 (G2201) Study – Low-Grade Glioma Cohort

The safety and efficacy of TAFINLAR in combination with trametinib for the treatment of BRAF V600E mutation-positive low-grade glioma (LGG) in pediatric patients aged 1 to < 18 years of age were evaluated in the multi-center, open-label trial (Study CDRB436G2201; NCT02684058). Patients with LGG (WHO grades 1 and 2) who required first systemic therapy were randomized in a 2:1 ratio to dabrafenib plus trametinib (D + T) or carboplatin plus vincristine (C + V).

BRAF mutation status was identified prospectively via a local assessment or a central laboratory test. In addition, retrospective testing of available tumor samples by the central laboratory was performed to evaluate BRAF V600E mutation status.

Patients received age- and weight-based dosing of TAFINLAR and trametinib until loss of clinical benefit or until unacceptable toxicity. Carboplatin and vincristine were dosed based on body surface area at doses 175 mg/m^2 and 1.5 mg/m^2 (0.05 mg/kg for patients < 12 kg), respectively, as one 10-week induction course followed by eight 6-week cycles of maintenance therapy.

The major efficacy outcome measure was overall response rate (ORR) by independent review based on RANO LGG (2017) criteria. Additional efficacy outcome measures were progression-free survival and overall survival. The primary analysis was performed when all patients had completed at least 32 weeks of therapy.

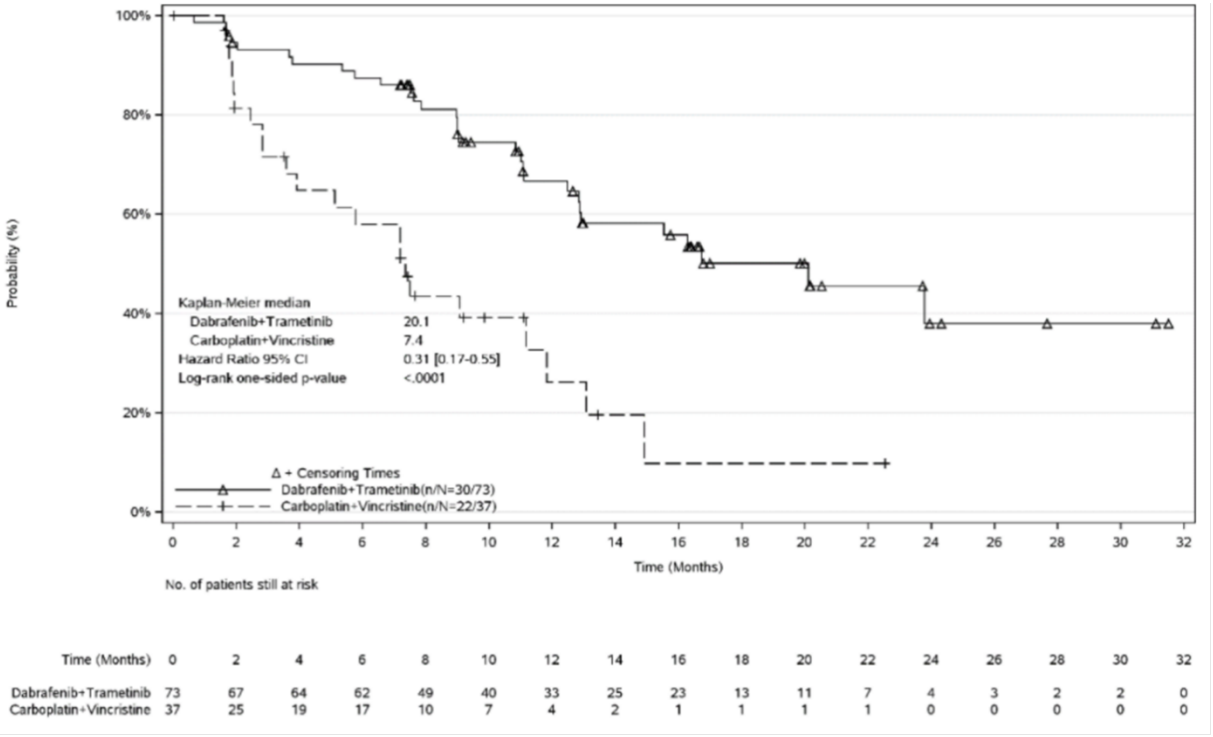
In the LGG cohort, 110 patients were randomized to D + T (n = 73) or C + V (n = 37). Median age was 9.5 years (range: 1 to 17); 60% were female. Study G2201 showed a statistically significant improvement in ORR and PFS in LGG patients randomized to D + T compared to those randomized to C + V. Efficacy results are shown in Table 26.

Table 26. Efficacy Results Based on Independent Review in Study G2201 (LGG Cohort)

	TAFINLAR plus Trametinib N = 73	**Carboplatin plus Vincristine N = 37**
Overall Response Rate		
ORR% (95% CI)[a]	46.6 (34.8, 58.6)	10.8 (3.0, 25.4)
P value	< 0.001	
Complete response, n (%)	2 (2.7)	1 (2.7)
Partial response, n (%)	32 (44)	3 (8)
Duration of Response		
Median (95% CI)[b], months	23.7 (14.5, NE)	NE (6.6, NE)
% with observed DoR ≥ 12 months	56	50
% with observed DoR ≥ 24 months	15	25
Progression-Free Survival		
Median (95% CI)[b], months	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI)[c]	0.31 (0.17, 0.55)	
P value	< 0.001	

Abbreviations: CI, confidence interval; DoR, duration of response; NE, not estimable; ORR, overall response rate.
[a] Based on Clopper-Pearson exact confidence interval.
[b] Based on Kaplan-Meier method.
[c] Based on proportional hazards model.

Figure 5. Kaplan-Meier Curves for Progression-Free Survival in Study G2201 (LGG Cohort)



At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was one death on the C + V arm. The OS results at interim analysis did not reach statistical significance.

16 HOW SUPPLIED/STORAGE AND HANDLING

TAFINLAR Capsules:

50 mg capsules: Dark red capsule imprinted with 'GS TEW' and '50 mg' available in bottles of 120 with child resistant closures (NDC 0078-0682-66). Each bottle contains a silica gel desiccant.

75 mg capsules: Dark pink capsule imprinted with 'GS LHF' and '75 mg' available in bottles of 120 with child resistant closures (NDC 0078-0681-66). Each bottle contains a silica gel desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Store and dispense in the original bottle with the desiccant.

TAFINLAR Tablets for Oral Suspension:

10 mg tablets for oral suspension: white to slightly yellow, round biconvex 6 mm tablet debossed with "D" on one side and "NVR" on the other side. Available in bottles of 210 with child resistant closures (NDC 0078-1154-21). Each bottle contains 2 silica gel desiccants.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Store and dispense in the original bottle with the desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

New Primary Cutaneous and Non-Cutaneous Malignancies

Advise patients that TAFINLAR increases the risk of developing new primary cutaneous and non-cutaneous malignancies. Advise patients to contact their healthcare provider immediately for any new lesions, changes to

existing lesions on their skin, or signs and symptoms of other malignancies *[see Warnings and Precautions (5.1)]*.

Hemorrhage

Advise patients that TAFINLAR administered with trametinib increases the risk of intracranial and gastrointestinal hemorrhage. Advise patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual bleeding or hemorrhage *[see Warnings and Precautions (5.3)]*.

Cardiomyopathy

Advise patients that TAFINLAR can cause cardiomyopathy and to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Uveitis

Advise patients that TAFINLAR can cause uveitis, including iritis and iridocyclitis and to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.5)]*.

Serious Febrile Reactions

Advise patients that TAFINLAR can cause pyrexia, including serious febrile reactions. Inform patients that the incidence and severity of pyrexia are increased when TAFINLAR is administered with trametinib. Instruct patients to contact their healthcare provider if they develop a fever while taking TAFINLAR *[see Warnings and Precautions (5.6)]*.

Serious Skin Toxicities

Advise patients that TAFINLAR can cause serious skin toxicities and to contact their healthcare provider for progressive or intolerable rash. Advise patients to contact their healthcare provider immediately if they develop signs and symptoms of a severe skin reaction *[see Warnings and Precautions (5.7)]*.

Hyperglycemia

Advise patients that TAFINLAR can impair glucose control in diabetic patients resulting in the need for more intensive hypoglycemic treatment and to contact their healthcare provider to report symptoms of severe hyperglycemia *[see Warnings and Precautions (5.8)]*.

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

Advise patients that TAFINLAR may cause hemolytic anemia in patients with G6PD deficiency. Advise patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.12), Use in Specific Populations (8.1, 8.3)]*.
- Advise females to contact their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment and for 2 weeks after discontinuation of treatment with TAFINLAR.
- Advise male patients with female partners of reproductive potential to use condoms during treatment with TAFINLAR and for 2 weeks after the last dose.

Lactation

Advise women not to breastfeed during treatment with TAFINLAR and for 2 weeks after the last dose of TAFINLAR *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential of the potential risk for impaired fertility with TAFINLAR *[see Use in Specific Populations (8.3)]*.

Administration

Instruct patients to take TAFINLAR at least 1 hour before or at least 2 hours after a meal *[see Dosage and Administration (2.3)]*.

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T2023-XX

MEDICATION GUIDE

TAFINLAR® (TAFF-in-lar)
(dabrafenib)
capsules

TAFINLAR® (TAFF-in-lar)
(dabrafenib)
tablets for oral suspension

Important information: If your healthcare provider prescribes TAFINLAR for you to be taken with trametinib, also read the Patient Information leaflet that comes with trametinib.

What is the most important information I should know about TAFINLAR?

TAFINLAR may cause serious side effects, including:

Risk of new cancers. TAFINLAR, when used alone or with trametinib, may cause skin cancers, called cutaneous squamous cell carcinoma (cuSCC), keratoacanthoma, basal cell carcinoma, or melanoma.

Talk with your healthcare provider about your risk for these cancers.

Check your skin and tell your healthcare provider right away about any skin changes, including a:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

Your healthcare provider should check your skin before treatment with TAFINLAR, every 2 months during treatment with TAFINLAR, and for up to 6 months after you stop taking TAFINLAR to look for any new skin cancers.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with TAFINLAR.

See **"What are the possible side effects of TAFINLAR?"** for more information about side effects.

What is TAFINLAR?

TAFINLAR is a prescription medicine used:

- alone or in combination with a medicine called trametinib to treat a type of skin cancer called melanoma:
  - that has spread to other parts of the body or cannot be removed by surgery, **and**
  - that has a certain type of abnormal “BRAF” gene.
- in combination with trametinib, to help prevent melanoma that has a certain type of abnormal “BRAF” gene from coming back after the cancer has been removed by surgery.
- in combination with trametinib to treat a type of lung cancer called non-small cell lung cancer (NSCLC):
  - that has spread to other parts of the body, **and**
  - that has a certain type of abnormal “BRAF” gene.
- in combination with trametinib to treat a type of thyroid cancer called anaplastic thyroid cancer (ATC):
  - that has spread to other parts of the body and you have no satisfactory treatment options, **and**
  - that has a certain type of abnormal “BRAF” gene.
- in combination with trametinib to treat solid tumors in adults and children 1 year and older:
  - that cannot be removed with surgery or have spread to other parts of the body, and that have gotten worse (progressed) and you have no satisfactory treatment options, **and**
  - that have a certain type of abnormal “BRAF” gene.
- in combination with trametinib to treat a type of brain tumor called glioma in children 1 year and older:
  - that is low-grade glioma (LGG), **and**
  - that have a certain type of abnormal “BRAF” gene, **and**
  - who require a medicine by mouth or injection (systemic therapy).

TAFINLAR is not for use in treating people with colorectal cancer or wild-type BRAF solid tumors.

Your healthcare provider will perform a test to make sure that TAFINLAR is right for you.

It is not known if TAFINLAR used in combination with trametinib is safe and effective in children less than 1 year of age.

It is not known if TAFINLAR used alone is safe and effective in children.

Before you take TAFINLAR, tell your healthcare provider about all of your medical conditions, including if you:

- have had bleeding problems
- have heart problems
- have eye problems
- have liver or kidney problems
- have diabetes

- plan to have surgery, dental, or other medical procedures
- have a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme
- are pregnant or plan to become pregnant. TAFINLAR can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will do a test to see if you are pregnant before starting treatment with TAFINLAR.
  - You should use effective birth control (contraception) during treatment with TAFINLAR and for 2 weeks after your last dose of TAFINLAR.
  - Birth control methods that contain hormones (such as birth control pills, injections, or transdermal systems) may not work as well during treatment with TAFINLAR and you could become pregnant. You should use another effective method of birth control during treatment with TAFINLAR.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with TAFINLAR.

  Males (including those who have had a vasectomy) with a female partner who is able to become pregnant:
  - Use condoms during sexual intercourse during treatment with TAFINLAR and for at least 2 weeks after your last dose of TAFINLAR.
- are breastfeeding or plan to breastfeed. It is not known if TAFINLAR passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of TAFINLAR. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take TAFINLAR?

- Take TAFINLAR exactly as your healthcare provider tells you. Do not change your dose or stop TAFINLAR unless your healthcare provider tells you.
- Your healthcare provider may change your dose of TAFINLAR, temporarily stop, or completely stop your treatment with TAFINLAR if you develop certain side effects.

TAFINLAR capsules:

- Take TAFINLAR 2 times a day, at the same time each day, about 12 hours apart.
- Take TAFINLAR at least 1 hour before or 2 hours after a meal.
- Take TAFINLAR capsules whole. Do not open, crush, or break TAFINLAR capsules.
- If TAFINLAR capsules are prescribed for your child 6 years of age or older, your child's healthcare provider will adjust their dose as your child grows.
- Tell your healthcare provider if you or your child is not able to swallow TAFINLAR capsules whole.
- If you miss a dose of TAFINLAR, take it as soon as you remember. **Do not take a missed dose of TAFINLAR if it is less than 6 hours before your next scheduled dose.** Just skip the missed dose and take the next dose of TAFINLAR at your regular time.
- If you vomit after taking a dose of TAFINLAR, do not take an additional dose. Take the next dose of TAFINLAR at your regular time.

TAFINLAR tablets for oral suspension:

- If TAFINLAR tablets for oral suspension are prescribed for your child 1 year of age or older, your child's healthcare provider will adjust their dose as your child grows.
- TAFINLAR tablets for oral suspension are to be taken as a suspension only.
- **Do not** swallow whole, chew or crush TAFINLAR tablets for oral suspension.
- See the "Instructions for Use" that comes with the medicine for instructions on how to correctly prepare and take or give a dose of the oral suspension.
- After the TAFINLAR tablets for oral suspension are dispersed into an oral suspension, take or give the medicine right away from a cup, oral dosing syringe or feeding tube.
- Take or give TAFINLAR oral suspension 2 times a day, at the same time each day, about 12 hours apart.
- Take or give each dose of TAFINLAR oral suspension at least 1 hour before or 2 hours after a meal.
- Throw away the prepared oral suspension if it is not used within 30 minutes.

- If you miss a dose of TAFINLAR, take or give it as soon as you remember. **Do not take or give a missed dose of TAFINLAR if it is less than 6 hours before your next scheduled dose.** Just skip the missed dose and take or give the next dose of TAFINLAR at the regular time.
- If vomiting happens after giving or taking a dose of TAFINLAR, do not take or give an additional dose. Take or give the next dose of TAFINLAR at the regular time.

What are the possible side effects of TAFINLAR?

TAFINLAR may cause serious side effects, including:

- **See "What is the most important information I should know about TAFINLAR?"**
- **bleeding problems.** TAFINLAR, when taken with trametinib, can cause serious bleeding problems, especially in your brain or stomach, that can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
  - headaches, dizziness, or feeling weak
  - cough up blood or blood clots
  - vomit blood or your vomit looks like "coffee grounds"
  - red or black stool that looks like tar
- **heart problems**, including heart failure. Your healthcare provider should check your heart function before and during treatment with TAFINLAR. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:
  - feeling like your heart is pounding or racing
  - shortness of breath
  - swelling of your ankles or feet
  - feeling lightheaded
- **eye problems**. TAFINLAR can cause severe eye problems that can lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
  - blurred vision, loss of vision, or other vision changes
  - see color dots
  - halo (see blurred outline around objects)
  - eye pain, swelling, or redness
- **fever**. Fever is common during treatment with TAFINLAR, but may also be serious. When taking TAFINLAR with trametinib, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever.

  Call your healthcare provider right away if you get a fever during treatment with TAFINLAR.

  Your healthcare provider may temporarily or permanently stop your treatment or change your dose of TAFINLAR with trametinib if you have fevers. Your healthcare provider will treat you as needed for your fever and any signs and symptoms of infection and should check your kidney function during and after you have had severe fever.
- **serious skin reactions**. Skin rash is a common side effect of TAFINLAR. TAFINLAR can also cause other skin reactions. In some cases, these rashes and other skin reactions can be severe or serious and may need to be treated in a hospital or lead to death.

  Tell your healthcare provider if you get a skin rash or acne that bothers you or worsens.

  Tell your healthcare provider right away if you develop any of the following signs or symptoms of a severe skin reaction, including:
  - blisters or peeling of your skin
  - mouth sores
  - blisters on your lips, or around your mouth or eyes
  - high fever or flu-like symptoms
  - enlarged lymph nodes
- **increased blood sugar (hyperglycemia)**. Some people may develop high blood sugar or worsening diabetes during treatment with TAFINLAR. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with TAFINLAR. Your diabetes medicine may need to be changed. Tell your healthcare provider if you have any of the following symptoms of severe high blood sugar:
  - increased thirst
  - urinating more often than normal, or urinating an increased amount of urine

- **TAFINLAR may cause healthy red blood cells to break down too early in people with G6PD deficiency**. This may lead to a type of anemia called hemolytic anemia where the body does not have enough healthy red blood cells. Tell your healthcare provider if you have any of the following signs or symptoms:
  - yellow skin (jaundice)
  - weakness or dizziness
  - shortness of breath
- **hemophagocytic lymphohistiocytosis (HLH)**. TAFINLAR when taken with trametinib may increase the risk of a type of overactivity of the immune system (hemophagocytic lymphohistiocytosis) that can cause fever, swollen glands, bruising, or skin rash. If you experience a combination of these symptoms, call your healthcare provider right away.

The most common side effects of TAFINLAR when taken alone include:

- thickening of the outer layers of the skin
- headache
- fever
- joint aches
- warts
- hair loss
- redness, swelling, peeling, or tenderness of hands or feet

The most common side effects of TAFINLAR when taken with trametinib in people with melanoma that has spread to other parts of the body or cannot be removed by surgery include:

- fever
- rash
- headache
- chills
- joint aches
- cough

The most common side effects of TAFINLAR when taken with trametinib to help prevent melanoma from coming back after the cancer has been removed by surgery include:

- fever
- tiredness
- nausea
- headache
- rash
- chills
- diarrhea
- vomiting
- joint aches
- muscle aches

The most common side effects of TAFINLAR when taken with trametinib in people with NSCLC include:

- fever
- tiredness
- nausea
- vomiting
- diarrhea
- dry skin
- decreased appetite
- rash
- swelling of face, arms, and legs
- chills
- bleeding
- cough
- shortness of breath

The most common side effects of TAFINLAR when taken with trametinib in adults with solid tumors that cannot be removed by surgery or have spread to other parts of the body include:

- fever
- tiredness
- nausea
- rash
- chills
- headache
- bleeding
- cough
- vomiting
- constipation
- diarrhea
- muscle and joint aches
- swelling of your arms and legs

The most common side effects of TAFINLAR when taken with trametinib in children 1 year of age and older with solid tumors that cannot be removed by surgery or have spread to other parts of the body include:

- fever
- rash
- vomiting
- tiredness
- dry skin
- cough
- diarrhea
- acne
- headache
- stomach-area (abdominal) pain
- nausea
- bleeding
- constipation
- skin infection around fingernails or toenails

The most common side effects of TAFINLAR when taken with trametinib in children 1 year of age and older with low-grade glioma include:

- fever
- rash
- headache
- vomiting
- muscle and bone pain
- tiredness
- dry skin
- diarrhea
- nausea
- bleeding
- stomach-area (abdominal) pain
- acne

TAFINLAR may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

TAFINLAR may cause lower sperm counts in males. This could affect the ability to father a child. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of TAFINLAR.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

How should I store TAFINLAR?

TAFINLAR Capsules:

- Store TAFINLAR capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TAFINLAR capsules in the original bottle.
- The bottle of TAFINLAR capsules contains a cannister with a drying agent (desiccant) to help keep your medicine dry. Do not throw away the desiccant cannister.

TAFINLAR tablets for oral suspension:

- Store the bottle of TAFINLAR tablets for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- Store the bottle of TAFINLAR tablets for oral suspension, along with the two plastic cannisters inside the original packaging, with the cap tightly closed. The cannisters contain a drying agent (desiccant) to help keep your medicine dry.
- TAFINLAR tablets for oral suspension come in a bottle with a child-resistant cap.
- Throw away (dispose of) any mixed oral suspension if it is not taken or given within 30 minutes after it is prepared.

Keep TAFINLAR and all medicines out of the reach of children.

General information about the safe and effective use of TAFINLAR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TAFINLAR for a condition for which it was not prescribed. Do not give TAFINLAR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TAFINLAR that is written for health professionals.

What are the ingredients in TAFINLAR?

TAFINLAR Capsules:

Active ingredient: dabrafenib
Inactive ingredients: colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.
Capsule shells: hypromellose, red iron oxide (E172), titanium dioxide (E171).

TAFINLAR Tablets for oral suspension:

Active ingredient: dabrafenib
Inactive ingredients: acesulfame potassium, artificial berry flavor, colloidal silicone dioxide, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose.

Distributed by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936
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For more information, go to www.us.tafinlarmekinist.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2023

T2023-XX

INSTRUCTIONS FOR USE
TAFINLAR® (TAFF-in-lar)
(dabrafenib)
tablets for oral suspension

This "Instructions for Use" contains information on how to prepare and take or give TAFINLAR tablets for oral suspension as an oral suspension.

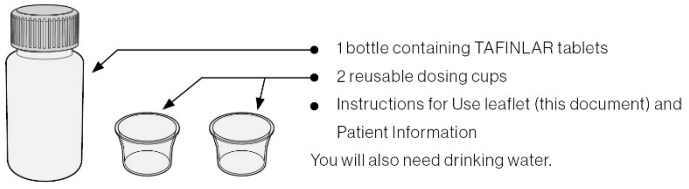
Important information you need to know before taking or giving TAFINLAR tablets for oral suspension (TAFINLAR tablets).

- Read this "Instructions for Use" carefully before you prepare and use TAFINLAR tablets for the first time and each time you get a refill. There may be new information.
- This "Instructions for Use" does not take the place of talking with your healthcare provider about you or your child's medical condition and treatment.
- Your healthcare provider or pharmacist should show you how to prepare and take or give a dose of TAFINLAR tablets correctly. Always take or give TAFINLAR tablets exactly as your healthcare provider tells you to.
- If you have any questions about how to prepare and take or give a dose of TAFINLAR tablets, talk to the healthcare provider or pharmacist.
- Always use the dosing cup that comes with your TAFINLAR tablets pack. If your pack does not contain a dosing cup, contact the healthcare provider or pharmacist.
- Use only clean water to rinse. **Do not** use soap or dishwashing liquid to clean the dosing cup.
- If at any time TAFINLAR oral suspension gets on your or your child's skin, wash the area well with soap and water.
- If at any time TAFINLAR oral suspension gets in your or your child's eyes, rinse the eyes well with cool water.
- If you spill any TAFINLAR oral suspension, follow the instructions at the end of this Instructions for Use in the section called "How to clean up any spilled TAFINLAR oral suspension."

The TAFINLAR tablets pack should contain:

You will receive the TAFINLAR tablets prescription in a sealed bottle which contains tablets. The TAFINLAR tablets must be mixed in water before taking or giving a dose of TAFINLAR oral suspension. The tablets break apart (disperse) in the water and may not fully dissolve. Follow the instructions below to mix the tablets in water.

- 1 bottle containing TAFINLAR tablets
- 2 reusable dosing cups
- Instructions for Use leaflet (this document) and Patient Information



You will also need drinking water.

For taking or giving a dose of the mixed TAFINLAR oral suspension by swallowing, go to Section A. For taking or giving a dose of the mixed TAFINLAR oral suspension through a feeding tube or using an oral syringe, go to Section B.

SECTION A. Preparing and taking or giving a dose of the mixed TAFINLAR oral suspension by swallowing directly from the dosing cup.

If any of the TAFINLAR oral suspension comes into contact with your skin or eyes, when you are following the steps below, follow instructions below in **Section E. "How to clean up any spilled TAFINLAR oral suspension."**

To prepare and take or give a dose of TAFINLAR oral suspension, you will need:

- the prescribed number of tablets
- 1 dosing cup
- 1 teaspoon
- drinking water

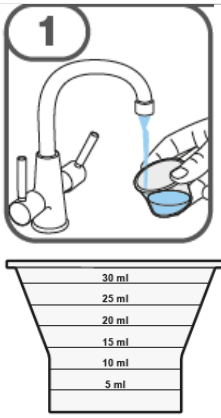
To take or give a dose of TAFINLAR oral suspension by mouth (swallowing the oral suspension), you or your child can drink it directly from the dosing cup.

Step 1. Wash and dry your hands before preparing TAFINLAR tablets as an oral suspension.

- Add cool drinking water up to the markings on the dosing cup, as follows:

Note: The amount of water does not need to be exact.

- If the prescribed dose is 1 to 4 tablets, you will need about 5 mL of water.
- If the prescribed dose is 5 to 15 tablets, you will need about 10 mL of water.

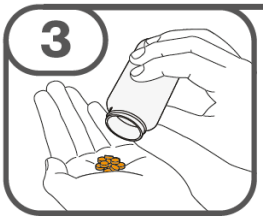


Step 2. Remove the bottle cap by pushing down and turning counter-clockwise in the direction of the arrow, as shown.

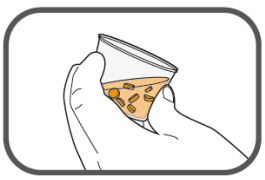
- **Do not** throw away (dispose of) the cap.
- If you are opening the bottle for the first time, remove the seal from the bottle.

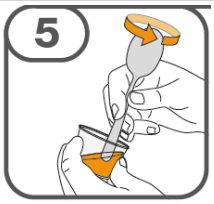
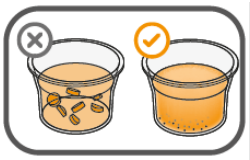


Step 3. Count out the prescribed number of tablets into your hand.



- Add the prescribed number of tablets into the water in your dosing cup.



• The bottle contains 2 plastic canisters to keep the tablets dry. If either canister falls out when you are taking out the tablets, re-insert it back into the bottle.	
Step 4. Place the cap back onto the bottle and turn it clockwise in the direction of the arrow, as shown to close it.	
Step 5. With one hand, tilt the dosing cup. • With your other hand, gently stir the water and tablets with the handle of a teaspoon until the tablets break apart (disperse). • It may take **3 minutes** or more for the tablets to disperse. After the tablets disperse, the oral suspension should be cloudy white, but may contain small pieces. • **Take or give the TAFINLAR oral suspension no later than 30 minutes after the tablets have been dispersed in water.** • If more than 30 minutes have passed, dispose of the TAFINLAR oral suspension following local regulations and restart from the beginning of Section A. If you are not sure how to dispose of the TAFINLAR oral suspension, ask your healthcare provider or pharmacist.	 
Step 6. Drink the TAFINLAR oral suspension from the dosing cup. **Important:** After swallowing, there will be some medicine (residue) still inside the cup. The residue may be difficult to see. Follow **Steps 7 through 9** to take or give any medicine residue still in the cup so that you give the full dose of TAFINLAR.	
Step 7. **Add about 5 mL of water** to the empty dosing cup.	
Step 8. **Stir** with the handle of a teaspoon to loosen the remaining medicine residue.	
Step 9. Drink the water and residue mixture.	

- **If the prescribed dose is 1 to 4 tablets: Do Steps 7 through 9 one time.**
- **If the prescribed dose is 5 to 15 tablets: Do Steps 7 through 9 two times.**

It is important to take or give **all of the medicine residue so that you get the full dose of TAFINLAR**.

Step 10. Go to **Section C. Cleaning the dose cup and syringe (if used).**

SECTION B. Preparing and giving TAFINLAR tablets as an oral suspension via feeding tube or oral syringe.

Important administration information.

Make sure all the tablets are dispersed before administering the TAFINLAR oral suspension.

The minimum feeding tube size you may use to administer the TAFINLAR oral suspension:

- If the prescribed dose is 1 to 3 tablets, the minimum size feeding tube that may be used is 10 French.
- If the prescribed dose is 4 to 15 tablets, the minimum size feeding tube that may be used is 12 French.
- If any of the TAFINLAR oral suspension comes into contact with your skin or eyes when you are following the steps below, follow the instructions in the section "Important information you need to know before taking or giving TAFINLAR for oral suspension."
- If any of the TAFINLAR oral suspension spills, follow the instruction in the section "**How to clean up any spilled TAFINLAR oral suspension."**
- Wash and dry your hands before giving a dose of TAFINLAR oral suspension.

Step 1. **Follow Steps 1 through 5 in Section A to disperse the TAFINLAR tablets.** If using a feeding tube, flush the tube with drinking water then continue with step 2 below.

Step 2. **Draw up all of the TAFINLAR oral suspension** from the dosing cup into a syringe by pulling back on the plunger. Be sure to use a syringe that can be used with the feeding tube or to give the TAFINLAR oral suspension by mouth. Ask your healthcare provider if you are not sure what syringe to use.



Step 3. If giving the dose through a feeding tube, give the TAFINLAR oral suspension into the feeding tube according to the feeding tube manufacturer's instructions.

If giving a dose of TAFINLAR oral suspension using an oral syringe, place the open end of the oral syringe inside the mouth with the tip pointing toward the inside of either cheek. If you are giving a dose of the TAFINLAR oral suspension to a child, make sure they are sitting upright.

Slowly push the plunger all the way down on the plunger to give the full dose.

Warning: Giving TAFINLAR oral suspension directly into the throat or pushing down on the plunger too fast may cause choking.



Step 4. **Add about 5 mL of water** to the empty dosing cup.	
Step 5. **Stir** to loosen the medicine residue inside the cup.	
Step 6. **Draw up** the water and medicine residue mixture.	
Step 7. **Give the water and medicine residue mixture through** the solution into the feeding tube or into the inside of the cheek.	
• It is important to **give all of the medicine that is left in the syringe and feeding tube (residue)**. **Repeat Step 4 through Step 7 three times to make sure that you give a full dose of TAFINLAR**.	
Step 8. After repeating **Step 4 through Step 7** three times, flush the feeding tube with drinking water. Then go to the cleaning steps in Section C.	
Section C. Cleaning the dosing cup and syringe (if used).	
Use only clean water to rinse the dosing cup. Do not use soap or dishwashing liquid when cleaning the dosing cup.	
Step 1. Rinse the dosing cup under clean cool water right away after dosing. • Shake off excess water then wipe dry using clean paper towels. **Note:** Keep the dosing cup away from other kitchen items.	
Step 2. Rinse the teaspoon in clean cold water then wash in warm soapy water and dry using clean paper towels. • You can also wash the teaspoon in a dishwasher.	

Step 3. Clean the oral syringe or the other syringe, as instructed by your healthcare provider, according to the manufacturer's instructions.



Section D. How to throw away (dispose of) TAFINLAR tablets that are expired or no longer needed, or old dosing cups.

- Throw away (dispose of) unused tablets or suspension, or old dosing cups into the trash. Do not pour suspension down the drain.
- Ask your healthcare provider or pharmacist about how to safely throw away (dispose of) TAFINLAR if you are not sure.

Section E. How to clean up any spilled TAFINLAR oral suspension.

If you accidentally spill any TAFINLAR oral suspension, clean up the spill as follows:

1. Put on plastic gloves.
2. Soak up the spilled TAFINLAR oral suspension completely using an absorbent material, such as paper towels soaked with either a mixture of water and household disinfectant or with ethanol 70% (or higher grade).
3. Repeat the cleaning with fresh soaked absorbent material at least three times until the area is clean.
4. Dry the area with paper towels.
5. Throw away all the disposable materials used to clean the spillage into a sealable plastic bag.
6. Dispose of the bags into the trash.
7. Wash your hands well with soap and water.

How should I store TAFINLAR tablets for oral suspension?

- Store the TAFINLAR tablets bottle with the two plastic canisters inside and the cap tightly closed. The canisters help keep the medicine dry and protect it from moisture.
- Store the bottle and dosing cups in the original packaging to protect from light and moisture.
- Store at 68°F to 77°F (20°C to 25°C).

Keep TAFINLAR tablets and all medicines out of the reach of children.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: May 2023

T2023-XX

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 50 mg hard capsules
Tafinlar 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tafinlar 50 mg hard capsules

Each hard capsule contains dabrafenib mesilate equivalent to 50 mg of dabrafenib.

Tafinlar 75 mg hard capsules

Each hard capsule contains dabrafenib mesilate equivalent to 75 mg of dabrafenib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Tafinlar 50 mg hard capsules

Opaque dark red capsules, approximately 18 mm long, with capsule shell imprinted with “GS TEW” and “50 mg”.

Tafinlar 75 mg hard capsules

Opaque dark pink capsules, approximately 19 mm long, with capsule shell imprinted with “GS LHF” and “75 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Non-small cell lung cancer (NSCLC)

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

4.2 Posology and method of administration

Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.

Before taking dabrafenib, patients must have confirmation of tumour BRAF V600 mutation using a validated test.

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC. Dabrafenib should therefore not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC (see sections 4.4 and 5.1).

Posology

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily.

Duration of treatment
Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity (see Table 2). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

Missed doses
If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next scheduled dose.

If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, the dose of trametinib should only be taken if it is more than 12 hours until the next scheduled dose.

Dose modification
Two dabrafenib capsule strengths, 50 mg and 75 mg, are available to effectively manage dose modification requirements.

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Tables 1 and 2).

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section 4.4).

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level (see section 4.4).

Recommended dose level reductions and recommendations for dose modifications are provided in Tables 1 and 2, respectively.

Table 1 Recommended dose level reductions

Dose level	**Dabrafenib dose** Used as monotherapy or in combination with trametinib	**Trametinib dose*** Only when used in combination with dabrafenib
Starting dose	150 mg twice daily	2 mg once daily
1st dose reduction	100 mg twice daily	1.5 mg once daily
2nd dose reduction	75 mg twice daily	1 mg once daily
3rd dose reduction	50 mg twice daily	1 mg once daily
Dose adjustment for dabrafenib below 50 mg twice daily is not recommended, whether used as monotherapy or in combination with trametinib. Dose adjustment for trametinib below 1 mg once daily is not recommended, when used in combination with dabrafenib.		

*For dosing instructions for treatment with trametinib monotherapy, see trametinib SmPC, Posology and Method of administration.

Table 2 Dose modification schedule based on the grade of any adverse events (AE) (excluding pyrexia)

Grade (CTC-AE)*	**Recommended dabrafenib dose modifications** Used as monotherapy or in combination with trametinib
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed 150 mg twice daily.

Pyrexia
If a patient's temperature is ≥38°C therapy should be interrupted (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4). Dabrafenib, or both dabrafenib and trametinib when used in combination, should be restarted if the patient is symptom free for at least 24 hours, either 1) at the same dose level, or 2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for uveitis, RAS mutation positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

Uveitis

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

RAS-mutation-positive non-cutaneous malignancies

The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction

If dabrafenib is being used in combination with trametinib and absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN), please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib.

Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)

If patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on combination therapy with dabrafenib and trametinib, please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for confirmed cases of RVO or RPED.

Interstitial lung disease (ILD)/Pneumonitis

In patients treated with dabrafenib in combination with trametinib with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations, please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for cases of ILD or pneumonitis.

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. There are no clinical data in subjects with severe renal impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Dabrafenib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with trametinib.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. Dabrafenib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with trametinib.

Special populations

Non-Caucasian patients

Limited safety and efficacy data have been collected on dabrafenib in non-Caucasian patients. The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. No dabrafenib dose adjustment is needed in Asian patients.

Elderly
No adjustment of the initial dose is required in patients >65 years of age.

Paediatric population
The safety and efficacy of dabrafenib in children and adolescents (<18 years) have not yet been established. No clinical data are available. Studies in juvenile animals have shown adverse effects of dabrafenib which had not been observed in adult animals (see section 5.3).

Method of administration

Tafinlar is for oral use. The capsules are to be swallowed whole with water. They should not be chewed or opened and should not be mixed with food or liquids due to chemical instability of dabrafenib.

It is recommended that the doses of dabrafenib be taken at similar times every day, leaving an interval of approximately 12 hours between doses. When dabrafenib and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal.

If a patient vomits after taking dabrafenib, the patient should not retake the dose and should take the next scheduled dose.

Please refer to trametinib SmPC for information on method of administration when given in combination with dabrafenib.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When dabrafenib is given in combination with trametinib, the SmPC of trametinib must be consulted prior to intiation of combination treatment. For additional information on warnings and precautions associated with trametinib treatment, please refer to the trametinib SmPC.

BRAF V600 testing

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC therefore dabrafenib should not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC (see sections 4.2 and 5.1).

Dabrafenib in combination with trametinib in patients with melanoma who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 5.1). Therefore, other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

New malignancies

New malignancies, cutaneous and non-cutaneous, can occur when dabrafenib is used as monotherapy or in combination with trametinib.

Cutaneous malignancies

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with dabrafenib alone and in combination with trametinib (see section 4.8). In the Phase III clinical trials MEK115306 and MEK116513 in patients with unresectable or metastatic melanoma, cuSCC occurred in 10% (22/211) of patients receiving dabrafenib as a monotherapy and in 18% (63/349) of patients receiving vemurafenib as a monotherapy, respectively. In the integrated safety population of patients with melanoma and advanced NSCLC, cuSCC occurred in 2% (19/1076) of patients receiving dabrafenib in combination with trametinib. The median time to diagnosis of the first occurrence of cuSCC in study MEK115306 was 223 days (range 56 to 510 days) in the combination therapy arm and 60 days (range 9 to 653 days) in the dabrafenib monotherapy arm. In the Phase III study BRF115532 (COMBI-AD) in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving dabrafenib in combination with trametinib as compared to 1% (5/432) of patients receiving placebo developed cuSCC. The median time to onset of the first occurrence of cuSCC in the combination arm of the adjuvant treatment study was approximately 18 weeks and was 33 weeks in the placebo arm.

It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment or, if taken in combination, dabrafenib and trametinib should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

New primary melanoma

New primary melanomas have been reported in clinical trials in patients treated with dabrafenib. In clinical trials in unresectable or metastatic melanoma,these cases were identified within the first 5 months of dabrafenib as monotherapy. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancies

In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAP kinase) signalling in BRAF wild-type cells with RAS mutations when exposed to BRAF inhibitors. This may lead to increased risk of non-cutaneous malignancies with dabrafenib exposure (see section 4.8) when RAS mutations are present. RAS-associated malignancies have been reported in clinical trials, both with another BRAF inhibitor (chronic myelomonocytic leukaemia and non-cutaneous SCC of the head and neck) as well as with dabrafenib monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with dabrafenib in combination with the MEK inhibitor, trametinib (colorectal cancer, pancreatic cancer).

Prior to initiation of treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen computerised tomography (CT) scan. During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations are recommended before and at the end of treatment or when considered clinically indicated. Complete blood cell counts and blood chemistry should be performed as clinically indicated.

The benefits and risks should be considered before administering dabrafenib in patients with a prior or concurrent cancer associated with RAS mutations. No dose modification of trametinib is required when taken in combination with dabrafenib.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Haemorrhage

Haemorrhagic events, including major haemorrhagic and fatal haemorrhages, have occurred in patients taking the combination of dabrafenib with trametinib (see section 4.8). Please refer to the trametinib SmPC (see section 4.4) for additional information.

Visual impairment

In clinical trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.

No dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

RPED and RVO may occur with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED.

Pyrexia

Fever has been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib (see section 4.8). In 1% of patients in clinical trials with dabrafenib monotherapy, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in subjects with normal baseline renal function (see section 4.8). The onset of these serious non-infectious febrile events was typically within the first month of dabrafenib as monotherapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

The incidence and severity of pyrexia are increased with combination therapy. In the combination therapy arm of study MEK115306 in patients with unresectable or metastatic melanoma, pyrexia was reported in 57% (119/209) of patients with 7% Grade 3, as compared to the dabrafenib monotherapy arm with 33% (69/211) of patients reporting pyrexia, 2% Grade 3. In the Phase II study BRF113928 in patients with advanced NSCLC the incidence and severity of pyrexia were increased slightly when dabrafenib was used in combination with trametinib (48%, 3% Grade 3) as compared to dabrafenib monotherapy (39%, 2% Grade 3). In the Phase III study BRF115532 in the adjuvant treatment of melanoma, the incidence and severity of pyrexia were higher in the dabrafenib in combination with trametinib arm (67%; 6% Grade 3/4) as compared to the placebo arm (15%; <1% Grade 3).

For patients with unresectable or metastatic melanoma who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events.

Therapy (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination) should be interrupted if the patient's temperature is ≥38ºC (see section 5.1). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2).

LVEF reduction/Left ventricular dysfunction

Dabrafenib in combination with trametinib has been reported to decrease LVEF (see section 4.8). Please refer to the trametinib SmPC for additional information (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib.

Renal failure

Renal failure has been identified in <1% of patients treated with dabrafenib alone and in ≤1% of patients treated with dabrafenib in combination with trametinib. Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported (see section 4.8). Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN) therefore caution should be used in this setting (see section 5.2).

Hepatic events

Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib (see section 4.8). It is recommended that patients receiving treatment with dabrafenib in combination with trametinib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib. Liver monitoring may be continued thereafter as clinically indicated. Please refer to the trametinib SmPC for additional information.

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension (see section 4.8). Please refer to the trametinib SmPC for additional information.

Interstitial lung disease (ILD)/Pneumonitis

Cases of pneumonitis or ILD have been reported in clinical trials with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC section 4.4 for additional information. If dabrafenib is being used in combination with trametinib then therapy with dabrafenib may be continued at the same dose.

Rash

Rash has been observed in about 24% of patients in clinical trials when dabrafenib is used in combination with trametinib (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions. Please refer to the trametinib SmPC section 4.4 for additional information.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib SmPC section 4.4 for additional information.

Pancreatitis

Pancreatitis has been reported in <1% of patients treated with dabrafenib as monotherapy and in combination with trametinib in unresectable or metastatic melanoma clinical trials and about 4% of patients treated with dabrafenib in combination with trametinib in the NSCLC clinical trial. One of the events occurred on the first day of dabrafenib dosing of a metastatic melanoma patient and recurred following re-challenge at a reduced dose. In the adjuvant treatment of melanoma trial, pancreatitis was

reported in <1% (1/435) of patients receiving dabrafenib in combination with trametinib, and no patients receiving placebo. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

Deep vein thrombosis/Pulmonary embolism

Pulmonary embolism or deep vein thrombosis can occur when dabrafenib is used in combination with trametinib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib/trametinib combination therapy. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be withdrawn.

Gastrointestinal disorders

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib SmPC for additional information (see section 4.4).

Sarcoidosis

Cases of sarcoidosis have been reported in patients treated with dabrafenib in combination with trametinib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with dabrafenib and trametinib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

Haemophagocytic lymphohistiocytosis

In post-marketing experience, haemophagocytic lymphohistiocytosis (HLH) has been observed in patients treated with dabrafenib in combination with trametinib. Caution should be taken when dabrafenib is administered in combination with trametinib. If HLH is confirmed, administration of dabrafenib and trametinib should be discontinued and treatment for HLH initiated.

Effects of other medicinal products on dabrafenib

Dabrafenib is a substrate of CYP2C8 and CYP3A4. Potent inducers of these enzymes should be avoided when possible as these agents may decrease the efficacy of dabrafenib (see section 4.5).

Effects of dabrafenib on other medicinal products

Dabrafenib is an inducer of metabolising enzymes which may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A drug utilisation review (DUR) is therefore essential when initiating dabrafenib treatment. Concomitant use of dabrafenib with medicinal products that are sensitive substrates of certain metabolising enzymes or transporters (see section 4.5) should generally be avoided if monitoring for efficacy and dose adjustment is not possible.

Concomitant administration of dabrafenib with warfarin results in decreased warfarin exposure. Caution should be exercised and additional International Normalised Ratio (INR) monitoring is

recommended when dabrafenib is used concomitantly with warfarin and at discontinuation of dabrafenib (see section 4.5).

Concomitant administration of dabrafenib with digoxin may result in decreased digoxin exposure. Caution should be exercised and additional monitoring of digoxin is recommended when digoxin (a transporter substrate) is used concomitantly with dabrafenib and at discontinuation of dabrafenib (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on dabrafenib

Dabrafenib is a substrate for the metabolising enzymes CYP2C8 and CYP3A4, while the active metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are therefore likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible. Use caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are co-administered with dabrafenib. Avoid co-administration of dabrafenib with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4.

Administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily, with dabrafenib 75 mg twice daily, resulted in a 71% increase in dabrafenib AUC and a 33% increase in dabrafenib C_{max} relative to administration of dabrafenib 75 mg twice daily alone. Co-administration resulted in increases in hydroxy- and desmethyl-dabrafenib AUC (increases of 82% and 68%, respectively). A decrease of 16% in AUC was noted for carboxy-dabrafenib.

Administration of gemfibrozil (a CYP2C8 inhibitor) 600 mg twice daily, with dabrafenib 75 mg twice daily, resulted in a 47% increase in dabrafenib AUC but did not alter dabrafenib C_{max} relative to administration of dabrafenib 75 mg twice daily alone. Gemfibrozil had no clinically relevant effect on the systemic exposure to dabrafenib metabolites (≤13%).

Administration of rifampin (a CYP3A4/CYP2C8 inducer) 600 mg once daily with dabrafenib 150 mg twice daily resulted in a decrease in repeat dose dabrafenib C_{max} (27%) and AUC (34%). No relevant change in AUC was noted for hydroxy-dabrafenib. There was an increase in AUC of 73% for carboxy-dabrafenib and a decrease in AUC of 30% for desmethyl-dabrafenib.

Co-administration of repeat doses of dabrafenib 150 mg twice daily and the pH-elevating agent rabeprazole 40 mg once daily resulted in a 3% increase in AUC and a 12% decrease in dabrafenib C_{max}. These changes in dabrafenib AUC and C_{max} are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g. proton pump inhibitors, H_2-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

Effect of dabrafenib on other medicinal products

Dabrafenib is an enzyme inducer and increases the synthesis of drug-metabolising enzymes including CYP3A4, CYP2Cs and CYP2B6 and may increase the synthesis of transporters. This results in reduced plasma levels of medicinal products metabolised by these enzymes, and may affect some transported medicinal products. The reduction in plasma concentrations can lead to lost or reduced clinical effect of these medicinal products. There is also a risk of increased formation of active metabolites of these medicinal products. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGTs (glucuronide conjugating enzymes). The transport protein Pgp may also be induced as well as other transporters, e.g. MRP-2. Induction of OATP1B1/1B3 and BCRP is not likely based on the observations from a clinical study with rosuvastatin.

In vitro, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4. In a clinical drug interaction study, C_{max} and AUC of oral midazolam (a CYP3A4 substrate) decreased by 47% and 65%, respectively with co-administration of repeat-dose dabrafenib.

Administration of dabrafenib 150 mg twice daily and warfarin resulted in a decrease in AUC of S- and R- warfarin of 37% and 33%, respectively, compared to administration of warfarin alone. C_{max} of S- and R-warfarin increased 18% and 19%.

Interactions with many medicinal products eliminated through metabolism or active transport is expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

The number of affected medicinal products is expected to be large; although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, methadone)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, see section 4.4)
- Antiepileptic (e.g. carbamazepine, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin, see section 4.4)
- Corticosteroids (e.g. dexamethasone, methylprednisolone)
- HIV antivirals (e.g. amprenavir, atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)
- Hormonal contraceptives (see section 4.6)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Upon discontinuation of dabrafenib offset of induction is gradual, concentrations of sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, UDP glucuronosyl transferase (UGT) and transporter substrates (e.g. Pgp or MRP-2) may increase and patients should be monitored for toxicity and dose of these agents may need to be adjusted.

In vitro, dabrafenib is a mechanism based inhibitor of CYP3A4. Therefore, transient inhibition of CYP3A4 may be observed during the first few days of treatment.

Effects of dabrafenib on substance transport systems

Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1), OATP1B3 and BCRP. Following co-administration of a single dose of rosuvastatin (OATP1B1, OATP1B3 and BCRP substrate) with repeat-dose dabrafenib 150 mg twice daily in 16 patients, C_{max} of rosuvastatin increased 2.6-fold whereas the AUC was only minimally changed (7% increase). The increased C_{max} of rosuvastatin is unlikely to have clinical relevance.

Combination with trametinib

Co-administration of repeat dosing of trametinib 2 mg once daily and dabrafenib 150 mg twice daily resulted in no clinically meaningful changes in trametinib or dabrafenib C_{max} and AUC with increases of 16 and 23%, respectively, in dabrafenib C_{max} and AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when trametinib is

administered in combination with dabrafenib, a CYP3A4 inducer, using a population pharmacokinetic analysis.

When dabrafenib is used in combination with trametinib refer to the guidance for medicinal product interactions found in sections 4.4 and 4.5 of dabrafenib and trametinib SmPC.

Effect of food on dabrafenib

Patients should take dabrafenib as monotherapy or in combination with trametinib at least one hour prior to or two hours after a meal due to the effect of food on dabrafenib absorption (see section 5.2).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective methods of contraception during therapy and for 2 weeks following discontinuation of dabrafenib and 16 weeks following the last dose of trametinib when given in combination with dabrafenib. Dabrafenib may decrease the efficacy of oral or any systemic hormonal contraceptives and an effective alternative method of contraception should be used (see section 4.5).

Pregnancy

There are no data from the use of dabrafenib in pregnant women. Animal studies have shown reproductive toxicity and embryo-foetal developmental toxicities, including teratogenic effects (see section 5.3). Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. If the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the foetus. Please see trametinib SmPC (see section 4.6) when used in combination with trametinib.

Breast-feeding

It is not known whether dabrafenib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding child cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue dabrafenib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for dabrafenib as monotherapy or in combination with trametinib. Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals (see section 5.3). Male patients taking dabrafenib as monotherapy or in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Please see trametinib SmPC (see section 4.6) when used in combination with trametinib.

4.7 Effects on ability to drive and use machines

Dabrafenib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of dabrafenib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should be made aware of the potential for fatigue and eye problems to affect these activities.

4.8 Undesirable effects

Summary of the safety profile

The safety of dabrafenib monotherapy is based on the integrated safety population from five clinical trials, BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680, which included 578 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with dabrafenib 150 mg twice daily. The most common adverse reactions (incidence ≥15%) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash, and vomiting.

The safety of dabrafenib in combination with trametinib has been evaluated in the integrated safety population of 1076 patients with BRAF V600 mutant unresectable or metastatic melanoma, Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment) and advanced NSCLC treated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III clinical trials, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), 435 were treated with the combination in the adjuvant treatment of Stage III BRAF V600 mutant melanoma after complete resection in a randomised Phase III study BRF115532 (COMBI-AD) and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928 (see section 5.1).

The most common adverse reactions (incidence ≥20%) for dabrafenib in combination with trametinib were: pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash.

Tabulated list of adverse reactions

Adverse reactions associated with dabrafenib obtained from clinical studies and post-marketing surveillance are tabulated below for dabrafenib monotherapy (Table 3) and dabrafenib in combination with trametinib (Table 4). Adverse drug reactions are listed below by MedDRA system organ class ranked by frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions with dabrafenib monotherapy

System organ class	Frequency (all grades)	Adverse reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very common	Papilloma
	Common	Cutaneous squamous cell carcinoma
		Seborrhoeic keratosis
		Acrochordon (skin tags)
		Basal cell carcinoma
	Uncommon	New primary melanoma
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
Eye disorders	Uncommon	Uveitis
Respiratory, thoracic and mediastinal disorders	Very common	Cough

Gastrointestinal disorders	Very common	Nausea
		Vomiting
		Diarrhoea
	Common	Constipation
	Uncommon	Pancreatitis
Skin and subcutaneous tissue disorders	Very common	Hyperkeratosis
		Alopecia
		Rash
		Palmar-plantar erythrodysaesthesia syndrome
	Common	Dry skin
		Pruritus
		Actinic keratosis
		Skin lesion
		Erythema
		Photosensitivity
	Uncommon	Panniculitis
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
Renal and urinary disorders	Uncommon	Renal failure, acute renal failure
		Nephritis
General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
		Chills
		Asthenia
	Common	Influenza-like illness

Table 4 Adverse reactions with dabrafenib in combination with trametinib

System organ class	Frequency (all grades)	Adverse reactions
Infections and infestations	Very common	Nasopharyngitis
	Common	Urinary tract infection
		Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma[a]
		Papilloma[b]
		Seborrhoeic keratosis
	Uncommon	New primary melanoma[c]
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Common	Neutropenia
		Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[d]
		Sarcoidosis
	Rare	Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia

Nervous system disorders	Very common	Headache
		Dizziness
Eye disorders	Common	Vision blurred
		Visual impairment
		Uveitis
	Uncommon	Chorioretinopathy
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
	Uncommon	Bradycardia
	Not known	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[e]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
	Uncommon	Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain[f]
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Colitis
	Rare	Gastrointestinal perforation
Skin and subcutaneous disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema[g]
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity
	Not known	Stevens-Johnson syndrome
		Drug reaction with eosinophilia and systemic symptoms
		Dermatitis exfoliative generalised
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms[h]
Renal and urinary disorders	Uncommon	Renal failure
		Nephritis

General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
		Influenza-like illness
	Common	Mucosal inflammation
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased

[a] Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma
[b] Papilloma, skin papilloma
[c] Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III
[d] Includes drug hypersensitivity
[e] Bleeding from various sites, including intracranial bleeding and fatal bleeding
[f] Abdominal pain upper and abdominal pain lower
[g] Erythema, generalised erythema
[h] Muscle spasms, musculoskeletal stiffness

Description of selected adverse reactions

Cutaneous squamous cell carcinoma
For dabrafenib monotherapy in study MEK115306, cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 10% of patients and approximately 70% of the events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. In the integrated safety population for dabrafenib in combination with trametinib, 2% of patients developed cuSCC and the events occurred later than with dabrafenib monotherapy with a median time to onset of 18-31 weeks. All patients receiving dabrafenib as monotherapy or in combination with trametinib who developed cuSCC continued on treatment without dose modification.

New primary melanoma
New primary melanomas have been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib in melanoma studies. Cases were managed with excision and did not require treatment modification (see section 4.4). No new primary melanoma was reported from the Phase II NSCLC study (BRF113928).

Non-cutaneous malignancy
Activation of MAP-kinase signalling in BRAF wild type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations (see section 4.4). Non-cutaneous malignancies were reported in 1% (6/586) of patients in the integrated safety population of dabrafenib monotherapy, and <1% (8/1076) of patients in the integrated safety population of dabrafenib in combination with trametinib. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy and in combination with trametinib. Patients should be monitored as clinically appropriate.

Haemorrhage
Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking dabrafenib in combination with trametinib. Please refer to the trametinib SmPC.

LVEF reduction/Left ventricular dysfunction
Decreased LVEF has been reported in 6% (65/1076) of patients in the integrated safety population of dabrafenib in combination with trametinib. Most cases were asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function. Please refer to the trametinib SmPC.

Pyrexia
Fever has been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib; the incidence and severity of pyrexia are increased with the combination therapy (see section 4.4). For patients who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events. In 1% of patients receiving dabrafenib as monotherapy in the integrated safety population, serious non-infectious febrile events were identified as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in subjects with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care (see sections 4.2 and 4.4).

Hepatic events
Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC.

Hypertension
Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate.

Arthralgia
Arthralgia was reported very commonly in the integrated safety population of dabrafenib monotherapy (25%) and dabrafenib in combination with trametinib (25%) although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%) and no Grade 4 occurrences being reported.

Hypophosphataemia
Hypophosphataemia has been reported commonly in the integrated safety population of dabrafenib monotherapy (7%) and of dabrafenib in combination with trametinib (4%). It should be noted that approximately half of these occurrences with dabrafenib monotherapy (4%) and 1% with dabrafenib in combination with trametinib were Grade 3 in severity.

Pancreatitis
Pancreatitis has been reported in dabrafenib monotherapy and in combination with trametinib. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis (see section 4.4).

Renal failure
Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon; however dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN). Caution should be used in this setting (see section 4.4).

Special populations

Elderly
Of the total number of patients in the integrated safety population of dabrafenib monotherapy (n=578), 22% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger

subjects (<65), more subjects ≥65 years old had adverse reactions that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse reactions compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these subjects and younger subjects.

In the integrated safety population of dabrafenib in combination with trametinib (n=1076), 265 patients (25%) were ≥65 years of age, 62 patients (6%) were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all clinical trials. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

Dabrafenib in combination with trametinib in patients with brain metastases

The safety and efficacy of the combination of dabrafenib and trametinib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. The safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for an overdose of dabrafenib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, B-Raf serine-threonine kinase (BRAF) inhibitors, ATC code: L01EC02

Mechanism of action

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. The most commonly observed BRAF mutation is V600E which accounts for approximately 90% of the BRAF mutations that are seen in melanoma.

Preclinical data generated in biochemical assays demonstrated that dabrafenib inhibits BRAF kinases with activating codon 600 mutations (Table 5).

Table 5 Kinase inhibitory activity of dabrafenib against RAF kinases

Kinase	Inhibitory concentration 50 (nM)
BRAF V600E	0.65
BRAF V600K	0.50
BRAF V600D	1.8
BRAF WT	3.2
CRAF WT	5.0

Dabrafenib demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK) and inhibited cell growth of BRAF V600 mutant melanoma cell lines, *in vitro* and in animal models.

In subjects with BRAF V600 mutation positive melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Combination with trametinib
Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib has shown anti-tumour activity in BRAF V600 mutation positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

Determination of BRAF mutation status
Before taking dabrafenib or combination with trametinib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the Phase II and III clinical trials, screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO). The IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only subjects with BRAF V600E or V600K mutation positive tumours were eligible for study participation.

Subsequently, all patient samples were re-tested using the bioMerieux (bMx) THxID BRAF validated assay, which has CE marking. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical trials with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical trials (n=876) that were mutation positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94%.

Clinical efficacy and safety

Unresectable or metastatic melanoma
- *Dabrafenib in combination with trametinib*

Treatment-naïve patients
The efficacy and safety of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two Phase III trials and one supportive Phase I/II study.

MEK115306 (COMBI-d):
MEK115306 was a Phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was progression-free survival (PFS), with a key secondary endpoint of overall survival (OS). Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 423 subjects were randomised 1:1 to either combination (N=211) or dabrafenib (N=212). Most subjects were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of subjects had Stage IVM1c disease (67%). Most subjects had LDH ≤ULN (65%), Eastern Cooperative Oncology Group (ECOG) performance status of 0 (72%), and visceral disease (73%) at baseline. The majority of subjects had a BRAF V600E mutation (85%). Subjects with brain metastases were not included in the trial.

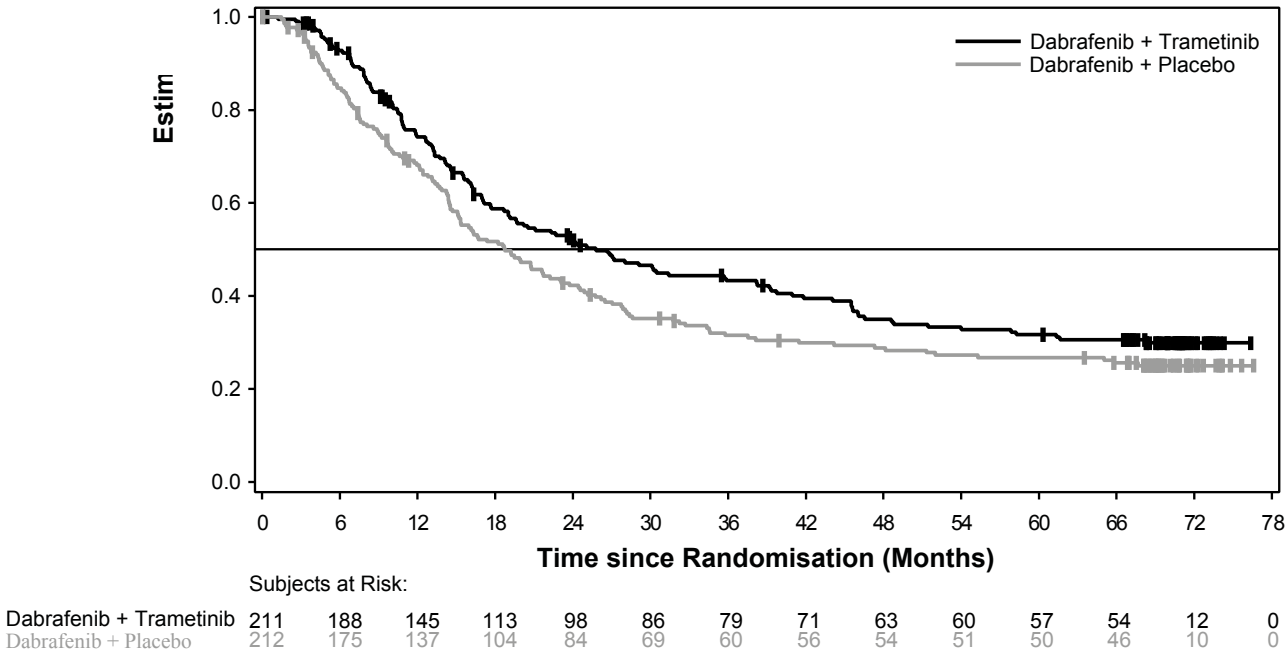
Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 6. From an OS analysis at 5 years, the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 6, Figure 1). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 1). The 5-year overall survival rate was 40% (95% CI: 31.2, 48.4) in the combination arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 6 Overall Survival results for Study MEK115306 (COMBI-d)

	OS analysis (data cut-off: 12-Jan-2015)		**5-year OS analysis (data cut-off: 10-Dec-2018)**	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
Number of patients				
Died (event), n (%)	99 (47)	123 (58)	135 (64)	151 (71)
Estimates of OS (months)				
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.80 (0.63, 1.01)	
p-value	0.011		NA	
Overall survival estimate, % (95% CI)	**Dabrafenib + Trametinib (n=211)**		**Dabrafenib + Placebo (n=212)**	
At 1 year	74 (66.8, 79.0)		68 (60.8, 73.5)	
At 2 years	52 (44.7, 58.6)		42 (35.4, 48.9)	
At 3 years	43 (36.2, 50.1)		31 (25.1, 37.9)	
At 4 years	35 (28.2, 41.8)		29 (22.7, 35.2)	
At 5 years	32 (25.1, 38.3)		27 (20.7, 33.0)	

NR = Not reached, NA = Not applicable

Figure 1 Kaplan-Meier overall survival curves for Study MEK115306 (ITT population)



Improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. Improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to dabrafenib monotherapy (Table 7).

Table 7 Efficacy results for Study MEK115306 (COMBI-d)

	Primary analysis (data cut-off: 26-Aug-2013)		Updated analysis (data cut-off: 12-Jan-2015)		5-year analysis (data cut-off: 10-Dec-2018)	
Endpoint	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
PFS[a]						
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	160 (76)	166 (78)
Median PFS (months) (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)		0.73 (0.59, 0.91)	
P value	0.035		<0.001[f]		NA	
ORR[b] % (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	69 (62.5, 75.4)	54 (46.8, 60.6)
ORR difference (95% CI)	15[e] (5.9, 24.5)		15[e] (6.0, 24.5)		NA	
P value	0.0015		0.0014[f]		NA	
DoR[c] **(months)** Median (95% CI)	9.2[d] (7.4, NR)	10.2[d] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1, 13.8)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d – At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing
e – ORR difference calculated based on the ORR result not rounded
f – Updated analysis was not pre-planned and the p-value was not adjusted for multiple testing
NR = Not reached
NA = Not applicable

MEK116513 (COMBI-v):
Study MEK116513 was a 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was OS with a key secondary endpoint of PFS. Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 704 subjects were randomised 1:1 to either combination or vemurafenib. Most subjects were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of subjects had Stage IV M1c disease (61% overall). Most subjects had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at Baseline. Overall, 54% of subjects had <3 disease sites at baseline. The majority of subjects had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the trial.

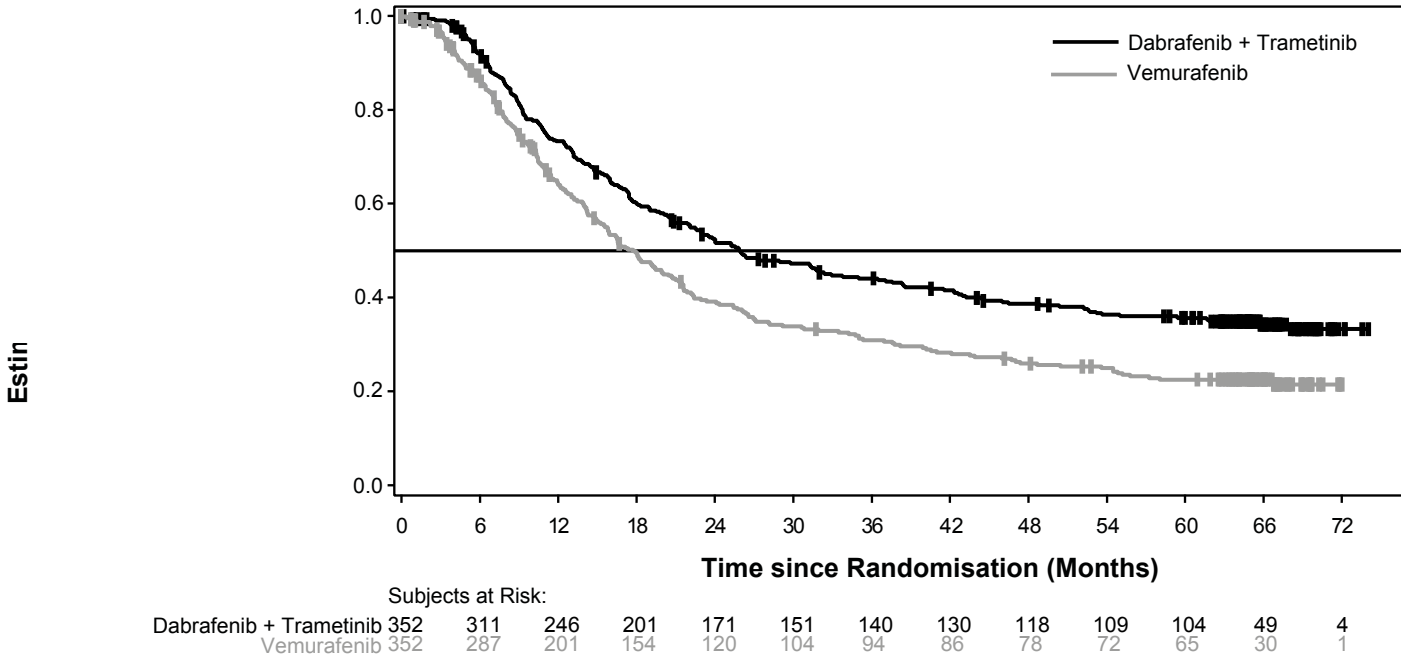
Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 8. From an OS analysis at 5 years, the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5-year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 8, Figure 2). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 2). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 8 Overall Survival results for Study MEK116513 (COMBI-v)

	OS analysis data cut-off: 13-Mar-2015)		5-year OS analysis (data cut-off: 08-Oct-2018)	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Number of patients				
Died (event), n (%)	155 (44)	194 (55)	216 (61)	246 (70)
Estimates of OS (months)				
Median (95% CI)	25.6 (22.6, NR)	18.0 (15.6, 20.7)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Adjusted hazard ratio (95% CI)	0.66 (0.53, 0.81)		0.70 (0.58, 0.84)	
p-value	<0.001		NA	
Overall survival estimate, % (95% CI)	**Dabrafenib + Trametinib (n=352)**		**Vemurafenib (n=352)**	
At 1 year	72 (67, 77)		65 (59, 70)	
At 2 years	53 (47.1, 57.8)		39 (33.8, 44.5)	
At 3 years	44 (38.8, 49.4)		31 (25.9, 36.2)	
At 4 years	39 (33.4, 44.0)		26 (21.3, 31.0)	
At 5 years	36 (30.5, 40.9)		23 (18.1, 27.4)	

NR = Not reached, NA = Not applicable

Figure 2 Kaplan-Meier overall survival curves for Study MEK116513



Improvements for the secondary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to vemurafenib monotherapy. Improvements were also observed for ORR and a longer DoR was observed in the combination arm compared to vemurafenib monotherapy (Table 9).

Table 9 Efficacy results for Study MEK116513 (COMBI-v)

	Primary analysis (Data cut-off: 17-Apr-2014)		5-year analysis (Data cut-off: 08-Oct-2018)	
Endpoint	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
PFS[a]				
Progressive disease or death, n (%)	166 (47)	217 (62)	257 (73)	259 (74)
Median PFS (months) (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.62 (0.52, 0.74)	
P value	<0.001		NA	
ORR[b] % (95% CI)	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (62.2, 72.2)	53 (47.2, 57.9)
ORR difference (95% CI)	13 (5.7, 20.2)		NA	
P value	0.0005		NA	
DoR[c] (months) Median (95% CI)	13.8[d] (11.0, NR)	7.5[d] (7.3, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d – At the time of the reporting the majority (59% of dabrafenib+trametinib and 42% of vemurafenib) of investigator-assessed responses were still ongoing
NR = Not reached
NA = Not applicable

Prior BRAF inhibitor therapy
There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor.

Part B of study BRF113220 included a cohort of 26 patients that had progressed on a BRAF inhibitor. The trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor. The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 45 patients who crossed over from dabrafenib monotherapy to the trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination in Part C of this study. In these patients a 13% (95 CI: 5.0, 27.0) confirmed response rate was observed with a median PFS of 3.6 months (95% CI: 2, 4).

Patients with brain metastases
The efficacy and safety of dabrafenib in combination with trametinib in patients with BRAF mutant-positive melanoma that has metastasised to the brain was studied in a non-randomised, open-label, multicentre, Phase II study (COMBI-MB study). A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.

- Cohort B: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or1.
- Cohort C: patients with BRAFV600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort D: patients with BRAFV600D/E/K/R mutant melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1 or 2.

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Intracranial response assessed by the investigator in Cohorts B, C and D were secondary endpoints of the study. Due to small sample size reflected by wide 95% CIs, the results in Cohorts B, C, and D should be interpreted with caution. Efficacy results are summarised in Table 10.

Table 10 Efficacy data by investigator assessment from COMBI-MB study

	All treated patients population			
Endpoints/ assessment	**Cohort A N=76**	**Cohort B N=16**	**Cohort C N=16**	**Cohort D N=17**
Intracranial response rate, % (95 % CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	59% (32.9, 81.6)
Duration of intracranial response, median, months (95% CI)				
	6.5 (4.9, 8.6)	7.3 (3.6, 12.6)	8.3 (1.3, 15.0)	4.5 (2.8, 5.9)
Overall response rate, % (95% CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
Progression-free survival, median, months (95% CI)				
	5.7 (5.3, 7.3)	7.2 (4.7, 14.6)	3.7 (1.7, 6.5)	5.5 (3.7, 11.6)
Overall survival, median, months (95% CI)				
	10.8 (8.7, 17.9)	24.3 (7.9, NR)	10.1 (4.6, 17.6)	11.5 (6.8, 22.4)

CI = Confidence Interval
NR = Not reached

- *Dabrafenib monotherapy*

The efficacy of dabrafenib in the treatment of adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in 3 clinical trials (BRF113683 [BREAK-3], BRF113929 [BREAK-MB], and BRF113710 [BREAK-2]) including patients with BRAF V600E and/or V600K mutations.

Included in these clinical trials were in total 402 subjects with BRAF V600E and 49 subjects with BRAF V600K mutation. Patients with melanoma driven by BRAF mutations other than V600E were excluded from the confirmatory trial and with respect to patients with the V600K mutation in single arm clinical trials the activity appears lower than in V600E tumours.

No data is available in patients with melanoma harbouring BRAF V600 mutations others than V600E and V600K. Efficacy of dabrafenib in subjects previously treated with a protein kinase inhibitor has not been investigated.

Previously untreated patients (results from the Phase III study [BREAK-3])
The efficacy and safety of dabrafenib were evaluated in a Phase III randomised, open-label study [BREAK 3] comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Patients with melanoma driven by BRAF mutations other than V600E were excluded.

The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to PFS per investigator assessment. Patients on the DTIC arm were allowed to cross over to dabrafenib after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6% were Caucasian; the median age was 52 years with 21% of patients being ≥65 years, 98.4% had ECOG status of 0 or 1, and 97% of patients had metastatic disease.

At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR=0.30; 95% Cl 0.18, 0.51; p < 0.0001) was achieved. Efficacy results from the primary analysis and a post-hoc analysis with 6-months additional follow up are summarised in Table 11. OS data from a further post-hoc analysis based on a 18 December 2012 data cut are shown in Figure 3.

Table 11 Efficacy in previously untreated patients (BREAK-3 Study, 25 June 2012)

	Data as of December 19, 2011		**Data as of June 25, 2012**	
	Dabrafenib N=187	**DTIC N=63**	**Dabrafenib N=187**	**DTIC N=63**
Progression-free survival				
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.9 (5.2,9.0)	2.7 (1.5,3.2)
HR (95% CI)	0.30 (0.18, 0.51) P < 0.0001		0.37 (0.24, 0.58) P < 0.0001	
Overall response[a]				
% (95% CI)	53 (45.5, 60.3)	19 (10.2, 30.9)	59 (51.4, 66.0)	24 (14, 36.2)
Duration of response				
Median, months (95% CI)	N=99 5.6 (4.8, NR)	N=12 NR (5.0, NR)	N=110 8.0 (6.6, 11.5)	N=15 7.6 (5.0, 9.7)

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR: not reached
[a] Defined as confirmed complete + partial response.

As of 25 June 2012 cut-off, thirty five subjects (55.6%) of the 63 randomised to DTIC had crossed over to dabrafenib and 63% of subjects randomised to dabrafenib and 79% of subjects randomised to DTIC had progressed or died. Median PFS after cross-over was 4.4 months.

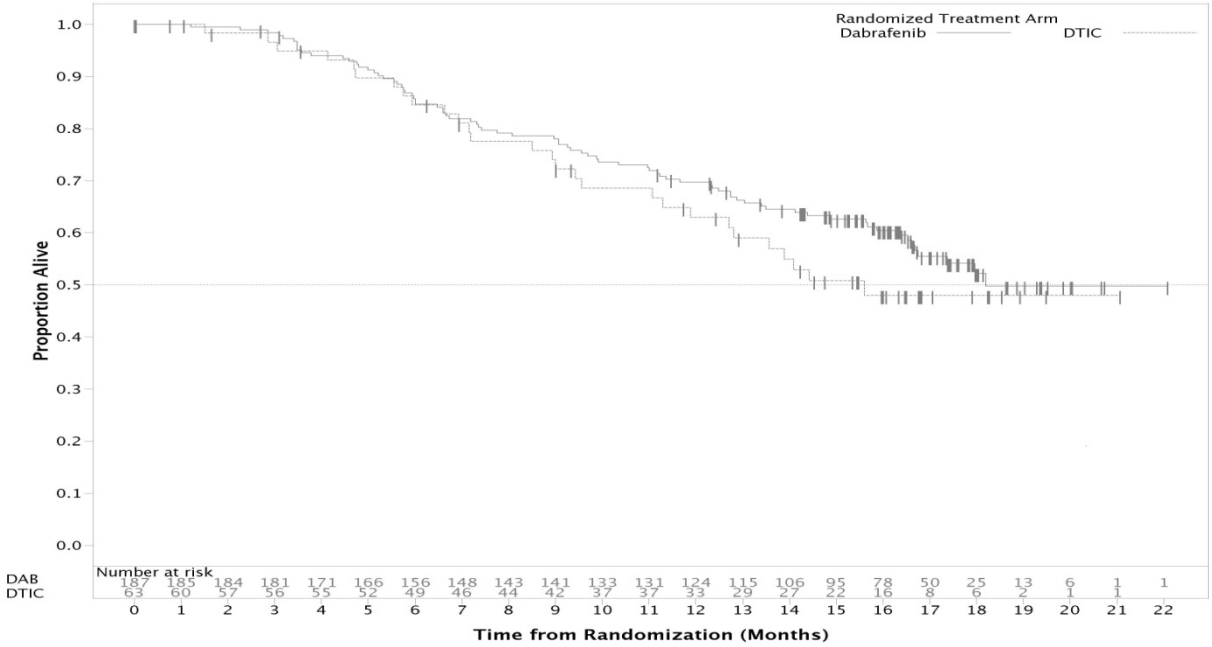
Table 12 Survival data from the primary analysis and post-hoc analyses

Cut-off date	**Treatment**	**Number of deaths (%)**	**Hazard ratio (95% CI)**
December 19, 2011	DTIC	9 (14%)	0.61 (0.25, 1.48) (a)
	dabrafenib	21 (11%)	
June 25, 2012	DTIC	21 (33%)	0.75 (0.44, 1.29) (a)
	dabrafenib	55 (29%)	
December 18, 2012	DTIC	28 (44%)	0.76 (0.48, 1.21) (a)
	dabrafenib	78 (42%)	

(a) Patients were not censored at the time of cross-over

OS data from a further post-hoc analysis based on the 18 December 2012 data cut demonstrated a 12-month OS rate of 63% and 70% for DTIC and dabrafenib treatments, respectively.

Figure 3 Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)



Patients with brain metastases (results from the Phase II study (BREAK-MB)
BREAK-MB was a multicentre, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Subjects were enrolled into Cohort A (subjects with no prior local therapy for brain metastasis) or Cohort B (subjects who received prior local therapy for brain metastasis).

The primary endpoint of the study was overall intracranial response rate (OIRR) in the V600E patient population, as assessed by investigators. The confirmed OIRR and other efficacy results per investigator assessment are presented in Table 13.

Table 13 Efficacy data in patients with brain metastases (BREAK-MB Study)

	All Treated Subjects Population			
	BRAF V600E (Primary)		BRAF V600K	
	Cohort A N=74	Cohort B N=65	Cohort A N=15	Cohort B N=18
Overall intracranial response rate,% (95% CI)[a]				
	39% (28.0, 51.2) P < 0.001[b]	31% (19.9, 43.4) P < 0.001[b]	7% (0.2, 31.9)	22% (6.4, 47.6)
Duration of intracranial response, median, months (95% CI)				
	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9 (NR, NR)	N=4 3.8 (NR, NR)
Overall response,% (95% CI)[a]				
	38% (26.8, 49.9)	31% (19.9, 43.4)	0 (0, 21.8)	28% (9.7, 53.5)
Duration of response, median, months (95% CI)				
	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
Progression-free survival, median, months (95% CI)				
	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
Overall survival, median, months (95% CI)				
Median, months	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Abbreviations: CI: confidence interval; NR: not reached; NA: not applicable

a Confirmed response.

b This study was designed to support or reject the null hypothesis of OIRR ≤10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥ 30% in BRAF V600E mutation positive subjects.

Patients who were previously untreated or failed at least one prior systemic therapy (results from the Phase II [BREAK-2])

BRF113710 (BREAK-2) was a multicentre, single-arm study that enrolled 92 subjects with metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma.

The investigator assessed confirmed response rate in patients with BRAF V600E metastatic melanoma (n=76) was 59% (95% CI: 48.2, 70.3) and the median DoR was 5.2 months (95% CI: 3.9, not calculable) based on a median follow-up time of 6.5 months. In patients with BRAF V600K mutation positive metastatic melanoma (n=16) the response rate was 13% (95% CI: 0.0, 28.7) with a median DoR of 5.3 months (95% CI: 3.7, 6.8). Although limited by the low number of patients, median OS appeared consistent with data in patients with BRAF V600E positive tumours.

Adjuvant treatment of Stage III melanoma

BRF115532 (COMBI-AD)

The efficacy and safety of dabrafenib in combination with trametinib were studied in a Phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with Stage III (Stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC) cutaneous melanoma with a BRAF V600 E/K mutation, following complete resection.

Patients were randomised 1:1 to receive either combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) or two placebos for a period of 12 months. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomisation. Any prior systemic anti-cancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease-free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients were stratified by BRAF mutation status (V600E versus V600K) and stage of disease prior to surgery using the American Joint Committee on Cancer (AJCC) 7th edition Melanoma Staging System (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size

and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint), freedom from relapse (FFR) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%). At the time of the primary analysis, the median duration of follow-up (time from randomisation to last contact or death) was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Table 14. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with a median RFS of 16.6 months for the placebo arm and not yet reached for the combination arm (HR: 0.47; 95% confidence interval: (0.39, 0.58); $p=1.53\times10^{-14}$). The observed RFS benefit was consistently demonstrated across subgroups of patients including age, sex and race. Results were also consistent across stratification factors for disease stage and BRAF V600 mutation type.

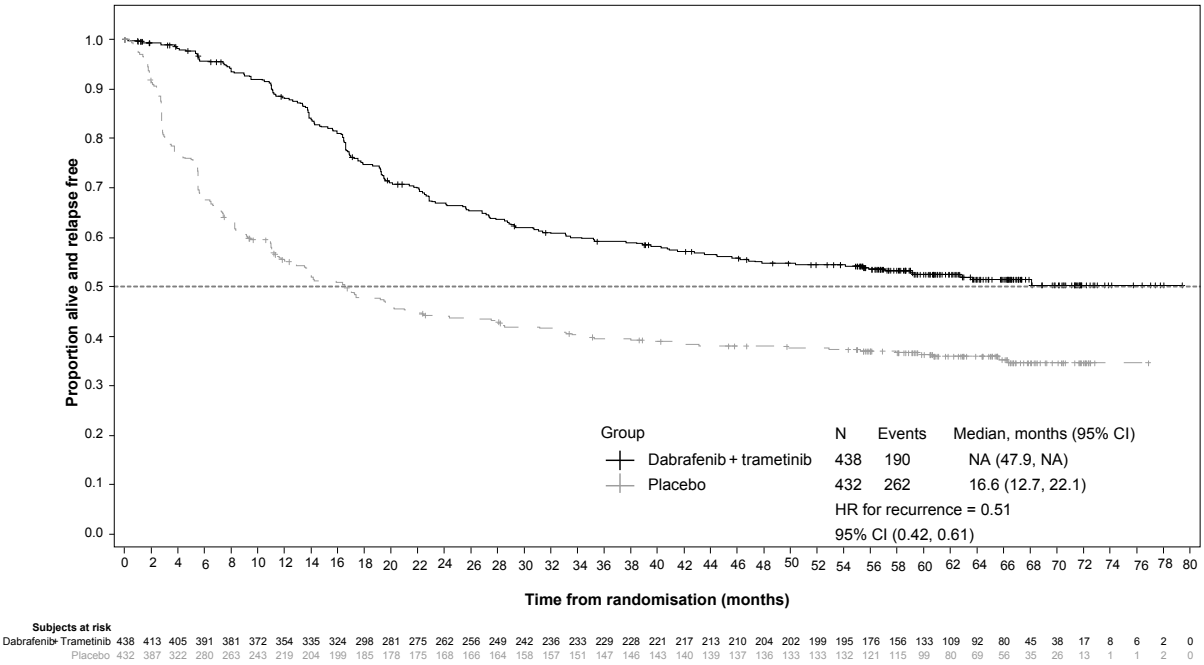
Table 14 Investigator-assessed RFS results for Study BRF115532 (COMBI-AD primary analysis)

RFS parameter	**Dabrafenib + Trametinib N=438**	**Placebo N=432**
Number of events, n (%)	166 (38%)	248 (57%)
Recurrence	163 (37%)	247 (57%)
Relapsed with distant metastasis	103 (24%)	133 (31%)
Death	3 (<1%)	1 (<1%)
Median (months)	NE	16.6
(95% CI)	(44.5, NE)	(12.7, 22.1)
Hazard ratio[1]	0.47	
(95% CI)	(0.39, 0.58)	
p-value[2]	1.53×10^{-14}	
1-year rate (95% CI)	0.88 (0.85, 0.91)	0.56 (0.51, 0.61)
2-year rate (95% CI)	0.67 (0.63, 0.72)	0.44 (0.40, 0.49)
3-year rate (95% CI)	0.58 (0.54, 0.64)	0.39 (0.35, 0.44)

[1] Hazard ratio is obtained from the stratified Pike model.
[2] P-value is obtained from the two-sided stratified logrank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)
NE = not estimable

Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 (95% CI: 0.42, 0.61) (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm.

Figure 4 Kaplan-Meier RFS curves for Study BRF115532 (ITT population, updated results)



Based on 153 events (60 [14%] in the combination arm and 93 [22%] in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomisation were 97% and 91% in the combination arm and 94% and 83% in the placebo arm, respectively).

<u>*Non-small cell lung cancer*</u>

Study BRF113928

The efficacy and safety of dabrafenib in combination with trametinib was studied in a Phase II, three-cohort, multicentre, non-randomised and open-label study in which patients with stage IV BRAF V600E mutant NSCLC were enrolled. The primary endpoint was ORR using the RECIST 1.1 assessed by the investigator. Secondary endpoints included DoR, PFS, OS, safety and population pharmacokinetics. ORR, DoR and PFS were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis.

Cohorts were enrolled sequentially:

- Cohort A: Monotherapy (dabrafenib 150 mg twice daily), 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.
- Cohort B: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 59 patients enrolled. 57 patients had 1-3 lines of previous systemic treatment for their metastatic disease. 2 patients had no previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 34 patients. All patients received study medicinal product as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy cohorts B and C, most patients were Caucasian (>90%), and similar female versus male (54% versus 46%), with a median age of 64 years in second line or higher patients and 68 years in the first line patients. Most patients (94%) enrolled in the combination therapy treated cohorts had an ECOG performance status of 0 or 1. 26 (28%) had never smoked. The majority of patients had a non-squamous histology. In the previously

treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

At the time of the primary analysis, the primary endpoint of investigator-assessed ORR in the first line population was 61.1% (95% CI, 43.5%, 76.9%), and in the previously treated population was 66.7% (95% CI, 52.9%, 78.6%). These met the statistical significance to reject the null hypothesis that the ORR of dabrafenib in combination with trametinib for this NSCLC population was less than or equal to 30%. The ORR results assessed by IRC were consistent with the investigator assessment. The efficacy of the combination with trametinib was superior when indirectly compared to dabrafenib monotherapy in Cohort A. The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 15.

Table 15 Summary of efficacy in the combination treatment cohorts based on investigator and independent radiology review

Endpoint	**Analysis**	**Combination 1st line N=36[1]**	**Combination 2nd line plus N=57[1]**
Overall confirmed response n (%) (95% CI)	By Investigator By IRC	23 (63.9%) (46.2, 79.2) 23 (63.9%) (46.2, 79.2)	39 (68.4%) (54.8, 80.1) 36 (63.2%) (49.3, 75.6)
Median DoR Months (95% CI)	By Investigator By IRC	10.2 (8.3, 15.2) 15.2 (7.8, 23.5)	9.8 (6.9, 18.3) 12.6 (5.8, 26.2)
Median PFS Months (95% CI)	By Investigator By IRC	10.8 (7.0, 14.5) 14.6 (7.0, 22.1)	10.2 (6.9, 16.7) 8.6 (5.2, 16.8)
Median OS Months (95% CI)	-	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)

[1] Data cut-off: 7 January 2021

QT prolongation

Worst-case QTc prolongation of >60 millisecond (msec) was observed in 3% of dabrafenib-treated subjects (one >500 msec in the integrated safety population). In the Phase III study MEK115306 no patients treated with trametinib in combination with dabrafenib had worst-case QTcB prolongation to >500 msec; QTcB was increased more than 60 msec from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1%) treated with trametinib in combination with dabrafenib had a QTcB Grade 3 increase (>500 msec). Two of these patients had a QTcB Grade 3 increase (>500 msec) that was also an increase >60 msec from baseline.

The potential effect of dabrafenib on QT prolongation was assessed in a dedicated multiple dose QT study. A supratherapeutic dose of 300 mg dabrafenib twice daily was administered in 32 subjects with BRAF V600 mutation-positive tumours. No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed.

Other studies - pyrexia management analysis
Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)
Pyrexia is observed in patients treated with dabrafenib and trametinib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia (fever ≥38.5°C). In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both medicinal products when patient's temperature is ≥38°C (COMBI-Aplus), or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of

grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with dabrafenib in one or more subsets of the paediatric population in melanoma and solid malignant tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Dabrafenib is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95% (90% CI: 81, 110%). Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. A decrease in exposure was observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, AUC(0-τ) and predose concentration (Cτ) were 1478 ng/ml, 4341 ng*hr/ml and 26 ng/ml, respectively.

Administration of dabrafenib with food reduced the bioavailability (C_{max} and AUC decreased by 51% and 31% respectively) and delayed absorption of dabrafenib capsules when compared to the fasted state.

Distribution

Dabrafenib binds to human plasma protein and is 99.7% bound. The steady-state volume of distribution following intravenous microdose administration is 46 L.

Biotransformation

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidised via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolised by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hrs while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21-22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib while the activity of carboxy-dabrafenib is not likely to be significant.

In vitro evaluation of drug-drug interaction potential

Dabrafenib is a substrate of human P-glycoprotein (Pgp) and human BCRP *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of Pgp or BCRP is low. Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of Pgp *in vitro*.

Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 *in vitro*, and dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) *in vitro,* the risk of a drug-drug interaction at these transporters is minimal based on clinical exposure of dabrafenib and its metabolites.

Elimination

Terminal half-life of dabrafenib following an intravenous single microdose is 2.6 hours. Dabrafenib terminal half-life after a single oral dose is 8 hours due to absorption-limited elimination after oral administration (flip-flop pharmacokinetics). IV plasma clearance is 12 l/hr.

After an oral dose, the major route of elimination of dabrafenib is metabolism, mediated via CYP3A4 and CYP2C8. Dabrafenib related material is excreted primarily in faeces, with 71% of an oral dose recovered in faeces; 23% of the dose was recovered in urine in the form of metabolites only.

Special patient populations

Hepatic impairment
A population pharmacokinetic analysis indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) do not significantly affect dabrafenib oral clearance. In addition, mild hepatic impairment as defined by bilirubin and AST did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, administration of dabrafenib should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2).

Renal impairment
A population pharmacokinetic analysis suggests that mild renal impairment does not affect oral clearance of dabrafenib. Although data in moderate renal impairment are limited these data may indicate no clinically relevant effect. No data are available in subjects with severe renal impairment (see section 4.2).

Elderly
Based on the population pharmacokinetic analysis, age had no significant effect on dabrafenib pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40% greater exposure in subjects ≥75 years of age, relative to subjects <75 years old.

Body weight and gender
Based on the population pharmacokinetic analysis, gender and weight were found to influence dabrafenib oral clearance; weight also impacted oral volume of distribution and distributional clearance. These pharmacokinetic differences were not considered clinically relevant.

Race
The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. There are insufficient data to evaluate the potential effect of other races on dabrafenib pharmacokinetics.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of dabrafenib in paediatric patients.

5.3 Preclinical safety data

Carcinogenicity studies with dabrafenib have not been conducted. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

In combined female fertility, early embryonic and embryo-foetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on oestrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects and variation in thymic shape were seen at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC).

Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period (see section 4.6).

Cardiovascular effects, including coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage and atrial fibrovascular proliferation were seen in dogs (≥2 times clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥0.5 and 0.6 times clinical exposure for rats and mice respectively). Hepatic effects, including hepatocellular necrosis and inflammation, were observed in mice (≥0.6 times clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥20 mg/kg/day (≥9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

Reversible haematological effects have been observed in dogs and rats given dabrafenib. In studies of up to 13 weeks, decreases in reticulocyte counts and/or red cell mass were observed in dogs and rats (≥10 and 1.4 times clinical exposure, respectively).

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) and testicular toxicity (degeneration and tubular dilation) were observed (≥0.2 times adult human clinical exposure based on AUC).

Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and *in vivo* at doses ≥100 mg/kg (>44 times clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice.

Combination with trametinib

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastrointestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Magnesium stearate
Colloidal silicone dioxide

Capsule shell

Red iron oxide (E172)
Titanium dioxide (E171)
Hypromellose (E464)

Printing ink

Black iron oxide (E172)
Shellac
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque white high density polyethylene (HDPE) bottle with polypropylene screw cap and a silica gel desiccant.

Each bottle contains either 28 or 120 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Tafinlar 50 mg hard capsules

EU/1/13/865/001
EU/1/13/865/002

Tafinlar 75 mg hard capsules

EU/1/13/865/003
EU/1/13/865/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013
Date of latest renewal: 08 May 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Lek Pharmaceuticals d.d.
Verovškova ulica 57
1526, Ljubljana
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
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GLAXO WELLCOME, S.A.
Avda. Extremadura, 3, Pol. Ind. Allendeduero
09400, Aranda de Duero (Burgos)
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 50 mg hard capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains dabrafenib mesilate equivalent to 50 mg dabrafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/001 28 capsules
EU/1/13/865/002 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tafinlar 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 50 mg capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains dabrafenib mesilate equivalent to 50 mg dabrafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/001 28 capsules
EU/1/13/865/002 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 75 mg hard capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains dabrafenib mesilate equivalent to 75 mg dabrafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/003 28 capsules
EU/1/13/865/004 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tafinlar 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tafinlar 75 mg capsules
dabrafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains dabrafenib mesilate equivalent to 75 mg dabrafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/865/003 28 capsules
EU/1/13/865/004 120 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tafinlar 50 mg hard capsules
Tafinlar 75 mg hard capsules
dabrafenib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tafinlar is and what it is used for
2. What you need to know before you take Tafinlar
3. How to take Tafinlar
4. Possible side effects
5. How to store Tafinlar
6. Contents of the pack and other information

1. What Tafinlar is and what it is used for

Tafinlar is a medicine that contains the active substance dabrafenib. It is used either on its own or in combination with another medicine containing trametinib in adults to treat a type of skin cancer called melanoma that has spread to other parts of the body, or cannot be removed by surgery.

Tafinlar in combination with trametinib is also used to prevent melanoma from coming back after it has been removed by surgery.

Tafinlar in combination with trametinib is also used to treat a type of lung cancer called non-small cell lung cancer (NSCLC).

Both cancers have a particular change (mutation) in a gene called BRAF at the V600 position. This mutation in the gene may have caused the cancer to develop. Your medicine targets proteins made from this mutated gene and slows down or stops the development of your cancer.

2. What you need to know before you take Tafinlar

Tafinlar should only be used to treat melanomas and NSCLC with the BRAF mutation. Therefore before starting treatment your doctor will test for this mutation.

If your doctor decides that you will receive treatment with the combination of Tafinlar and trametinib, **read the trametinib leaflet carefully as well as this leaflet.**

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

Do not take Tafinlar
- **if you are allergic** to dabrafenib or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you.

Warnings and precautions
Talk to your doctor before taking Tafinlar. Your doctor needs to know if you:
- have any **liver problems.**
- have or have ever had any **kidney problems**.
  Your doctor may take blood samples to monitor your liver and kidney function while you are taking Tafinlar.
- **have had a different type of cancer other than melanoma or NSCLC**, as you may be at greater risk of developing other skin and non-skin cancers when taking Tafinlar.

Before you take Tafinlar in combination with trametinib your doctor also needs to know if you:
- have heart problems such as heart failure or problems with the way your heart beats.
- have eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid leakage (chorioretinopathy).
- have any lung or breathing problems, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue.
- have or have had any gastrointestinal problems such as diverticulitis (inflamed pouches in the colon) or metastases to the gastrointestinal tract.

Check with your doctor if you think any of these may apply to you.

Conditions you may need to look out for
Some people taking Tafinlar develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you're taking this medicine. Some of these symptoms (bleeding, fever, changes to your skin and eye problems) are briefly mentioned in this section, but more detailed information is found in section 4, "Possible side effects".

Bleeding
Taking Tafinlar in combination with trametinib can cause serious bleeding including in your brain, the digestive system (such as stomach, rectum or intestine), lungs, and other organs, and can lead to death. Symptoms may include:
- headaches, dizziness, or feeling weak
- passing blood in the stools or passing black stools
- passing blood in the urine
- stomach pain
- coughing / vomiting up blood

Tell your doctor as soon as possible if you get any of these symptoms.

Fever
Taking Tafinlar or the combination of Tafinlar and trametinib may cause fever, although it is more likely if you are taking the combination treatment (see also section 4). In some cases, people with fever may develop low blood pressure, dizziness or other symptoms.

Tell your doctor immediately if you get a temperature above 38ºC or if you feel a fever coming on while you are taking this medicine.

Heart disorder
Tafinlar can cause heart problems, or make existing heart problems worse (see also "Heart conditions" in section 4), in people taking Tafinlar in combination with trametinib.

Tell your doctor if you have a heart disorder. Your doctor will run tests to check that your heart is working properly before and during your treatment with Tafinlar in combination with trametinib. Tell your doctor immediately if it feels like your heart is pounding, racing, or beating irregularly, or if you experience dizziness, tiredness, light-headedness, shortness of breath or swelling in the legs. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Changes in your skin which may indicate new skin cancer
Your doctor will check your skin before you start taking this medicine and regularly while you are taking it. **Tell your doctor immediately** if you notice any changes to your skin while taking this medicine or after treatment (see also section 4).

Eye problems
You should have your eyes examined by your doctor while you are taking this medicine.
Tell your doctor immediately if you get eye redness and irritation, blurred vision, eye pain or other vision changes during your treatment (see also section 4).
Tafinlar when given in combination with trametinib can cause eye problems including blindness. Trametinib is not recommended if you have ever had blockage of the vein draining the eye (retinal vein occlusion). Tell your doctor immediately if you get the following symptoms of eye problems: blurred vision, loss of vision or other vision changes, coloured dots in your vision or halos (seeing blurred outline around objects) during your treatment. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

➔ **Read the information about fever, changes in your skin and eye problems in section 4 of this leaflet. Tell your doctor, pharmacist or nurse if you get any of the signs and symptoms listed.**

Liver problems
Tafinlar in combination with trametinib can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal. Your doctor will monitor you periodically. Signs that your liver may not be working properly may include:
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin

Tell your doctor as soon as possible if you get any of these symptoms

Muscle pain
Tafinlar in combination with trametinib can result in the breakdown of muscle (rhabdomyolysis). **Tell your doctor** as soon as possible if you get any of these symptoms.
- muscle pain
- dark urine due to kidney damage

If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Hole in the stomach or intestine (perforation)
Taking the combination of Tafinlar and trametinib may increase the risk of developing holes in the gut wall. **Tell your doctor** as soon as possible if you have severe abdominal pain.

Serious skin reactions
Serious skin reactions have been reported in people taking Tafinlar in combination with trametinib. Tell your doctor immediately if you notice any changes to your skin (see section 4 for symptoms to be aware of).

Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes
An inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis). Common symptoms of sarcoidosis may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints and tender bumps on your skin. Tell your doctor if you get any of these symptoms.

Immune system disorders
Tafinlar in combination with trametinib may in rare instances cause a condition (haemophagocytic lymphohistiocytosis or HLH) in which the immune system makes too many infection-fighting cells, called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems. Tell your doctor immediately if you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time.

Children and adolescents
Tafinlar is not recommended for children and adolescents. The effects of Tafinlar in people younger than 18 years old are not known.

Other medicines and Tafinlar
Before starting treatment, tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

Some medicines may affect how Tafinlar works, or make it more likely that you will have side effects. Tafinlar can also affect how some other medicines work. These include:
- **birth control medicines** (*contraceptives)* containing hormones, such as pills, injections, or patches
- warfarin and acenocoumarol, medicines used to **thin the blood**
- digoxin, used to treat **heart conditions**
- medicines to treat **fungal infections**, such as ketoconazole, itraconazole, voriconazole and posaconazole
- some calcium channel blockers, used to treat **high blood pressure**, such as diltiazem, felodipine, nicardipine, nifedipine or verapamil
- medicines to treat **cancer,** such as cabazitaxel
- some medicines to **lower fat (lipids)** in the blood stream, such as gemfibrozil
- some medicines used to treat certain **psychiatric conditions**, such as haloperidol
- some **antibiotics**, such as clarithromycin, doxycyline and telithromycin
- some medicines **for tuberculosis** (TB), such as rifampicin
- some medicines that reduce **cholesterol** levels, such as atorvastatin and simvastatin
- some **immunosuppressants**, such as cyclosporin, tacrolimus and sirolimus
- some **anti-inflammatory** medicines, such as dexamethasone and methylprednisolone
- some medicines to treat **HIV**, such as ritonavir, amprenavir, indinavir, darunavir, delavirdine, efavirenz, fosamprenavir, lopinavir, nelfinavir, tipranavir, saquinavir and atazanavir
- some medicines used for **pain relief**, such as fentanyl and methadone
- medicines to treat seizures (**epilepsy**), such as phenytoin, phenobarbital, primidone, valproic acid or carbamazepine
- **antidepressant** medicines such as nefazodone and the herbal medicine St John's wort (*Hypericum perforatum)*

➔ **Tell your doctor, pharmacist or nurse** if you are taking any of these (or if you are not sure). Your doctor may decide to adjust your dose.

Keep a list of the medicines you take, so you can show it to your doctor, pharmacist or nurse.

Pregnancy, breast-feeding and fertility
Tafinlar is not recommended during pregnancy.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine. Tafinlar is not recommended during pregnancy, since it may potentially harm an unborn baby.
- If you are a woman who could become pregnant you must use a reliable birth control method while you are taking Tafinlar and for at least 2 weeks after you stop taking it and for at least 16 weeks following the last dose of trametinib when given in combination with Tafinlar.

- Birth control medicines containing hormones (such as pills, injections or patches) may not work as well while you are taking Tafinlar or combination treatment (Tafinlar as well as trametinib). You need to use another effective method of birth control so you do not become pregnant while you are taking this medicine. Ask your doctor, pharmacist or nurse for advice.
- If you do become pregnant while you are taking this medicine, tell your doctor immediately.

Tafinlar is not recommended while breast-feeding.
It is not known whether the ingredients of this medicine can pass into breast milk.
If you are breast-feeding, or planning to breast-feed, you must tell your doctor. You and your doctor will decide if you will take this medicine or breast-feed.

Fertility – both men and women
Animal studies have shown that the active substance dabrafenib may permanently reduce male fertility. In addition, men who are taking Tafinlar may have a reduced sperm count and their sperm count may not return to normal levels after they stop taking this medicine.

Prior to starting treatment with Tafinlar, talk to your doctor about options to improve your chances to have children in the future.

Taking Tafinlar with trametinib: trametinib may impair fertility in both men and women.

If you have any further questions on the effect of this medicine on sperm count, ask your doctor, pharmacist or nurse.

Driving and using machines
Tafinlar can have side effects that may affect your ability to drive or use machines.
Avoid driving or using machines if you have problems with your vision or if you feel tired or weak, or if your energy levels are low.
Descriptions of these effects can be found in sections 2 and 4.
Discuss with your doctor, pharmacist or nurse if you are unsure about anything. Even your disease, symptoms and treatment situation may affect your ability to drive or use machines.

3. How to take Tafinlar

Always take this medicine exactly as your doctor, pharmacist or nurse has told you to. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
The usual dose of Tafinlar either used alone or in combination with trametinib is two 75 mg capsules twice a day (corresponding to a daily dose of 300 mg). The recommended dose of trametinib, when used in combination with Tafinlar, is 2 mg once a day.

Your doctor may decide that you should take a lower dose if you get side effects.

Tafinlar are also available as 50 mg capsules if a dose reduction is recommended.

Don’t take more Tafinlar than your doctor has recommended, since this may increase the risk of side effects.

How to take it
Swallow the capsules whole with water, one after the other.

Don’t chew or crush the capsules, since they will otherwise lose their effect.

Take Tafinlar twice a day, on an empty stomach. This means that
- after taking Tafinlar, you must wait **at least 1 hour** before eating, or
- after eating, you must wait **at least 2 hours** before taking Tafinlar.

Take Tafinlar in the morning and evening, about 12 hours apart. Take your morning and evening doses of Tafinlar at the same times every day. This will increase the chance of remembering to take the capsules.

Don't take the morning and evening doses of Tafinlar at the same time.

If you take more Tafinlar than you should
If you take too many capsules of Tafinlar, **contact your doctor, pharmacist or nurse for advice.** If possible, show them the Tafinlar pack with this leaflet.

If you forget to take Tafinlar
If the missed dose is less than 6 hours late, take it as soon as you remember.
If the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time.
Then carry on taking your capsules at regular times as usual.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Tafinlar
Take Tafinlar for as long as your doctor recommends. Do not stop unless your doctor, pharmacist or nurse advises you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

How should you take Tafinlar in combination with trametinib
- Take Tafinlar in combination with trametinib exactly as your doctor, nurse or pharmacist tells you. Do not change your dose or stop Tafinlar or trametinib unless your doctor, nurse or pharmacist tells you to.
- Take **Tafinlar twice daily** and take **trametinib once daily**. It may be good for you to get into the habit of taking both medicines at the same times each day. The Tafinlar doses should be about 12 hours apart. Trametinib when given in combination with Tafinlar should be taken with **either** the morning dose of Tafinlar **or** the evening dose of Tafinlar.
- Take Tafinlar and trametinib on an empty stomach, at least one hour before or two hours after a meal. Take whole with a full glass of water.
- If you miss a dose of Tafinlar or trametinib, take it as soon as you remember. Do not make up for missed doses and just take your next dose at your regular time:
    - If it is less than 6 hours to your next scheduled dose of Tafinlar, which is taken twice daily.
    - If it is less than 12 hours to your next scheduled dose of trametinib, which is taken once daily.
- If you take too much Tafinlar or trametinib, immediately contact your doctor, nurse or pharmacist. Take Tafinlar capsules and trametinib tablets with you when possible. If possible, show them the Tafinlar and trametinib pack with each leaflet.
- If you get side effects your doctor may decide that you should take lower doses of Tafinlar and / or trametinib. Take the doses of Tafinlar and trametinib exactly as your doctor, nurse or pharmacist tells you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects
Bleeding problems
Tafinlar can cause serious bleeding problems, especially in your brain when taken in combination with trametinib. Call your doctor or nurse and get medical help right away if you have any unusual signs of bleeding, including:
- headaches, dizziness, or weakness
- coughing up of blood or blood clots
- vomit containing blood or that looks like "coffee grounds"
- red or black stools that look like tar

Fever
Taking Tafinlar may cause fever in more than 1 in 10 people. **Tell your doctor, pharmacist or nurse immediately if you get a fever (temperature 38ºC or above) or if you feel a fever coming on while you are taking this medicine**. They will carry out tests to find out if there are other causes for the fever and treat the problem.

In some cases, people with fever may develop low blood pressure and dizziness. If the fever is severe, your doctor may recommend that you stop taking Tafinlar, or Tafinlar and trametinib, while they treat the fever with other medicines. Once the fever is controlled, your doctor may recommend that you start taking Tafinlar again.

Heart conditions
Tafinlar can affect how well your heart pumps blood when taken in combination with trametinib. It is more likely to affect people who have an existing heart problem. You will be checked for any heart problems while you are taking Tafinlar in combination with trametinib. Signs and symptoms of heart problems include:
- feeling like your heart is pounding, racing, or beating irregularly
- dizziness
- tiredness
- feeling lightheaded
- shortness of breath
- swelling in the legs

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

Changes in your skin
Serious skin reactions have been reported in people taking Tafinlar in combination with trametinib (frequency not known). If you notice any of the following:
- reddish patches on the trunk that are circular or target-shaped, with central blisters. Skin peeling. Ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).
- widespread rash, fever, and enlarged lymph nodes (DRESS-syndrome or drug hypersensitivity syndrome).

  ➔ **stop using the medicine and seek medical attention immediately.**

Patients taking Tafinlar may commonly (may affect up to 1 in 10 people) develop a different type of skin cancer called *cutaneous squamous cell carcinoma (cuSCC)*. Others may develop a type of skin cancer called *basal cell carcinoma (BCC)*. Usually, these skin changes remain local and can be removed with surgery and treatment with Tafinlar can be continued without interruption.

Some people taking Tafinlar may also notice that new melanomas have appeared. These melanomas are usually removed by surgery and treatment with Tafinlar can be continued without interruption.

Your doctor will check your skin before you start taking Tafinlar, then check it again every month while you are taking this medicine and for 6 months after you stop taking it. This is to look for any new skin cancers.

Your doctor will also check your head, your neck, your mouth, your lymph glands and you will have scans of your chest and stomach area (called CT scans) regularly. You may also have blood tests. These checks are to detect if any other cancer, including squamous cell carcinoma, develops inside your body. Pelvic examinations (for women) and anal examinations are also recommended before and at the end of your treatment.

Check your skin regularly whilst taking Tafinlar
If you notice any of the following:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change of a mole in size or colour
  - ➔ **Tell your doctor, pharmacist or nurse as soon as possible** if you get any of these symptoms - either for the first time or if they get worse.

Skin reactions (rash) can happen while taking Tafinlar in combination with trametinib. **Talk to your doctor** if you get a skin rash while taking Tafinlar in combination with trametinib.

Eye problems
Patients taking Tafinlar alone can uncommonly (may affect up to 1 in 100 people) develop an eye problem called uveitis, which could damage your vision if it is not treated. This may occur commonly (may affect up to 1 in 10 people) in patients taking Tafinlar in combination with trametinib.

Uveitis may develop rapidly and the symptoms include:

- eye redness and irritation
- blurred vision
- eye pain
- increased sensitivity to light
- floating spots before the eyes
  - ➔ **Contact your doctor, pharmacist or nurse immediately** if you get these symptoms.

Tafinlar can cause eye problems when taken in combination with trametinib. Trametinib is not recommended if you have ever had a blockage of the vein draining the eye (retinal vein occlusion). Your doctor may advise an eye examination before you take Tafinlar in combination with trametinib and while you are taking it. Your doctor may ask you to stop taking trametinib or refer you to a specialist, if you develop signs and symptoms in your vision that include:

- loss of vision
- eye redness and irritation
- coloured dots in your vision
- halo (seeing a blurred outline around objects)
- blurred vision
  - ➔ **Contact your doctor, pharmacist or nurse immediately if you get these symptoms.**

It is very important to tell your doctor, pharmacist or nurse immediately if you develop these symptoms, especially if you have a painful, red eye that does not clear up quickly. They may arrange for you to see a specialist eye doctor for a complete eye examination.

Immune system disorders
If you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time, tell your doctor immediately. It may be a sign of a condition where the immune system

makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis), see section 2 (frequency rare).

Possible side effects in patients taking Tafinlar alone

The side effects that you may see when you take Tafinlar alone are as follows:

Very common side effects (may affect more than 1 in 10 people)
- Papilloma (a type of skin tumour which is usually not harmful)
- Decreased appetite
- Headache
- Cough
- Feeling sick (nausea), being sick (vomiting)
- Diarrhoea
- Thickening of the outer layers of the skin
- Unusual hair loss or thinning
- Rash
- Reddening and swelling of the palms, fingers and soles of the feet (see "Changes in your skin" earlier in section 4)
- Joint pain, muscle pain, or pain in the hands or feet
- Fever (see "Fever" earlier in section 4)
- Lack of energy
- Chills
- Feeling weak

Common side effects (may affect up to 1 in 10 people)
- Skin effects including cutaneous squamous cell carcinoma (a type of skin cancer), wart-like growths, skin tags, uncontrolled skin growths or lesions (basal cell carcinoma), dry skin, itching or redness of skin, patches of thick, scaly, or crusty skin (actinic keratosis), skin lesions, skin reddening, increased sensitivity of the skin to sun
- Constipation
- Flu-like illness

Common side effects that may show up in your blood tests
- Low levels of phosphate (hypophosphataemia) in the blood
- Increase in blood sugar level (hyperglycaemia)

Uncommon side effects (may affect up to 1 in 100 people)
- New melanoma
- Allergic reaction (hypersensitivity)
- Inflammation of the eye (uveitis, see "Eye problems" earlier in section 4))
- Inflammation of the pancreas (causing strong abdominal pain)
- Inflammation of the fatty layer under the skin (panniculitis)
- Kidney problems, kidney failure
- Inflammation of kidneys

Possible side effects when Tafinlar and trametinib are taken together

When you take Tafinlar and trametinib together you may get any of the side effects given in the lists above, although the frequency may change (increase or decrease).

You may also get **additional side effects due to taking trametinib** at the same time as Tafinlar.

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

Please also read the trametinib package leaflet for details of the side effects you may get with trametinib.

The side effects that you may see when you take Tafinlar in combination with trametinib are as follows:

Very common side effects (may affect more than 1 in 10 people)
- Nasal and throat inflammation
- Decreased appetite
- Headache
- Dizziness
- High blood pressure (hypertension)
- Bleeding, at various sites in the body, which may be mild or serious (haemorrhage)
- Cough
- Stomach ache
- Constipation
- Diarrhoea
- Feeling sick (nausea), being sick (vomiting)
- Rash, dry skin, itching, skin reddening
- Joint pain, muscle pain, or pain in the hands or feet
- Muscle spasms
- Lack of energy, feeling weak
- Chills
- Swelling of the hands or feet (oedema peripheral)
- Fever
- Flu-like illness

Very common side effects that may show up in your blood tests
- Abnormal blood test results related to the liver

Common side effects (may affect up to 1 in 10 people)
- Infection of the urinary system
- Skin effects including infection of the skin (cellulitis), inflammation of hair follicles in the skin, nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles, skin rash with pus-filled blisters, cutaneous squamous cell carcinoma (a type of skin cancer), papilloma (a type of skin tumour which is usually not harmful), wart-like growths, increased sensitivity of the skin to sun (see also “Changes in your skin” earlier in section 4)
- Dehydration (low levels of water or fluid)
- Blurred vision, eyesight problems, inflammation of the eye (uveitis)
- Heart pumping less efficiently
- Low blood pressure (hypotension)
- Localised tissue swelling
- Shortness of breath
- Dry mouth
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Acne-like problems
- Thickening of the outer layer of the skin (hyperkeratosis), patches of thick, scaly, or crusty skin (actinic keratosis), chapping or cracking of the skin
- Increased sweating, night sweats
- Unusual hair loss or thinning
- Red, painful hands and feet
- Inflammation of the fatty layer under the skin (panniculitis)
- Inflammation of the mucosa
- Swelling of the face

Common side effects that may show up in your blood tests
- Low levels of white blood cells
- Decrease in number of red blood cells (anaemia), blood platelets (cells that help blood to clot), and a type of white blood cells (leukopenia)
- Low levels of sodium (hyponatraemia) or phosphate (hypophosphataemia) in the blood
- Increase in blood sugar level
- Increase in creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- Increase in some substances (enzymes) produced by the liver

Uncommon side effects (may affect up to 1 in 100 people)
- Appearance of new skin cancer (melanoma)
- Skin tags
- Allergic reactions (hypersensitivity)
- Eye changes including swelling in the eye caused by fluid leakage (chorioretinopathy), separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal detachment) and swelling around the eyes
- Heart rate that is lower than the normal range and/or a decrease in heart rate
- Inflammation of the lung (pneumonitis)
- Inflammation of pancreas
- Inflammation of the intestines (colitis)
- Kidney failure
- Inflammation of the kidneys
- Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)

Rare side effects (may affect up to 1 in 1000 people)
- A hole (perforation) in the stomach or intestines

Not known (frequency cannot be estimated from the available data)
- Inflammation of the heart muscle (myocarditis) which can result in breathlessness, fever, palpitations and chest pain
- Inflamed, flaky skin (exfoliative dermatitis)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tafinlar

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tafinlar contains
- The active substance is dabrafenib. Each hard capsule contains dabrafenib mesilate equivalent to 50 mg or 75 mg of dabrafenib.
- The other ingredients are: microcrystalline cellulose, magnesium stearate, colloidal silicone dioxide, red iron oxide (E172), titanium dioxide (E171), and hypromellose (E464). Further, the capsules are printed with black ink that contains black iron oxide (E172) shellac and propylene glycol.

What Tafinlar looks like and contents of the pack
Tafinlar 50 mg hard capsules are opaque dark red and imprinted with “GS TEW” and “50 mg”.
Tafinlar 75 mg hard capsules are opaque dark pink and imprinted with “GS LHF” and “75 mg”.

The bottles are opaque white plastic with threaded plastic closures.

The bottles also include a silica gel desiccant in a small cylinder shaped container. The desiccant must be kept inside the bottle and must not be eaten.

Tafinlar 50 mg and 75 mg hard capsules are available in packs containing 28 or 120 capsules. Not all pack sizes may be marketed in your country.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

販売名	タフィンラーカプセル 50mg／タフィンラーカプセル 75mg	メキニスト錠 0.5mg／メキニスト錠 2mg	コセルゴカプセル 10mg／コセルゴカプセル 25mg
一般的名称	ダブラフェニブメシル酸塩	トラメチニブ ジメチルスルホキシド付加物	セルメチニブ硫酸塩
会社名	ノバルティスファーマ株式会社	ノバルティスファーマ株式会社	アレクシオンファーマ合同会社
効能・効果	○*BRAF* 遺伝子変異を有する悪性黒色腫 ○*BRAF* 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌	○*BRAF* 遺伝子変異を有する悪性黒色腫 ○*BRAF* 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌	神経線維腫症 1 型における叢状神経線維腫
添付文書改訂日	2023 年 1 月改訂	2023 年 1 月改訂	2022 年 11 月改訂
備 考	—	—	—

販売名	ビラフトビカプセル 50mg／ビラフトビカプセル 75mg	メクトビ錠 15mg	ゼルボラフ錠 240mg
一般的名称	エンコラフェニブ	ビニメチニブ	ベムラフェニブ
会社名	小野薬品工業株式会社	小野薬品工業株式会社	中外製薬株式会社
効能・効果	○*BRAF* 遺伝子変異を有する根治切除不能な悪性黒色腫 ○がん化学療法後に増悪した *BRAF* 遺伝子変異を有する治癒 切除不能な進行・再発の結腸・直腸癌	○*BRAF* 遺伝子変異を有する根治切除不能な悪性黒色腫 ○がん化学療法後に増悪した *BRAF* 遺伝子変異を有する治癒 切除不能な進行・再発の結腸・直腸癌	*BRAF* 遺伝子変異を有する根治切除不能な悪性黒色腫
添付文書改訂日	2022 年 12 月改訂	2020 年 11 月改訂	2022 年 12 月改訂
備 考	—	—	—

*2022年11月改訂（第2版）
2022年9月作成（第1版）

神経線維腫症1型治療剤（MEK阻害剤）
セルメチニブ硫酸塩

日本標準商品分類番号
* 874299

貯　　法：室温保存
有効期間：3年

劇薬、処方箋医薬品注）

コセルゴ® カプセル 10mg
コセルゴ® カプセル 25mg
Koselugo® Capsules

	カプセル10mg	カプセル25mg
承認番号	30400AMX00430000	30400AMX00431000
* 販売開始	2022年11月	

注）注意－医師等の処方箋により使用すること

1. 警告

本剤は、緊急時に十分対応できる医療施設において、本剤についての十分な知識と神経線維腫症1型の治療の十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。

2. 禁忌（次の患者には投与しないこと）

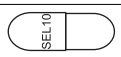
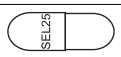
2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 妊婦又は妊娠している可能性のある女性［9.5参照］
2.3 重度の肝機能障害（Child-Pugh分類C）のある患者［9.3.1、16.6.2参照］

3. 組成・性状

3.1 組成

販売名	コセルゴカプセル10mg	コセルゴカプセル25mg
有効成分	1カプセル中 セルメチニブ硫酸塩 12.1mg （セルメチニブとして10mg）	1カプセル中 セルメチニブ硫酸塩 30.25mg （セルメチニブとして25mg）
添加剤	内容物： コハク酸トコフェロールポリエチレングリコール カプセル： ヒプロメロース、カラギーナン、塩化カリウム、酸化チタン	内容物： コハク酸トコフェロールポリエチレングリコール カプセル： ヒプロメロース、カラギーナン、塩化カリウム、酸化チタン、青色2号、黄色三二酸化鉄

3.2 製剤の性状

販売名		コセルゴカプセル10mg	コセルゴカプセル25mg
剤形		硬カプセル剤	硬カプセル剤
色調		キャップ、ボディ：白色	キャップ、ボディ：青色
外形		 4号カプセル	 4号カプセル
大きさ	長径	約14mm	約14mm
	短径	約5mm	約5mm
重量		約158mg	約188mg
識別コード		SEL 10	SEL 25

4. 効能又は効果

神経線維腫症1型における叢状神経線維腫

5. 効能又は効果に関連する注意

5.1 疼痛や外観上の変形等の臨床症状を有し、重大な合併症のリスクを伴うことなく切除できない叢状神経線維腫を有する神経線維腫症1型患者に対し投与すること。［17.1.1、17.1.2参照］

6. 用法及び用量

通常、小児にはセルメチニブとして1回25mg/m^2（体表面積）を1日2回空腹時に経口投与するが、患者の状態により適宜減量する。ただし、1回量は50mgを上限とする。

7. 用法及び用量に関連する注意

7.1 食事の影響により本剤のC_{max}及びAUCが低下するため、食事の1時間前から食後2時間までの間の服用は避けること。［16.2.2参照］
7.2 3歳未満及び19歳以上の患者における有効性及び安全性は確立していない。［9.7、17.1.1、17.1.2参照］
7.3 18歳以下で本剤により薬物治療を開始した患者において、18歳を超えて継続投与する場合には、治療上の有益性と危険性を考慮して慎重に投与すること。
7.4 体表面積から換算した本剤の投与量は以下の表のとおりとする。

体表面積（m^2）	投与量
0.55 - 0.69	朝20mg/夜10mg
0.70 - 0.89	1回20mg 1日2回
0.90 - 1.09	1回25mg 1日2回
1.10 - 1.29	1回30mg 1日2回
1.30 - 1.49	1回35mg 1日2回
1.50 - 1.69	1回40mg 1日2回
1.70 - 1.89	1回45mg 1日2回
≧ 1.90	1回50mg 1日2回

7.5 本剤投与により副作用が発現した場合には、以下の基準を参考に、本剤を休薬、減量又は中止すること。2段階減量後に忍容性が認められない場合、投与を中止すること。

副作用の発現により減量する場合の投与量

体表面積（m^2）	1段階減量（1回用量）		2段階減量（1回用量）	
	朝	夜	朝	夜
0.55 - 0.69	10mg	10mg	10mg/日	
0.70 - 0.89	20mg	10mg	10mg	10mg
0.90 - 1.09	25mg	10mg	10mg	10mg
1.10 - 1.29	25mg	20mg	20mg	10mg
1.30 - 1.49	25mg	25mg	25mg	10mg
1.50 - 1.69	30mg	30mg	25mg	20mg
1.70 - 1.89	35mg	30mg	25mg	20mg
≧ 1.90	35mg	35mg	25mg	25mg

副作用発現時の用量調節基準

副作用	程度注）	処置
左室駆出率（LVEF）低下	投与前から10%以上低下かつ正常下限値以下で無症候性	回復するまで休薬し、再開する場合、用量を1段階減量して投与する。
	症候性又はGrade3以上	投与を中止する。

眼障害	網膜色素上皮剥離又は中心性漿液性網膜症	回復するまで休薬し、再開する場合、用量を1段階減量して投与する。
	網膜静脈閉塞	投与を中止する。
筋障害	Grade1又は忍容可能なGrade2のCK上昇又は筋症状	患者の状態に注意しながら投与を継続する。
	忍容不能なGrade2又はGrade3のCK上昇又は筋症状	Grade1以下に回復するまで休薬し、再開する場合、用量を1段階減量して投与する。
	Grade4のCK上昇	Grade1以下に回復するまで休薬し、再開する場合、用量を1段階減量して投与する。また、投与中止を検討する。
	横紋筋融解症	投与を中止する。
下痢	Grade1又は忍容可能なGrade2	患者の状態に注意しながら投与を継続する。
	忍容不能なGrade2又はGrade3	Grade1以下に回復するまで休薬し、再開する場合、用量を1段階減量して投与する。
	Grade4	投与を中止する。
上記以外の副作用	Grade1又は忍容可能なGrade2	患者の状態に注意しながら投与を継続する。
	忍容不能なGrade2又はGrade3	Grade1以下に回復するまで休薬し、再開する場合、用量を1段階減量して投与する。
	Grade4	Grade1以下に回復するまで休薬し、再開する場合、用量を1段階減量して投与する。また、投与中止を検討する。

注)GradeはCTCAE ver.4.03に準じる。

7.6 中等度の肝機能障害(Child-Pugh分類B)のある患者では、7.7項の表を参考に、本剤1回20mg/m^{2}の1日2回投与とすること。[9.3.2、16.6.2参照]

7.7 強い又は中程度のCYP3A阻害剤若しくはフルコナゾールとの併用は可能な限り避けること。やむを得ず併用する場合には、以下の表に従い、1回20mg/m^{2}の1日2回投与とし、併用中に副作用が発現した場合には、1回15mg/m^{2}の1日2回投与に減量すること。[10.2、16.7.1、16.7.2、16.7.4参照]

1回20mg/m^2 1日2回及び1回15mg/m^2 1日2回の投与量

体表面積(m^2)	20mg/m^2(1回用量)		15mg/m^2(1回用量)	
	朝	夜	朝	夜
0.55 - 0.69	10mg	10mg	10mg/日	
0.70 - 0.89	20mg	10mg	10mg	10mg
0.90 - 1.09	20mg	20mg	20mg	10mg
1.10 - 1.29	25mg	25mg	25mg	10mg
1.30 - 1.49	30mg	25mg	25mg	20mg
1.50 - 1.69	35mg	30mg	25mg	25mg
1.70 - 1.89	35mg	35mg	30mg	25mg
≧ 1.90	40mg	40mg	30mg	30mg

7.8 10mgカプセルと25mgカプセルの生物学的同等性は示されていないため、1回50mgを投与する際には10mgカプセルを使用しないこと。

8. 重要な基本的注意

8.1 心機能障害があらわれることがあるので、本剤投与開始前及び投与中は定期的に心機能検査(心エコー等)を行い、患者の状態(LVEFの変動を含む)を確認すること。[9.1.1、11.1.1参照]

8.2 眼障害があらわれることがあるので、本剤投与中は定期的に眼の異常の有無を確認すること。また、眼の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。[11.1.2参照]

8.3 肝機能障害があらわれることがあるので、本剤投与中は定期的に肝機能検査を行うこと。[11.1.4参照]

8.4 横紋筋融解症、ミオパチーがあらわれることがあるので、本剤投与中は定期的にCK、クレアチニン等の検査を行い、筋肉痛、脱力感、CK上昇、血中及び尿中ミオグロビン上昇等に十分注意すること。[11.1.5参照]

8.5 貧血、ヘモグロビン減少、好中球減少、リンパ球減少、血小板減少があらわれることがあるので、本剤投与中は定期的に血液検査(血球数算定、白血球分画等)を行うこと。[11.1.6参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 心疾患又はその既往歴のある患者

症状が悪化するおそれがある。[8.1、11.1.1参照]

9.3 肝機能障害患者

9.3.1 重度の肝機能障害患者(Child-Pugh分類C)

投与しないこと。本剤の血中濃度が上昇するおそれがある。[2.3、16.6.2参照]

9.3.2 中等度の肝機能障害患者(Child-Pugh分類B)

本剤を減量するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇するおそれがある。[7.6、16.6.2参照]

9.4 生殖能を有する者

9.4.1 妊娠可能な女性に対しては、本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。[9.5参照]

9.4.2 パートナーが妊娠する可能性がある男性に対しては、本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には投与しないこと。マウスを用いた胚・胎児発生に関する試験では、胚・胎児死亡、催奇形性、胎児重量の減少が認められ、臨床曝露量(25mg/m^2 1日2回投与、初回投与時)に対する安全域は2.8倍であった。マウスを用いた出生前及び出生後の発生に関する試験では、出生児に未成熟な開眼及び口蓋裂等の奇形が認められ、臨床曝露量(25mg/m^2 1日2回投与、初回投与時)に対する安全域は0.4倍未満であった。[2.2、9.4.1参照]

9.6 授乳婦

授乳しないことが望ましい。本剤又は本剤の代謝物がヒトの母乳中に移行するかどうかは不明であるが、動物試験(マウス)で授乳中の母動物へ本剤を投与した際、本剤及び本剤の代謝物が乳汁中に排泄されることが認められている。

9.7 小児等

低出生体重児、新生児、乳児又は3歳未満の幼児、体表面積0.55m^{2}未満の小児を対象とした有効性及び安全性を指標とした臨床試験は実施していない。[7.2、17.1.1、17.1.2参照]

10. 相互作用

本剤は、主にCYP3Aにより代謝され、CYP2C19も関与する。[16.4参照]

10.2 併用注意(併用に注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
強い又は中程度のCYP3A阻害剤 クラリスロマイシン エリスロマイシン イトラコナゾール等 グレープフルーツジュース [7.7、16.7.1、16.7.4参照]	本剤の副作用が増強されるおそれがあるため、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、減量するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	これらの薬剤等がCYP3Aを阻害することにより、本剤の代謝が阻害され、本剤の血中濃度が上昇する可能性がある。
フルコナゾール [7.7、16.7.2参照]	本剤の副作用が増強されるおそれがあるため、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、減量するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	CYP2C19及びCYP3Aを阻害することにより、本剤の代謝が阻害され、本剤の血中濃度が上昇する可能性がある。
強い又は中程度のCYP3A誘導剤 フェニトイン リファンピシン カルバマゼピン等 [16.7.3、16.7.4参照]	本剤の効果が減弱するおそれがあるため、これらの薬剤との併用は可能な限り避けること。	これらの薬剤等がCYP3Aを誘導することにより、本剤の代謝が促進され、本剤の血中濃度が低下する可能性がある。
セイヨウオトギリソウ(St. John's Wort、セント・ジョーンズ・ワート)含有食品	本剤の効果が減弱するおそれがあるため、摂取しないよう注意すること。	
ビタミンE含有製剤(サプリメント等)	ビタミンEの摂取を控えるよう指導すること。	添加剤であるコハク酸トコフェロールポリエチレングリコールとして、本剤10mgには32mg、本剤25mgには36mgのビタミンEが含まれる。ビタミンEの高用量摂取により、出血のリスクを増強させる可能性がある。
抗凝固剤 抗血小板剤 ワルファリン アスピリン等	プロトロンビン時間国際標準比(INR)値等の血液凝固能の検査、臨床症状の観察を頻回に行い、これらの薬剤の用量を調節すること。	

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 心機能障害

駆出率減少(14.5%)、左室機能不全(頻度不明)等の心機能障害があらわれることがある。[8.1、9.1.1参照]

11.1.2 眼障害

網膜色素上皮剥離(頻度不明)、中心性漿液性網膜症(頻度不明)、網膜静脈閉塞(頻度不明)等の眼障害があらわれることがある。[8.2参照]

11.1.3 消化管障害

嘔吐(66.1%)、下痢(59.7%)、悪心(53.2%)等の消化管障害があらわれることがある。

11.1.4 肝機能障害

AST(32.3%)、ALT(25.8%)、ビリルビン(1.6%)等の上昇を伴う肝機能障害があらわれることがある。[8.3参照]

11.1.5 横紋筋融解症(頻度不明)

[8.4参照]

11.1.6 貧血及び血球減少

貧血(33.9%)、好中球減少(22.6%)、リンパ球減少(11.3%)、血小板減少(9.7%)等があらわれることがある。[8.5参照]

11.1.7 間質性肺疾患(頻度不明)

11.2 その他の副作用

	10%以上	1%～10%未満
眼	-	霧視
呼吸器	-	呼吸困難
消化器	口内炎	口内乾燥
皮膚	発疹(75.8%)、ざ瘡様皮膚炎(53.2%)、皮膚乾燥(51.6%)、爪囲炎、脱毛・毛髪変色	-
その他	血中CK増加(62.9%)、疲労・無力症、低アルブミン血症、発熱、血中クレアチニン増加	高血圧、末梢性浮腫、顔面浮腫

14. 適用上の注意

14.1 薬剤調製時の注意

吸湿により添加剤が加水分解され本剤の品質に影響を及ぼす可能性があるため、分包せずボトルのまま交付すること。

14.2 薬剤交付時の注意

患者又は保護者等に対し以下の点に注意するよう指導すること。

・カプセルは噛んだり、溶かしたり、開けたりせずに、そのまま水とともに服用すること。

・ボトルから乾燥剤は取り出さず、使用の都度密栓すること。[20.1、20.2参照]

15. その他の注意

15.2 非臨床試験に基づく情報

マウスを用いた反復投与毒性試験において、臨床曝露量の約22倍で盲腸及び結腸の穿孔が認められ、回復性は確認されていない。また、ラットを用いた反復投与毒性試験において、臨床曝露量の約9倍で骨端軟骨異形成が認められ、回復性は確認されていない。

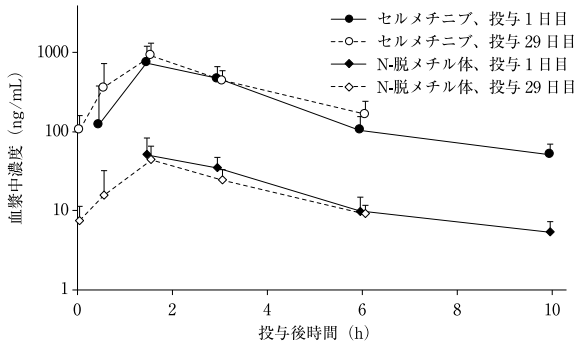
16. 薬物動態

16.1 血中濃度

16.1.1 国内第I相試験(D1346C00013試験)

3歳以上18歳以下の叢状神経線維腫を有する日本人神経線維腫症1型患者12例に本剤25mg/m^{2}を1日2回空腹時に反復経口投与したとき、投与1日目及び29日目のセルメチニブ及び活性代謝物であるN-脱メチル体の血漿中濃度推移及び薬物動態パラメータは以下のとおりであった[1)]。

3歳以上18歳以下の叢状神経線維腫を有する日本人神経線維腫症1型患者に本剤25mg/m²を1日2回空腹時に反復経口投与したときの血漿中濃度推移(算術平均値＋標準偏差)



3歳以上18歳以下の叢状神経線維腫を有する日本人神経線維腫症1型患者に本剤25mg/m²を1日2回空腹時に反復経口投与したときの薬物動態パラメータ

測定対象	測定日	例数	C_{max} (ng/mL)	T_{max}[a] (h)	$AUC_{0\text{-}6h}$ (ng·h/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)
セルメチニブ	投与1日目	12	783.1 (52.70)	1.49 [0.50, 3.05]	1926 (41.64)	2523 (24.23)[b]
	投与29日目	11	869.4 (53.53)	1.47 [0.42, 2.87]	2396 (40.32)	—
N-脱メチル体	投与1日目	12	55.47 (49.13)	1.52 [1.37, 3.05]	140.8 (38.86)	188.7 (24.32)[c]
	投与29日目	11	40.90 (53.10)	1.47 [0.42, 2.87]	123.6 (37.34)	—

幾何平均値(変動係数%)、—：評価せず
a)中央値[範囲]、b)8例、c)7例

16.1.2 海外第I相試験(D1532C00057試験第I相パート)

3歳以上18歳以下の叢状神経線維腫を有する外国人神経線維腫症1型患者13例に本剤20又は25mg/m²を空腹時に単回経口投与したとき注)のセルメチニブ及び活性代謝物であるN-脱メチル体の薬物動態パラメータは以下のとおりであった。

3歳以上18歳以下の叢状神経線維腫を有する外国人神経線維腫症1型患者に本剤20又は25mg/m²を空腹時に単回経口投与したときの薬物動態パラメータ

測定対象	投与量	例数	C_{max} (ng/mL)	T_{max}[a] (h)	$AUC_{0\text{-}12h}$ (ng·h/mL)	$T_{1/2}$[b] (h)
セルメチニブ	20mg/m²	9	754.7 (47.53)	1.08 [0.98, 3.00]	1898 (18.83)	9.41±4.59
	25mg/m²	4	928.4 (18.17)	1.04 [1.00, 2.00]	2199 (14.83)	6.16±0.88
N-脱メチル体	20mg/m²	9	58.05 (70.87)	1.08 [0.98, 3.00]	163.3 (28.84)	9.44±10.24
	25mg/m²	4	56.02 (35.27)	1.04 [1.00, 2.00]	150.9 (24.33)	4.47±2.49

幾何平均値(変動係数%)
a)中央値［範囲］、b)算術平均値±標準偏差

16.2 吸収

16.2.1 バイオアベイラビリティ

健康成人12例に本剤75mgを単回経口投与したとき注)、絶対バイオアベイラビリティは62%であった[2](外国人データ)。

16.2.2 食事の影響

健康成人34例に本剤75mgを高脂肪食の摂取後に単回経口投与したとき注)、絶食下投与と比較して、C_{max}は50%低下し、AUCは16%低下し、T_{max}は約1.5時間延長した[3](外国人データ)。[7.1参照]

健康成人24例に本剤50mgを低脂肪食の摂取後に単回経口投与したとき注)、絶食下投与と比較して、C_{max}は60%低下し、AUCは38%低下し、T_{max}は約0.9時間延長した[4](外国人データ)。[7.1参照]

16.3 分布

In vitro 試験において、セルメチニブのヒト血漿蛋白結合率は98.4%であった。セルメチニブは主にヒト血清アルブミンに対して結合し(96.1%)、α1-酸性糖蛋白への結合率は27.2%であった[5]。

16.4 代謝

セルメチニブは主にCYP3Aにより代謝され、CYP2C19も関与する(代謝における推定寄与率：25%及び15%[6])。また、セルメチニブのグルクロン酸抱合にはUGT1A1及びUGT1A3が寄与することが示唆された。[10.参照]

健康成人6例にセルメチニブの^{14}C標識体75mgを単回経口投与したとき注)、ヒト血漿中の主なセルメチニブ関連成分は、未変化体のセルメチニブ(投与放射能の約40%)、イミダゾインダゾール体のグルクロン酸抱合体(22%)であった。その他、セルメチニブのグルクロン酸抱合体(7%)、N-脱メチルカルボン酸体(3.6%)、活性代謝物であるN-脱メチル体(2.9%)等が認められた[7](外国人データ)。

16.5 排泄

健康成人6例にセルメチニブの^{14}C標識体75mgを単回経口投与したとき注)、投与後9日間で投与量の59%の放射能標識体が糞中から回収され(未変化体は投与量の19%)、33%が尿中から回収された(未変化体は投与量の1%未満)[7](外国人データ)。

16.6 特定の背景を有する患者

16.6.1 腎機能障害

腎機能が正常な成人被験者11例及び末期腎不全の成人被験者12例に本剤50mgを単回経口投与したとき注)、腎機能が正常な被験者に比べて末期腎不全の被験者では、C_{max}は16%低く、AUCは28%低く、非結合形のC_{max}は13%高く、非結合形のAUCは3%低かった。末期腎不全の被験者におけるN-脱メチル体のAUCはセルメチニブの約20%であり、腎機能が正常な被験者よりやや高かった[8](外国人データ)。

16.6.2 肝機能障害

肝機能が正常な成人被験者(8例)及び軽度の肝機能障害を有する成人被験者(Child-Pugh分類A、8例)に本剤50mgを、中等度の肝機能障害を有する成人被験者(Child-Pugh分類B、8例)に本剤50mg又は25mgを、並びに重度の肝機能障害を有する成人被験者(Child-Pugh分類C、8例)に本剤20mgを単回経口投与したとき注)、肝機能が正常な被験者に比べて軽度の肝機能障害を有する被験者では用量補正AUC及び用量補正非結合形AUCはそれぞれ86%及び69%であったが、中等度の肝機能障害を有する被験者ではそれぞれ159%及び141%、重度の肝機能障害を有する被験者ではそれぞれ157%及び317%と高かった[8](外国人データ)。[2.3、7.6、9.3.1、9.3.2参照]

16.7 薬物相互作用

16.7.1 イトラコナゾール

健康成人24例にイトラコナゾール(強力なCYP3A阻害剤)200mgを1日2回11日間反復経口投与し、投与8日目に本剤25mgを単回経口投与したとき注)、本剤単独投与時と比較してイトラコナゾール併用時ではC_{max}及びAUCはそれぞれ19%及び49%上昇した[9](外国人データ)。[7.7、10.2参照]

16.7.2 フルコナゾール

健康成人22例にフルコナゾール(CYP2C19阻害剤かつ中程度のCYP3A阻害剤)を投与1日目に400mgを単回経口投与した後、投与2日目以降は200mgを1日1回10日間反復経口投与し、投与8日目に本剤25mgを単回経口投与したとき注)、本剤単独投与時と比較してフルコナゾール併用時ではC_{max}及びAUCはそれぞれ26%及び53%上昇した[9](外国人データ)。[7.7、10.2参照]

16.7.3 リファンピシン

健康成人22例にリファンピシン(強力なCYP3A誘導剤)600mg

を1日1回11日間反復経口投与し、投与8日目に本剤75mgを単回経口投与したとき注)、本剤単独投与時と比較してリファンピシン併用時ではC_{max}及びAUCはそれぞれ26%及び51%低下した[9](外国人データ)。[10.2参照]

16.7.4 エリスロマイシン、ジルチアゼム、エファビレンツ

生理学的薬物速度論モデルによるシミュレーションにおいて、本剤25mgを単独投与したときに対し注)、中程度のCYP3A阻害剤であるエリスロマイシン(500mg 1日3回投与)又はジルチアゼム(60mg 1日3回投与)との併用時では、セルメチニブのAUC及びC_{max}はそれぞれ約30%～40%及び約20%上昇すると推定された。また、本剤75mgを単独投与したときに対し注)、中程度のCYP3A誘導剤であるエファビレンツ(600mg 1日1回投与)との併用時では、セルメチニブのAUC及びC_{max}はそれぞれ38%及び22%低下すると推定された[6]。[7.7、10.2参照]

注)本剤の承認用法及び用量は「通常、小児にはセルメチニブとして1回25mg/m^2(体表面積)を1日2回空腹時に経口投与するが、患者の状態により適宜減量する。ただし、1回量は50mgを上限とする。」である。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 海外第II相試験(D1532C00057試験第II相パート層1)

3歳以上18歳以下の疼痛や外観上の変形、運動機能障害、気道機能障害等の臨床症状を有し生命維持に必要な構造を巻き込んでいる等により重大な合併症のリスクを伴うことなく切除できない叢状神経線維腫(Plexiform neurofibroma)を有する神経線維腫症1型患者(悪性末梢神経鞘腫瘍を合併する患者は除外)50例を対象に、本剤1回25mg/m^2(体表面積1.9m^{2}以上の場合は50mg)を1日2回空腹時に経口投与する非盲検試験を実施した[10]。主要評価項目であるResponse Evaluation in Neurofibromatosis and Schwannomatosis(REiNS)基準[11]に基づく奏効率(例数)[95%信頼区間]は66.0%(33/50例)[51.2, 78.8]であった注)。なお、最良総合効果は部分奏効(確定)33例、部分奏効(未確定)4例、及び安定11例であった。総投与期間の中央値は2.2年であった。(データカットオフ日:2018年6月29日)[5.1、7.2、9.7参照]

本剤が投与された50例中49例(98.0%)に有害事象が認められ、主な有害事象は、嘔吐43例(86.0%)、血中CK増加39例(78.0%)、下痢37例(74.0%)及び悪心36例(72.0%)であった。(データカットオフ日:2021年3月31日)

17.1.2 国内第I相試験(D1346C00013試験)

3歳以上18歳以下の疼痛や外観上の変形、運動機能障害等の臨床症状を有し生命維持に必要な構造を巻き込んでいる等により重大な合併症のリスクを伴うことなく切除できない叢状神経線維腫(Plexiform neurofibroma)を有する神経線維腫症1型患者(悪性末梢神経鞘腫瘍を合併する患者は除外)12例を対象に、本剤1回25mg/m^2(体表面積1.9m^{2}以上の場合は50mg)を1日2回空腹時に経口投与する非盲検単群試験を実施した[1]。REiNS基準に基づく奏効率(例数)[95%信頼区間]は33.3%(4/12例)[9.9, 65.1]であり、最良総合効果は部分奏効(確定)4例(33.3%)、部分奏効(未確定)2例(16.7%)、安定4例(33.3%)、病勢進行2例(16.7%)であった注)。[5.1、7.2、9.7参照]

本剤が投与された12例全例に有害事象が認められ、主な有害事象は、湿疹7例(58.3%)、ざ瘡様皮膚炎6例(50.0%)、下痢及び爪囲炎各5例(41.7%)、嘔吐、皮膚乾燥及び口内炎各4例(33.3%)であった。(12カ月間投与データ)

注)完全奏効:標的病変の消失、部分奏効:標的叢状神経線維腫腫瘍容積がベースラインから20%以上減少、安定:ベースラインからの腫瘍容積の変化が部分奏効及び病勢進行の基準に合致しない、病勢進行:標的叢状神経線維腫腫瘍容積がベースライン又は最良効果判定時から20%以上増加。初回部分奏効後3カ月以降に実施した再評価で奏効を確定した。奏効率は、完全奏効又は部分奏効(確定)が認められた患者の割合とした。

18. 薬効薬理

18.1 作用機序

セルメチニブは、MEK1/2を阻害することにより、MEKの基質であるERKのリン酸化を阻害し、RASにより調節されるRAF/MEK/ERK経路のシグナル伝達を抑制することで、NF1における神経線維腫の増殖を抑制すると考えられる[12]。

18.2 神経線維腫の増殖抑制作用

シュワン細胞特異的に*NF1*遺伝子を欠失させた遺伝子改変マウス神経線維腫モデルにおいて、セルメチニブは神経線維腫組織内におけるERKのリン酸化を阻害し、神経線維腫の増殖を抑制した[13]。

19. 有効成分に関する理化学的知見

一般的名称:

セルメチニブ硫酸塩(Selumetinib Sulfate)(JAN)

化学名:

5-[(4-Bromo-2-chlorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide monosulfate

分子式:

$C_{17}H_{15}BrClFN_4O_3 \cdot H_2SO_4$

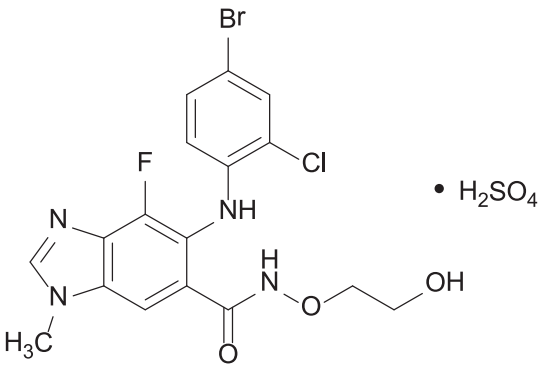
分子量:

555.76

性状:

白色～黄色の粉末である。メタノールに溶けにくく、エタノールに極めて溶けにくく、水にほとんど溶けない。

化学構造式:



20. 取扱い上の注意

20.1 湿気を避けるため、乾燥剤を同封した元の容器にて保存し、使用の都度、密栓すること。[14.2参照]

20.2 容器から乾燥剤を取り出さないこと。[14.2参照]

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤の使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

〈コセルゴカプセル10mg〉

28カプセル[ボトル、バラ、乾燥剤入り]

〈コセルゴカプセル25mg〉

28カプセル[ボトル、バラ、乾燥剤入り]

23. 主要文献

1)社内資料:セルメチニブの小児期の神経線維腫症1型患者を対象とした国内第I相試験(D1346C00013)(2022年9月26日承認、CTD 2.7.6.2.1)

2)社内資料:絶対バイオアベイラビリティ(D1532C00080)

（2022年9月26日承認、CTD 2.7.6.2.17）
3）Tomkinson H, et al. Clin Ther. 2017;39(11):2260-2275.e1.
4）社内資料：食事の影響（参考）（D1532C00089）（2022年9月26日承認、CTD 2.7.6.2.23）
5）社内資料：血漿蛋白結合（*in vitro* 試験）（2022年9月26日承認、CTD 2.6.4.4.1）
6）Cohen-Rabbie S, et al. J Clin Pharmacol. 2021;61(11):1493-1504.
7）Dymond AW, et al. Clin Ther. 2016;38(11):2447-2458.
8）Dymond AW, et al. J Clin Pharmacol. 2017;57(5):592-605.
9）Dymond AW, et al. Eur J Clin Pharmacol. 2017;73(2):175-184.
10）社内資料：セルメチニブの小児期の神経線維腫症1型患者を対象とした海外第Ⅱ相試験（D1532C00057試験第Ⅱ相パート層1）（2022年9月26日承認、CTD 2.7.6.2.2）
11）Dombi E, et al. Neurology. 2013;81 (Suppl 1):S33-S40.
12）Caunt CJ, et al. Nat Rev Cancer. 2015;15(10):577-592.
13）Dombi E, et al. N Engl J Med. 2016;375(26):2550-2260.

24. 文献請求先及び問い合わせ先

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メディカル インフォメーション センター
〒108-0023
東京都港区芝浦三丁目1番1号
田町ステーションタワーN
TEL:0120-577-657

*25. 保険給付上の注意

本剤は新医薬品であるため、厚生労働省告示第333号（令和4年11月15日付）に基づき、2023年11月末日までは、投薬期間は1回28日分を限度とされている。

26. 製造販売業者等

26.1 製造販売元

アレクシオンファーマ合同会社
〒108-0023
東京都港区芝浦三丁目1番1号
田町ステーションタワーN

＊＊2022年12月改訂（第4版）
＊2022年 5 月改訂

貯　　法：室温保存
＊有効期間：4年

日本標準商品分類番号 874291

	ビラフトビ カプセル 50mg	ビラフトビ カプセル 75mg
承認番号	23100AMX00007000	30200AMX00747000
販売開始	2019年2月	2020年11月

―抗悪性腫瘍剤―
BRAF阻害剤
エンコラフェニブカプセル

劇薬、処方箋医薬品[注)]

ビラフトビ®カプセル50mg
ビラフトビ®カプセル75mg

BRAFTOVI® Capsules

注）注意－医師等の処方箋により使用すること

1. 警告

本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

＊＊3. 1 組成

販売名	ビラフトビカプセル50mg	ビラフトビカプセル75mg
有効成分	1カプセル中 エンコラフェニブ50mg	1カプセル中 エンコラフェニブ75mg
添加剤	コポビドン、ポリオキシエチレン（160）ポリオキシプロピレン（30）グリコール、結晶セルロース、コハク酸、クロスポビドン、軽質無水ケイ酸、ステアリン酸マグネシウム	
	カプセルにゼラチン、酸化チタン、黒酸化鉄、三二酸化鉄、黄色三二酸化鉄を含有する。	

3. 2 製剤の性状

販売名		ビラフトビカプセル 50mg	ビラフトビカプセル 75mg
剤形		硬カプセル剤	
外形			
号数		0号	00号
長径(mm)		約21.7	約23.3
短径(mm)		約7.3	約8.2
質量(mg)		約429.0	約617.5
色調	頭部	赤褐色不透明	薄い黄赤色不透明
	胴部	薄い黄赤色不透明	白色不透明
識別コード		LGX 50mg	LGX 75mg

4. 効能又は効果

○*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫
○がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌

5. 効能又は効果に関連する注意

〈効能共通〉

5. 1 十分な経験を有する病理医又は検査施設における検査により、*BRAF*遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

5. 2「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

5. 3 本剤の術後補助療法における有効性及び安全性は確立していない。

〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

5. 4 本剤の一次治療における有効性及び安全性は確立していない。

6. 用法及び用量

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

ビニメチニブとの併用において、通常、成人にはエンコラフェニブとして450mgを1日1回経口投与する。なお、患者の状態により適宜減量する。

〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

セツキシマブ（遺伝子組換え）との併用、又はビニメチニブ及びセツキシマブ（遺伝子組換え）との併用において、通常、成人にはエンコラフェニブとして300mgを1日1回経口投与する。なお、患者の状態により適宜減量する。

7. 用法及び用量に関連する注意

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

7. 1 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。

7. 2 本剤単独投与時の忍容性を検討した臨床試験では、1日1回450mg投与は本剤の最大耐用量を上回る可能性が示唆されている。ビニメチニブを休薬又は中止した場合には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。［17.1.1参照］

減量して投与を継続する場合の投与量

減量レベル※1	投与量
通常投与量	450mg 1日1回
1段階減量	300mg 1日1回
2段階減量	200mg 1日1回
3段階減量	投与中止

※1：減量を要した副作用がGrade 1以下に回復し、他に合併する副作用がない場合には、減量時と逆の段階を経て増量可能

副作用発現時の用量調節基準

副作用	程度※2	処置
網膜疾患、ぶどう膜炎	Grade 2	Grade 1以下に回復するまで休薬。再開する場合、同量又は1段階減量して投与。
	Grade 3	Grade 2以下に回復するまで休薬。再開する場合、1段階減量して投与。Grade 3が継続する場合、投与中止。
	Grade 4	投与中止。
網膜静脈閉塞	Grade 1以上	投与中止。
眼障害（上記以外）	Grade 3	Grade 1以下に回復するまで休薬。28日以内で回復し再開する場合、1段階減量して投与。28日以内で回復しない場合、投与中止。
	Grade 4	投与中止。
AST増加、ALT増加	Grade 2（血清ビリルビン上昇を伴わない場合）	14日を超えて継続する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。

副作用	程度※2	処置
AST増加、ALT増加	Grade 2（血清ビリルビン上昇を伴う場合）	Grade 1以下に回復するまで休薬。7日以内で回復し再開する場合、1段階減量して投与。7日以内で回復しない場合、投与中止。
	Grade 3（血清ビリルビン上昇を伴わない場合）	Grade 1以下に回復するまで休薬。14日以内で回復し再開する場合、同量で投与。14日超で回復し再開する場合、1段階減量して投与。
	Grade 3（血清ビリルビン上昇を伴う場合）及びGrade 4	投与中止。
血清CK上昇	Grade 3-4（血清クレアチニン上昇を伴う場合）	Grade 1以下に回復するまで休薬。28日以内で回復し再開する場合、1段階減量して投与。28日以内で回復しない場合、投与中止。
心電図QT延長	500msを超えるQTc値が認められ、かつ投与前からの変化が60ms以下の場合	QTc値が500msを下回るまで休薬。再開する場合、1段階減量して再開すること。ただし、再発した場合、投与中止。
	500msを超えるQTc値が認められ、かつ投与前からの変化が60msを超える場合	投与中止。
皮膚炎	Grade 2	症状が継続又は悪化する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。
	Grade 3	Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1 段階減量して投与。
	Grade 4	投与中止。
手掌・足底発赤知覚不全症候群	Grade 2	14日を超えて継続する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与することを考慮。
	Grade 3	Grade 1以下に回復するまで休薬。再開する場合、1段階減量して投与。ただし、再発を繰り返す場合、1段階減量して投与又は投与中止することも考慮。
上記以外の副作用	Grade 2	Grade 2が継続する場合、休薬又は減量を考慮。
	Grade 3	Grade 1以下に回復するまで休薬を考慮。28日以内で回復し再開する場合、1段階減量して投与することを考慮。
	Grade 4	投与中止。

※2：Grade はNCI-CTCAE ver4.03に準じる。

〈がん化学療法後に増悪した *BRAF* 遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

7. 3 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。

7. 4 ビニメチニブ及びセツキシマブ（遺伝子組換え）との併用において、ビニメチニブ及びセツキシマブ（遺伝子組換え）の両剤を休薬又は中止した場合には、本剤をそれぞれ休薬又は中止すること。

7. 5 セツキシマブ（遺伝子組換え）との併用において、セツキシマブ（遺伝子組換え）を休薬又は中止した場合には、本剤をそれぞれ休薬又は中止すること。

7. 6 併用する他の抗悪性腫瘍剤の選択に際しては、「17. 臨床成績」の項の内容を熟知し、関連学会の最新のガイドライン等を参考にした上で、患者の状態に応じて、ビニメチニブの併用の必要性を判断すること。

減量して投与を継続する場合の投与量

減量レベル※3	投与量
通常投与量	300mg 1日1回
1段階減量	225mg 1日1回
2段階減量	150mg 1日1回
3段階減量	投与中止

※3：減量を要した副作用がGrade 1以下に回復し、他に合併する副作用がない場合には、減量時と逆の段階を経て増量可能

副作用発現時の用量調節基準

副作用	程度※4	処置
網膜疾患、ぶどう膜炎	Grade 2	Grade 1以下に回復するまで休薬。再開する場合、同量又は1段階減量して投与。
	Grade 3	Grade 2以下に回復するまで休薬。再開する場合、1段階減量して投与。Grade 3が継続する場合、投与中止。
	Grade 4	投与中止。
網膜静脈閉塞	Grade 1以上	投与中止。
眼障害（上記以外）	Grade 3	Grade 1以下に回復するまで休薬。21日以内で回復し再開する場合、1段階減量して投与。21日以内で回復しない場合、投与中止。
	Grade 4	投与中止。
AST増加、ALT増加	Grade 2（血清ビリルビン上昇を伴わない場合）	14日を超えて継続する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 2（血清ビリルビン上昇を伴う場合）	Grade 1以下に回復するまで休薬。7日以内で回復し再開する場合、1段階減量して投与。7日以内で回復しない場合、投与中止。
	Grade 3（血清ビリルビン上昇を伴わない場合）	Grade 1以下に回復するまで休薬。14日以内で回復し再開する場合、同量で投与。14日超で回復し再開する場合、1段階減量して投与。
	Grade 3（血清ビリルビン上昇を伴う場合）及びGrade 4	投与中止。
血清CK上昇	Grade 3-4（血清クレアチニン上昇を伴う場合）	Grade 1以下に回復するまで休薬。21日以内で回復し再開する場合、1段階減量して投与。21日以内で回復しない場合、投与中止。
心電図QT延長	500msを超えるQTc値が認められ、かつ投与前からの変化が60ms以下の場合	QTc値が500msを下回るまで休薬。再開する場合、1段階減量して再開すること。ただし、再発した場合、投与中止。
	500msを超えるQTc値が認められ、かつ投与前からの変化が60msを超える場合	投与中止。
皮膚炎	Grade 2	症状が継続又は悪化する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。
	Grade 3	Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 4	投与中止。
手掌・足底発赤知覚不全症候群	Grade 2	14日を超えて継続する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与することを考慮。
	Grade 3	Grade 1以下に回復するまで休薬。再開する場合、1段階減量して投与。ただし、再発を繰り返す場合、1段階減量して投与又は投与中止することも考慮。
上記以外の副作用	Grade 2	Grade 2が継続する場合、休薬又は減量を考慮。
	Grade 3	Grade 1以下に回復するまで休薬を考慮。21日以内で回復し再開する場合、1段階減量して投与することを考慮。
	Grade 4	投与中止。

※4：Grade はNCI-CTCAE ver4.03に準じる。

8. 重要な基本的注意

8. 1 皮膚悪性腫瘍があらわれることがあるので、定期的に皮膚の状態を確認すること。また、皮膚の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。［11.1.1 参照］

8. 2 皮膚以外の部位に悪性腫瘍があらわれるおそれがあるので、観察を十分に行い、異常が認められた場合には、適切な処置を行うこと。

8. 3 重篤な眼障害が報告されているので、定期的に眼の異常の有無を確認すること。また、眼の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。［11.1.2 参照］

8. 4 肝機能障害があらわれることがあるので、本剤投与中は定期的に肝機能検査を行い、患者の状態を確認すること。［11.1.4 参照］

8. 5 心機能障害があらわれることがあるので、本剤投与開始前及び本剤投与中は適宜心機能検査（心エコー等）を行い、患者の状態（左室駆出率（LVEF）の変動を含む）を確認すること。［9.1.1、11.1.3 参照］

8. 6 横紋筋融解症があらわれることがあるので、本剤投与中は定期的にCK、クレアチニン等の検査を行い、筋肉痛、脱力感、CK上昇、血中及び尿中ミオグロビン上昇等に十分注意すること。［11.1.5 参照］

8. 7 高血圧クリーゼがあらわれることがあるので、血圧の推移等に十分注意して投与すること。［11.1.6 参照］

9. 特定の背景を有する患者に関する注意

9. 1 合併症・既往歴等のある患者

9. 1. 1 心疾患又はその既往歴のある患者

症状が悪化するおそれがある。［8.5、11.1.3 参照］

9. 3 肝機能障害患者

本剤の減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇するとの報告がある。［16.6.1 参照］

9. 4 生殖能を有する者

妊娠可能な女性には、本剤投与中及び最終投与後一定期間、適切な避妊を行うよう指導すること。［9.5 参照］

9. 5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた動物試験において臨床曝露量の27倍に相当する用量で胎児体重の低値、骨化遅延又は骨格変異、ウサギを用いた動物試験において臨床曝露量の180倍に相当する用量で胎児体重の低値、骨化遅延が認められた。［9.4 参照］

9. 6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒト乳汁中への移行は不明である。

9. 7 小児等

小児等を対象とした臨床試験は実施していない。

9. 8 高齢者

患者の状態を十分に観察しながら慎重に投与すること。一般に生理機能が低下している。

10. 相互作用

本剤は主にCYP3A4により代謝される。［16.4.1 参照］

10. 2 併用注意（併用に注意すること）

	薬剤名等	臨床症状・措置方法	機序・危険因子
	CYP3A阻害剤 リトナビル、クラリスロマイシン、ポサコナゾール、ジルチアゼム等 ［16.7.1 参照］	本剤の血中濃度が上昇し、副作用の発現が増強されるおそれがあるので、CYP3A阻害作用のない薬剤への代替を考慮すること。やむを得ずCYP3A阻害剤を併用する場合には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	これらの薬剤との併用により、本剤の代謝が阻害され、血中濃度が上昇するおそれがある。
*	OATP1B1、OATP1B3又はBCRP基質 ロスバスタチン、アトルバスタチン、メトトレキサート等 ［16.7.2 参照］	OATP1B1、OATP1B3又はBCRPの基質となる薬剤と併用する場合は、これらの薬剤の血中濃度が上昇するおそれがある。	本剤がOATP1B1、OATP1B3及びBCRPを阻害することにより、これらの薬剤の血中濃度が上昇するおそれがある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11. 1 重大な副作用

11. 1. 1 皮膚悪性腫瘍

基底細胞癌（0.3%）、ケラトアカントーマ（0.5%）、新たな原発性悪性黒色腫（頻度不明）等の皮膚悪性腫瘍があらわれることがある。［8.1 参照］

11. 1. 2 眼障害

網膜障害（10.0%）、ぶどう膜炎（虹彩炎、虹彩毛様体炎を含む）（1.4%）等の眼障害があらわれることがある。［8.3 参照］

11. 1. 3 心機能障害

左室機能不全（0.5%）、駆出率減少（2.9%）等の心機能障害があらわれることがある。［8.5、9.1.1 参照］

11. 1. 4 肝機能障害

AST（4.1%）、ALT（5.2%）、γ-GTP（4.1%）、ビリルビン（0.5%）等の上昇を伴う肝機能障害があらわれることがある。［8.4 参照］

11. 1. 5 横紋筋融解症（0.2%）

［8.6 参照］

11. 1. 6 高血圧（2.4%）、**高血圧クリーゼ**（0.2%）

［8.7 参照］

11. 1. 7 出血

消化管出血（2.7%）等の出血があらわれることがある。

11. 1. 8 手掌・足底発赤知覚不全症候群（7.9%）

悪性黒色腫に対する本剤の単独投与時にビニメチニブとの併用投与時と比較して、手掌・足底発赤知覚不全症候群等の発現頻度が増加する傾向が認められているので、ビニメチニブを中止し本剤を継続する場合は、観察を十分に行い、これらの事象の発現に十分に注意すること。

11. 2 その他の副作用

	5%以上	5%未満
血液及びリンパ系障害	貧血	リンパ球減少、好中球減少
心臓障害		動悸、期外収縮、僧帽弁閉鎖不全症
耳及び迷路障害		耳鳴、回転性めまい
眼障害	霧視	眼瞼炎、色視症、眼乾燥、眼の障害、眼刺激、羞明、硝子体浮遊物、変視症、視力障害、結膜炎
胃腸障害	下痢(33.3%)、悪心(28.9%)、嘔吐、腹痛、便秘、口内炎	腹部不快感、腹部膨満、大腸炎、口内乾燥、消化不良、鼓腸、胃食道逆流性疾患、膵炎、アミラーゼ増加
全身障害	疲労(25.1%)、無力症、発熱	悪寒、冷感、インフルエンザ様疾患、浮腫(末梢性浮腫等)、末梢腫脹、全身健康状態低下、乾燥症、倦怠感
免疫系障害		過敏症
感染症及び寄生虫症		毛包炎、爪真菌症、咽頭炎、ヘルペス感染、カンジダ感染、胃腸炎
代謝及び栄養障害	食欲減退	高コレステロール血症、血中リン減少、高カリウム血症、高トリグリセリド血症、高尿酸血症、低アルブミン血症、リパーゼ増加、低ナトリウム血症
筋骨格系及び結合組織障害	関節痛、筋肉痛、血中CK増加	関節炎、背部痛、筋力低下、成長痛、筋骨格痛、四肢痛、頚部痛、四肢不快感、筋痙縮
精神・神経系障害	頭痛	顔面麻痺、視野欠損、不安、不眠症、睡眠障害、異常感覚、錯感覚、失神、傾眠、末梢性ニューロパチー、浮動性めまい、味覚異常
腎及び尿路障害		血中クレアチニン増加、頻尿
呼吸器、胸郭及び縦隔障害		咳嗽、呼吸困難、胸水、発声障害

	5%以上	5%未満
皮膚及び皮下組織障害	ざ瘡様皮膚炎(29.0%)、発疹(湿疹、丘疹等)(25.9%)、脱毛症、皮膚乾燥、過角化、そう痒症	皮膚炎、毛髪障害、毛質異常、多汗症、寝汗、光線過敏性反応、蕁麻疹、尋常性白斑、皮膚腫瘤、皮膚色素減少、皮膚色素過剰、脂肪織炎、紅斑、掌蹠角皮症、皮膚病変
血管障害		低血圧、ほてり
その他	メラノサイト性母斑	体重減少、体重増加、アクロコルドン、脂漏性角化症、乳頭腫、扁平上皮癌

14. 適用上の注意

14. 1 薬剤交付時の注意

14. 1. 1 PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

14. 1. 2 本剤は吸湿性があるので、服用直前までPTPシートから取り出さないこと。

15. その他の注意

15. 2 非臨床試験に基づく情報

15. 2. 1 ラットにおいて、臨床曝露量の3.3倍に相当する用量から雄性生殖器への影響（精細管変性、精子数減少等）が認められた。

15. 2. 2 カニクイザルにおいて、臨床曝露量の1.5倍に相当する用量で網膜への影響（黄斑部における網膜剥離）が認められた。

15. 2. 3 *In vitro* 光毒性試験において陽性結果が得られた。

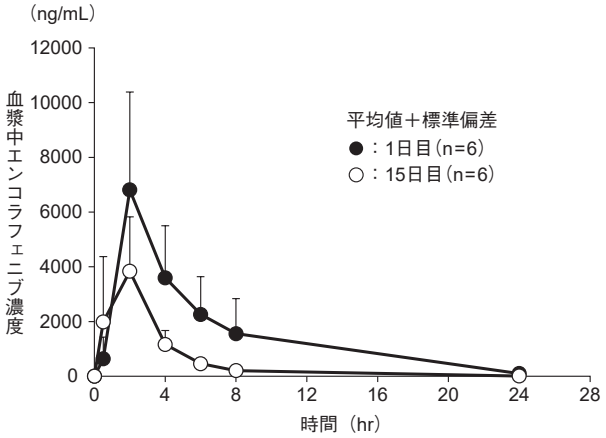
16. 薬物動態

16. 1 血中濃度

16. 1. 1 反復投与

〈*BRAF* 遺伝子変異を有する根治切除不能な悪性黒色腫〉

BRAF 遺伝子変異を有する悪性黒色腫患者（6例）にエンコラフェニブ450mgを1日1回反復投与したときのエンコラフェニブの血漿中濃度推移及び薬物動態パラメータを以下に示す。エンコラフェニブの血漿中濃度は15日以内に定常状態に達し、累積係数は0.438倍であった[1]（外国人データ）。



試験日（日）	Cmax (ng/mL)	Tmax (hr)	AUC_{tau} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$T_{1/2}$ (hr)
1 (n=6)	6650 ±3220	2 (2, 2.33)	38500 ±24100	39100 ±25100	2.92 (2.32, 4.98)
15 (n=6)	4330 ±2070	2 (0.5, 2)	13800 ±5050	13900 ±5050	3.19 (2.82, 3.56)

平均値±標準偏差、Tmax及び$T_{1/2}$は中央値（最小値、最大値）

〈がん化学療法後に増悪した *BRAF* 遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

BRAF 遺伝子変異を有する結腸・直腸癌患者（37例、日本人を含む）にビニメチニブ及びセツキシマブ（遺伝子組換え）との併用でエンコラフェニブ300mgを1日1回反復投与したときのエンコラフェニブの薬物動態パラメータを以下に示す[2]。

試験日（日）	Cmax (ng/mL)	Tmax (hr)	AUClast (ng·hr/mL)
1 (n=34)	3950 ±2270	2 (0.883, 6.25)	13100 ±7170
29 (n=29)	3010 ±1750	2 (0.950, 5.73)	7650 ±3980

平均値±標準偏差、Tmaxは中央値（最小値、最大値）

16. 2 吸収

16. 2. 1 食事の影響

健康成人（31例）にエンコラフェニブ100mgを空腹又は食後（高脂肪食）に単回投与[注)]したとき、空腹時と比較して、食後投与時のエンコラフェニブのCmax及び$AUC_{0-\infty}$はそれぞれ64.0及び95.9%であった[3]（外国人データ）。

16. 3 分布

エンコラフェニブのヒト血漿中蛋白結合率は86.1%、ヒト血液/血漿中濃度比は0.75であった[4]（*in vitro*）。

16. 4 代謝

16. 4. 1 *In vitro*

エンコラフェニブの主な代謝経路はCYP3A4による*N*-脱アルキル化及びそれに続くグルクロン酸抱合であり、CYP2C19及びCYP2D6も一部関与する[5,6]。[10. 参照]

16. 4. 2 *In vivo*

健康成人（4例）に^{14}C-エンコラフェニブ100mgを単回投与[注)]したとき、投与後24時間までの血漿中において、主に未変化体、M12.8（*N*-脱アルキル化及び加水分解を受けた代謝物のグルクロン酸抱合体）及びM42.5A（*N*-脱アルキル化体）が検出された（血漿中の総放射能に対する割合はそれぞれ27.5、23.0及び15.5%）[7]（外国人データ）。

16. 5 排泄

健康成人（4例）に^{14}C-エンコラフェニブ100mgを単回投与[注)]したとき、投与後144時間までに投与放射能量の47.2%が糞中に、47.2%が尿中に排泄された。尿中には投与後48時間までに投与放射能の1.8%が未変化体として排泄された[7]（外国人データ）。

16. 6 特定の背景を有する患者

16. 6. 1 肝機能障害患者

軽度肝機能障害患者（6例、Child-Pughスコア5～6）又は肝機能正常者（6例）にエンコラフェニブ50mgを単回投与[注)]したとき、肝機能正常者と比較して、軽度肝機能障害患者の血漿中非結合形エンコラフェニブのCmax及び$AUC_{0-\infty}$はそれぞれ1.21及び1.55倍であった[8]（外国人データ）。[9.3 参照]

16. 7 薬物相互作用

16. 7. 1 ポサコナゾール及びジルチアゼムとの併用

健康成人（16例）にポサコナゾール400mgの1日2回9日間反復投与時にエンコラフェニブ50mgを併用投与[注)]したとき、エンコラフェニブ単独投与時と比較して、エンコラフェニブのCmax及び$AUC_{0-\infty}$はそれぞれ168.4及び283.4%であった。また、健康成人（16例）にジルチアゼム240mgの1日1回4日間反復投与時にエンコラフェニブ50mgを併用投与[注)]したとき、エンコラフェニブ単独投与時と比較して、エンコラフェニブのCmax及び$AUC_{0-\infty}$はそれぞれ144.7及び183.0%であった[9]（外国人データ）。[10.2 参照]

＊16. 7. 2 ロスバスタチンとの併用

悪性腫瘍患者（10例）にエンコラフェニブ450mgを1日1回とビニメチニブ45mgを1日2回反復投与時にロスバスタチン10mgを併用投与（1日目、14日目）したとき、ロスバスタチン単独投与時と比較して、1日目のロスバスタチンのCmax及び$AUC_{0\text{-last}}$はそれぞれ434%及び279%、14日目の

ロスバスタチンのCmax及び$AUC_{0\text{-last}}$はそれぞれ268％及び157％であった（外国人データ）。［10.2参照］

16. 7. 3 その他

(1) ラベプラゾールとの併用

健康成人（11例）にエンコラフェニブ100mgをラベプラゾール20mgと併用[注)]したとき、エンコラフェニブ単独投与時と比較して、エンコラフェニブのCmax及び$AUC_{0\text{-}\infty}$はそれぞれ94.2及び96.6％であり、ラベプラゾール併用による胃内pH上昇はエンコラフェニブの薬物動態に影響を及ぼさなかった[10]（外国人データ）。

(2) エンコラフェニブはCYP1A2、CYP2B6、CYP2C8、CYP2C9、CYP2C19、CYP2D6及びCYP3Aを可逆的に阻害し、IC_{50}値はそれぞれ22、1、20～30、5、50、25及び8～15μmol/Lであった（*in vitro*）。また、エンコラフェニブはCYP3Aを時間依存的に阻害し、K_I値は20.5μmol/L、k_{inact}値は0.0527 min^{-1}であった[11]（*in vitro*）。

エンコラフェニブはCYP1A2、CYP2B6、CYP2C9を誘導した[12]（*in vitro*）。エンコラフェニブはCYP3A4を誘導し、EC_{50}値は10.2μmol/L、Emax値は169倍であった[13]（*in vitro*）。

(3) エンコラフェニブはUGT1A1を阻害し、IC_{50}値は1～7μmol/Lであった[14]（*in vitro*）。なお、エンコラフェニブはUGT1A1の基質であるビニメチニブの薬物動態に大きな影響を与えなかった（*in vivo*）。

(4) エンコラフェニブはP-gpの基質である[15]。エンコラフェニブはBCRP、OCT1、OATP1B1、OATP1B3、OCT2、OAT1及びOAT3を阻害し、IC_{50}値はそれぞれ10～25、12.7、5.35、6.16、2.05、4.20及び0.92μmol/Lであった[16～19]（*in vitro*）。

注）本剤の承認された用法及び用量は、以下の通りである。

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

ビニメチニブとの併用において、通常、成人にはエンコラフェニブとして450mgを1日1回経口投与する。

〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

セツキシマブ（遺伝子組換え）との併用、又はビニメチニブ及びセツキシマブ（遺伝子組換え）との併用において、通常、成人にはエンコラフェニブとして300mgを1日1回経口投与する。

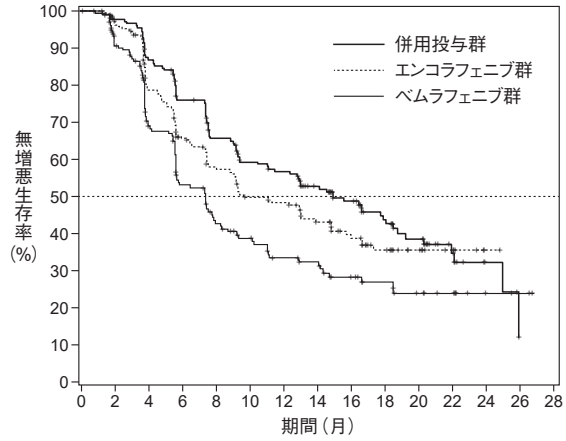
17. 臨床成績

17. 1 有効性及び安全性に関する試験

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

17. 1. 1 国際共同第Ⅲ相試験（CMEK162B2301試験）

BRAF V600E/K変異を有する根治切除不能な悪性黒色腫患者577例（日本人患者11例を含む。本剤とビニメチニブの併用投与群192例、ベムラフェニブ群191例、本剤単独投与群194例）を対象に、ベムラフェニブを対照として本剤（450mg[※1]を1日1回）とビニメチニブ（1回45mgを1日2回）を併用投与したときの有効性及び安全性を検討した。主要評価項目である中央判定による無増悪生存期間（中央値［95％信頼区間］）の主要解析結果は、本剤とビニメチニブ併用投与群で14.9［11.0～18.5］ヵ月、ベムラフェニブ群で7.3［5.6～8.2］ヵ月であり、本剤とビニメチニブの併用投与はベムラフェニブに対し統計学的に有意な延長を示した（ハザード比0.54［95％信頼区間：0.41～0.71］、p<0.0001［層別log-rank検定］、2016年5月19日データカットオフ）[20]。また、安全性評価対象となった192例中169例（88.0％）に副作用（臨床検査値の異常を含む）が認められた。主な副作用は、悪心59例（30.7％）、下痢52例（27.1％）、疲労48例（25.0％）、血中CK増加41例（21.4％）であった。［7.2参照］



at risk数

併用投与群	192	171	151	128	107	92	87	70	57	41	28	14	4	0
エンコラフェニブ群	194	162	125	99	84	71	68	55	41	28	17	10	1	0
ベムラフェニブ群	191	149	101	75	56	45	36	32	23	18	13	10	4	3	0

※1：本剤単独投与時の忍容性を検討した国際共同第Ⅰ相試験の結果、1日1回450mg投与で認められた用量制限毒性に基づき、次相以降の本剤単独投与の推奨用量は1日1回300mg投与と決定された一方、CMEK162B2301試験では、ビニメチニブを休薬又は中止した場合にも本剤は減量せずに継続することが可能な規定とされた。

〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

17. 1. 2 国際共同第Ⅲ相試験（ARRAY-818-302試験）

一次治療又は二次治療後に増悪したBRAF V600E変異を有する治癒切除不能な進行・再発の結腸・直腸癌患者665例（日本人患者20例を含む）を対象に、FOLFIRI[※2]及びセツキシマブ[※3]の併用投与又はイリノテカン[※4]及びセツキシマブ[※3]の併用投与（対照群）を対照として①本剤[※5]、ビニメチニブ[※6]及びセツキシマブ[※3]の併用投与（3剤群）又は②本剤[※5]及びセツキシマブ[※3]の併用投与（2剤群）の有効性及び安全性を検討した。主要評価項目である全生存期間及び奏効率の結果[※7]を以下に示す。対照群に対して3剤群及び2剤群は、全生存期間を統計学的に有意に延長し、奏効率は統計学的に有意に高値であった（2019年2月11日データカットオフ）[2]。また、3剤群及び2剤群においてそれぞれ安全性評価対象となった222例中208例（93.7％）及び216例中191例（88.4％）に副作用（臨床検査値の異常を含む）が認められた。主な副作用は、3剤群で下痢118例（53.2％）、ざ瘡様皮膚炎107例（48.2％）、悪心79例（35.6％）、疲労61例（27.5％）、嘔吐57例（25.7％）、2剤群でざ瘡様皮膚炎60例（27.8％）、疲労49例（22.7％）、悪心44例（20.4％）であった。

※2：2週間を1サイクルとして、第1日目に①イリノテカン180mg/m^2を90分かけて静脈内投与、②ホリナート400mg/m^2を120分かけて静脈内投与、③フルオロウラシル400mg/m^2を急速静脈内投与した後、フルオロウラシル2,400mg/m^2を46～48時間かけて静脈内投与

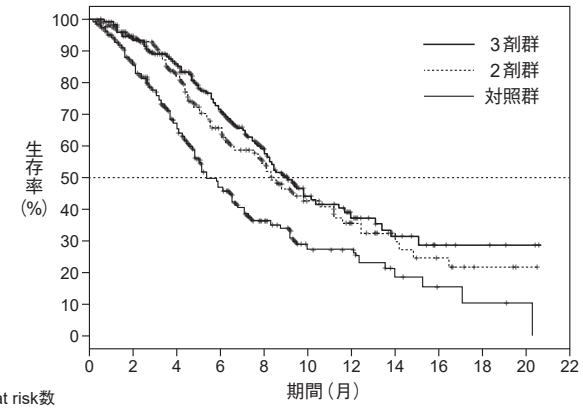
※3：初回のみ400mg/m^2を120分かけて、その後250mg/m^2を60分かけて毎週静脈内投与

※4：2週間を1サイクルとして、180mg/m^2を90分かけて静脈内投与

※5：300mgを1日1回投与

※6：1回45mgを1日2回投与

※7：本試験では、主要目的として、対照群に対する3剤群の奏効率及び全生存期間の優越性が検証された後、階層的な検定手順に従い、副次目的である対照群に対する2剤群の全生存期間及び奏効率の解析が実施された



at risk数

3剤群	224	186	141	103	69	37	24	14	6	4	2	0
2剤群	220	184	133	87	57	33	21	12	8	3	1	0
対照群	221	158	102	60	34	18	15	7	4	2	1	0

		3剤群	2剤群	対照群
全生存期間	症例数	224例	220例	221例
	中央値（月） [95%信頼区間]	9.0 [8.0, 11.4]	8.4 [7.5, 11.0]	5.4 [4.8, 6.6]
	ハザード比※8 [95%信頼区間] p値※9	0.52 [0.39, 0.70] <0.0001	0.60 [0.45, 0.79] 0.0002	-
奏効率※10	症例数※11	111例	113例	107例
	奏効率（%） [95%信頼区間]	26.1 [18.2, 35.3]	20.4 [13.4, 29.0]	1.9 [0.2, 6.6]
	p値※12	<0.0001	<0.0001	-

※8：層別 Cox 比例ハザードモデル（対照群との比較）
※9：層別 log-rank 検定（対照群との比較）
※10：RECIST ガイドライン 1.1 版に基づく中央判定による CR 又は PR
※11：本試験に最初に登録された 331 例が解析対象とされた
※12：Cochran-Mantel-Haenszel 検定（対照群との比較）

なお、部分集団解析による 2 剤群に対する 3 剤群のハザード比［95% 信頼区間］※13 は、ECOG PS 1 の集団（3 剤群 109 例、2 剤群 107 例）で 0.71［0.51, 0.99］、転移臓器数≧3 の集団（3 剤群 111 例、2 剤群 103 例）で 0.63［0.45, 0.90］、CRP 値＞1mg/dL の集団（3 剤群 95 例、2 剤群 79 例）で 0.65［0.46, 0.92］、原発巣が未切除又は不完全切除の集団（3 剤群 91 例、2 剤群 97 例）で 0.55［0.38, 0.79］であり、3 剤群で OS が良好な傾向が認められた。一方、ECOG PS 0 の集団（3 剤群 115 例、2 剤群 113 例；0.99［0.66, 1.47］）、転移臓器数≦2 の集団（3 剤群 113 例、2 剤群 117 例；1.04［0.72, 1.50］）、CRP 値≦1mg/dL の集団（3 剤群 122 例、2 剤群 139 例）；1.02［0.71, 1.46］）、原発巣が完全切除の集団（3 剤群 133 例、2 剤群 123 例）；1.00［0.71, 1.41］）では、2 剤群と 3 剤群の OS は同程度であった（2019 年 8 月 15 日データカットオフ）。

※13：全体集団において単変量 Cox 回帰モデル等により同定された、OS に影響を及ぼすと考えられる 5 つの患者背景因子（CRP 値＞1 mg/dL、肝転移あり、CEA 値＞5μg/L、CA19-9 値＞35U/mL 及び転移臓器数≧3）で調整した結果

18. 薬効薬理

18. 1 作用機序

エンコラフェニブは、ヒト BRAF V600E のキナーゼ活性を阻害した[21]。また、エンコラフェニブは、BRAF V600E 変異を有するヒト悪性黒色腫由来 A375 細胞株において、MAPK 経路のシグナル伝達分子（MEK 及び ERK）のリン酸化を阻害した[22,23]。

18. 2 抗腫瘍効果

18. 2. 1 *In vitro*

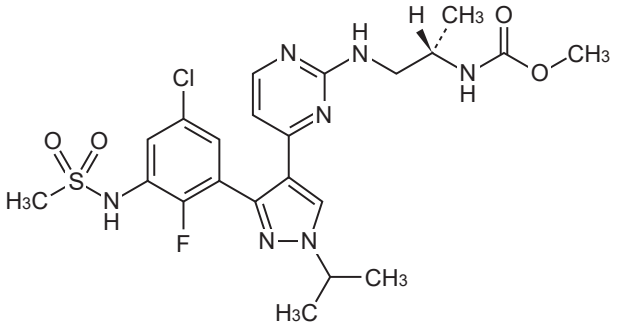
エンコラフェニブは、BRAF V600E 変異を有するヒト悪性黒色腫由来 A375 細胞株及び BRAF V600E 変異を有するヒト結腸・直腸癌由来細胞株（COLO 205、HT-29 等）の増殖を抑制した[24,25]。また、エンコラフェニブと MEK 阻害剤であるビニメチニブとの併用により、各薬剤単独と比較して、BRAF V600E 変異を有するヒト悪性黒色腫由来細胞株（A375、COLO 800 等）、BRAF V600K 変異を有するヒト悪性黒色腫由来 IGR-1 細胞株、BRAF V600E 変異を有するヒト結腸・直腸癌由来細胞株（COLO 205、HT-29 等）に対する増殖抑制作用が増強した[26,27]。

18. 2. 2 *In vivo*

エンコラフェニブは、A375 細胞株及び COLO 205 細胞株を皮下移植したヌードマウスにおいて、腫瘍増殖抑制作用を示した[28,29]。また、エンコラフェニブとビニメチニブとの併用により、各薬剤単独と比較して、BRAF V600E 変異を有するヒト悪性黒色腫患者由来 HMEX1906 腫瘍組織片を皮下移植したヌードマウスにおける腫瘍増殖抑制作用が増強した[30]。さらに、①エンコラフェニブとセツキシマブとの併用、並びに②エンコラフェニブ、ビニメチニブ及びセツキシマブの併用により、①セツキシマブ単独及び②エンコラフェニブ又はセツキシマブ単独と比較して、HT-29 細胞株を皮下移植したヌードマウスにおける腫瘍増殖抑制作用がそれぞれ増強した[31]。

19. 有効成分に関する理化学的知見

一般名：エンコラフェニブ（Encorafenib）
化学名：Methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate
分子式：$C_{22}H_{27}ClFN_7O_4S$
分子量：540.01
性　状：本品は白色～ほとんど白色の粉末であり、エタノール（99.5）に溶けにくく、水にほとんど溶けない。
化学構造式：



21. 承認条件

21. 1 医薬品リスク管理計画を策定の上、適切に実施すること。
〈*BRAF* 遺伝子変異を有する根治切除不能な悪性黒色腫〉
21. 2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

〈ビラフトビカプセル 50mg〉
42 カプセル［6 カプセル（PTP）×7］
60 カプセル［6 カプセル（PTP）×10］
〈ビラフトビカプセル 75mg〉
42 カプセル［6 カプセル（PTP）×7］

23. 主要文献

1）小野薬品工業：海外第Ⅰ相（CLGX818X2101）試験成績（社内資料；2019 年 1 月 8 日承認、CTD2.7.6.10、CTD2.7.2.2.1.2）
2）小野薬品工業：国際共同第Ⅲ相（ARRAY-818-302）試験成績（社内資料；2020 年 11 月 27 日承認、CTD2.7.6.6、CTD2.7.2.2.3.1）
3）小野薬品工業：海外第Ⅰ相（ARRAY-818-102）試験成績（社内資料；2019 年 1 月 8 日承認、CTD2.7.6.1、CTD2.7.1.2）
4）小野薬品工業：*In vitro* 血漿蛋白結合及び血球移行性（社内資料；2019 年 1 月 8 日承認、CTD2.7.2.2）
5）小野薬品工業：*In vitro* 代謝（社内資料；2019 年 1 月 8 日承認、CTD2.7.2.2、CTD2.7.2.3）
6）小野薬品工業：代謝酵素の推定（社内資料；2019 年 1 月 8 日承認、CTD2.7.2.2、CTD2.7.2.3）

7）小野薬品工業：海外マスバランス（CLGX818A2101）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.6）
8）小野薬品工業：肝機能障害患者における海外第Ⅰ相（ARRAY-818-101）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.13、CTD2.7.2.2.1.2）
9）小野薬品工業：海外第Ⅰ相（ARRAY-818-105）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.18、CTD2.7.2.2.1.2）
10）小野薬品工業：海外第Ⅰ相（ARRAY-162-105）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.15、CTD2.7.2.2.1.2）
11）小野薬品工業：CYP阻害作用（社内資料；2019年1月8日承認、CTD2.7.2.2）
12）小野薬品工業：CYP誘導作用（1）（社内資料；2019年1月8日承認、CTD2.7.2.2）
13）小野薬品工業：CYP誘導作用（2）（社内資料；2019年1月8日承認、CTD2.7.2.2）
14）小野薬品工業：UGT1A1阻害作用（社内資料；2019年1月8日承認、CTD2.7.2.2）
15）小野薬品工業：トランスポーター基質検討（社内資料；2019年1月8日承認、CTD2.7.2.2）
16）小野薬品工業：排出トランスポーター阻害作用（社内資料；2019年1月8日承認、CTD2.7.2.2）
17）小野薬品工業：肝取込みトランスポーター阻害作用（1）（社内資料；2019年1月8日承認、CTD2.7.2.2）
18）小野薬品工業：肝取込みトランスポーター阻害作用（2）（社内資料；2019年1月8日承認、CTD2.7.2.2）
19）小野薬品工業：腎取込みトランスポーター阻害作用（社内資料；2019年1月8日承認、CTD2.7.2.2）
20）小野薬品工業：国際共同第Ⅲ相（CMEK162B2301）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.19、CTD2.7.6.20）
21）小野薬品工業：BRAFに対する阻害活性（社内資料；2019年1月8日承認、CTD2.6.2.2）
22）小野薬品工業：MEKのリン酸化に対する阻害作用（社内資料；2019年1月8日承認、CTD2.6.2.2）
23）小野薬品工業：ERKのリン酸化に対する阻害作用（社内資料；2019年1月8日承認、CTD2.6.2.2）
24）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞の増殖に対する抑制作用（社内資料；2019年1月8日承認、CTD2.6.2.2）
25）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞の増殖に対する抑制作用（社内資料；2020年11月27日承認、CTD2.6.2.2）
26）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞の増殖に対するビニメチニブとの併用効果（社内資料；2019年1月8日承認、CTD2.6.2.2）
27）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞の増殖に対するビニメチニブとの併用効果（社内資料；2020年11月27日承認、CTD2.6.2.2）
28）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞移植マウスにおける抗腫瘍効果（社内資料；2019年1月8日承認、CTD2.6.2.2）
29）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞移植マウスにおける抗腫瘍効果（社内資料；2020年11月27日承認、CTD2.6.2.2）
30）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞移植マウスにおけるビニメチニブとの併用効果（社内資料；2019年1月8日承認、CTD2.6.2.2）
31）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞移植マウスにおけるビニメチニブ及びセツキシマブとの併用効果（社内資料；2020年11月27日承認、CTD2.6.2.2）

24. 文献請求先及び問い合わせ先

小野薬品工業株式会社　くすり相談室
〒541-8564 大阪市中央区久太郎町1丁目8番2号
電話 0120-626-190

26. 製造販売業者等

26. 1 製造販売

小野薬品工業株式会社
大阪市中央区久太郎町1丁目8番2号

26. 2 提携

＊2020年11月改訂（第1版、効能変更、用法変更）

貯　　法：室温保存
有効期間：5年

日本標準商品分類番号 874291

承認番号	23100AMX00006000
販売開始	2019年2月

―抗悪性腫瘍剤―
MEK阻害剤
ビニメチニブ錠

劇薬、処方箋医薬品注）

メクトビ®錠15mg

MEKTOVI® Tablets

注）注意－医師等の処方箋により使用すること

1. 警告

本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

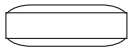
本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

有効成分	1錠中 ビニメチニブ15mg
添加剤	乳糖水和物、結晶セルロース、クロスカルメロースナトリウム、ステアリン酸マグネシウム、軽質無水ケイ酸、ポリビニルアルコール（部分けん化物）、マクロゴール4000、酸化チタン、タルク、黄色三二酸化鉄、黒酸化鉄

3.2 製剤の性状

剤　形	フィルムコーティング錠		
外　形	表面	裏面	側面
			
長径(mm)	約12.3		
短径(mm)	約5.3		
厚さ(mm)	約4.2		
質量(mg)	約247.7		
色　調	黄色～暗黄色		
識別コード	15		

4. 効能又は効果

○*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫
＊○がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌

5. 効能又は効果に関連する注意

〈効能共通〉

＊5.1 十分な経験を有する病理医又は検査施設における検査により、*BRAF*遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

5.2「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

5.3 本剤の術後補助療法における有効性及び安全性は確立していない。

＊〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

＊5.4 本剤の一次治療における有効性及び安全性は確立していない。

6. 用法及び用量

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

エンコラフェニブとの併用において、通常、成人にはビニメチニブとして1回45mgを1日2回経口投与する。なお、患者の状態により適宜減量する。

＊〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

エンコラフェニブ及びセツキシマブ（遺伝子組換え）との併用において、通常、成人にはビニメチニブとして1回45mgを1日2回経口投与する。なお、患者の状態により適宜減量する。

7. 用法及び用量に関連する注意

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

7.1 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。

7.2 エンコラフェニブを休薬又は中止した場合には、本剤をそれぞれ休薬又は中止すること。

減量して投与を継続する場合の投与量

減量レベル※1	投与量
通常投与量	45mg 1日2回
1段階減量	30mg 1日2回
2段階減量	15mg 1日2回
3段階減量	投与中止

※1：減量を要した副作用がGrade 1以下に回復し、他に合併する副作用がない場合には、減量時と逆の段階を経て増量可能

副作用発現時の用量調節基準

副作用	程度※2	処置
網膜疾患、ぶどう膜炎	Grade 2	Grade 1以下に回復するまで休薬。再開する場合、同量又は1段階減量して投与。
	Grade 3	Grade 2以下に回復するまで休薬。再開する場合、1段階減量して投与。Grade 3が継続する場合、投与中止。
	Grade 4	投与中止。
網膜静脈閉塞	Grade 1以上	投与中止。
眼障害（上記以外）	Grade 3	Grade 1以下に回復するまで休薬。28日以内で回復し再開する場合、1段階減量して投与。28日以内で回復しない場合、投与中止。
	Grade 4	投与中止。
AST増加、ALT増加	Grade 2（血清ビリルビン上昇を伴わない場合）	Grade 1以下に回復するまで休薬。14日以内で回復し再開する場合、同量で投与。14日超で回復し再開する場合、1段階減量して投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 2（血清ビリルビン上昇を伴う場合）	Grade 1以下に回復するまで休薬。7日以内で回復し再開する場合、1段階減量して投与。7日以内で回復しない場合、投与中止。

副作用	程度※2	処置
AST増加、ALT増加	Grade 3（血清ビリルビン上昇を伴わない場合）	Grade 1以下に回復するまで休薬。再開する場合、1段階減量して投与。
	Grade 3（血清ビリルビン上昇を伴う場合）及びGrade 4	投与中止。
血清CK上昇	Grade 3（筋症状又はクレアチニン上昇を伴う場合）及びGrade 4	Grade 1以下に回復するまで休薬。28日以内で回復し再開する場合、1段階減量して投与。28日以内で回復しない場合、投与中止。
駆出率減少	左室駆出率が投与前より10%以上減少、又は正常下限を下回る場合	回復するまで休薬。28日以内で回復し再開する場合、1段階減量して投与。28日以内で回復しない場合、投与中止。
	Grade 3-4	投与中止。
心電図QT延長	500msを超えるQTc値が認められ、かつ投与前からの変化が60ms以下の場合	QTc値が500msを下回るまで休薬。再開する場合、1段階減量して再開すること。ただし、再発した場合、投与中止。
	500msを超えるQTc値が認められ、かつ投与前からの変化が60msを超える場合	投与中止。
皮膚炎	Grade 2	症状が継続又は悪化する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 3	Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 4	投与中止。
上記以外の副作用	Grade 2	Grade 2が継続する場合、休薬又は減量を考慮。
	Grade 3	Grade 1以下に回復するまで休薬を考慮。28日以内で回復し再開する場合、1段階減量して投与することを考慮。
	Grade 4	投与中止。

※2：GradeはNCI-CTCAE ver4.03に準じる。

＊〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

＊7.3 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。

＊7.4 エンコラフェニブを休薬又は中止した場合には、本剤をそれぞれ休薬又は中止すること。

減量して投与を継続する場合の投与量

減量レベル※3	投与量
通常投与量	45mg 1日2回
1段階減量	30mg 1日2回
2段階減量	15mg 1日2回
3段階減量	投与中止

※3：減量を要した副作用がGrade 1以下に回復し、他に合併する副作用がない場合には、減量時と逆の段階を経て増量可能

副作用発現時の用量調節基準

副作用	程度※4	処置
網膜疾患、ぶどう膜炎	Grade 2	Grade 1以下に回復するまで休薬。再開する場合、同量又は1段階減量して投与。
	Grade 3	Grade 2以下に回復するまで休薬。再開する場合、1段階減量して投与。Grade 3が継続する場合、投与中止。
	Grade 4	投与中止。
網膜静脈閉塞	Grade 1以上	投与中止。
眼障害（上記以外）	Grade 3	Grade 1以下に回復するまで休薬。21日以内で回復し再開する場合、1段階減量して投与。21日以内で回復しない場合、投与中止。
	Grade 4	投与中止。
AST増加、ALT増加	Grade 2（血清ビリルビン上昇を伴わない場合）	Grade 1以下に回復するまで休薬。14日以内で回復し再開する場合、同量で投与。14日超で回復し再開する場合、1段階減量して投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
AST増加、ALT増加	Grade 2（血清ビリルビン上昇を伴う場合）	Grade 1以下に回復するまで休薬。7日以内で回復し再開する場合、1段階減量して投与。7日以内で回復しない場合、投与中止。
	Grade 3（血清ビリルビン上昇を伴わない場合）	Grade 1以下に回復するまで休薬。再開する場合、1段階減量して投与。
	Grade 3（血清ビリルビン上昇を伴う場合）及びGrade 4	投与中止。
血清CK上昇	Grade 3（筋症状又はクレアチニン上昇を伴う場合）及びGrade 4	Grade 1以下に回復するまで休薬。21日以内で回復し再開する場合、1段階減量して投与。21日以内で回復しない場合、投与中止。
駆出率減少	左室駆出率が投与前より10%以上減少、又は正常下限を下回る場合	回復するまで休薬。21日以内で回復し再開する場合、1段階減量して投与。21日以内で回復しない場合、投与中止。
	Grade 3-4	投与中止。
心電図QT延長	500msを超えるQTc値が認められ、かつ投与前からの変化が60ms以下の場合	QTc値が500msを下回るまで休薬。再開する場合、1段階減量して再開すること。ただし、再発した場合、投与中止。
	500msを超えるQTc値が認められ、かつ投与前からの変化が60msを超える場合	投与中止。
皮膚炎	Grade 2	症状が継続又は悪化する場合、Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 3	Grade 1以下に回復するまで休薬。再開する場合、同量で投与。ただし、再発した場合、休薬し回復後に1段階減量して投与。
	Grade 4	投与中止。
上記以外の副作用	Grade 2	Grade 2が継続する場合、休薬又は減量を考慮。
	Grade 3	Grade 1以下に回復するまで休薬を考慮。21日以内で回復し再開する場合、1段階減量して投与することを考慮。
	Grade 4	投与中止。

※4：GradeはNCI-CTCAE ver4.03に準じる。

8. 重要な基本的注意

8.1 重篤な眼障害が報告されているので、定期的に眼の異常の有無を確認すること。また、眼の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。［11.1.1参照］

8.2 肝機能障害があらわれることがあるので、本剤投与中は定期的に肝機能検査を行い、患者の状態を確認すること。［11.1.3参照］

8.3 心機能障害があらわれることがあるので、本剤投与開始前及び本剤投与中は適宜心機能検査（心エコー等）を行い、患者の状態（左室駆出率（LVEF）の変動を含む）を確認すること。［9.1.1、11.1.2参照］

8.4 横紋筋融解症があらわれることがあるので、本剤投与中は定期的にCK、クレアチニン等の検査を行い、筋肉痛、脱力感、CK上昇、血中及び尿中ミオグロビン上昇等に十分注意すること。［11.1.4参照］

8.5 高血圧クリーゼがあらわれることがあるので、血圧の推移等に十分注意して投与すること。［11.1.5参照］

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 心疾患又はその既往歴のある患者

症状が悪化するおそれがある。［8.3、11.1.2参照］

9.3 肝機能障害患者

9.3.1 中等度以上の肝機能障害のある患者

本剤の減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇するとの報告がある。［16.6.1参照］

9. 4 生殖能を有する者

妊娠可能な女性には、本剤投与中及び最終投与後一定期間、適切な避妊を行うよう指導すること。[9.5 参照]

9. 5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた動物試験において臨床曝露量の 10 倍に相当する用量から胎児体重の低値及び骨化遅延、ウサギを用いた動物試験において臨床曝露量の 1.4 倍に相当する用量から流産、着床後胚損失率の増加、生存胎児数の減少及び胎児体重の低値、1.9 倍に相当する用量で催奇形性（心室中隔欠損及び血管異常）が認められた。[9.4 参照]

9. 6 授乳婦

授乳しないことが望ましい。乳汁移行に関するデータはないが、本剤は BCRP の基質であるため、乳汁移行の可能性がある。

9. 7 小児等

小児等を対象とした臨床試験は実施していない。

9. 8 高齢者

患者の状態を十分に観察しながら慎重に投与すること。一般に生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11. 1 重大な副作用

＊11. 1. 1 眼障害

網膜障害（15.0%）、ぶどう膜炎（虹彩炎、虹彩毛様体炎を含む）(2.2%）等の眼障害があらわれることがある。[8.1 参照]

＊11. 1. 2 心機能障害

左室機能不全（0.7%）、駆出率減少（4.3%）等の心機能障害があらわれることがある。[8.3、9.1.1 参照]

＊11. 1. 3 肝機能障害

AST（5.3%）、ALT（7.0%）、γ-GTP（6.3%）、ビリルビン（0.7%）等の上昇を伴う肝機能障害があらわれることがある。[8.2 参照]

＊11. 1. 4 横紋筋融解症（0.2%）

[8.4 参照]

＊11. 1. 5 高血圧（3.1%）、**高血圧クリーゼ**（0.2%）

[8.5 参照]

＊11. 1. 6 出血

消化管出血（3.9%）等の出血があらわれることがある。

11. 2 その他の副作用

	5%以上	5%未満
血液及びリンパ系障害	貧血	リンパ球減少、好中球減少
心臓障害		動悸、期外収縮、僧帽弁閉鎖不全症
耳及び迷路障害		耳鳴、回転性めまい
＊ 眼障害	霧視	眼瞼炎、色視症、眼乾燥、眼の障害、眼刺激、羞明、硝子体浮遊物、変視症、視力障害、結膜炎
＊ 胃腸障害	下痢(41.1%)、悪心(33.3%)、嘔吐(21.3%)、腹痛、便秘、口内炎	腹部不快感、腹部膨満、大腸炎、口内乾燥、消化不良、鼓腸、胃食道逆流性疾患、膵炎、アミラーゼ増加
＊ 全身障害	疲労(26.3%)、無力症、発熱	悪寒、冷感、インフルエンザ様疾患、浮腫(末梢性浮腫等)、末梢腫脹、全身健康状態低下、乾燥症、倦怠感
免疫系障害		過敏症
＊ 感染症及び寄生虫症		毛包炎、爪真菌症、咽頭炎、ヘルペス感染、カンジダ感染、胃腸炎
＊ 代謝及び栄養障害	食欲減退	高コレステロール血症、血中リン減少、高カリウム血症、高トリグリセリド血症、高尿酸血症、低アルブミン血症、リパーゼ増加、低ナトリウム血症
筋骨格系及び結合組織障害	関節痛、筋痙縮、筋肉痛、血中CK増加	関節炎、背部痛、筋力低下、成長痛、筋骨格痛、四肢痛、頚部痛、四肢不快感
＊ 精神・神経系障害	味覚異常、頭痛	顔面麻痺、視野欠損、不安、不眠症、睡眠障害、異常感覚、錯感覚、失神、傾眠、末梢性ニューロパチー、浮動性めまい、嗜眠
＊ 腎及び尿路障害		血中クレアチニン増加、頻尿、急性腎障害
呼吸器、胸郭及び縦隔障害		咳嗽、呼吸困難、胸水
＊ 皮膚及び皮下組織障害	ざ瘡様皮膚炎(28.7%)、発疹(湿疹、丘疹等)(26.6%)、脱毛症、皮膚乾燥、過角化、そう痒症	皮膚炎、毛髪障害、毛質異常、多汗症、寝汗、光線過敏性反応、蕁麻疹、尋常性白斑、皮膚腫瘤、皮膚色素減少、皮膚色素過剰、脂肪織炎、紅斑、掌蹠角皮症、皮膚剥脱
血管障害		低血圧、ほてり
その他		体重減少、体重増加、アクロコルドン、メラノサイト性母斑、脂漏性角化症、乳頭腫、扁平上皮癌

14. 適用上の注意

14. 1 薬剤交付時の注意

PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15. 2 非臨床試験に基づく情報

15. 2. 1 ラットにおいて、臨床曝露量の 4.4 倍に相当する用量から血中リンの高値を伴う諸臓器（腺胃、下垂体等）の鉱質沈着が認められた。

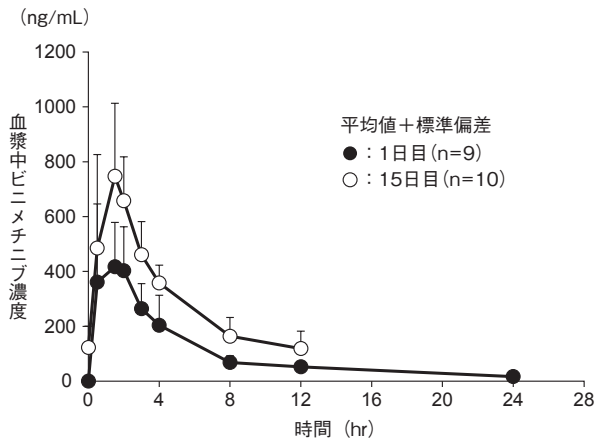
15. 2. 2 *In vitro* 光毒性試験において陽性結果が得られた。また、マウスを用いた動物試験において光感作性が認められた。

16. 薬物動態

16. 1 血中濃度

16. 1. 1 反復投与

日本人の固形がん患者にビニメチニブ 45mg を 1 日 1 回又は 1 日 2 回反復投与した※1 ときのビニメチニブの血漿中濃度推移及び薬物動態パラメータを以下に示す。ビニメチニブの血漿中濃度は 14 日以内に定常状態に達し、累積係数は 1.80 倍であった[1)]。



試験日（日）	Cmax（ng/mL）	Tmax（hr）	$AUC_{0\text{-}12h}$（ng·hr/mL）	$AUC_{0\text{-}\infty}$（ng·hr/mL）	$T_{1/2}$（hr）
1（n=9）	559±145	1.5（0.5, 4）	2030±475	2650±698	8.24±3.78
15（n=9）	805±274	1.5（0.5, 2）	3670±1100	3380±370※2	4.11±1.13

平均値±標準偏差、Tmaxは中央値（最小値、最大値）
※1：1日目は1回投与し、2日目以降15日目まで1日2回投与した。
※2：n=5

16. 2 吸収

16. 2. 1 食事の影響

健康成人（12例）にビニメチニブ45mgを空腹又は食後（高脂肪食）に単回投与注）したとき、空腹時と比較して、食後投与時のビニメチニブのCmax及び$AUC_{0\text{-}\infty}$はそれぞれ0.828及び0.993倍であった[2]（外国人データ）。

16. 3 分布

ビニメチニブのヒト血漿中蛋白結合率は97.2%、ヒト血液/血漿中濃度比は0.718であった[3]（*in vitro*）。

16. 4 代謝

16. 4. 1 *In vitro*

ビニメチニブの主な代謝経路はUGT1A1によるグルクロン酸抱合であり、CYP1A2及びCYP2C19による*N*-脱メチル化も一部関与する[4, 5]。

16. 4. 2 *In vivo*

健康成人（6例）に^{14}C-ビニメチニブ45mgを単回投与注）したとき、投与後24時間までの血漿中において、主に未変化体、M10.2（グルクロン酸抱合体）及びM3（*N*-脱メチル化体）が検出された（血漿中の総放射能に対する割合はそれぞれ60.2、5.5及び7.3%）[6]（外国人データ）。

16. 5 排泄

健康成人（6例）に^{14}C-ビニメチニブ45mgを単回投与注）したとき、投与後360時間までに投与放射能量の62.3%が糞中に、31.4%が尿中に排泄された。尿中には投与後360時間までに投与放射能量の6.5%が未変化体として排泄された[6]（外国人データ）。

16. 6 特定の背景を有する患者

16. 6. 1 肝機能障害患者

肝機能障害患者※3（軽度：6例、中等度：6例、重度：5例）又は肝機能正常者（10例）にビニメチニブ45mg（重度肝機能障害患者は15mg）を単回投与注）したとき、軽度、中等度及び重度肝機能障害患者の血漿中非結合形ビニメチニブの投与量で補正した$AUC_{0\text{-}120h}$は、肝機能正常者のそれぞれ1.22、3.80及び3.48倍であった。また、軽度、中等度及び重度肝機能障害患者の血漿中非結合形ビニメチニブの投与量で補正したCmaxは、肝機能正常者のそれぞれ1.28、2.63及び2.68倍であった[7]（外国人データ）。［9.3.1参照］

※3：NCI-ODWG（National Cancer Institute - Organ Dysfunction Working Group）基準による分類（2011年8月時点）

16. 6. 2 腎機能障害患者

ビニメチニブの消失に腎排泄の寄与は小さい。重度腎機能障害患者（eGFR≦29mL/min/1.73m^2、6例）又は腎機能正常者（6例）にビニメチニブ45mgを単回投与注）したとき、重度腎機能障害患者の血漿中非結合形ビニメチニブのCmax及び$AUC_{0\text{-}\infty}$は、腎機能正常者のそれぞれ1.43及び1.53倍であった[8]（外国人データ）。

16. 7 薬物相互作用

16. 7. 1 その他

（1）ラベプラゾールとの併用

健康成人（15例）にビニメチニブ45mgをラベプラゾール20mgと併用投与注）したとき、ビニメチニブ単独投与時と比較して、ビニメチニブのCmax及び$AUC_{0\text{-}\infty}$はそれぞれ82.6及び104.2%であり、ラベプラゾール併用による胃内pH上昇はビニメチニブの薬物動態に影響を及ぼさなかった[9]（外国人データ）。

（2）ミダゾラムとの併用

健康成人（11例）にビニメチニブ30mgを1日2回2週間反復投与注）した後にミダゾラム4mgを併用投与したとき、ミダゾラム単独投与時と比較して、ビニメチニブ2週間投与後のミダゾラムのCmax及び$AUC_{0\text{-}\infty}$はそれぞれ0.925及び1.10倍であり、ビニメチニブの明確なCYP3A4誘導作用は認められなかった[10]（外国人データ）。

（3）*In vitro*

ビニメチニブはCYP2B6を可逆的に阻害し、Ki値は1.73 μmol/Lであった[11]。ビニメチニブはP-gp及びBCRPの基質である[12, 13]。

（4）*In vivo*

ビニメチニブは主にUGT1A1により代謝される。ビニメチニブの薬物動態は、UGT1A1阻害作用を有するエンコラフェニブとの併用による大きな影響を受けなかった。なお、UGT1A1を介した臨床薬物相互作用試験は実施していない。

＊注）本剤の承認された用法及び用量は、以下の通りである。
〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉
エンコラフェニブとの併用において、通常、成人にはビニメチニブとして1回45mgを1日2回経口投与する。
〈がん化学療法後に増悪した*BRAF*遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉
エンコラフェニブ及びセツキシマブ（遺伝子組換え）との併用において、通常、成人にはビニメチニブとして1回45mgを1日2回経口投与する。

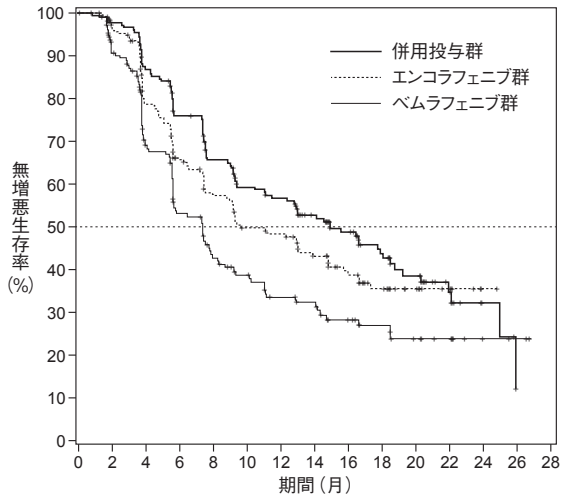
17. 臨床成績

17. 1 有効性及び安全性に関する試験

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

17. 1. 1 国際共同第Ⅲ相試験（CMEK162B2301試験）

BRAF V600E/K変異を有する根治切除不能な悪性黒色腫患者577例（日本人患者11例を含む。本剤とエンコラフェニブ併用投与群192例、ベムラフェニブ群191例、エンコラフェニブ単独投与群194例）を対象に、ベムラフェニブを対照として本剤（1回45mgを1日2回）とエンコラフェニブ（450mgを1日1回）を併用投与したときの有効性及び安全性を検討した。主要評価項目である中央判定による無増悪生存期間（中央値［95%信頼区間］）の主要解析結果は、本剤とエンコラフェニブの併用投与群で14.9［11.0～18.5］ヵ月、ベムラフェニブ群で7.3［5.6～8.2］ヵ月であり、本剤とエンコラフェニブの併用投与はベムラフェニブに対し統計学的に有意な延長を示した（ハザード比0.54［95%信頼区間：0.41～0.71］、p<0.0001［層別log-rank検定］、2016年5月19日データカットオフ）[14]。また、安全性評価対象となった192例中169例（88.0%）に副作用（臨床検査値の異常を含む）が認められた。主な副作用は、悪心59例（30.7%）、下痢52例（27.1%）、疲労48例（25.0%）、血中CK増加41例（21.4%）であった。



at risk数

併用投与群	192	171	151	128	107	92	87	70	57	41	28	14	4	0
エンコラフェニブ群	194	162	125	99	84	71	68	55	41	28	17	10	1	0
ベムラフェニブ群	191	149	101	75	56	45	36	32	23	18	13	10	4	3	0

＊〈がん化学療法後に増悪した *BRAF* 遺伝子変異を有する治癒切除不能な進行・再発の結腸・直腸癌〉

＊17. 1. 2 国際共同第Ⅲ相試験（ARRAY-818-302 試験）

一次治療又は二次治療後に増悪したBRAF V600E変異を有する治癒切除不能な進行・再発の結腸・直腸癌患者665例（日本人患者20例を含む）を対象に、FOLFIRI※1及びセツキシマブ※2の併用投与又はイリノテカン※3及びセツキシマブ※2の併用投与（対照群）を対照として①エンコラフェニブ※4、本剤※5及びセツキシマブ※2の併用投与（3剤群）又は②エンコラフェニブ※4及びセツキシマブ※2の併用投与（2剤群）注）の有効性及び安全性を検討した。主要評価項目である全生存期間及び奏効率の結果※6を以下に示す。対照群に対して3剤群及び2剤群は、全生存期間を統計学的に有意に延長し、奏効率は統計学的に有意に高値であった（2019年2月11日データカットオフ）[15]。また、3剤群及び2剤群においてそれぞれ安全性評価対象となった222例中208例（93.7%）及び216例中191例（88.4%）に副作用（臨床検査値の異常を含む）が認められた。主な副作用は、3剤群で下痢118例（53.2%）、ざ瘡様皮膚炎107例（48.2%）、悪心79例（35.6%）、疲労61例（27.5%）、嘔吐57例（25.7%）、2剤群でざ瘡様皮膚炎60例（27.8%）、疲労49例（22.7%）、悪心44例（20.4%）であった。

※1：2週間を1サイクルとして、第1日目に①イリノテカン180mg/m² を90分かけて静脈内投与、②ホリナート400mg/m² を120分かけて静脈内投与、③フルオロウラシル400mg/m² を急速静脈内投与した後、フルオロウラシル2,400mg/m² を46～48時間かけて静脈内投与

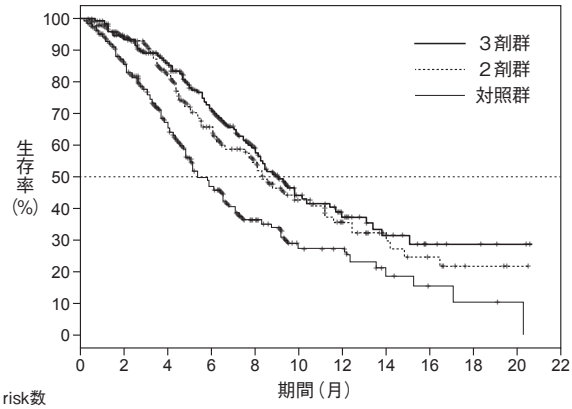
※2：初回のみ400mg/m² を120分かけて、その後250mg/m² を60分かけて毎週静脈内投与

※3：2週間を1サイクルとして、180mg/m² を90分かけて静脈内投与

※4：300mgを1日1回投与

※5：1回45mgを1日2回投与

※6：本試験では、主要目的として、対照群に対する3剤群の奏効率及び全生存期間の優越性が検証された後、階層的な検定手順に従い、副次目的である対照群に対する2剤群の全生存期間及び奏効率の解析が実施された。



at risk数

3剤群	224	186	141	103	69	37	24	14	6	4	2	0
2剤群	220	184	133	87	57	33	21	12	8	3	1	0
対照群	221	158	102	60	34	18	15	7	4	2	1	0

		3剤群	2剤群	対照群
全生存期間	症例数	224例	220例	221例
	中央値（月）[95%信頼区間]	9.0 [8.0, 11.4]	8.4 [7.5, 11.0]	5.4 [4.8, 6.6]
	ハザード比※7 [95%信頼区間] p値※8	0.52 [0.39, 0.70] ＜0.0001	0.60 [0.45, 0.79] 0.0002	–
奏効率※9	症例数※10	111例	113例	107例
	奏効率（%）[95%信頼区間]	26.1 [18.2, 35.3]	20.4 [13.4, 29.0]	1.9 [0.2, 6.6]
	p値※11	＜0.0001	＜0.0001	–

※7：層別Cox比例ハザードモデル（対照群との比較）

※8：層別log-rank検定（対照群との比較）

※9：RECISTガイドライン1.1版に基づく中央判定によるCR又はPR

※10：本試験に最初に登録された331例が解析対象とされた

※11：Cochran-Mantel-Haenszel検定（対照群との比較）

なお、部分集団解析による2剤群に対する3剤群のハザード比［95%信頼区間］※12は、ECOG PS 1の集団（3剤群109例、2剤群107例）で0.71［0.51, 0.99］、転移臓器数≧3の集団（3剤群111例、2剤群103例）で0.63［0.45, 0.90］、CRP値＞1mg/ dLの集団（3剤群95例、2剤群79例）で0.65［0.46, 0.92］、原発巣が未切除又は不完全切除の集団（3剤群91例、2剤群97例）で0.55［0.38, 0.79］であり、3剤群でOSが良好な傾向が認められた。一方、ECOG PS 0の集団（3剤群115例、2剤群113例；0.99［0.66, 1.47］）、転移臓器数≦2の集団（3剤群113例、2剤群117例；1.04［0.72, 1.50］）、CRP値≦1 mg/ dLの集団（3剤群122例、2剤群139例）；1.02［0.71, 1.46］）、原発巣が完全切除の集団（3剤群133例、2剤群123例）；1.00［0.71, 1.41］）では、2剤群と3剤群のOSは同程度であった（2019年8月15日データカットオフ）。

※12：全体集団において単変量Cox回帰モデル等により同定された、OSに影響を及ぼすと考えられる5つの患者背景因子（CRP値＞1 mg/dL、肝転移あり、CEA値＞5μg/L、CA19-9値＞35U/mL及び転移臓器数≧3）で調整した結果

18. 薬効薬理

18. 1 作用機序

ビニメチニブは、ヒトMEK1及びMEK2の活性化及びキナーゼ活性を阻害した[16]。また、ビニメチニブは、BRAF V600E変異を有するヒト悪性黒色腫由来細胞株（A375、COLO 800等）において、MAPK経路のシグナル伝達分子（ERK）のリン酸化を阻害した[17]。

18. 2 抗腫瘍効果

＊18. 2. 1 *In vitro*

ビニメチニブは、BRAF V600E変異を有するヒト悪性黒色腫由来細胞株（A375、COLO 800等）、BRAF V600D変異を有するヒト悪性黒色腫由来WM-115細胞株、BRAF V600K変異を有するヒト悪性黒色腫由来IGR-1細胞株及びBRAF V600E変異を有するヒト結腸・直腸癌由来細胞株（COLO 205、HT-29等）の増殖を抑制した[18,19]。また、ビニメチニブとBRAF阻害剤であるエンコラフェニブとの併用により、各薬剤単独と比較して、BRAF V600E変異を有するヒト悪性黒色腫由来細胞株（A375、COLO 800等）、BRAF V600K変異を有するヒト悪性黒色腫由来IGR-1細胞株、BRAF V600E変異を有するヒト結腸・直腸癌由来細胞株（COLO 205、HT-29等）に対する増殖抑制作用が増強した[20,21]。

＊18. 2. 2 *In vivo*

ビニメチニブは、A375細胞株及びCOLO 205細胞株を皮下移植したヌードマウスにおいて、腫瘍増殖抑制作用を示した[22,23]。また、ビニメチニブとエンコラフェニブとの併用により、各薬剤単独と比較してBRAF V600E変異を有するヒト悪性黒色腫患者由来HMEX1906腫瘍組織片を皮下移植したヌードマウスにおける腫瘍増殖抑制作用が増強した[24]。さらに、ビニメチニブ、エンコラフェニブ及びセツキシマブの併用により、エンコラフェニブ又はセツキシマブ単独と比較して、HT-29細胞株を皮下移植したヌードマウスにおける腫瘍増殖抑制作用が増強した[25]。

19. 有効成分に関する理化学的知見

一般名：ビニメチニブ（Binimetinib）

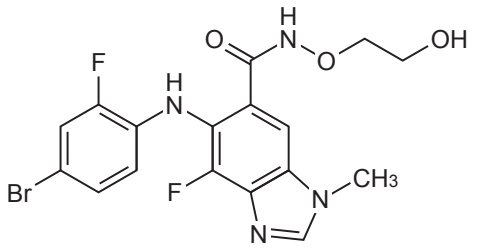
化学名：5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide

分子式：$C_{17}H_{15}BrF_2N_4O_3$

分子量：441.23

性　状：本品は白色～灰白色の粉末であり、エタノール（99.5）に溶けにくく、水にほとんど溶けない。

化学構造式：



21. 承認条件

21. 1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈*BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫〉

21. 2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

30錠［10錠（PTP）×3］
100錠［10錠（PTP）×10］

23. 主要文献

1）小野薬品工業：国内第Ⅰ相（CMEK162X1101）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.8、CTD2.7.2.2.2.2）
2）小野薬品工業：海外第Ⅰ相（CMEK162A2103）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.16）
3）小野薬品工業：*In vitro*血漿蛋白結合及び血球移行性（社内資料；2019年1月8日承認、CTD2.6.4.4）
4）小野薬品工業：*In vitro*代謝（社内資料；2019年1月8日承認、CTD2.6.4.5）
5）小野薬品工業：代謝酵素の推定（社内資料；2019年1月8日承認、CTD2.6.4.5）
6）小野薬品工業：海外マスバランス（CMEK162A2102）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.5）
7）小野薬品工業：肝機能障害患者における海外第Ⅰ相（CMEK162A2104）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.12、CTD2.7.2.2.2.2）
8）小野薬品工業：腎機能障害患者における海外第Ⅰ相（ARRAY-162-106）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.11）
9）小野薬品工業：海外第Ⅰ相（ARRAY-162-105）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.15）
10）小野薬品工業：海外第Ⅰ相（CMEK162A2105）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.17、CTD2.7.2.2.2.2）
11）小野薬品工業：CYP阻害作用（社内資料；2019年1月8日承認、CTD2.6.4.5）
12）小野薬品工業：P-gp基質検討（社内資料；2019年1月8日承認、CTD2.6.4.7）
13）小野薬品工業：BCRP基質検討（社内資料；2019年1月8日承認、CTD2.6.4.7）
14）小野薬品工業：国際共同第Ⅲ相（CMEK162B2301）試験成績（社内資料；2019年1月8日承認、CTD2.7.6.19、CTD2.7.6.20）
＊15）小野薬品工業：国際共同第Ⅲ相（ARRAY-818-302）試験成績（社内資料；2020年11月27日承認、CTD2.7.6.6）
16）小野薬品工業：MEKに対する阻害活性（社内資料；2019年1月8日承認、CTD2.6.2.2）
17）小野薬品工業：ERKのリン酸化に対する阻害作用（社内資料；2019年1月8日承認、CTD2.6.2.2）
18）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞の増殖に対する抑制作用（社内資料；2019年1月8日承認、CTD2.6.2.2）
＊19）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞の増殖に対する抑制作用（社内資料；2020年11月27日承認、CTD2.6.2.2）
20）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞の増殖に対するエンコラフェニブとの併用効果（社内資料；2019年1月8日承認、CTD2.6.2.2）
＊21）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞の増殖に対するエンコラフェニブとの併用効果（社内資料；2020年11月27日承認、CTD2.6.2.2）
22）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞移植マウスにおける抗腫瘍効果（社内資料；2019年1月8日承認、CTD2.6.2.2）
＊23）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞移植マウスにおける抗腫瘍効果（社内資料；2020年11月27日承認、CTD2.6.2.2）
24）小野薬品工業：BRAF変異ヒト悪性黒色腫細胞移植マウスにおけるエンコラフェニブとの併用効果（社内資料；2019年1月8日承認、CTD2.6.2.2）
＊25）小野薬品工業：BRAF変異ヒト結腸・直腸癌細胞移植マウスにおけるエンコラフェニブ及びセツキシマブとの併用効果（社内資料；2020年11月27日承認、CTD2.6.2.2）

24. 文献請求先及び問い合わせ先

小野薬品工業株式会社　くすり相談室
〒541-8564 大阪市中央区久太郎町1丁目8番2号
電話 0120-626-190

26. 製造販売業者等

26. 1 製造販売

小野薬品工業株式会社
大阪市中央区久太郎町1丁目8番2号

26. 2 提携

ARRAY

2022年12月改訂（第2版）
＊2020年5月改訂（第1版）

貯　　法：室温保存
有効期間：3年

日本標準商品分類番号
874291

承認番号	22600AMX01406
販売開始	2015年2月

抗悪性腫瘍剤　BRAF阻害剤
ベムラフェニブ錠
劇薬、処方箋医薬品注)

ゼルボラフ®錠240mg
ZELBORAF® Tablets

CHUGAI
Roche ロシュ グループ

注)注意－医師等の処方箋により使用すること

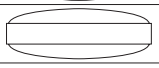
1．警告
本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2．禁忌（次の患者には投与しないこと）
本剤の成分に対し過敏症の既往歴のある患者

3．組成・性状
3.1 組成

販　売　名	ゼルボラフ錠240mg
有効成分	1錠中 ベムラフェニブ　240mg
添加剤	ヒプロメロース酢酸エステルコハク酸エステル、クロスカルメロースナトリウム、軽質無水ケイ酸、ステアリン酸マグネシウム、ヒドロキシプロピルセルロース、ポリビニルアルコール（部分けん化物）、酸化チタン、マクロゴール4000、タルク、三二酸化鉄

3.2 製剤の性状

販　売　名		ゼルボラフ錠240mg
剤形		フィルムコーティング錠
色調		帯赤白色～だいだい白色
外形	表面	
	裏面	
	側面	
長　径		約19.1mm
短　径		約9.7mm
厚　さ		約7.4mm
質　量		870mg
識別コード		VEM

4．効能又は効果
***BRAF*遺伝子変異を有する根治切除不能な悪性黒色腫**

5．効能又は効果に関連する注意
＊5.1 十分な経験を有する病理医又は検査施設における検査により、*BRAF*遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断薬等を用いること。
5.2「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で適応患者の選択を行うこと。
5.3 本剤の術後補助化学療法における有効性及び安全性は確立していない。

6．用法及び用量
通常、成人にはベムラフェニブとして1回960mgを1日2回経口投与する。

7．用法及び用量に関連する注意
7.1 副作用が発現した場合には、表1の規定を参考にして減量・休薬すること。ただし、有棘細胞癌（皮膚の扁平上皮癌）又は新たな原発性悪性黒色腫が発現した場合には、外科的切除等の適切な処置を行った上で、減量・休薬することなく治療の継続を可能とする。また、QT間隔延長が発現した場合には、表2の規定を参考にして減量・休薬すること。[8.1、8.3、9.1.1、11.1.1、11.1.2、11.1.6参照]

表1：減量・休薬の規定

NCI-CTCAE注1)によるGrade判定		治療期間中の処置
Grade 1又は忍容可能なGrade 2		減量・休薬不要
忍容不能なGrade 2又はGrade 3	初回発現	休薬 Grade 1以下又はベースラインまで軽快後、1回720mg（1日2回）で投与を再開注2)
	2回目発現	休薬 Grade 1以下又はベースラインまで軽快後、1回480mg（1日2回）で投与を再開注3)
	3回目発現	投与中止
Grade 4	初回発現	原則投与中止 治療継続が患者にとって望ましいと判断された場合には、休薬 Grade 1以下又はベースラインまで軽快後、1回480mg（1日2回）で投与を再開注3)
	2回目発現	投与中止

注1）NCI-CTCAE v4.0によりGradeを判定
注2）休薬前に1回720mgに減量されていた場合には1回480mgとする。
注3）休薬前に1回480mgに減量されていた場合には本剤の投与を中止する。

表2：QT間隔延長に基づく減量・休薬の規定

QT間隔		治療期間中の処置
QTc値が500msを超え、かつ、ベースライン値からの延長が60msを超える場合		投与中止
QTc値が500msを超え、かつ、ベースライン値からの延長が60ms以下の場合	初回発現	休薬 QTc値が500ms以下まで軽快後、1回720mg（1日2回）で投与を再開注2)
	2回目発現	休薬 QTc値が500ms以下まで軽快後、1回480mg（1日2回）で投与を再開注3)
	3回目発現	投与中止

7.2 食後に本剤を投与した場合、C_{max}及びAUCが増加するとの報告がある。食事の影響を避けるため、食事の1時間前から食後2時間までの間の服用は避けることが望ましい。[16.2.1参照]
7.3 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

8．重要な基本的注意
8.1 有棘細胞癌があらわれることがあるので、定期的に皮膚の状態を確認すること。また、皮膚の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。[7.1、11.1.1参照]
8.2 皮膚以外の部位に扁平上皮癌があらわれることがあるので、観察を十分に行うこと。[11.1.2参照]

8.3 QT間隔延長があらわれることがあるので、本剤の投与開始前には心電図検査及び電解質測定を行うこと。投与開始前にQTcのベースライン値が500msを超える場合又は補正できない電解質異常が認められる場合には投与を避けること。本剤投与期間中は定期的に心電図検査及び電解質測定を行うこと。[7.1、9.1.1、11.1.6参照]

8.4 肝不全、肝機能障害、黄疸等の肝障害又はALT、AST、ビリルビンの上昇等があらわれることがあるので、患者の状態に応じて定期的に肝機能検査を行うこと。[11.1.7参照]

8.5 急性腎障害があらわれることがあるので、投与開始前及び投与中に定期的に腎機能検査を行うこと。[11.1.8参照]

8.6 光線過敏症があらわれることがあるので、外出時には帽子や衣類等による遮光や日焼け止め効果の高いサンスクリーンの使用により、日光やUV光線の照射を避けるよう患者を指導すること。

8.7 ブドウ膜炎等の重篤な眼障害が報告されているので、定期的に眼の異常の有無を確認すること。また、眼の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 QT間隔延長のおそれ又はその既往歴のある患者

QT間隔延長が起こるおそれがある。[7.1、8.3、11.1.6参照]

9.3 肝機能障害患者

9.3.1 重度の肝機能障害のある患者

重度の肝機能障害のある患者を対象とした臨床試験は実施していない。

9.4 生殖能を有する者

妊娠可能な女性には、本剤投与中及び本剤投与終了後一定期間は適切な避妊を行うよう指導すること。[9.5参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。妊娠ラット及びウサギを用いた胚・胎児発生に関する試験において、胚・胎児への影響は認められていないが、最大投与量におけるAUCは臨床曝露量の約1.2倍（ラット）及び約0.5倍（ウサギ）であった。[9.4参照]

9.6 授乳婦

授乳しないことが望ましい。乳汁移行に関するデータはないが、ベムラフェニブは乳癌耐性蛋白（BCRP）の基質であるため、乳汁移行の可能性がある。[16.7.6参照]

9.7 小児等

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下していることが多い。

10. 相互作用

ベムラフェニブは主にCYP3A4で代謝され、CYP3A4を誘導し、CYP1A2、CYP2C9及びP-糖蛋白（P-gp）を阻害することが示されている。[16.4、16.7.6参照]

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP3A4の基質となる薬剤 ミダゾラム、アトルバスタチン、シンバスタチン等 [16.7.1参照]	これらの薬剤の血漿中濃度が低下する可能性がある。	併用薬剤の代謝が誘導され血漿中濃度が低下する可能性がある。
CYP3A4を誘導する薬剤 リファンピシン、フェニトイン、カルバマゼピン等 [16.7.2参照]	ベムラフェニブの血漿中濃度が低下し、本剤の有効性が減弱するおそれがあることから、誘導作用のない薬剤への代替を考慮すること。	ベムラフェニブの代謝が誘導され血漿中濃度が低下する可能性がある。
* CYP3A4を阻害する薬剤 イトラコナゾール、ポサコナゾール、クラリスロマイシン等 [16.7.3参照]	ベムラフェニブの血漿中濃度が上昇する可能性がある。CYP3A4阻害剤と併用する場合は、必要に応じ本剤の減量を考慮すること。	ベムラフェニブの代謝が阻害され血漿中濃度が上昇する可能性がある。
CYP1A2の基質となる薬剤 カフェイン、テオフィリン、チザニジン　等 [16.7.1、16.7.4参照]	これらの薬剤の血漿中濃度が上昇する可能性がある。	併用薬剤の代謝が阻害され血漿中濃度が上昇する可能性がある。
CYP2C9の基質となる薬剤 ワルファリン　等 [16.7.1参照]	これらの薬剤の血漿中濃度が上昇する可能性がある。	併用薬剤の代謝が阻害され血漿中濃度が上昇する可能性がある。
P-gpの基質となる薬剤 ジゴキシン　等 [16.7.5参照]	これらの薬剤の血漿中濃度が上昇する可能性がある。	本剤のP-gp阻害作用により併用薬剤の血漿中濃度が上昇する可能性がある。
QT間隔延長を引き起こすことが知られている薬剤 イミプラミン、ピモジド　等	QT間隔延長作用を増強する可能性がある。	本剤及びこれらの薬剤はいずれもQT間隔を延長させるおそれがあるため、併用により作用が増強する可能性がある。
抗不整脈薬 キニジン、プロカインアミド、ジソピラミド、ソタロール　等		
放射線照射	放射線照射の併用又は本剤投与前後の放射線照射により放射線皮膚障害、放射線性肺臓炎等の放射線照射リコール反応、放射線増感作用があらわれることがある。	放射線毒性を増強させる可能性がある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 有棘細胞癌

皮膚有棘細胞癌（18.7%）、ケラトアカントーマ（10.6%）、ボーエン病（0.6%）があらわれることがある。[7.1、8.1参照]

11.1.2 悪性腫瘍（二次発癌）

扁平上皮癌（皮膚以外）（頻度不明）、原発性悪性黒色腫（1.1%）等があらわれることがある。[7.1、8.2参照]

11.1.3 アナフィラキシー（頻度不明）、**過敏症**（0.9%）

アナフィラキシーを含む重篤な過敏症があらわれることがある。

11.1.4 皮膚粘膜眼症候群（Stevens-Johnson症候群）（0.3%）、**中毒性表皮壊死融解症（Toxic Epidermal Necrolysis；TEN）**（頻度不明）、**多形紅斑**（0.3%）、**紅皮症（剥脱性皮膚炎等）**（0.9%）

皮膚粘膜眼症候群、中毒性表皮壊死融解症等の重篤な皮膚障害があらわれることがある。

11.1.5 薬剤性過敏症症候群（頻度不明）

初期症状として発疹、発熱が認められ、更に肝機能障害、リンパ節腫脹、白血球増加、好酸球増多、異型リンパ球出現等を伴う遅発性の重篤な過敏症状があらわれることがある。本剤の投与中止後も発疹、発熱、肝機能障害等の症状が再燃あるいは遷延化することがあるので注意すること。

11.1.6 QT間隔延長（2.0%）

［7.1、8.3、9.1.1参照］

11.1.7 肝不全（頻度不明）、**肝機能障害**（2.0%）、**黄疸**（頻度不明）

肝不全、肝機能障害、黄疸等の肝障害があらわれることがある。［8.4参照］

11.1.8 急性腎障害（頻度不明）

［8.5参照］

11.2 その他の副作用

	5%以上	1～5%未満	1%未満	頻度不明
皮膚	発疹（湿疹、丘疹等）（54.0%）、光線過敏症（46.0%）、脱毛症（46.0%）、過角化（25.9%）、そう痒症（21.8%）、皮膚乾燥、紅斑、日光性角化症、脂漏性角化症、手足症候群、毛孔性角化症、皮膚病変、毛包炎	ざ瘡様皮膚炎、皮膚剥脱、ざ瘡、メラノサイト性母斑、稗粒腫、皮膚嚢腫、全身性皮疹、結節性紅斑、掌蹠角皮症、色素沈着障害、皮膚炎、皮膚肥厚、毛質異常、蕁麻疹、日光皮膚炎、毛髪成長異常、アレルギー性皮膚炎、寝汗、多汗症、皮膚腫瘤、皮膚変色	せつ、顔面腫脹、休止期脱毛、苔癬様角化症、熱傷、皮膚刺激、皮膚毒性、皮膚疼痛、脂肪織炎	
耳		回転性めまい		
眼		ブドウ膜炎、眼充血、流涙増加、眼乾燥、結膜炎、羞明、眼刺激、霧視	眼痛	網膜静脈閉塞
筋・骨格	関節痛（49.4%）、筋骨格痛、四肢痛	筋骨格硬直、関節炎、関節腫脹、背部痛、筋力低下、筋痙縮	関節滲出液、頚部痛、変形性関節症、腱痛、デュプイトラン拘縮	
血液・凝固		貧血、リンパ球減少、血小板減少、好中球減少	好酸球増加症、白血球減少	
呼吸器		呼吸困難、咽頭喉頭痛、上気道感染（鼻咽頭炎、副鼻腔炎、上気道感染等）		
消化器	悪心（26.1%）、下痢（21.3%）、嘔吐、腹痛	口内炎、逆流性食道炎、口唇炎、便秘、口内乾燥、消化不良、腹部膨満	鼓腸、口唇腫脹、腹部不快感、嚥下障害、膵炎	
肝臓	血中ビリルビン増加、Al-P上昇、ALT上昇、AST上昇	γ-GTP増加		
心・血管系	ほてり	リンパ浮腫	血管炎、動悸	
精神神経系	頭痛、味覚異常、末梢神経障害	不眠症、浮動性めまい、知覚過敏、嗜眠	傾眠、振戦	顔面神経麻痺
生殖器		乳頭痛		
代謝	食欲減退	低カリウム血症、脱水	高コレステロール血症	
その他	疲労（43.7%）、皮膚乳頭腫（21.6%）、浮腫（全身性浮腫、末梢性浮腫）、発熱、体重減少	疼痛、乾燥症、棘細胞腫、悪寒、乳頭腫、アクロコルドン、インフルエンザ様疾患、カンジダ症、胸痛、全身健康状態低下、眼瞼乳頭腫、小結節	ヘルペスウイルス感染、腫瘤、転倒、乳頭腫ウイルス感染、膿瘍	

14. 適用上の注意

14.1 薬剤交付時の注意

PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 海外市販後の自発報告において、*RAS*遺伝子変異を有する慢性骨髄単球性白血病の進行が報告されている[1]。

15.1.2 本剤とイピリムマブを併用投与した海外第Ⅰ相臨床試験において、重度の肝機能障害が高頻度に発現し、忍容性が認められなかった[2]。

15.2 非臨床試験に基づく情報

イヌ39週間毒性試験において、忍容性低下のため早期（投与10日目）に終了した900mg/kg/日の1例に限局的な骨髄壊死が報告されており、この時のAUCは臨床曝露量の約0.5倍であった。

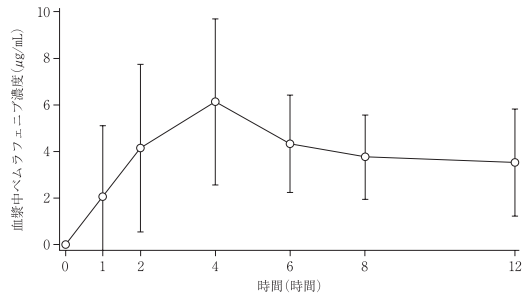
16. 薬物動態

16.1 血中濃度

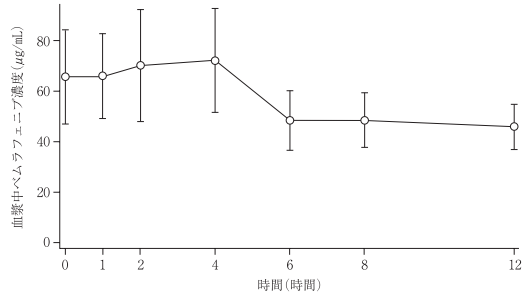
16.1.1 単回及び反復投与

悪性黒色腫患者9例を対象にベムラフェニブとして960mgを単回経口投与したときの血漿中ベムラフェニブ濃度の推移を以下の図に示した。また、引き続き15日目までベムラフェニブとして1回960mgを1日2回反復経口投与した7例の血漿中ベムラフェニブ濃度推移図を示すと共に、薬物動態パラメータを単回投与時（1日目）の結果と併せて表に示した。

単回投与時（1日目）と反復投与時（15日目）のAUC、C_{max}から算出した蓄積係数は、それぞれ20.5、16.5を示した[3]。



1日目の血漿中ベムラフェニブ濃度推移（平均値±標準偏差）



15日目の血漿中ベムラフェニブ濃度推移（平均値±標準偏差）

単回又は反復投与時のベムラフェニブの薬物動態パラメータ

		n	$AUC_{0\text{-}12}$ (μg·h/mL)	C_{max} (μg/mL)	$t_{1/2}$ (h)	T_{max} (h)
960mg/回	1日目	9	46.4 (57.8%)	6.40 (54.9%)	12.7 (18.2%)[a)]	3.88 (3.83-5.98)
	15日目	7	669 (24.2%)	73.3 (28.7%)	60.8 (82.4%)[b)]	2.12 (0.900-4.02)

平均値（CV%）

T_{max}：中央値（最小値－最大値）

a）n=6、b）n=4

悪性黒色腫患者52例を対象にベムラフェニブとして240、480、720[注)]又は960mgを単回経口投与し、その後15日目まで、1日2回反復経口投与したところ、投与15日目までに多くの症例が定常状態に達していた。単回投与時、反復投与時ともに240mg[注)]から960mgの範囲で線形性が認められた[4)]（外国人データ）。

注）承認された用法及び用量は、通常1回 960mgを1日2回経口投与である。

16.2 吸収

16.2.1 食事の影響

悪性黒色腫患者16例を対象にベムラフェニブとして960mgを単回経口投与したとき、食後（高脂肪・高カロリー食）投与では絶食時投与と比較して、C_{max}が2.5倍、AUC_{inf}が4.6倍に増加し、T_{max}の中央値は4時間から7.5時間に延長した[5)]（外国人データ）。[7.2参照]

＊16.2.2 絶対的バイオアベイラビリティ

悪性腫瘍患者4例を対象にベムラフェニブの絶対的バイオアベイラビリティを検討したところ、57.8%（幾何平均値）であった[6)]（外国人データ）。

16.3 分布

16.3.1 蛋白結合率

ベムラフェニブは、血清アルブミン及びα_1-酸性糖蛋白と結合し、蛋白結合率はいずれも99%以上であった[7)]（*in vitro*）。

16.3.2 分布容積

母集団薬物動態解析によると、悪性黒色腫患者のみかけの分布容積は、90.9L（個体間変動64.8%）であった[8)]（外国人データ）。

16.4 代謝

悪性黒色腫患者7例を対象にベムラフェニブとして1回960mgを1日2回14日間連日反復投与し、15日目に^{14}C-ベムラフェニブ960mgを単回経口投与したところ、血漿中放射能の95%がベムラフェニブ、代謝物は5%未満であった[9)]（外国人データ）。

ヒト肝ミクロソームでは、ベムラフェニブは主にCYP3A4で代謝された[10)]（*in vitro*）。[10.参照]

16.5 排泄

悪性黒色腫患者7例を対象にベムラフェニブとして1回960mgを1日2回14日間連日反復投与し、15日目に^{14}C-ベムラフェニブ960mgを単回経口投与したところ、放射能の94%が糞中に排泄され、尿中に排泄されたのは1%未満であった[9)]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害

悪性黒色腫患者458例を対象に母集団薬物動態解析を実施し、腎機能に関連するクレアチニンクリアランスで共変量探索を実施した結果、クレアチニンクリアランスは共変量として組み込まれなかった[8)]（外国人データ）。

16.6.2 肝機能障害

悪性黒色腫患者458例を対象に母集団薬物動態解析を実施し、肝機能に関連するALT、Al-P、AST、総ビリルビン、肝転移の有無で共変量探索を実施した結果、これらの変数は共変量として組み込まれなかった[8)]（外国人データ）。

16.7 薬物相互作用

16.7.1 カフェイン、デキストロメトルファン、ミダゾラム、オメプラゾール、S-ワルファリン

悪性黒色腫患者20例を対象に5種のCYP分子種（CYP1A2、CYP2D6、CYP3A4、CYP2C19、CYP2C9）の基質となるカクテル薬剤を用いて、本剤が各CYP分子種の基質となる薬剤の薬物動態に与える影響を検討した結果を表に示す[11)]（外国人データ）。[10.2参照]

CYPの各分子種の基質となる薬剤の
薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	併用、非併用時の幾何平均値の比	幾何平均値の比の90%信頼区間
カフェイン (CYP1A2)	$AUC_{0\text{-}last}$	2.56	(2.24-2.93)
	C_{max}	1.05	(0.98-1.13)
デキストロメトルファン (CYP2D6)	$AUC_{0\text{-}last}$	1.47	(1.21-1.78)
	C_{max}	1.36	(1.07-1.72)
ミダゾラム (CYP3A4)	$AUC_{0\text{-}last}$	0.61	(0.50-0.74)
	C_{max}	0.65	(0.54-0.78)
オメプラゾール (CYP2C19)	$AUC_{0\text{-}last}$	1.13	(0.92-1.37)
	C_{max}	1.17	(0.92-1.49)
S-ワルファリン (CYP2C9)	$AUC_{0\text{-}last}$	1.18	(1.12-1.24)
	C_{max}	1.00	(0.93-1.08)

（カフェインはn=19，他はn=20）

16.7.2 リファンピシン

悪性腫瘍患者23例を対象にCYP3A4を誘導するリファンピシンを用いて、CYP3A4の誘導剤がベムラフェニブの薬物動態に与える影響を検討した結果を表に示す[12)]（外国人データ）。[10.2参照]

リファンピシン併用又は非併用時のベムラフェニブの薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	併用、非併用時の幾何平均値の比	幾何平均値の比の90%信頼区間
ベムラフェニブ (CYP3A4)	$AUC_{0\text{-}last}$	0.614	(0.484-0.780)
	C_{max}	1.11	(0.908-1.36)

(n=23)

＊16.7.3 イトラコナゾール

悪性腫瘍患者8例を対象にCYP3A4を阻害するイトラコナゾールを用いて、CYP3A4の阻害剤がベムラフェニブの薬物動態に与える影響を検討した結果を表に示す[13)]（外国人データ）。[10.2参照]

イトラコナゾール併用又は非併用時のベムラフェニブの薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	併用、非併用時の幾何平均値の比	幾何平均値の比の90%信頼区間
ベムラフェニブ	$AUC_{0\text{-}tau}$	1.400	(1.210-1.610)
	C_{max}	1.400	(1.210-1.610)

(n=8)

16.7.4 チザニジン

悪性腫瘍患者16例を対象にCYP1A2の基質であるチザニジンを用いて、本剤がCYP1A2の基質となる薬剤の薬物動態に与える影響を検討した結果を表に示す[14)]（外国人データ）。[10.2参照]

チザニジンの薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	併用、非併用時の幾何平均値の比	幾何平均値の比の90%信頼区間
チザニジン (CYP1A2)	$AUC_{0\text{-}last}$	4.22	(3.37-5.28)
	C_{max}	2.15	(1.71-2.71)

(n=16)

16.7.5 ジゴキシン

悪性腫瘍患者29例を対象にP-gpの基質であるジゴキシンを用いて、本剤がP-gpの基質となる薬剤の薬物動態に与える影響を検討した結果を表に示す[15]（外国人データ）。［10.2参照］

ジゴキシンの薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	併用、非併用時の幾何平均値の比	幾何平均値の比の90%信頼区間
ジゴキシン（P-gp）	$AUC_{0\text{-last}}$	1.82	(1.63-2.02)
	C_{max}	1.47	(1.30-1.65)

(n=26)

16.7.6 その他

*In vitro*試験において、ベムラフェニブはP-gp及びBCRPの基質であること、並びにCYP2C8、P-gp、BCRP及び胆汁酸排泄ポンプ（BSEP）を阻害することが示されている[16),17)]。［9.6、10.参照］

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内第Ⅰ/Ⅱ相試験（JO28178試験）

BRAF V600変異を有する[注1)]根治切除不能な悪性黒色腫患者11例を対象とし、本剤1回960mgを1日2回空腹時（投与前2時間、投与後1時間絶食）に連日投与する第Ⅰ/Ⅱ相試験を実施した。有効性評価の対象となった8例における奏効率[注2)]は75.0%（95%信頼区間：34.9-96.8）であった[18)]。安全性評価対象例11例中11例（100%）に副作用が認められた。主な副作用は、関節痛10例（90.9%）、発疹（湿疹、丘疹等）10例（90.9%）、筋骨格痛7例（63.6%）、脱毛症7例（63.6%）、疲労6例（54.5%）等であった。

注1）コンパニオン診断薬として製造販売承認されているコバス®BRAF V600変異検出キットを用いて検査された。

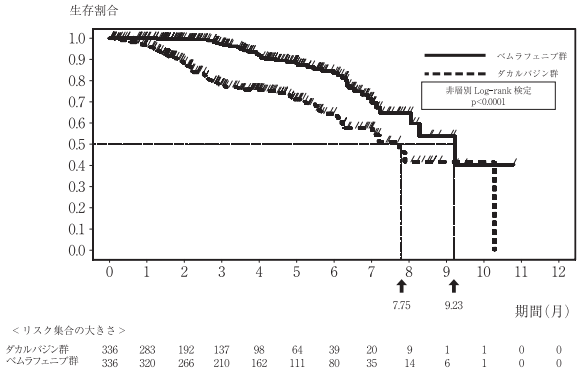
注2) RECIST（ver1.1）ガイドラインによる判定（CR+PR）

17.1.2 海外第Ⅲ相試験（NO25026試験）

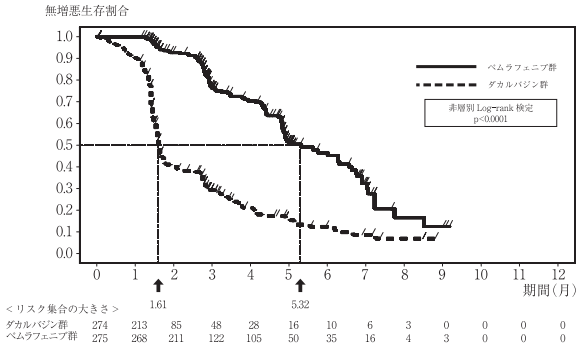
化学療法歴のないBRAF V600変異を有する[注1)]根治切除不能なⅢ期/Ⅳ期の悪性黒色腫患者675例を対象とし、ダカルバジン1000mg/m^{2}を3週毎に投与[注3)]する群と本剤1回960mgを1日2回連日投与する群を比較した第Ⅲ相非盲検ランダム化比較試験の成績（2010年12月30日データカットオフ）を以下に示す。

OS解析において、ダカルバジン投与群に対する本剤投与群のハザード比は0.37（95%信頼区間：0.26-0.55）であり、Kaplan-Meier法で推定した中央値は、ダカルバジン投与群7.75カ月（95%信頼区間：6.28-10.28）、本剤投与群9.23カ月（95%信頼区間：8.05-未到達）と、統計学的に有意なOSの延長が確認された（非層別Log-rank検定、p<0.0001）。また、PFS解析において、ダカルバジン投与群に対する本剤投与群のハザード比は0.26（95%信頼区間：0.20-0.33）であり、Kaplan-Meier法で推定した中央値はダカルバジン投与群1.61カ月（95%信頼区間：1.58-1.74）、本剤投与群5.32カ月（95%信頼区間：4.86-6.57）と、統計学的に有意なPFSの延長が確認された（非層別Log-rank検定、p<0.0001）[19)]。

注3）承認された用法・用量外である。



全生存期間（OS）のKaplan-Meier曲線
（2010年12月30日 カットオフ）



無増悪生存期間（PFS）のKaplan-Meier曲線
（2010年12月30日 カットオフ）

本剤投与群の安全性評価対象例337例中329例（97.6%）に副作用が認められた。主な副作用は、発疹（湿疹、丘疹等）178例（52.8%）、関節痛162例（48.1%）、光線過敏症157例（46.6%）、脱毛症153例（45.4%）、疲労146例（43.3%）等であった（2012年2月1日 カットオフ）。

17.3 その他

17.3.1 QT間隔に及ぼす影響

悪性黒色腫患者128例を対象に心電図の中央判定を行った結果、QTcの補正はQTcPが適切であると判断された。サイクル2及びそれ以降にスクリーニング時からのQTcの変化量は、12～15msの延長がみられ、サイクル6 Day1で15.1ms（上側95%信頼区間：17.7ms）の延長がみられた（1サイクル：21日）[20)]（外国人データ）。

18. 薬効薬理

18.1 作用機序

ベムラフェニブは、BRAF V600変異（V600E、V600D、V600R、V600K、V600G、V600M）を含む活性化変異型のBRAFキナーゼ活性を阻害することにより[21)]、BRAF活性化によるMEK及びERKのリン酸化を阻害し、BRAF V600変異を有する腫瘍の増殖を抑制すると考えられる[22)]。

18.2 抗腫瘍効果

ベムラフェニブは、*in vitro*において、BRAF V600E変異を有するヒト悪性黒色腫由来Colo829及びA375細胞株並びにBRAF V600D変異を有するヒト悪性黒色腫由来WM2664細胞株に対して増殖抑制作用を示した。また、BRAF V600E変異を有するヒト悪性黒色腫由来細胞株（LOX、Colo829及びA375）を皮下移植したヌードマウスにおいて、ベムラフェニブ投与による腫瘍増殖抑制作用が示された[22)]。

19. 有効成分に関する理化学的知見

一般的名称：ベムラフェニブ（Vemurafenib）（JAN）

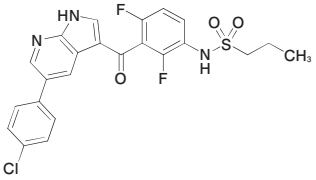
化学名：*N*-{3-[5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-carbonyl]-2,4-difluorophenyl}propane-1-sulfonamide

分子式：$C_{23}H_{18}ClF_2N_3O_3S$

分子量：489.92

性　状：白色の粉末又は塊のある粉末である。*N*,*N*-ジメチルアセトアミドに溶けやすく、アセトンに溶けにくく、エタノールに極めて溶けにくく、水にはほとんど溶けない。

構造式：



融　点：約271℃

20．取扱い上の注意

湿気を避けて保存すること（PTP包装のまま保存すること）。

21．承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22．包装

56錠（PTP8錠×7）

23．主要文献

1）Callahan MK, et al. N Engl J Med. 2012;367(24):2316-21.
2）Ribas A, et al. N Engl J Med. 2013;368(14):1365-6.
3）患者を対象とする国内臨床試験（JO28178）（2014年12月26日承認、CTD2.7.2.2.3.1）
4）Grippo JF, et al. Cancer Chemother Pharmacol. 2014;73(1):103-11.
5）社内資料：食事の影響試験（NP25396）
6）社内資料：絶対的バイオアベイラビリティ試験（GO28395試験）
7）*In vitro*血漿蛋白結合及び血球移行性（2014年12月26日承認、CTD2.7.2.2.1.1.1）
8）母集団薬物動態解析（2014年12月26日承認、CTD2.7.2.3.4）
9）Goldinger SM, et al. Pharmacol Res Perspect. 2015;3(2):e00113.
10）代謝関与酵素（2014年12月26日承認、CTD2.7.2.2.1.2.3）
11）社内資料：海外臨床薬物相互作用試験（NP22676）
12）社内資料：リファンピシンとの海外臨床薬物相互作用試験（GO28052）
13）社内資料：イトラコナゾールとの海外臨床薬物相互作用試験（GO29475）
14）社内資料：チザニジンとの海外臨床薬物相互作用試験（GO28396）
15）社内資料：ジゴキシンとの海外臨床薬物相互作用試験（GO28394）
16）トランスポーターを介した*in vitro*輸送（2014年12月26日承認、CTD2.7.2.2.1.3.3）
17）薬物代謝酵素阻害（2014年12月26日承認、CTD2.7.2.2.1.3.2）
18）国内第Ⅰ/Ⅱ相臨床試験（JO28178）（2014年12月26日承認、CTD2.7.3.2.4）
19）Chapman PB, et al. N Engl J Med. 2011;364(26):2507-16.
20）薬物動態、QT延長評価サブスタディ（NP22657）（2014年12月26日承認、CTD2.7.2.2.3.6.1）
21）変異BRAFキナーゼに対する阻害活性（2014年12月26日承認、CTD2.6.2.2.1.1）
22）Yang H, et al. Cancer Res. 2010;70(13):5518-27.

24．文献請求先及び問い合わせ先

中外製薬株式会社　メディカルインフォメーション部
〒103-8324　東京都中央区日本橋室町2-1-1
電話：0120-189706
Fax ：0120-189705
https://www.chugai-pharm.co.jp/

26．製造販売業者等

26.1 製造販売元

中外製薬株式会社
東京都中央区日本橋室町2-1-1
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ダブラフェニブメシル酸塩

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タフィンラーカプセル 75mg

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	50mg	75mg
承認番号	22800AMX00372000	22800AMX00373000
販売開始年月	2016 年 6 月	2016 年 6 月

注）注意―医師等の処方箋により使用すること

1. 警告

1.1 本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 妊婦又は妊娠している可能性のある女性［9.5 参照］

3. 組成・性状

3.1 組成

タフィンラーカプセル 50mg

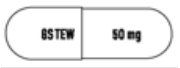
有効成分	1 カプセル中 ダブラフェニブメシル酸塩 59.25mg（ダブラフェニブとして 50mg）
添加剤	セルロース、ステアリン酸マグネシウム、無水ケイ酸 カプセル本体にヒプロメロース、三二酸化鉄、酸化チタン含有

タフィンラーカプセル 75mg

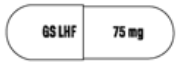
有効成分	1 カプセル中 ダブラフェニブメシル酸塩 88.88mg（ダブラフェニブとして 75mg）
添加剤	セルロース、ステアリン酸マグネシウム、無水ケイ酸 カプセル本体にヒプロメロース、三二酸化鉄、酸化チタン含有

3.2 製剤の性状

タフィンラーカプセル 50mg

外形	 
識別コード	GS TEW 50mg
性状	暗赤色不透明の 2 号硬カプセル
大きさ（約）	長径：18.0mm 短径：6.4mm 質量：0.242g

タフィンラーカプセル 75mg

外形	 
識別コード	GS LHF 75mg
性状	暗紅白色不透明の 1 号硬カプセル
大きさ（約）	長径：19.4mm 短径：6.9mm 質量：0.346g

4. 効能又は効果

○ *BRAF* 遺伝子変異を有する悪性黒色腫
○ *BRAF* 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌
○ 標準的な治療が困難な *BRAF* 遺伝子変異を有する進行・再発の固形腫瘍（結腸・直腸癌を除く）
○ *BRAF* 遺伝子変異を有する再発又は難治性の有毛細胞白血病

5. 効能又は効果に関連する注意

〈効能共通〉

5.1 十分な経験を有する病理医又は検査施設における検査により、*BRAF* 遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

〈悪性黒色腫〉

5.2 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で適応患者の選択を行うこと。［17.1.1-17.1.5 参照］

〈非小細胞肺癌〉

5.3 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で適応患者の選択を行うこと。［17.1.6 参照］

5.4 本剤の術後補助療法における有効性及び安全性は確立していない。

〈固形腫瘍〉

5.5 組織球症患者は本剤の投与対象となり得る。

5.6 臨床試験に組み入れられた患者のがん種等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施につ

いても慎重に検討し、適応患者の選択を行うこと。［17.1.7、17.1.8 参照］

5.7 本剤の手術の補助療法における有効性及び安全性は確立していない。

〈有毛細胞白血病〉

5.8 臨床試験に組み入れられた患者の前治療歴等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.7 参照］

6. 用法及び用量

〈悪性黒色腫〉

通常、成人にはダブラフェニブとして1回150mgを1日2回、空腹時に経口投与する。ただし、術後補助療法の場合には、トラメチニブと併用し、投与期間は12ヵ月間までとする。なお、患者の状態により適宜減量する。

〈非小細胞肺癌、有毛細胞白血病〉

トラメチニブとの併用において、通常、成人にはダブラフェニブとして1回150mgを1日2回、空腹時に経口投与する。なお、患者の状態により適宜減量する。

〈固形腫瘍〉

トラメチニブとの併用において、通常、ダブラフェニブとして以下の用量を1日2回、空腹時に経口投与する。なお、患者の状態により適宜減量する。

・成人には、1回150mg

・小児には、体重に合わせて次の用量

体重	26kg以上 38kg未満	38kg以上 43kg未満	43kg以上 51kg未満	51kg以上
1回 投与量	75mg	100mg	125mg	150mg

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 トラメチニブ以外の抗悪性腫瘍剤との併用における有効性及び安全性は確立していない。

7.2 食後に本剤を投与した場合、Cmax及びAUCが低下するとの報告がある。食事の影響を避けるため、食事の1時間前から食後2時間までの間の服用は避けること。［16.2.1 参照］

7.3 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。ただし、有棘細胞癌（皮膚の扁平上皮癌）又は新たな原発性悪性黒色腫が発現した場合には、外科的切除等の適切な処置を行った上で、休薬、減量することなく治療を継続することができる。

休薬、減量及び中止基準

NCI-CTCAE 注1) による Grade 判定	処置
忍容不能な Grade 2 又は Grade 3	休薬 Grade 1以下まで軽快後、1段階減量して投与を再開
Grade 4	原則投与中止 治療継続が患者にとって望ましいと判断された場合には、Grade 1以下まで軽快後、1段階減量して投与を再開

注1）NCI-CTCAE v4.0により Grade を判定

用量調節の目安（成人）

用量調節段階注2)	1回投与量（1日2回）
通常投与量	150mg
1段階減量	100mg
2段階減量	75mg
3段階減量	50mg
4段階減量	投与中止

注2）適切な処置により副作用が管理できた場合には、減量時と逆の段階を経て増量可

用量調節の目安（小児）

用量調節段階注2)	1回投与量（1日2回）			
通常投与量	75mg	100mg	125mg	150mg
1段階減量	50mg	75mg	100mg	100mg
2段階減量	投与中止	50mg	75mg	75mg
3段階減量	―	投与中止	50mg	50mg
4段階減量	―	―	投与中止	投与中止

〈固形腫瘍〉

7.4 26kg未満の小児患者における有効性及び安全性は確立していない。

8. 重要な基本的注意

8.1 発熱が高頻度に認められ、重度の脱水、低血圧を伴う例も報告されているので、患者の状態を十分に観察し、異常が認められた場合には減量、休薬や解熱剤の投与など適切な処置を行うこと。

8.2 有棘細胞癌（皮膚の扁平上皮癌）、新たな原発性悪性黒色腫があらわれることがあるので、定期的に皮膚の状態を確認すること。また、皮膚の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。［11.1.1 参照］

8.3 皮膚以外の部位に悪性腫瘍があらわれることがあるので、観察を十分に行い、異常が認められた場合には、適切な処置を行うこと。［11.1.2 参照］

8.4 心障害があらわれることがあるので、本剤投与開始前には、患者の心機能を確認すること。本剤投与中は適宜心機能検査（心エコー等）を行い、患者の状態（左室駆出率（LVEF）の変動を含む）を十分に観察すること。［9.1.1、11.1.3 参照］

8.5 ぶどう膜炎（虹彩炎を含む）等の重篤な眼障害が報告されているので、定期的に眼の異常の有無を確認すること。また、眼の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。

8.6 肝機能障害があらわれることがあるので、本剤投与中は定期的に肝機能検査を行うこと。［9.3.1、11.1.4 参照］

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 心疾患又はその既往歴のある患者

症状が悪化するおそれがある。［8.4、11.1.3 参照］

9.3 肝機能障害患者

9.3.1 中等度以上の肝機能障害患者

本剤の曝露量が増加する可能性がある。［8.6、11.1.4 参照］

9.4 生殖能を有する者

9.4.1 妊娠可能な女性には、本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。［9.5 参照］

9.4.2 パートナーが妊娠する可能性のある男性には、本剤投与中及び投与終了後一定期間は避妊を行うよう指導するこ

と。マウス、ラット及びイヌでは雄性生殖器に悪影響が認められている。[15.2.2 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には投与しないこと。動物実験では、ラットにおいて母動物の体重増加量・胎児体重の低値、骨化遅延が 20mg/kg/日（臨床曝露量（AUC）の約 0.3 倍）以上の群でみられ、黄体数・着床数の低値、着床前・後死亡率の高値、生存胎児数の低値、心室中隔欠損及び胸腺分離が 300mg/kg/日（臨床曝露量（AUC）の約 1.9 倍）群で認められている。[2.2、9.4.1 参照]

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒトの乳汁中への移行は不明である。

9.7 小児等

〈悪性黒色腫、非小細胞肺癌、有毛細胞白血病〉
小児等を対象とした臨床試験は実施していない。
〈固形腫瘍〉
低出生体重児、新生児を対象とした臨床試験は実施していない。また、6 歳未満の患者に対する本剤の用法及び用量について、十分な検討は行われていない。

9.8 高齢者

患者の状態を観察しながら注意して投与すること。一般に生理機能が低下している。

10. 相互作用

本剤は CYP2C8 及び 3A4 の基質となる。また、本剤は CYP2C9 及び 3A4 を誘導することが示されている。[16.7.1 参照]

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP3A 阻害剤 ケトコナゾール（経口剤は国内未承認） クラリスロマイシン リトナビル等 [16.7.2 参照]	本剤の血中濃度が上昇するおそれがあるので、CYP3A 阻害作用のない薬剤への代替を考慮すること。やむを得ず CYP3A 阻害剤と本剤を併用投与する場合には、患者の状態を慎重に観察し、副作用の発現・増強に注意すること。	これらの薬剤が CYP3A を阻害することにより、本剤の代謝が阻害され、血中濃度が上昇するおそれがある。
CYP2C8 阻害剤 ゲムフィブロジル（国内未承認）等 [16.7.2 参照]	本剤の血中濃度が上昇するおそれがあるので、CYP2C8 阻害作用のない薬剤への代替を考慮すること。やむを得ず CYP2C8 阻害剤と本剤を併用投与する場合には、患者の状態を慎重に観察し、副作用の発現・増強に注意すること。	これらの薬剤が CYP2C8 を阻害することにより、本剤の代謝が阻害され、血中濃度が上昇するおそれがある。
CYP3A 及び CYP2C8 誘導剤 リファンピシン等 [16.7.2 参照]	本剤の血中濃度が低下するおそれがあるので、CYP3A 及び CYP2C8 誘導作用のない薬剤への代替を考慮すること。	これらの薬剤が CYP3A 及び CYP2C8 を誘導することにより、本剤の代謝が促進され、血中濃度が低下する可能性がある。
CYP3A 基質 ミダゾラム 経口避妊薬（ノルエチステロン・エチニルエストラジオール等） デキサメタゾン等 [16.7.2 参照]	CYP3A により代謝される薬剤と併用する場合は、これらの薬剤の血中濃度が低下し、有効性が減弱する可能性がある。	本剤が CYP3A を誘導することにより、これらの薬剤の血中濃度が低下する可能性がある。
CYP2C9 基質 ワルファリン等 [16.7.2 参照]	CYP2C9 により代謝される薬剤と併用する場合は、これらの薬剤の血中濃度が低下し、有効性が減弱する可能性がある。	本剤が CYP2C9 を誘導することにより、これらの薬剤の血中濃度が低下する可能性がある。
OATP1B1 及び OATP1B3 基質 HMG-CoA 還元酵素阻害剤（ロスバスタチン）等 [16.7.2 参照]	OATP1B1 及び OATP1B3 の基質となる薬剤と併用する場合は、これらの薬剤の血中濃度が上昇するおそれがある。	本剤が OATP1B1 及び OATP1B3 を阻害することにより、これらの薬剤の血中濃度が上昇するおそれがある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用[注 1)、注 2)、注 3)]

11.1.1 有棘細胞癌

皮膚有棘細胞癌（0.5%、1.6%）、ケラトアカントーマ（0.2%、3.7%）、ボーエン病（0.5%、頻度不明）があらわれることがある。臨床試験において、有毛細胞白血病患者では他がん種の患者よりも有棘細胞癌の発現頻度に高い傾向が認められた（皮膚有棘細胞癌（5.5%、頻度不明）、扁平上皮癌（5.5%、頻度不明））[注 4)]。[8.2 参照]

11.1.2 悪性腫瘍（二次発癌）

原発性悪性黒色腫（0.1%、1.1%）等の悪性腫瘍（二次発癌）があらわれることがある。臨床試験において、有毛細胞白血病患者では他がん種の患者よりも悪性腫瘍（二次発癌）の発現頻度に高い傾向が認められた（基底細胞癌（12.7%、頻度不明））[注 4)]。[8.3 参照]

11.1.3 心障害

心不全（0.1%、0.5%）、左室機能不全（0.2%、1.4%）、駆出率減少（5.9%、4.7%）等の重篤な心障害があらわれることがある。[8.4、9.1.1 参照]

11.1.4 肝機能障害

ALT（11.3%、1.6%）、AST（11.5%、0.5%）等の上昇を伴う肝機能障害があらわれることがある。[8.6、9.3.1 参照]

11.1.5 静脈血栓塞栓症（0.3%、頻度不明）

11.1.6 脳血管障害

脳出血（0.1%、頻度不明）、脳血管発作（いずれも頻度不明）等の脳血管障害があらわれることがある。

注 1）重大な副作用の発現頻度は、トラメチニブとの併用時、本剤単独投与時の順に記載した。

11.2 その他の副作用

トラメチニブとの併用時[注 2)]

	10%以上	1%～10%未満	1%未満	頻度不明
感染症	－	毛包炎、膿疱性皮疹	蜂巣炎、尿路感染、上咽頭炎、爪囲炎	－
血　液	－	好中球減少症、貧血、血小板減少症、白血球減少症	－	－
代　謝	－	食欲減退、脱水、低ナトリウム血症、低リン血症、高血糖	－	－
神経系	頭痛	浮動性めまい	－	－
眼	－	霧視、ぶどう膜炎、視力障害	網膜色素上皮剥離、網脈絡膜症、網膜剥離、眼窩周囲浮腫	－
心・血管	－	高血圧、低血圧、出血（鼻出血、歯肉出血等）	リンパ浮腫、徐脈、QT/QTc 間隔延長	心拍数減少
呼吸器	－	咳嗽、呼吸困難	肺臓炎、間質性肺炎	－
消化器	悪心、下痢、嘔吐	便秘、腹痛、口内乾燥、口内炎	膵炎	－
肝胆道系	－	ALP 増加、γ－GTP 増加	－	－
皮　膚	発疹、皮膚乾燥	そう痒症、ざ瘡様皮膚炎、紅斑、日光角化症、寝汗、過角化、脱毛症、手掌・足底発赤知覚不全症候群、皮膚病変、多汗症、脂肪織炎、皮膚亀裂、光線過敏症	－	－
筋骨格系	関節痛、筋肉痛	四肢痛、筋痙縮、血中 CK 増加	横紋筋融解症	－
腎	－	－	腎炎、腎不全、尿細管間質性腎炎、急性腎障害	－
全　身	発熱（50.1%）、疲労、悪寒、無力症	末梢性浮腫、インフルエンザ様疾患、粘膜の炎症	顔面浮腫	－
その他	－	脂漏性角化症	乳頭腫、アクロコルドン、過敏症	－

本剤単独投与時[注 3)]

	10%以上	1%～10%未満	1%未満	頻度不明
感染症	－	鼻咽頭炎	－	－
代　謝	－	高血糖、食欲減退、低リン酸血症	－	－
神経系	頭痛	－	－	－
心・血管	－	－	－	QT/QTc 間隔延長
眼	－	－	－	ぶどう膜炎
呼吸器	－	咳嗽	－	－
消化器	－	悪心、嘔吐、下痢、便秘	膵炎	－
皮　膚	発疹、過角化（34%）、	そう痒症、皮膚乾燥、日	－	脂肪織炎

	脱毛症、手掌・足底発赤知覚不全症候群	光角化症、皮膚病変、紅斑、光線過敏症		
筋骨格系	関節痛	筋肉痛、四肢痛	－	－
腎	－	－	－	腎不全、急性腎障害、尿細管間質性腎炎
全　身	疲労、発熱、無力症	悪寒、インフルエンザ様疾患	－	－
その他	－	乳頭腫、アクロコルドン、脂漏性角化症	－	過敏症

注 2）トラメチニブとの併用時の副作用頻度は臨床試験（MEK115306 試験、MEK116513 試験、F2301 試験、E2201 試験及び X2201 試験）に基づき記載した。
注 3）本剤単独投与時の副作用頻度は海外臨床試験（BRF113683 試験）に基づき記載した。
注 4）X2201 試験の有毛細胞白血病患者（55 例）で発現した副作用頻度に基づき記載した。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 臨床試験において、RAS 遺伝子変異を有する腫瘍の発現が報告されている。

15.2 非臨床試験に基づく情報

15.2.1 変異型 RAS を伴う野生型 BRAF 細胞を BRAF 阻害剤で処理することにより、MAPK シグナル伝達の活性化が示されている[1]。

15.2.2 マウス、ラット及びイヌにおいて精巣／精巣上体に悪影響（精上皮の変性、精細管萎縮、精子数減少等）が 5mg/kg/日（臨床曝露量（AUC）の約 0.2 倍）以上の群でみられ、ラット及びイヌでは休薬後においても回復性は認められなかった。[9.4.2 参照]

15.2.3 マウス、ラット及びイヌにおいて心臓又は血管への悪影響（冠動脈の変性／壊死、出血、房室弁の肥大／出血、心房の線維血管性増殖、肝動脈の変性、血管／血管周囲炎等）が 15mg/kg/日（臨床曝露量（AUC）の約 0.5 倍）以上の群でみられた。

15.2.4 イヌにおいて気管支肺胞の炎症が 20mg/kg/日（臨床曝露量（AUC）の約 8.4 倍）以上の群でみられた。

15.2.5 *In vitro* 3T3 光毒性試験で陽性を示し、また、ヘアレスマウスを用いた *in vivo* 試験で 100mg/kg（臨床曝露量（Cmax）の約 31 倍）以上の群で光毒性反応がみられた。

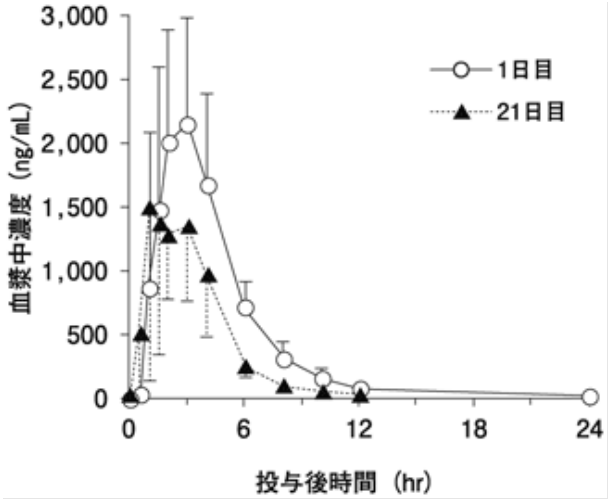
15.2.6 幼若ラットにおいて、成長・発達への影響（骨長の短縮、膣開口の早期化）が 1mg/kg/日／ 3mg/kg/日（生後 7～21 日の投与量／生後 22～35 日の投与量）（成人の臨床曝露量（AUC）の約 0.2 倍）以上の群でみられた。また、同用量群で成熟動物では認められなかった腎臓への影響（尿細管変性等）等がみられた。

16. 薬物動態

16.1 血中濃度

16.1.1 単回及び反復投与

日本人固形癌患者 12 例にダブラフェニブ 75～150mg（ヒプロメロースカプセル）を空腹時に単回経口投与した時、血漿中ダブラフェニブ濃度は投与 1.0～4.0 時間後に最大となった[2]。その後、血漿中ダブラフェニブ濃度は二相性を示して低下し、消失半減期は約 5～15 時間であった。Cmax 及び AUC_{0-12h} は 75mg 群と 100mg 群の間では投与量増加に伴い増加したが、100mg 群と 150mg 群は同程度であった。反復投与後の血漿中ダブラフェニブの AUC_{0-12h} は単回投与時と比べて約 40%減少し、ダブラフェニブ代謝の自己誘導が示唆された。血漿中ダブラフェニブ濃度は、投与開始後 21 日目までには定常状態に達すると考えられた。外国人固形癌患者 4 例のマイクロドーズ試験で、ダブラフェニブ 150mg を単回経口投与した時の、[^{14}C] ダブラフェニブ 50μg を単回静脈内投与に対する絶対的バイオアベイラビリティは 94.5%であった[3]。



日本人固形癌患者にダブラフェニブ 150mg を単回及び反復経口投与したときの血漿中ダブラフェニブ濃度推移（平均値＋標準偏差、1 日目：n=6、21 日目：n=5）

日本人固形癌患者にダブラフェニブ 75～150mg を単回及び反復経口投与したときの血漿中ダブラフェニブの薬物動態パラメータ

	投与量（mg）	例数（n）	Cmax（μg/mL）	Tmax（hr）	AUC_{0-12h}（μg・hr/mL）	$T_{1/2}$（hr）
1 日目	75	3	1.39（29.9）	4.0（3.0－4.0）	4.63（35.6）	15.2（2,140.1）
	100	3	3.81（32.2）	1.0（0.9－2.0）	11.4（42.9）	13.1（55.4）
	150	6	2.41（40.1）	2.5（1.0	9.24（29.3）	5.07（47.0）[a]

				－ 4.0)		
21 日目	75	3	1.43 (75. 5)	3.0 (1.5 － 4.0)	2.85 (41. 5)	－
	100	3	2.90 (22. 1)	1.0 (0.9 － 2.0)	6.02 (17. 3)	－
	150	5	2.08 (37. 0)	1.5 (1.0 － 3.0)	5.90 (33. 3)	－

幾何平均値（変動係数%）、Tmax は中央値（最小値-最大値）

a：n=5

16.2 吸収

16.2.1 食事の影響

外国人固形癌患者 14 例にダブラフェニブ 150mg を高脂肪・高カロリー食摂食後に単回経口投与した時、AUC 及び Cmax は絶食下に比べてそれぞれ約 31 及び 51%低下した。また、食後の Tmax（6 時間）は絶食下（2 時間）に比べて遅延した[4]。［7.2 参照］

16.3 分布

ダブラフェニブのヒト血漿蛋白結合率は 99.7%であった[5]（*in vitro*）。

16.4 代謝

16.4.1 *In vitro*

ダブラフェニブは主に CYP2C8 及び 3A4 により水酸化体に代謝され、更に CYP3A4 によりカルボン酸体に代謝された。また、カルボン酸体は非酵素的に脱メチル化された[6]。

16.4.2 *In vivo*

血漿中には、主にカルボン酸体が検出された（血中放射能の約 54%）（外国人）[7]。その他には t-ブチル基が酸化された水酸化体、脱カルボン酸化された脱メチル体が検出された[2),7)]（外国人及び日本人）。

16.5 排泄

外国人固形癌患者 4 例に［^{14}C］ダブラフェニブの 95mg（懸濁液）を単回経口投与した時、尿糞中には投与量の 93.8%が回収された（投与後 240 時間）。放射能の主排泄経路は糞中（投与量の約 71.1%）であり、尿中には 22.7%が回収された[7]。

16.6 特定の背景を有する患者

16.6.1 小児

海外第Ⅰ相試験（A2102 試験及び X2101 試験）及び国際共同第Ⅱ相試験（G2201 試験）に組み入れられた 109 例（6 歳以上 18 歳未満）のデータを用いた母集団薬物動態解析の結果、①26kg 以上 38kg 未満の患者に 75mg、②38kg 以上 43kg 未満の患者に 100mg、③43kg 以上 51kg 未満の患者に 125mg、④51kg 以上の患者に 150mg をそれぞれ 1 日 2 回反復経口投与した際の、ダブラフェニブの Cmax（μg/mL）及び $AUC_{0\text{-}12h}$（μg・hr/mL）の中央値は、①1.29 及び 4.35、②1.48 及び 5.20、③1.65 及び 6.05 並びに④1.50 及び 5.25 と推定された。

16.7 薬物相互作用

16.7.1 *In vitro*

ダブラフェニブは CYP2B6 及び 3A4 を誘導した[8]。また、ダブラフェニブは CYP2C8 及び 2C19 を阻害した（IC_{50} 値：それぞれ 8.2 及び 22.4μmol/L）[9]。ダブラフェニブは Pgp 及び BCRP の基質であった[10]。［10. 参照］

16.7.2 *In vivo*

(1) ケトコナゾール

外国人固形癌患者 16 例に CYP3A4 の阻害作用を有するケトコナゾール（経口剤は国内未承認）400mg の 1 日 1 回反復経口投与をダブラフェニブ 75mg[注)] の 1 日 2 回反復経口投与と併用したときのダブラフェニブの AUC 及び Cmax は、ダブラフェニブ単独投与に比べてそれぞれ約 71 及び 33%増加した[11]。［10.2 参照］

(2) ゲムフィブロジル

外国人固形癌患者 17 例に CYP2C8 の阻害作用を有するゲムフィブロジル（国内未承認）600mg の 1 日 2 回反復経口投与をダブラフェニブ 75mg[注)] の 1 日 2 回反復経口投与と併用したとき、ダブラフェニブ単独投与に比べてダブラフェニブの AUC は約 47%増加したものの、Cmax は変化しなかった[12]。［10.2 参照］

(3) ワルファリン

外国人固形癌患者 14 例にダブラフェニブ 150mg の 1 日 2 回反復経口投与とワルファリン（S 体：CYP2C9 の基質、R 体：CYP3A4 及び CYP1A2 の基質）15mg 単回経口投与を併用したときのワルファリンの AUC は、ワルファリン単独投与に比べて、S 体で約 37%、R 体で約 33%減少した。また、ワルファリンの Cmax はワルファリン単独投与に比べて、S 体で約 18%、R 体で約 19%増加した[13]。［10.2 参照］

(4) ミダゾラム

外国人固形癌患者 12 例にダブラフェニブ 150mg の 1 日 2 回反復経口投与とミダゾラム（CYP3A の基質）3mg の単回経口投与を併用したときのミダゾラムの AUC 及び Cmax は、ミダゾラム単独投与に比べてそれぞれ約 74 及び 61%減少した[14]。［10.2 参照］

(5) リファンピシン

外国人固形癌患者 17 例に CYP3A 及び CYP2C8 の誘導作用を有するリファンピシン 600mg の 1 日 1 回反復経口投与をダブラフェニブ 150mg の 1 日 2 回反復投与と併用したとき、ダブラフェニブ単独投与に比べて、ダブラフェニブの Cmax は 27%、AUC は 34%減少した[15]。［10.2 参照］

(6) ロスバスタチン

外国人がん患者 16 例にロスバスタチン（OATP1B1 及び OATP1B3 の基質）10mg の単回経口投与をダブラフェニブ 150mg の 1 日 2 回経口投与と併用したとき、ダブラフェニブ非併用投与に比べて、ロスバスタチンの Cmax は 94%、AUC は 22%増加した。また、ダブラフェニブ 150mg を 1 日 2 回 14 日間反復投与した後にロスバスタチン 10mg を単回経口投与したとき、ダブラフェニブ非併用投与に比べて、ロスバスタチンの Cmax は 156%増加、AUC は 7%増加した[16]。［10.2 参照］

(7) その他の薬剤

トラメチニブ

外国人固形癌患者 17 例にトラメチニブ 2mg の 1 日 1 回反復経口投与とダブラフェニブ 150mg の 1 日 2 回反復経口投与を併用した時、血漿中ダブラフェニブの Cmax 及び AUC は、ダブラフェニブ単独投与時に比べて、それぞれ約 16 及び 23%増加した[17]。

ラベプラゾール

外国人固形癌患者 17 例にラベプラゾール（プロトンポンプ阻害剤）40mg の 1 日 1 回反復経口投与をダブラフェニ

ブ 150mg の 1 日 2 回反復経口投与と併用したとき、ダブラフェニブ単独投与に比べてダブラフェニブの AUC は 3%増加し、Cmax は 12%減少した[15]。
注）本剤の承認用法・用量は、ダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時経口投与である。

17. 臨床成績

17.1 有効性及び安全性に関する試験

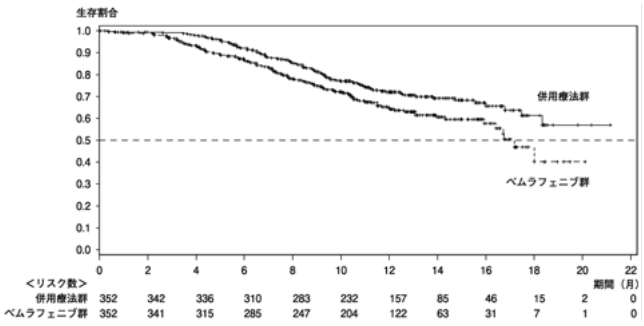
〈根治切除不能な悪性黒色腫〉

17.1.1 国内第Ⅰ/Ⅱ相臨床試験（MEK116885 試験）

BRAF V600E/K 変異を有する①進行固形癌患者（第Ⅰ相パート）及び②根治切除不能な悪性黒色腫患者（第Ⅱ相パート）（症例数：①6 例及び②6 例）を対象にダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）とトラメチニブ（2mg を 1 日 1 回連日投与）を併用する第Ⅰ/Ⅱ相非盲検非対照試験を実施した。第Ⅱ相パートにおける奏効率[注1)] は 83%（5/6 例）であった。
副作用発現頻度は、100%（12/12 例）であった。主な副作用は、発熱 66.7%（8/12 例）、AST 増加及び末梢性浮腫各 50.0%（6/12 例）であった[18]。［5.2 参照］
注 1）RECIST（ver 1.1）ガイドラインによる治験責任医師に基づく判定（CR+PR）

17.1.2 海外第Ⅲ相臨床試験（MEK116513 試験、COMBI-v）

BRAF V600E/K 変異を有する根治切除不能な悪性黒色腫患者 704 例を対象に、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）とトラメチニブ（2mg を 1 日 1 回連日投与）を併用する群（併用療法群 352 例）とベムラフェニブ（1 回 960mg を 1 日 2 回連日投与）を投与する群（ベムラフェニブ群 352 例）と比較した第Ⅲ相非盲検無作為化比較試験を実施した。全生存期間（OS）の中間解析において、ベムラフェニブ群と比較して併用療法群において統計学的に有意な延長が認められた［Kaplan-Meier 法で推定した中央値：併用療法群未到達、ベムラフェニブ群 17.2 ヵ月、ハザード比 0.69（95%信頼区間：0.53-0.89）、層別 log-rank 検定 p=0.005］。



全生存期間（OS）の Kaplan-Meier 曲線
（MEK116513 試験 ITT 集団、2014 年 4 月 17 日カットオフ）

ダブラフェニブとトラメチニブ併用療法群における副作用発現頻度は、91%（320/350 例）であった。主な副作用は、発熱 47%（163/350 例）、悪寒 28%（98/350 例）及び悪心 23%（81/350 例）であった[19]。［5.2 参照］

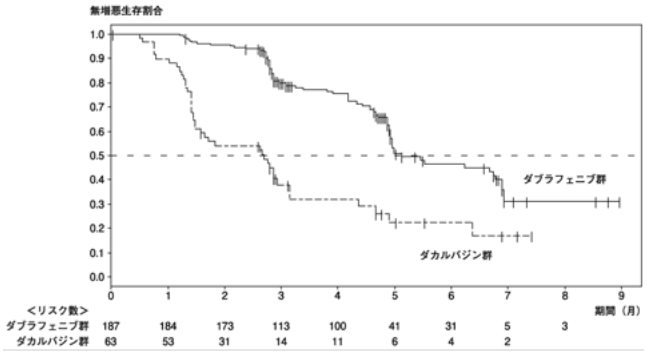
17.1.3 海外第Ⅲ相臨床試験（MEK115306 試験、COMBI-d）

BRAF V600E/K 変異を有する根治切除不能な悪性黒色腫患者 423 例を対象に、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）とトラメチニブ（2mg を 1 日 1 回連日投与）を併用する群（併用療法群 211 例）と、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）を投与する群（単剤療法群 212 例）を比較した第Ⅲ相二重盲検無作為化比較試験を実施した。無増悪生存期間（PFS）の解析において、単剤療法群と比較して併用療法群において統計学的に有意な延長が認められた［Kaplan-Meier 法で推定した中央値：併用療法群 9.3 ヵ月、単剤療法群 8.8 ヵ月、ハザード比 0.75（95%信頼区間：0.57-0.99）、層別 log-rank 検定 p=0.035］[20]。なお、OS の最終解析において、Kaplan-Meier 法で推定した中央値は併用療法群で 25.1 ヵ月、単剤療法群で 18.7 ヵ月であった［ハザード比 0.71（95%信頼区間：0.55-0.92）］。

ダブラフェニブとトラメチニブ併用療法群における副作用発現頻度は、併用療法群では、86%（179/209 例）であった。主な副作用は、発熱 47%（98/209 例）、悪寒 27%（57/209 例）及び疲労 25%（52/209 例）であった。単剤療法群では、88%（186/211 例）であった。主な副作用は、過角化 30%（63/211 例）、疲労 27%（56/211 例）及び脱毛症 25%（52/211 例）であった。［5.2 参照］

17.1.4 海外第Ⅲ相臨床試験（BRF113683 試験、BREAK-3）

BRAF V600E 変異を有する根治切除不能な悪性黒色腫患者 250 例を対象に、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）を投与する群（187 例）とダカルバジン 1,000mg/m^2（体表面積）を 3 週毎に静脈内投与する群（63 例）を比較した第Ⅲ相非盲検無作為化比較試験を実施した。PFS の解析において、ダカルバジン群と比較してダブラフェニブ投与群における統計学的に有意な延長が認められた［Kaplan-Meier 法で推定した中央値：ダブラフェニブ投与群 5.1 ヵ月、ダカルバジン群 2.7 ヵ月、ハザード比 0.30（95%信頼区間：0.18-0.51）、層別 log-rank 検定 p＜0.0001］。



無増悪生存期間（PFS）の Kaplan-Meier 曲線
（BRF113683 試験 ITT 集団、2011 年 12 月 19 日カットオフ）

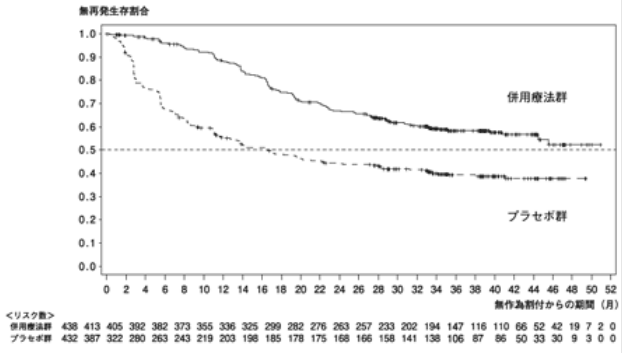
ダブラフェニブ投与群における副作用発現頻度は、88%（164/187 例）であった。主な副作用は、過角化 34%（63/187 例）、皮膚乳頭腫 21%（40/187 例）、脱毛症 20%（37/187 例）であった[21]。［5.2 参照］

〈悪性黒色腫の術後補助療法〉

17.1.5 国際共同第Ⅲ相臨床試験（F2301 試験、COMBI-AD）

BRAF V600E/K 変異を有する再発ハイリスク（American Joint Committee on Cancer（AJCC）Melanoma of the Skin Staging version 7 に基づく病期Ⅲa：リンパ節転移 1mm 超、Ⅲb、Ⅲc）の悪性黒色腫の術後患者 870 例（日本人患者 5 例を含む）を対象に、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）とトラメチニブ（2mg を 1 日 1 回連日投与）を併用する群（併用療法群 438 例）とプラセボ群（432 例）を比較した第Ⅲ相二重盲検無作為化比較試験を実施した。併用療法もしくはプラセボの投与期間

は 12 ヵ月間とした。無再発生存期間（RFS）の解析において、プラセボ群と比較して併用療法群において統計学的に有意な延長が認められた［Kaplan-Meier 法で推定した RFS の中央値：併用療法群未到達、プラセボ群 16.6 ヵ月、ハザード比 0.47（95%信頼区間：0.39-0.58）、層別 log-rank 検定 $p=1.53\times10^{-14}$］。



無再発生存期間（RFS）の Kaplan-Meier 曲線
（2017 年 6 月 30 日カットオフ）

ダブラフェニブとトラメチニブ併用療法群における副作用発現頻度は、91.5%（398/435 例（日本人患者 3 例を含む））であった。主な副作用は、発熱 56.1%（244/435 例）、疲労 39.1%（170/435 例）、悪寒 35.6%（155/435 例）であった[22]。［5.2 参照］

〈非小細胞肺癌〉

17.1.6 国際共同第Ⅱ相臨床試験（E2201 試験）

BRAF V600E 変異を有する切除不能な進行・再発の非小細胞肺癌患者を対象に、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）とトラメチニブ（2mg を 1 日 1 回連日投与）の併用投与（①白金系抗悪性腫瘍剤を含む化学療法歴のある患者 57 例（日本人患者 1 例を含む）、②化学療法歴のない患者 36 例）を検討する第Ⅱ相非盲検非対照試験を実施した。奏効率[注1)]（%）はそれぞれ①63.2（95%信頼区間：49.3-75.6）及び②61.1（95%信頼区間：43.5-76.9）であった。

ダブラフェニブとトラメチニブ併用療法群における副作用発現頻度は、89.2%（83/93 例（日本人患者 1 例を含む））であった。主な副作用は、発熱 49.5%（46/93 例）、悪心 38.7%（36/93 例）、嘔吐及び皮膚乾燥 26.9%（25/93 例）であった[23]。［5.3 参照］

〈固形腫瘍、有毛細胞白血病〉

17.1.7 国際共同第Ⅱ相臨床試験（X2201 試験、ROAR）

標準的な治療選択肢のない BRAF V600E 変異を有する固形腫瘍患者、BRAF V600E 変異を有する再発又は難治性の有毛細胞白血病患者[注2)]等（18 歳以上）を対象に、ダブラフェニブ（1 回 150mg を 1 日 2 回連日投与）とトラメチニブ（2mg を 1 日 1 回連日投与）の併用投与を検討する第Ⅱ相非盲検非対照試験を実施した。奏効率は、表のとおりであった。

がん種	例数（日本人患者数）	奏効率（%）（95%信頼区間）
甲状腺未分化癌[注1)]	36（2）	56（38.1-72.1）
胆道癌[注1)]	43（2）	53（37.7-68.8）
消化管間質腫瘍[注1)]	1（0）	0
WHO grade 1 又は 2 の神経膠腫（LGG）[注3)]	13（2）	69（38.6-90.9）
WHO grade 3 又は 4 の神経膠腫（HGG）[注4)]	45（1）	33（20.0-49.0）
小腸癌[注1)]	3（0）	67（9.4-99.2）
有毛細胞白血病[注5)]	55（0）	89（77.8-95.9）

ダブラフェニブとトラメチニブ併用療法群における副作用発現頻度は、88.8%（174/196 例（日本人患者 7 例を含む））であった。主な副作用は、発熱 41.8%（82/196 例）、疲労 27.0%（53/196 例）、悪寒 26.0%（51/196 例）であった[24]。［5.6、5.8 参照］

注 2）プリンアナログによる一次治療に不応若しくは当該治療の 1 年以内に再発した、又は 2 つ以上の治療後に増悪した有毛細胞白血病患者が対象とされた。

注 3）RANO LGG（2011）基準による治験責任医師に基づく判定（CR+PR+MR）

注 4）RANO HGG（2010）基準による治験責任医師に基づく判定（CR+PR）

注 5）NCCN のガイドライン、Consensus Resolution Criteria、及び過去の臨床試験の定義から改変した基準による治験責任医師に基づく判定（微小残存病変を伴う又は伴わない CR+PR）

17.1.8 海外第Ⅰ/Ⅱ相試験（小児 X2101 試験、パート D）

BRAF V600 変異を有する LGG 及びランゲルハンス細胞組織球症（LCH）患者（生後 1 ヵ月以上 18 歳未満）を対象に、ダブラフェニブ（12 歳未満：2.625mg/kg、12 歳以上：2.25mg/kg を 1 日 2 回連日投与）[注6)]とトラメチニブ（6 歳未満：0.032mg/kg、6 歳以上：0.025mg/kg を 1 日 1 回連日投与）の併用投与（①LGG：20 例、②LCH：10 例）を検討する第Ⅰ/Ⅱ相非盲検非対照試験を実施した。奏効率[注7)]（%）はそれぞれ①25.0（95%信頼区間：8.7-49.1）及び②60.0（95%信頼区間：26.2-87.8）であった[25]。

ダブラフェニブとトラメチニブ併用療法群における副作用発現頻度は、100%であった。主な副作用は発熱 53.3%（16/30 例）、疲労 36.7%（11/30 例）、皮膚乾燥 36.7%（11/30 例）であった。［5.6 参照］

注 6）小児に対する本剤の承認用法・用量は、体重 26kg 以上 38kg 未満の患者は 75mg、38kg 以上 43kg 未満の患者は 100mg、43kg 以上 51kg 未満の患者は 125mg、51kg 以上の患者は 150mg を 1 回投与量とし、1 日 2 回経口投与である。

注 7）①は RANO LGG（2011）基準による独立画像判定に基づく判定（CR＋PR）、②は Histiocyte Society Evaluations and Treatment Guidelines（Apr. 2009）（Minkov et al. 2009）による治験責任医師に基づく判定（CR＋Regressive disease）。

18. 薬効薬理

18.1 作用機序

ダブラフェニブは、BRAF 変異型（V600E、V600K 及び V600D）のキナーゼ活性を阻害した[26]。また、ダブラフェニブは、A375P F11 細胞株を移植したマウスの腫瘍組織において、RAF シグナル経路下流の ERK のリン酸化を阻害した[27]。

18.2 抗腫瘍効果

18.2.1 *In vitro*

(1) ダブラフェニブは、BRAF V600E 変異型を発現するヒト悪性黒色腫由来細胞株（UACC-257、SK-MEL-1、COLO-829 等）、ヒト非小細胞肺癌由来 MV522 細胞株及びヒト甲状腺未分化癌由来細胞株（8505C 及び 8305C）、BRAF V600K 変異型を発現するヒト悪性黒色腫由来細胞株（WW165、YUMAC、YULAC 及び YUSIT1）並びに BRAF V600D 変異型を発現するヒト悪性黒色腫由来 WM-115 細胞株の増殖を抑制した[28-30]。

(2) ダブラフェニブを、MEK1 及び MEK2 阻害薬であるトラメチニブと併用することにより、UACC-257、SK-MEL-1、COLO-829、MV522、8505C、8305C 細胞株等に対する増殖抑制作用は各薬剤単独処理と比較して増強した[28-30]。

18.2.2 *In vivo*

ダブラフェニブは、BRAF V600E 変異型を発現するヒト悪性黒色腫由来 A375P F11 細胞株を皮下移植したマウスにおいて、腫瘍増殖を抑制した[31]。また、ダブラフェニブとトラメチニブを併用投与することにより、各薬剤単独投与と比較して腫瘍増殖抑制作用が増強した[27]。

19. 有効成分に関する理化学的知見

一般的名称

ダブラフェニブメシル酸塩（Dabrafenib Mesilate）

化学名

N-｛3-［5-（2-Aminopyrimidin-4-yl）-2-（1,1-dimethylethyl）-1,3-thiazol-4-yl］-2-fluorophenyl｝-2,6-difluorobenzenesulfonamide monomethanesulfonate

分子式

$C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$

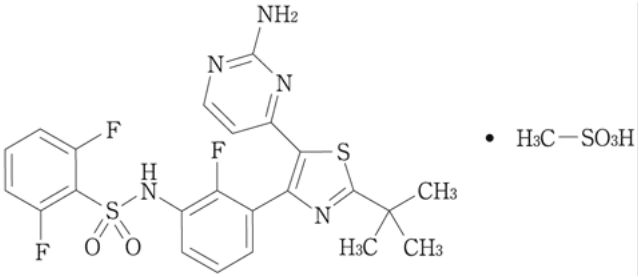
分子量

615.67

性状

白色～淡黄白色の粉末である。

化学構造式



21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

〈タフィンラーカプセル 50mg〉

28 カプセル［プラスチックボトル、乾燥剤入り］

〈タフィンラーカプセル 75mg〉

28 カプセル［プラスチックボトル、乾燥剤入り］

23. 主要文献

1) Hatzivassiliou,G.et al.：Nature. 2010；464（7287）:431-435 ［20160200］

2) 社内資料：国内第Ⅰ相試験におけるダブラフェニブの薬物動態（2016 年 3 月 28 日承認、CTD2.7.6 BRF116056 試験） ［20160201］

3) Denton,C.L.et al.：J.Clin.Pharmacol. 2013;53（9）:955-961 ［20160202］

4) Ouellet,D.et al.：J.Pharm.Sci.2013;102（9）:3100-3109 ［20160203］

5) 社内資料：血漿蛋白結合（2016 年 3 月 28 日承認、CTD2.7.2.2.1.1.1.） ［20160204］

6) 社内資料：*In vitro* 代謝（2016 年 3 月 28 日承認、CTD2.6.4.5.5.） ［20160205］

7) Bershas,D.A.et al.：Drug Metab.Dispos. 2013;41（12）:2215-2224 ［20160206］

8) 社内資料：CYP に対する *in vitro* 誘導作用（2016 年 3 月 28 日承認、CTD2.6.4.5.7.1.） ［20160207］

9) 社内資料：CYP に対する *in vitro* 阻害作用（2016 年 3 月 28 日承認、CTD2.6.4.5.7.2.2.） ［20160208］

10) 社内資料：トランスポーターによる *in vitro* 輸送（2016 年 3 月 28 日承認、CTD2.6.4.4.5.） ［20160209］

11) 社内資料：ケトコナゾールとの薬物相互作用（2016 年 3 月 28 日承認、CTD2.7.2.2.1.1.4.）［20160211］

12) 社内資料：ゲムフィブロジルとの薬物相互作用（2016 年 3 月 28 日承認、CTD2.7.2.2.1.1.4.） ［20160212］

13) 社内資料：ワルファリンとの薬物相互作用（2016 年 3 月 28 日承認、CTD2.7.2.2.1.1.4.） ［20160213］

14) 社内資料：ミダゾラムとの薬物相互作用（2016 年 3 月 28 日承認、CTD2.7.2.2.1.1.4.1.） ［20160214］

15) 社内資料：リファンピシン又はラベプラゾールとの薬物相互作用（2018 年 3 月 23 日承認、CTD2.7.2.2.1.1.） ［20170557］

16) 社内資料：ロスバスタチンとの薬物相互作用（2018 年 3 月 23 日承認、CTD2.7.2.2.1.2.） ［20170558］

17) 社内資料：ダブラフェニブとトラメチニブの薬物相互作用（2016 年 3 月 28 日承認、CTD2.7.2.2.1.3.） ［20160210］

18) 社内資料：国内第Ⅰ/Ⅱ相臨床試験（MEK116885 試験）（2016 年 3 月 28 日承認、CTD2.7.6 MEK116885 試験） ［20160215］

19) 社内資料：海外第Ⅲ相臨床試験（MEK116513 試験、COMBI-v）（2016 年 3 月 28 日承認、CTD2.7.6 MEK116513 試験（COMBI-v 試験)） ［20160216］

20) 社内資料：海外第Ⅲ相臨床試験（MEK115306 試験、COMBI-d）（2016 年 3 月 28 日承認、CTD2.7.6 MEK115306 試験（COMBI-d 試験)） ［20160217］

21) 社内資料：海外第Ⅲ相臨床試験（BRF113683 試験）（2016 年 3 月 28 日承認、CTD2.7.6 BRF113683 試験） ［20160218］

22) 社内資料：国際共同第Ⅲ相臨床試験（F2301 試験） ［20180229］

23) 社内資料：国際共同第Ⅱ相臨床試験（E2201 試験） ［20170555］

24) 社内資料：国際共同第Ⅱ相臨床試験（X2201 試験） ［XXXXXXXX］

25) 社内資料：海外第 I/Ⅱ相臨床試験（小児 X2101 試験） ［XXXXXXXX］

26) 社内資料：BRAF 阻害作用（2016 年 3 月 28 日承認、CTD2.6.2.2.1.1.1.） ［20160222］

27) King,A.J.et al.：PLoS One. 2013;8（7）:e67583 ［20160221］

28) 社内資料：BRAF 変異陽性ヒト悪性黒色腫由来細胞株の増殖に及ぼす影響 （2016 年 3 月 28 日承認、CTD2.6.2.2.1.5.）［20160219］

29）社内資料：BRAF 変異陽性ヒト非小細胞肺癌由来細胞株の増殖に及ぼす影響　(2018 年 3 月 23 日承認、CTD2.6.2.2.1.1.)［20170556］

30）社内資料：BRAF 変異陽性ヒト甲状腺未分化癌由来細胞株の増殖に及ぼす影響　(XX 年 X 月 XX 日承認、CTD2.6.2.2.1.1.)［XXXXXXXX］

31）社内資料：マウスにおけるヒト悪性黒色腫由来細胞の増殖抑制作用（2016 年 3 月 28 日承認、CTD2.6.2.2.2.1.2.）　［20160220］

24. 文献請求先及び問い合わせ先

ノバルティスファーマ株式会社　ノバルティスダイレクト
〒105-6333 東京都港区虎ノ門 1-23-1



26. 製造販売業者等

26.1 製造販売

ノバルティスファーマ株式会社
東京都港区虎ノ門 1-23-1

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略号一覧

略号	省略していない表現（英）	省略していない表現（日）
ASI	adenocarcinoma of small intestine	小腸腺癌
ATC	anaplastic thyroid cancer	甲状腺未分化癌
AUCtau	area under the drug plasma concentration-time curve during a dosing interval	投与間隔（tau）における血漿中薬物濃度–時間曲線下面積
BRAF	B-Raf proto-oncogene serine/threonine kinase	—
BTC	biliary tract cancer	胆道癌
HCL	hairy cell leukemia	有毛細胞白血病
HGG	high grade glioma	高グレード神経膠腫 (WHO grade 3 又は 4 の神経膠腫)
LCH	langerhans cell histiocytosis	ランゲルハンス細胞組織球症
LGG	low grade glioma	低グレード神経膠腫 (WHO grade 1 又は 2 の神経膠腫)
MAP	Managed Access Programs	—
MEK	mitogen-activated extracellular signal-regulated kinase kinase	—
MTD	maximum tolerated dose	最大耐用量
NCI-MATCH	National Cancer Institute’s - Molecular Analysis for Therapy Choice	—
NSCLC	non-small cell lung cancer	非小細胞肺癌
ORR	overall response rate	全奏効率
RP2D	recommended phase 2 dose	第 II 相試験推奨用量

1 4. 効能又は効果欄

1.1 4. 効能又は効果

BRAF V600E 遺伝子変異を有する進行・再発の固形腫瘍（標準的な治療が困難な場合に限る）

1.2 4. 効能又は効果の設定根拠

BRAF V600E 変異を有する 15 種類を超えるがん種を対象とした 4 つの臨床試験（成人 X2201 試験及び NCI-MATCH 試験サブプロトコール H（Arm H）（以降，XUS35T 試験），小児 A2102 試験及び X2101 試験）の結果から，代替治療選択肢がない患者においてダブラフェニブ／トラメチニブ併用療法の臨床的エビデンスが示された。さらに，これらの結果は，ノバルティス社が実施する薬剤の倫理提供のプログラム（MAP）及び医師主導試験を含めた文献レビューの結果からも裏付けられ，発がん性 BRAF V600E が組織非依存的に作用するドライバー変異であることを示唆している。日本人集団での有効性は，X2201 試験に組み入れられた被験者は 7 名と限定的であるものの，全体集団と同様に良好な結果が得られた。また，NCCH1901 研究では，日本人 57 名での貴重な使用経験が報告され，良好な結果が得られている（2.5-4.7 項）。

また，がん種横断適応を目的とした開発プログラムで検討した BRAF V600 変異陽性の成人及び小児患者におけるダブラフェニブ／トラメチニブ併用療法の安全性プロファイルは，臨床試験及び市販後の成人の悪性黒色腫，NSCLC で認められた安全性プロファイルと同様であった。J-RMP で規定された重要な特定されたリスク及び重要な潜在的リスクについても，小児及び成人患者ともに，既承認の適応症と同様に十分な観察と必要に応じてダブラフェニブ又はトラメチニブの休薬や減量，あるいは対症療法を行うことにより，そのリスクを最小化することが可能と考える（2.5-6.3 項）。

以上より，効能又は効果を「*BRAF* V600E 遺伝子変異を有する進行・再発の固形腫瘍（標準的な治療が困難な場合に限る）」とした。

審査期間中，国内の BRAF V600E 遺伝子変異を有する再発難治性 HCL の治療環境や医療ニーズを鑑み，本申請適応症の範囲に血液腫瘍である HCL を含めること，また LCH 等の組織球症が本申請適応症の範囲に含まれることを明確化する必要性が生じたため，効能・効果に「組織球症を含む」ことを明記するとともに，「*BRAF* V600E 遺伝子変異を有する再発又は難治性の有毛細胞白血病」を追加することとした（2.5-1.1 項）。

審査の過程で，医薬品医療機器総合機構との協議を踏まえ，効能又は効果を以下のとおり設定することとした。

標準的な治療が困難な *BRAF* 遺伝子変異を有する進行・再発の固形腫瘍（結腸・直腸癌を除く）
BRAF 遺伝子変異を有する再発又は難治性の有毛細胞白血病

2 5. 効能又は効果に関連する注意欄

2.1 5. 効能又は効果に関連する注意

〈効能共通〉

5.1 十分な経験を有する病理医又は検査施設における検査により、*BRAF* 遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断用~~薬等~~医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

5.2 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で適応患者の選択を行うこと。

〈非小細胞肺癌〉

5.3 本剤の術後補助療法における有効性及び安全性は確立していない。

〈固形腫瘍〉

5.4 結腸・直腸癌における有効性及び安全性は確立していない。

5.5 本剤の手術の補助療法における有効性及び安全性は確立していない。

（取り消し線：削除，下線：変更箇所）

2.2 5. 効能又は効果に関連する注意の設定根拠

本剤の作用機序及び臨床試験成績から，本剤により期待される効果を得るためには固形腫瘍における BRAF 遺伝子変異陽性を適切な検査により確認することが重要であると考えた。このことから，効能又は効果に関連する注意として，「十分な経験を有する病理医又は検査施設における検査により、*BRAF* 遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。」を設定した。悪性黒色腫及び NSCLC の腫瘍組織において BRAF 変異を検出する体外診断薬（コンパニオン診断薬）として臨床性能が確認されている試薬は，医薬品医療機器総合機構のウェブサイトに情報が掲載されており，固形腫瘍の体外診断薬についても掲載される予定である。また，今後も新しい診断薬，検査方法等が登場する場合にも掲載されることから，当該ウェブサイトを参照できるように，体外診断薬等を用いる既承認の薬剤の記載に準じて，「なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である： https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html」と記載した。

BRAF V600 変異を有する結腸・直腸癌の BRAF/MEK 阻害剤に対する臨床での治療感受性は，BRAF V600 変異を有する悪性黒色腫，NSCLC，ATC よりも低いことが示されている。さまざまな組織型の固形腫瘍に対する BRAF/MEK 阻害剤の有効性は，一様ではない可能性が考えられることから，臨床データパッケージに含まれる臨床試験及び既承認の適応症の臨床試験の結果を踏

まえ，がん種別に ORR を比較した。その結果，同一試験ではないため比較は困難であり解釈には限界があるものの，結腸・直腸癌を除いた BRAF V600 変異陽性のさまざまな腫瘍を有する患者で，一貫したダブラフェニブ／トラメチニブ併用療法の臨床的ベネフィットが示された。また，文献レビューからも，結腸・直腸癌以外の腫瘍で，BRAF V600 阻害剤に対する耐性を示す決定的なエビデンスは得られていない。以上より，結腸・直腸癌を除く，広範ながん種で一貫した臨床ベネフィットが示され，ダブラフェニブ／トラメチニブ併用療法のがん種横断適応的な適用が支持された。結腸・直腸癌のみが BRAF/MEK 阻害に対する特異な耐性機序を有すると考えることから，「結腸・直腸癌における有効性及び安全性は確立していない。」の記載を効能・効果に関連する注意として設定した（2.5-6.2.3 項）。

BRAF V600E 遺伝子変異を有する進行・再発の固形腫瘍患者における手術の補助療法としてのダブラフェニブ／トラメチニブ併用療法の有効性及び安全性成績は得られていないため，「本剤の手術の補助療法における本剤の有効性及び安全性は確立していない」を効能・効果に関連する使用上の注意として設定した。

審査の過程で，医薬品医療機器総合機構との協議を踏まえ，効能又は効果に関連する注意を以下のとおり設定することとした。

〈効能共通〉

5.1 十分な経験を有する病理医又は検査施設における検査により、BRAF 遺伝子変異が確認された患者に投与すること。検査にあたっては、承認された体外診断用~~薬等~~医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：

https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

〈悪性黒色腫〉

5.2「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で適応患者の選択を行うこと。

〈非小細胞肺癌〉

5.3「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で適応患者の選択を行うこと。

5.4 本剤の術後補助療法における有効性及び安全性は確立していない。

〈固形腫瘍〉

5.5 組織球症患者は本剤の投与対象となり得る。

5.6 臨床試験に組み入れられた患者のがん種等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。

5.7 本剤の手術の補助療法における有効性及び安全性は確立していない。

〈有毛細胞白血病〉

5.8 臨床試験に組み入れられた患者の前治療歴等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

（取り消し線：削除，下線：変更箇所）

3 6. 用法及び用量欄

3.1 6. 用法及び用量

〈悪性黒色腫〉

通常、成人にはダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時に経口投与する。ただし、術後補助療法の場合には、トラメチニブと併用し、投与期間は 12 ヵ月間までとする。なお、患者の状態により適宜減量する。

〈非小細胞肺癌，固形腫瘍〉

トラメチニブとの併用において、通常、成人にはダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時に経口投与する。なお、患者の状態により適宜減量する。

〈固形腫瘍〉

トラメチニブとの併用において、通常、小児にはダブラフェニブとして 1 回 75～150mg を 1 日 2 回、空腹時に経口投与する。1 回あたりの投与量は体重に基づき、下表により設定する。

体重（kg）	26～37	38～50	≧51
投与量（mg）	75	100	150

（下線：変更箇所）

3.2 6. 用法及び用量の設定根拠

成人患者を対象とした 2 試験（X2201 試験，XUS35T 試験）で用いたダブラフェニブ／トラメチニブ併用療法の用法・用量は，国内外で承認されている適応症（*BRAF* 遺伝子変異を有する悪性黒色腫，*BRAF* 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌）と同じ，ダブラフェニブ 150 mg を 1 日 2 回，トラメチニブ 2 mg を 1 日 1 回経口投与とした。なお，ダブラフェニブ及びトラメチニブの成人の用法・用量の設定根拠の詳細は，悪性黒色腫承認時資料（1.13.1-1）に示した（2.5-4.2 項）。X2201 試験の結果，さまざまな BRAF V600E 変異陽性の進行・再発の固形腫瘍に対し，ダブラフェニブ／トラメチニブ併用療法の高い奏効率が認められた。同一試験ではなく，対象集団も異なることから比較には限界があるものの，3 名以上が登録され，かつ既存治療（国内既承認薬に限定）又は標準治療のあるがん種では，主要評価項目である試験担当医師判定に基づく ORR は，既存治療等の ORR に比べ同等又は上回っており，臨床的意義が示された。（2.5-6.2.1 項）。

小児患者（1 歳以上 18 歳未満）を対象とした A2102 試験では，ダブラフェニブの開始用量（3 mg/kg/日）は体重補正した成人用量の 80%とした。X2101 試験では，トラメチニブの用量を 80 kg の成人に基づき算出し，小児患者（2 歳以上 18 歳未満）に対する開始用量（0.0125 mg/kg/日）は成人用量の 50%，2 番目の用量（0.025 mg/kg/ 日）は成人用量と等価，3 番目の用量（0.040 mg/kg/日）は成人における MTD と等価として設定の上，RP2D を検討した。各試験で決定したダブラフェニブ及びトラメチニブの RP2D を用い，ダブラフェニブ／トラメチニブ併用療法の RP2D を検討した（2.5-4.2 項）。その結果，ダブラフェニブ／トラメチニブ併用療法は，小児の再発又は難治性の BRAF V600 変異陽性の神経膠腫（LGG 及び HGG）及び LCH 患者に対して良好な有効性を示した。（2.5-6.2.2 項）。

小児に対するダブラフェニブ／トラメチニブ併用療法の推奨用法・用量は，小児患者対象の 2 試験（A2102 試験，X2101 試験）で設定した年齢区分別の用法・用量ではなく，上記 2 試験の小児患者（6 歳以上 18 歳未満）及び同じく小児患者対象の試験（G2201 試験）の小児患者での母集団薬物動態解析の結果に基づき，年齢を考慮しない体重区分（26～37 kg，38～50 kg，51 kg 以上）別に設定した。母集団薬物動態解析では，対象患者が確実に成人の定常状態での目標 Cavg（ダブラフェニブ 300 ng/mL，トラメチニブ 10 ng/mL）以上となる各体重区分における用法・用量を予測した。なお，母集団薬物動態解析モデルを用いた薬物動態予測の結果，17～25 kg の体重区分では，被験者の約 50%がダブラフェニブの目標 Cavg に達成しないと予想され，かつトラメチニブの用量設定が不可能であったことから，ダブラフェニブ／トラメチニブ併用療法の推奨用法・用量を，体重 26 kg 以上で設定した（2.7.3-4.2.2 項）。小児患者における推奨用法・用量は，母集団解析の結果を踏まえ，体重区分別に既承認のダブラフェニブカプセル（50 mg 及び 75 mg）及びトラメチニブ錠（0.5 mg 及び 2 mg）のうち同一含量の製剤のみを組み合わせて設定した。母集団薬物動態解析の結果に基づいて設定した体重区分別の用法・用量における AUCtau の 95 パーセンタイル値の最大値（ダブラフェニブ：8844.4 h*ng/mL，トラメチニブ：484.5 h*ng/mL）は，小児患者を対象とした 2 試験で観察された AUCtau の最大値（ダブラフェニブ：13800 h*ng/mL，トラメチニブ：865 h*ng/mL）を超えなかった。以上より，小児患者における体重区分別の用法・用量は適切であると考えた（2.5-3.2.2 項）。

X2201 試験の結果から，成人の BRAF V600E 変異陽性の固形腫瘍患者でダブラフェニブ／トラメチニブ併用療法でみられた有害事象の内容は，既承認の悪性黒色腫及び NSCLC を対象とした臨床試験成績と同様であり，X2201 試験に特有の安全性上の懸念，日本人特有の安全性上の懸念も認められなかった。また，A2102 試験及び X2101 試験の結果から，小児の BRAF V600E 変異陽性の固形腫瘍患者で，現時点で小児患者に特有の新たな安全性上の懸念は認められなかった。J-RMP で特定されたリスクに該当する事象の多くは治験薬の休薬又は減量，あるいは適切な処置により管理可能であった（2.5-5.7 項）。

以上より，*BRAF* V600E 遺伝子変異を有する進行・再発の固形腫瘍（標準的な治療が困難な場合に限る）での用法・用量を設定した。

審査の過程で，医薬品医療機器総合機構との協議を踏まえ，用法及び用量を以下のとおり設定することとした。

〈悪性黒色腫〉

通常、成人にはダブラフェニブとして 1 回 150 mg を 1 日 2 回、空腹時に経口投与する。ただし、術後補助療法の場合には、トラメチニブと併用し、投与期間は 12 カ月間までとする。なお、患者の状態により適宜減量する。

〈非小細胞肺癌、有毛細胞白血病〉

トラメチニブとの併用において、通常、成人にはダブラフェニブとして 1 回 150 mg を 1 日 2 回、空腹時に経口投与する。なお、患者の状態により適宜減量する。

〈固形腫瘍〉

トラメチニブとの併用において、通常、ダブラフェニブとして以下の用量を 1 日 2 回、空腹時に経口投与する。なお、患者の状態により適宜減量する。

・成人には、1 回 150 mg

・小児には、体重に合わせて次の用量

体重	26kg 以上 38kg 未満	38kg 以上 43kg 未満	43kg 以上 51kg 未満	51kg 以上
1 回投与量	75mg	100mg	125mg	150mg

（下線：変更箇所）

4 7. 用法及び用量に関連する注意欄

4.1 7. 用法及び用量に関連する注意

7.1 トラメチニブ以外の抗悪性腫瘍剤との併用における有効性及び安全性は確立していない。

7.2 食後に本剤を投与した場合、Cmax 及び AUC が低下するとの報告がある。食事の影響を避けるため、食事の 1 時間前から食後 2 時間までの間の服用は避けること。

7.3 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。ただし、有棘細胞癌（皮膚の扁平上皮癌）又は新たな原発性悪性黒色腫が発現した場合には、外科的切除等の適切な処置を行った上で、休薬、減量することなく治療を継続することができる。

休薬、減量及び中止基準

NCI-CTCAE 注 1) による Grade 判定	処置
忍容不能な Grade 2 又は Grade 3	休薬 Grade 1 以下まで軽快後、1 段階減量して投与を再開
Grade 4	原則投与中止 治療継続が患者にとって望ましいと判断された場合には、 Grade 1 以下まで軽快後、1 段階減量して投与を再開

注 1）NCI-CTCAE v4.0 により Grade を判定

用量調節の目安（成人）

用量調節段階注 2)	投与量
通常投与量	1 回 150mg（1 日 2 回）
1 段階減量	1 回 100mg（1 日 2 回）
2 段階減量	1 回 75mg（1 日 2 回）
3 段階減量	1 回 50mg（1 日 2 回）
4 段階減量	投与中止

注 2）適切な処置により副作用が管理できた場合には、減量時と逆の段階を経て増量可

用量調節の目安（小児）

用量調節段階[注2)]	投与量		
通常投与量	1回75mg（1日2回）	1回100mg（1日2回）	1回150mg（1日2回）
1段階減量	1回50mg（1日2回）	1回75mg（1日2回）	1回100mg（1日2回）
2段階減量	投与中止	1回50mg（1日2回）	1回75mg（1日2回）
3段階減量	―	投与中止	1回50mg（1日2回）
4段階減量	―	―	投与中止

7.4 小児において26kg未満の患者への有効性及び安全性は確立していない。

（下線：変更箇所）

4.2 7. 用法及び用量に関連する注意の設定根拠

各臨床試験では，治験薬との因果関係が示唆される有害事象が認められた場合，必要に応じて治験薬の休薬又は減量を段階的に行った。これらの段階的な用量調整により有害事象を管理することが可能であった。成人と同様に，小児においても利用可能な製剤の規格に合わせ，段階的な用量調節の目安を設定した。

母集団薬物動態解析モデルを用いた体重区分ごとの薬物動態予測により，26 kg未満の体重区分（17～25 kg）で，ダブラフェニブでは約50%の患者が目標Cavg（300 ng/mL）を達成しないと予想され，かつ，トラメチニブについて本体重区分の用量設定が不可能であったことから，ダブラフェニブの推奨用法・用量を体重26 kg以上の患者について設定した（2.7.2-3.4.2.1項）。そのため，「小児において26kg未満の患者への有効性及び安全性は確立していない」を用法及び用量に関連する注意として設定した。

審査の過程で，医薬品医療機器総合機構との協議を踏まえ，用法及び用量に関連する注意を以下のとおり設定することとした。

〈効能共通〉

7.1 トラメチニブ以外の抗悪性腫瘍剤との併用における有効性及び安全性は確立していない。

7.2 食後に本剤を投与した場合、Cmax及びAUCが低下するとの報告がある。食事の影響を避けるため、食事の1時間前から食後2時間までの間の服用は避けること。

7.3 本剤投与により副作用が発現した場合には、下記の基準を参考に、本剤を休薬、減量又は中止すること。ただし、有棘細胞癌（皮膚の扁平上皮癌）又は新たな原発性悪性黒色腫が発現した場合には、外科的切除等の適切な処置を行った上で、休薬、減量することなく治療を継続することができる。

休薬、減量及び中止基準

NCI-CTCAE 注 1) による Grade 判定	処置
忍容不能な Grade 2 又は Grade 3	休薬 Grade 1 以下まで軽快後、1 段階減量して投与を再開
Grade 4	原則投与中止 治療継続が患者にとって望ましいと判断された場合には、 Grade 1 以下まで軽快後、1 段階減量して投与を再開

注 1）NCI-CTCAE v4.0 により Grade を判定

用量調節の目安（成人）

用量調節段階注 2)	1 回投与量（1 日 2 回）
通常投与量	~~1 回 150mg（1 日 2 回）~~
1 段階減量	~~1 回 100mg（1 日 2 回）~~
2 段階減量	~~1 回 75mg（1 日 2 回）~~
3 段階減量	~~1 回 50mg（1 日 2 回）~~
4 段階減量	投与中止

注 2）適切な処置により副作用が管理できた場合には、減量時と逆の段階を経て増量可

用量調節の目安（小児）

用量調節段階注 2)	1 回投与量（1 日 2 回）			
通常投与量	75mg	100mg	125mg	150mg
1 段階減量	50mg	75mg	100mg	100mg
2 段階減量	投与中止	50mg	75mg	75mg
3 段階減量	—	投与中止	50mg	50mg
4 段階減量	—	—	投与中止	投与中止

〈固形腫瘍〉

7.4 26 kg 未満の小児患者における有効性及び安全性は確立していない。

（取り消し線：削除，下線：変更箇所）

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既承認の適応症に対する使用経験より特定された安全性プロファイルとがん種横断適応を目的とした開発プログラムで検討した BRAF V600 変異陽性の成人及び小児患者におけるダブラフェニブ／トラメチニブ併用療法の安全性プロファイルを比較した際，新たな安全性の懸念となる事象は認められなかったことから，「9. 特定の背景を有する患者に関する注意」，「11. 副作用」及び「15. その他の注意」以外の変更は不要と判断した。

以下に，今回改訂する「9. 特定の背景を有する患者に関する注意」，「11. 副作用」及び「15. その他の注意」の注意喚起について，設定根拠とともに記載した。

1 9. 特定の背景を有する患者に関する注意欄

1.1 9.7 小児等

9.7 小児等

〈悪性黒色腫、非小細胞肺癌、有毛細胞白血病〉

小児等を対象とした臨床試験は実施していない。

〈固形腫瘍〉

低出生体重児、新生児を対象とした臨床試験は実施していない。また、6 歳未満の患者に対する本剤の用法及び用量について、十分な検討は行われていない。

1.2 9.7 小児等の設定根拠

本剤の医薬品製造販売承認事項一部変更承認申請時点において，低出生体重児，新生児を対象とした臨床試験は実施しておらず，客観的な事実が確認できるよう設定した。また，小児患者に対する用法及び用量は 6 歳以上の患者の PK データに基づき構築された PPK モデルを用いて検討したこと等を考慮して設定した。

2 11. 副作用欄

2.1 11.1 重大な副作用

11.1 重大な副作用[注 1)、注 2)、注 3)]

11.1.1 有棘細胞癌

皮膚有棘細胞癌（0.5%、1.6%）、ケラトアカントーマ（0.2%、3.7%）、ボーエン病（0.5%、頻度不明）があらわれることがある。臨床試験において、有毛細胞白血病患者では他がん種の患者よりも有棘細胞癌の発現頻度に高い傾向が認められた（皮膚有棘細胞癌 （5.5%、頻度不明）、扁平上皮癌（5.5%、頻度不明））[注 4)]。［8.2 参照］

11.1.2 悪性腫瘍（二次発癌）

原発性悪性黒色腫（0.1%、1.1%）等の悪性腫瘍（二次発癌）があらわれることがある。臨床試験において、有毛細胞白血病患者では他がん種の患者よりも悪性腫瘍（二次発癌）の発現頻度に高い傾向が認められた（基底細胞癌（12.7%、頻度不明））注4)。［8.3 参照］

11.1.3 心障害

心不全（0.1%、0.5%）、左室機能不全（0.2%、1.4%）、駆出率減少（5.9%、4.7%）等の重篤な心障害があらわれることがある。［8.4、9.1.1 参照］

11.1.4 肝機能障害

ALT（11.3%、1.6%）、AST（11.5%、0.5%）等の上昇を伴う肝機能障害があらわれることがある。［8.6、9.3.1 参照］

11.1.5 静脈血栓塞栓症（0.3%、頻度不明）

11.1.6 脳血管障害

脳出血（0.1%、頻度不明）、脳血管発作（いずれも頻度不明）等の脳血管障害があらわれることがある。

注 1）重大な副作用の発現頻度は、トラメチニブとの併用時、本剤単独投与時の順に記載した。

2.2 11.1 重大な副作用の設定根拠

11.1.1，11.1.2 項：X2201 試験の有毛細胞白血病患者において，他のがん種と比較して観察期間が長い傾向が認められたこと，二次性悪性腫瘍が既知の副作用であるクラドリビンの前治療歴のある患者が 96%であったこと等を考慮する必要があるものの，他のがん種と比較して有棘細胞癌，悪性腫瘍（二次発癌）の発現率が高い傾向がみられたことから設定した。

上記以外について，現行の添付文書に記載されている内容の変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。なお，発現頻度は，既存の集計（MEK115306 試験，MEK116513 試験，F2301 試験及び E2201 試験）に加えて X2201 試験で認められた副作用の併合解析から算出し，その結果に基づき頻度を変更した。

各試験のカットオフは，以下のとおりである。

- MEK115306 試験（2015 年 1 月 12 日）
- MEK116513 試験（2014 年 4 月 17 日）
- E2201 試験（2016 年 8 月 8 日）
- F2301 試験（2017 年 6 月 30 日）
- X2201 試験（2021 年 12 月 10 日）

2.3 11.2 その他の副作用

11.2 その他の副作用

トラメチニブとの併用時[注2)]

	10%以上	1%～10%未満	1%未満	頻度不明
感染症	－	毛包炎、膿疱性皮疹	蜂巣炎、尿路感染、上咽頭炎、爪囲炎	－
血　液	－	好中球減少症、貧血、血小板減少症、白血球減少症	－	－
代　謝	－	食欲減退、脱水、低ナトリウム血症、低リン血症、高血糖	－	－
神経系	頭痛	浮動性めまい	－	－
眼	－	霧視、ぶどう膜炎、視力障害	網膜色素上皮剥離、網脈絡膜症、網膜剥離、眼窩周囲浮腫	－
心・血管	－	高血圧、低血圧、出血（鼻出血、歯肉出血等）	リンパ浮腫、徐脈、QT/QTc 間隔延長	心拍数減少
呼吸器	－	咳嗽、呼吸困難	肺臓炎、間質性肺炎	－
消化器	悪心、下痢、嘔吐	便秘、腹痛、口内乾燥、口内炎	膵炎	－
肝胆道系	－	ALP 増加、γ-GTP 増加	－	－
皮　膚	発疹、皮膚乾燥	そう痒症、ざ瘡様皮膚炎、紅斑、日光角化症、寝汗、過角化、脱毛症、手掌・足底発赤知覚不全症候群、皮膚病変、多汗症、脂肪織炎、皮膚亀裂、光線過敏症	－	－
筋骨格系	関節痛、筋肉痛	四肢痛、筋痙縮、血中 CK 増加	横紋筋融解症	－
腎	－	－	腎炎、腎不全、尿細管間質性腎炎、急性腎障害	－
全　身	発熱(50.1%)、疲労、悪寒、無力症	末梢性浮腫、インフルエンザ様疾患、粘膜の炎症	顔面浮腫	－
その他	－	脂漏性角化症	乳頭腫、アクロコルドン、過敏症	－

（略）

注 2）トラメチニブとの併用時の副作用頻度は臨床試験（MEK115306 試験、MEK116513 試験、F2301 試験、E2201 試験及び X2201 試験）に基づき記載した。
注 3）本剤単独投与時の副作用頻度は海外臨床試験（BRF113683 試験）に基づき記載した。
注 4）X2201 試験の有毛細胞白血病患者（55 例）で発現した副作用頻度に基づき記載した。

2.4 11.2 その他の副作用の設定根拠

現行の添付文書に記載されている内容について，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。なお，発現頻度は，既存の集計（MEK115306 試験，MEK116513 試験，F2301 試験及び E2201 試験）に加えて X2201 試験で認められた副作用の併合解析から算出し，その結果に基づき頻度を変更した。なお，「鼻咽頭炎」，「低リン酸血症」は MedDRA の Version up により「上咽頭炎」，「低リン血症」に用語を変更した。また，記載整備を行った。

各試験のカットオフは，以下のとおりである。

- MEK115306 試験（2015 年 1 月 12 日）
- MEK116513 試験（2014 年 4 月 17 日）
- E2201 試験（2016 年 8 月 8 日）
- F2301 試験（2017 年 6 月 30 日）
- X2201 試験（2021 年 12 月 10 日）

3 15 その他の注意欄

3.1 15.2 非臨床試験に基づく情報

15.2.6 幼若ラットにおいて、成長・発達への影響（骨長の短縮、膣開口の早期化）が 1 mg/kg/日／3 mg/kg/日（生後 7～21 日の投与量／生後 22～35 日の投与量）（成人の臨床曝露量（AUC）の約 0.2 倍）以上の群でみられた。また、同用量群で成熟動物では認められなかった腎臓への影響（尿細管変性等）等がみられた。

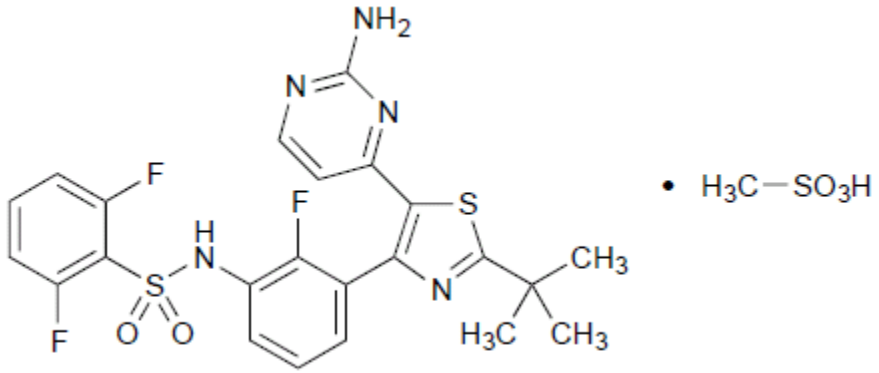
3.2 15.2 非臨床試験に基づく情報の設定根拠

幼若ラットを用いた毒性試験において，本剤の成人での臨床曝露量の約 0.2 倍に相当する用量で，成長・発達への影響（骨長の短縮、膣開口の早期化）への影響が毒性所見として認められたため記載した。

1.9 一般的名称に係る文書

既承認医薬品に係る資料を参照

<現行>

化学名・別名	【日本名】*N*-{3-[5-(2-アミノピリミジン-4-イル)-2-(1,1-ジメチルエチル)-1,3-チアゾール-4-イル]-2-フルオロフェニル}-2,6-ジフルオロベンゼンスルホンアミド一メタンスルホン酸塩 【英名】*N*-{3-[5-(2-Aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide monomethanesulfonate
構造式	
効能・効果	1. *BRAF* 遺伝子変異を有する悪性黒色腫 2. *BRAF* 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌
用法・用量	〈悪性黒色腫〉 通常、成人にはダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時に経口投与する。ただし、術後補助療法の場合には、トラメチニブと併用し、投与期間は 12 ヵ月間までとする。なお、患者の状態により適宜減量する。 〈非小細胞肺癌〉 トラメチニブとの併用において、通常、成人にはダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時に経口投与する。なお、患者の状態により適宜減量する。
劇薬等の指定	原体：劇薬，製剤：劇薬 処方箋医薬品
市販名及び有効成分・分量	原体：ダブラフェニブメシル酸塩 製剤：タフィンラーカプセル 50 mg（1 カプセル中ダブラフェニブとして 50 mg 含有） タフィンラーカプセル 75 mg（1 カプセル中ダブラフェニブとして 75 mg 含有）
毒性	ダブラフェニブメシル酸塩：

急性

概略の致死量	経口（mg/kg）
ラット	＞600
イヌ	＞80

反復投与

動物種	投与期間	投与経路	投与量（mg/kg/日）	無毒性量（mg/kg/日）
マウス	26 週	経口	15, 50, 150	＜15

≥15：好中球・リンパ球・好酸球・好塩基球・白血球数の高値，ALT／AST 高値，グルコース低値，肝臓の壊死／炎症，肝細胞肥大，クッパー細胞肥大／過形成，胆管周囲炎，色素沈着又は有糸分裂像増加，骨髄細胞密度増加，食道／前胃／舌の粘膜上皮過形成／角化亢進，炎症又は潰瘍，脾臓髄外造血増加，精巣の精子細胞滞留又は細胞残渣増加，精巣網拡張，血管壁壊死，血管／血管周囲炎，気道上皮内好酸球，細気管支上皮肥大

≥50：リンパ節の炎症／壊死，胸腺リンパ球減少

		150：体重／体重増加量低値，アルブミン低値，胆嚢の混合性炎症細胞浸潤又は上皮肥大／過形成
		ラット　4 週　経口　5, 20, 200　♂< 5, ♀200
		≥ 5：トリグリセリド低値，前胃／腺胃境界縁上皮の角化細胞変性，下顎／頸部リンパ節の赤血球増加，精巣の伸長精子細胞変性／滞留，精巣上体の細胞残屑 ≥ 20：心筋症 200：体重減少／体重増加量／摂餌量低値
		ラット　13 週　経口　20, 200, 400　< 20
		≥ 20：体重減少，体重増加量／摂餌量低値，皮膚病変（乾燥，剥離，腫脹，発赤），リンパ球数高値，リン低値，前・後肢足蹠部／趾間皮膚の表皮肥厚／角化亢進，前胃粘膜上皮過形成，粘膜筋板への下層増殖，精上皮変性／消失，精巣上体中の精子数減少／無精子 ≥ 200：好酸球数高値，総蛋白・トリグリセリド・アルブミンの低値，小葉中間帯肝細胞空胞化 400：削痩，脱水症状，好中球・単球数の高値，皮膚混合性炎症細胞浸潤
		イヌ　4 週　経口　1, 5, 50　5
		≥ 1：摂餌量低値，異常便（粘液／軟／水様／変色便） 50：皮膚の隆起，有茎性腫瘤，潰瘍，乳頭腫，表皮肥厚・角化亢進，三尖弁の肥厚・出血
		イヌ　13 週　経口　5, 20, 60/100 (♂/♀)　< 5
		≥ 5：皮膚病変（丘疹，発赤，痂皮形成），四肢腫脹，嘔吐，脱水症状，液状／黒色便，皮膚の表皮肥厚，混合性炎症細胞浸潤又はびらん／痂皮，精巣の精上皮変性／消失，精巣上体の精子数減少／無精子，膝窩リンパ節の形質細胞増加又は赤血球増加／赤血球貪食像増加 ≥20：体重・摂餌量減少，努力呼吸，浅呼吸，振戦，好中球・単球数の高値，ALP 高値，尿素，クレアチニン・アルブミン・コレステロール・リン・カリウムの低値，右心房壁の線維血管性増殖，胸骨骨髄過形成，胸腺のリンパ球減少，気管支肺胞炎症 60/100：重度の一般状態悪化（体重減少，食欲不振，削痩，脱水症状，液状便，嘔吐）のため試験 14/15 日に投与中止

副　作　用

国内試験

ダブラフェニブ単独投与の国内第 I 相臨床試験（BRF116056 試験）

副作用（臨床検査値異常変動を含む）発現率：12/12 例=100%

副作用（臨床検査値異常変動を含む）の種類：

脱毛症　6 例

発熱　6 例

関節痛　6 例　　等

ダブラフェニブとトラメチニブの併用による国内臨床試験（MEK116885 試験）

副作用（臨床検査値異常変動を含む）発現率：12/12 例=100%

副作用（臨床検査値異常変動を含む）の種類：

発熱　8 例

アスパラギン酸アミノトランスフェラーゼ増加　6 例

末梢性浮腫　6 例　　等

外国試験

	外国第 III 相試験（MEK115306 試験）のうち，ダブラフェニブ単剤投与群 副作用（臨床検査値異常変動を含む）発現率：186/211 例=88.2% 副作用（臨床検査値異常変動を含む）の種類： 過角化　63 例 疲労　56 例 脱毛症　52 例　　等 外国第 III 相試験（MEK115306 試験）のうち，ダブラフェニブとトラメチニブの併用投与群 副作用（臨床検査値異常変動を含む）発現率：179/209 例=85.6% 副作用（臨床検査値異常変動を含む）の種類： 発熱　98 例 悪寒　57 例 疲労　52 例　　等 国際共同試験 BRAF V600E/K 変異を有する再発ハイリスクの悪性黒色腫の術後患者を対象とした国際共同第 III 相臨床試験（F2301 試験）のトラメチニブとの併用投与群において，435 例（日本人患者 3 例を含む）中 398 例（91.5%）に臨床検査値異常を含む副作用が報告された。その主なものは，発熱 244 例（56.1%），疲労 170 例（39.1%），悪寒 155 例（35.6%）であった。 （効能又は効果の一変承認時までの集計） BRAF V600E 変異を有する切除不能な進行・再発の非小細胞肺癌患者を対象とした国際共同第 II 相臨床試験（E2201 試験）のトラメチニブとの併用投与群において，93 例（日本人患者 1 例を含む）中 83 例（89.2%）に臨床検査値異常を含む副作用が報告された。その主なものは，発熱 46 例（49.5%），悪心 36 例（38.7%），嘔吐 25 例（26.9%），皮膚乾燥 25 例（26.9%）であった。 （効能又は効果の一変承認時までの集計）
会　　社	ノバルティスファーマ株式会社　製剤：輸入

<削除・追加>二重取り消し線，二重下線部

化学名・別　　名	
構　造　式	
効能・効果	1. *BRAF* 遺伝子変異を有する悪性黒色腫 2. *BRAF* 遺伝子変異を有する切除不能な進行・再発の非小細胞肺癌 3. 標準的な治療が困難な *BRAF* 遺伝子変異を有する進行・再発の固形腫瘍（結腸・直腸癌を除く） 4. *BRAF* 遺伝子変異を有する再発又は難治性の有毛細胞白血病
用法・用量	〈悪性黒色腫〉 通常、成人にはダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時に経口投与する。ただし、術後補助療法の場合には、トラメチニブと併用し、投与期間は 12 ヵ月間までとする。なお、患者の状態により適宜減量する。 〈非小細胞肺癌、有毛細胞白血病〉 トラメチニブとの併用において、通常、成人にはダブラフェニブとして 1 回 150mg を 1 日 2 回、空腹時に経口投与する。なお、患者の状態により適宜減量する。 〈固形腫瘍〉 トラメチニブとの併用において、通常、ダブラフェニブとして以下の用量を 1 日 2 回、空腹時に経口投与する。なお、患者の状態により適宜減量する。 ・成人には、1 回 150mg ・小児には、体重に合わせて次の用量

<table>
<tr><td></td><td>
<table>
<tr><td>体重</td><td>26kg 以上
38kg 未満</td><td>38kg 以上
43kg 未満</td><td>43kg 以上
51kg 未満</td><td>51kg 以上</td></tr>
<tr><td>1 回
投与量</td><td>75mg</td><td>100mg</td><td>125mg</td><td>150mg</td></tr>
</table>
</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>国内試験
ダブラフェニブ単独投与の国内第 I 相臨床試験（BRF116056 試験）
副作用（臨床検査値異常変動を含む）発現率：12/12 例=100%
副作用（臨床検査値異常変動を含む）の種類：
脱毛症　6 例
発熱　6 例
関節痛　6 例　　等
ダブラフェニブとトラメチニブの併用による国内臨床試験（MEK116885 試験）
副作用（臨床検査値異常変動を含む）発現率：12/12 例=100%
副作用（臨床検査値異常変動を含む）の種類：
発熱　8 例
アスパラギン酸アミノトランスフェラーゼ増加　6 例
末梢性浮腫　6 例　　等

外国試験
外国第 III 相試験（MEK115306 試験）のうち，ダブラフェニブ単剤投与群
副作用（臨床検査値異常変動を含む）発現率：186/211 例=88.2%
副作用（臨床検査値異常変動を含む）の種類：
過角化　63 例
疲労　56 例
脱毛症　52 例　　等
外国第 III 相試験（MEK115306 試験）のうち，ダブラフェニブとトラメチニブの併用投与群
副作用（臨床検査値異常変動を含む）発現率：179/209 例=85.6%
副作用（臨床検査値異常変動を含む）の種類：
発熱　98 例
悪寒　57 例
疲労　52 例　　等
ダブラフェニブとトラメチニブの併用による外国第 I/II 相試験（小児 X2101 試験，パート D）
副作用（臨床検査値異常変動を含む）発現率：30/30 例=100%
副作用（臨床検査値異常変動を含む）の種類：
発熱　16 例
疲労　11 例
皮膚乾燥　11 例　　等</td></tr>
</table>

	国際共同試験： BRAF V600E/K 変異を有する再発ハイリスクの悪性黒色腫の術後患者を対象とした国際共同第 III 相臨床試験（F2301 試験）のトラメチニブとの併用投与群において，435 例（日本人患者 3 例を含む）中 398 例（91.5%）に臨床検査値異常を含む副作用が報告された。その主なものは，発熱 244 例（56.1%），疲労 170 例（39.1%），悪寒 155 例（35.6%）であった。 （効能又は効果の一変承認時までの集計） BRAF V600E 変異を有する切除不能な進行・再発の非小細胞肺癌患者を対象とした国際共同第 II 相臨床試験（E2201 試験）のトラメチニブとの併用投与群において，93 例（日本人患者 1 例を含む）中 83 例（89.2%）に臨床検査値異常を含む副作用が報告された。その主なものは，発熱 46 例（49.5%），悪心 36 例（38.7%），嘔吐 25 例（26.9%），皮膚乾燥 25 例（26.9%）であった。 （効能又は効果の一変承認時までの集計） 標準的な治療選択肢のない BRAF V600E 変異を有する固形腫瘍患者，BRAF V600E 変異を有する再発又は難治性の有毛細胞白血病患者等（18 歳以上）を対象とした国際共同第Ⅱ相臨床試験（X2201 試験）のトラメチニブとの併用投与群において，196 例（日本人患者 7 例を含む）中 174 例（88.8%）に臨床検査値異常を含む副作用が報告された。その主なものは，発熱 82 例（41.8%），疲労 53 例（27.0%），悪寒 51 例（26.0%）であった。
会　　社	

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3　第 5 部 8

1 第 3 部

該当資料なし

2 第 4 部

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考
4.2 試験報告書						
4.2.1 薬理試験						
4.2.1.1 効力を裏付ける試験						
4.2.1.1-1	RD-2017-00062	Combining the RAF inhibitor Dabrafenib and MEK1/2 inhibitor Trametinib in BRAFV600E-mutant human anaplastic thyroid cancer cell lines in vitro	20[redacted] 年[redacted] 月[redacted] 日	ノバルティス	海外	評価
4.2.1.2 副次的薬理試験						
—	—	該当資料なし	—	—	—	—
4.2.1.3 安全性薬理試験						
—	—	該当資料なし	—	—	—	—
4.2.1.4 薬力学的薬物相互作用試験						
—	—	該当資料なし	—	—	—	—
4.2.2 薬物動態試験						
—	—	該当資料なし	—	—	—	—
4.2.3 毒性試験						
4.2.3.1 単回投与毒性試験						
—	—	該当資料なし	—	—	—	—

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考
4.2.3.2 反復投与毒性試験						
―	―	該当資料なし	―	―	―	―
4.2.3.3 遺伝毒性試験						
―	―	該当資料なし	―	―	―	―
4.2.3.4 がん原性試験						
―	―	該当資料なし	―	―	―	―
4.2.3.5 生殖発生毒性試験						
4.2.3.5.1 受胎能及び着床までの初期胚発生に関する試験						
―	―	該当資料なし	―	―	―	―
4.2.3.5.2 胚・胎児発生に関する試験						
―	―	該当資料なし	―	―	―	―
4.2.3.5.3 出生前及び出生後の発生並びに母体の機能に関する試験						
―	―	該当資料なし	―	―	―	―
4.2.3.5.4 新生児を用いた試験						
4.2.3.5.4-1	2011N121500	GSK2118436A: Oral Juvenile Tolerability/Dose Range Finding Study in Rats	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	参考
4.2.3.5.4-2	2012N146940	GSK1120212B: Oral Juvenile Tolerability/Dose Range Finding Study in Rats	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	参考
4.2.3.5.4-3	2012N148838	GSK2118436A: Oral Juvenile Toxicity Study in Rats (From Day 7 to 35 of Age) Followed by a 6-week Off-drug Period	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	カナダ	海外	評価
	2012N148838-original	GSK2118436A: Oral Juvenile Toxicity Study in Rats (From Day 7 to 35 of Age) Followed by a 6-week Off-drug Period (Original Version)	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	カナダ	海外	評価
4.2.3.5.4-4	2013N165537	GSK1120212B: Oral Juvenile Toxicity Study in Rats (from Day 7 to 45 of age) followed by a 6-Week Off-Drug Period	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	評価
4.2.3.5.4-5	2014N204291	GSK2118436A: Oral Juvenile Investigative Study in the Female Rat	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	参考

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考
4.2.3.5.4-6	2013N164523	GSK2118436A: Oral Investigative Renal Study in Juvenile Rats	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	参考
4.2.3.6 局所刺激性試験						
―	―	該当資料なし	―	―	―	―
4.2.3.7 その他の毒性試験						
―	―	該当資料なし	―	―	―	―

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4.3-3	Bellhorn RW, Korte GE, Abrutyn D (1988) Spontaneous corneal degeneration in the rat. Lab Anim Sci; 38(1):46-50.	海外
4.3-4	Bershas DA, Ouellet D, Mamaril-Fishman DB, et al. (2013) Metabolism and disposition of oral dabrafenib in cancer patients: proposed participation of aryl nitrogen in carbon-carbon bond cleavage via decarboxylation following enzymatic oxidation. Drug Metab Dispos; 41(12):2215-24.	海外
4.3-5	Brown AP, Courtney CL, King LM, et al. (2005) Cartilage dysplasia and tissue mineralization in the rat following administration of a FGF receptor tyrosine kinase inhibitor. Toxicol Pathol; 33(4):449-55.	海外
4.3-6	Cargnello M and Roux PP (2011) Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev; 75(1):50-83.	海外
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4.3-8	Charles RP, Iezza G, Amendola E, et al. (2011) Mutationally activated $BRAF^{V600E}$ elicits papillary thyroid cancer in the adult mouse. Cancer Res; 71(11):3863-71.	海外
4.3-9	Cocco E, Scaltriti M, Drilon A. (2018) *NTRK* fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol; 15(12):731-47.	海外
4.3-10	Davies H, Bignell GR, Cox C, et al. (2002) Mutations of the *BRAF* gene in human cancer. Nature; 417:949-54.	海外
4.3-11	Dearden S, Stevens J, Wu YL, et al. (2013) Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol; 24:2371-6.	海外
4.3-12	Deng C, Wynshaw-Boris A, Zhou F, et al. (1996) Fibroblast growth factor receptor 3 is a negative regulator of bone growth. Cell; 84(6):911-21.	海外
4.3-13	Dhomen N, Reis-Filho JS, Dias SR, et al. (2009) Oncogenic Braf induces melanocyte senescence and melanoma in mice. Cancer Cell; 15(4):294-303.	海外

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4.3-16	Freireich EJ, Gehan EA, Rall DP, et al. (1966) Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep; 50(4):219-44.	海外
4.3-17	Galabova-Kovacs G, Matzen D, Piazzolla D, et al. (2006) Essential role of B-Raf in ERK activation during extraembryonic development. Proc Natl Acad Sci USA; 103(5):1325-30.	海外
4.3-18	Gao B, St Pierre MV, Stieger B, et al. (2004) Differential expression of bile salt and organic anion transporters in developing rat liver. J Hepatol; 41(2):201-8.	海外
4.3-19	Grossauer S, Koeck K, Murphy NE, et al. (2016) Concurrent MEK targeted therapy prevents MAPK pathway reactivation during $BRAF^{V600E}$ targeted inhibition in a novel syngeneic murine glioma model. Oncotarget; 7(46):75839-53.	海外
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4.3-23	Knauf JA, Ma X, Smith EP, et al. (2005) Targeted expression of BRAFV600E in thyroid cells of transgenic mice results in papillary thyroid cancers that undergo dedifferentiation. Cancer Res; 65(10):4238-45.	海外
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3 第 5 部

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.2 全臨床試験一覧表							
5.2	―	全臨床試験一覧表	―	―	国内	評価	―
5.3 臨床試験報告書							
5.3.1 生物薬剤学試験報告書							
5.3.1.1 バイオアベイラビリティ（BA）試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.1.2 比較 BA 試験及び生物学的同等性（BE）試験報告書							
5.3.1.2-1	CDRB436G2101 - clinical study report	A randomized, open-label, three-period cross-over study to investigate the relative bioavailability of two new oral suspension formulations of dabrafenib (10 x 10 mg dispersible tablets reconstituted in water) in comparison to dabrafenib HPMC capsules (2 x 50 mg) following a single oral dose of 100 mg in healthy adult volunteers	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
	CDRB436G2101 - Clinical Study Report Addendum 01	Addendum 01 to Clinical Study Report CDRB436G2101	20[redacted]年[redacted]月[redacted]日	米国	海外	―	―
	DMPK RCDRB436G2101	Bioanalytical Data Report: Determination of GSK2118436, GSK2285403, GSK2167542, and GSK2298683 in Human Plasma	20[redacted]年[redacted]月[redacted]日	米国	海外	―	―
	DMPK RCDRB436G2101-01	Bioanalytical Data Report Amendment no. 01: Determination of GSK2118436, GSK2285403, GSK2167542, and GSK2298683 in Human Plasma	20[redacted]年[redacted]月[redacted]日	米国	海外	―	―

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.1.2-2	MEK115892	Clinical Pharmacology Study Report for MEK115892: An Open-Label, Two-Period, Randomized, Crossover Study to Assess the Relative Bioavailability of GSK1120212 Tablet Formulation and the GSK1120212 Pediatric Oral Solution Formulation Following Single-Dose Administration to Adult Subjects with Solid Tumors	20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
	2012N154264_00	Determination of GSK1120212 in human plasma samples from MEK115892 by HPLC with MS/MS detection	20[redacted]年[redacted]月[redacted]日	米国	海外	－	－
5.3.1.3 *In Vitro-In Vivo* の関連を検討した試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.1.4 生物学的及び理化学的分析法検討報告書							
5.3.1.4-1	2012N132488_00	Re-Validation of a Method for the Determination of GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-2	2015N244953_00 Addendum 02	Validation of a Method for the Determination of GSK2118436, GSK2285403, GSK2167542, and GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-3	DMPK R1600155 Addendum 03	Validation of a Method for the Determination of GSK2118436, GSK2285403, GSK2167542, and GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-4	DMPK R1600155a Addendum 04	Validation of a Method for the Determination of GSK2118436, GSK2285403, GSK2167542, and GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-5	DMPK R1600155b Addendum 05	Validation of a Method for the Determination of GSK2118436, GSK2285403, GSK2167542, and GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.1.4-6	2014N220583_02 Addendum 01	Re-Validation of a Method for the Determination of GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-7	2012N132488_01 Addendum 01	Re-Validation of a Method for the Determination of GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-8	2016N275845_00 Addendum 02	Re-Validation of a Method for the Determination of GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-9	DMPK R2000094 Addendum 03	Re-Validation of a Method for the Determination of GSK1120212 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-10	2015N230769_00 Addendum 02	Validation of a Method for the Determination of GSK2298683 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国、中国	海外	参考	なし
5.3.1.4-11	DMPK R1900331 Addendum 03	Validation of a Method for the Determination of GSK2298683 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.1.4-12	DMPK R1900331a Addendum 04	Validation of a Method for the Determination of GSK2298683 in Human Plasma by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	海外	参考	なし
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.3 臨床薬物動態（PK）試験報告書							
5.3.3.1 健康被験者における PK 及び初期忍容性試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.3.2 患者における PK 及び初期忍容性試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.3.3 内因性要因を検討した PK 試験報告書							
―	―	該当資料なし	―	―	―	―	―

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.3.4 外因性要因を検討した PK 試験報告書							
—	—	該当資料なし	—	—	—	—	—
5.3.3.5 ポピュレーション PK 試験報告書							
5.3.3.5-1	Study No. CDRB436A2102, CTMT212X2101, CDRB436G2201	Population pharmacokinetics of dabrafenib and trametinib in pediatric patients aged 6 years and older Modeling Report	20[redacted]年[redacted]月[redacted]日	米国	海外	評価	あり（non-CDISC）
5.3.4 臨床薬力学（PD）試験報告書							
—	—	該当資料なし	—	—	—	—	—
5.3.5 有効性及び安全性試験報告書							
5.3.5.1 申請する適応症に関する比較対照試験報告書							
—	—	該当資料なし	—	—	—	—	—
5.3.5.2 非対照試験報告書							
5.3.5.2-1	DRB436X2201	DRB436X2201 総括報告書	2014 年 3 月 12 日～ 2021 年 12 月 10 日	日本，オーストリア，ベルギー，カナダ，デンマーク，フランス，ドイツ，イタリア，韓国，オランダ，ノルウェー，米国，スウェーデン，スペイン	国際共同	評価	あり
	DMPK RCDRB436X2201	DMPK RCDRB436X2201 Final Bioanalytical Data Report: Determination of GSK1120212, GSK2118436, GSK2285403, and GSK2167542 in Human Plasma Samples	20[redacted]年[redacted]月[redacted]日	米国	—	—	—

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5.2-2	DRB436A2102	DRB436A2102 総括報告書	2013 年 5 月 23 日 ～2020 年 12 月 4 日	オーストラリア，カナダ，デンマーク，ドイツ，フランス，スペイン，イギリス，米国	外国	評価	あり
	DMPK RCDRB436A2102	DMPK RCDRB436A2102 Bioanalytical data report: Determination of GSK2118436, GSK2167542, GSK2285403, and GSK2298683 in Human Plasma Samples by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	－	－	－
5.3.5.2-3	TMT212X2101	TMT212X2101 総括報告書	2015 年 1 月 15 日～ 2020 年 12 月 29 日	オーストラリア，カナダ，フランス，イギリス，米国	外国	評価	あり
	DMPK RCTMT212X2101	DMPK RCTMT212X2101 Final bioanalytical data report: Determination of GSK1120212, GSK2118436, GSK2167542, GSK2285403, and GSK2298683 in Human Plasma Samples from MEK116540 by HPLC with MS/MS Detection	20[redacted]年[redacted]月[redacted]日	米国	－	－	－
	－	Errata	－	－	－	－	－
5.3.5.2-4	XUS35T	XUS35T 総括報告書	2016 年 1 月 4 日 ～20[redacted]年[redacted]月[redacted]日 （データカットオフ日） 本報告時点で継続中	米国	外国	参考	－
5.3.5.3 複数の試験成績を併せて解析した報告書							
5.3.5.3-1	－	SCE Appendix 1 Report on Individual Patient Requests for dabrafenib + trametinib combination therapy treatment of rare BRAF V600 mutation-positive tumors	－	－	－	－	－
5.3.5.3-2	－	SCE Appendix 2 Literature review – Dabrafenib/Trametinib Use in Rare BRAF V600E Mutation-Positive Solid Tumors	－	－	－	－	－

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5.3-3	—	SCE Appendix 4 Statistical analyses in support of the Individual Patient Request report	—	—	—	—	—
5.3.5.3-4	—	SCS Appendix 1	—	—	—	—	—
5.3.5.3-5	—	ISS-Metastatic Melanoma	—	—	—	—	—
5.3.5.3-6	—	SCS Addendum-MekTaf NSCLC 90-day update	—	—	—	—	—
	—	SCS Addendum-MekTaf NSCLC 90-day update Appendix 1	—	—	—	—	—
5.3.5.3-7	—	SCS Appendix 1 jp	—	—	—	—	—
5.3.5.4 その他の臨床試験報告書							
5.3.5.4-1	NCCH1901	NCCH1901 第 5 回定期モニタリングレポート	—	—	—	—	—
		NCCH1901 第 5 回定期モニタリングレポート別紙	—	—	—	—	—
		NCCH1901 主たる解析レポート	—	—	—	—	—
		NCCH1901 研究実施計画書	—	—	—	—	—
5.3.6 市販後の使用経験に関する報告書							
5.3.6-1	—	Tafinlar PSUR (27Aug2020-26Aug2021)	2020 年 8 月 27 日～ 2021 年 8 月 26 日	—	—	—	—
5.3.6-2	—	Mekinist PSUR (30May2020-29May2021)	2020 年 5 月 30 日～ 2021 年 5 月 29 日	—	—	—	—
5.3.6-3	CDRB436B1401	CDRB436B1401	2016 年 6 月 1 日～ 2021 年 11 月 29 日	日本	国内	—	—
5.3.6-4	CDRB436E1402	CDRB436E1402	2018 年 3 月 23 日～ 2021 年 11 月 29 日	日本	国内	—	—
5.3.7 患者データ一覧表及び症例記録							
—	—	該当資料なし	—	—	—	—	—

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