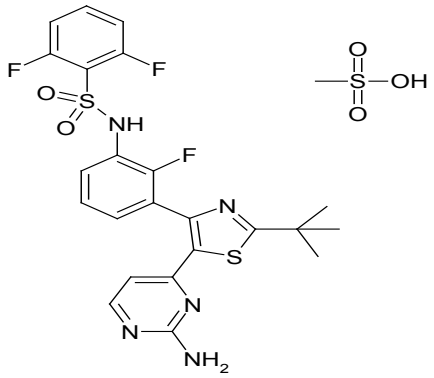
TAFINLAR[â] CAPSULES
PRODUCT INFORMATION

NAME OF THE MEDICINE

Dabrafenib mesilate



It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2$. CH_4O_3S and a molecular weight of 615.68.

CAS Registry Number: 1195768-06-9

DESCRIPTION

Dabrafenib mesilate is a nitrogen and sulphur containing heterocycle possessing an aromatic sulphonamide.

The chemical name for dabrafenib mesilate is N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulphonamide, methanesulphonate salt.

Dabrafenib mesilate is a white to slightly coloured solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media. The pKa of the sulfonamide moiety is 6.6, the pKa of the pyrimidine moiety is 2.2 and the pKa of the thiazole moiety is -1.5. The partition coefficient (log P) is 2.9.

The TAFINLAR Capsules contain 50 or 75 mg of dabrafenib mesilate as the active ingredient. The hard capsules also contain cellulose - microcrystalline, magnesium stearate, silica -colloidal anhydrous, iron oxide red, titanium dioxide, hypromellose, iron oxide black, shellac, butan-1-ol, isopropyl alcohol, propylene glycol, ammonium hydroxide

PHARMACOLOGY

Dabrafenib is an ATP-competitive inhibitor of RAF kinases with 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 a small number of other kinases, including wild-type BRAF and CRAF with IC_{50} values of 3.2 and 5.0nM, respectively. Mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including

approximately 50% of melanoma. The most commonly observed BRAF mutation, V600E, and the next most common, V600K, account for 95% of the BRAF mutations found in these cancers. A number of rare mutations also occur including V600D, V600G and V600R. Clinical inhibition of the MAPK pathway signalling depends on cellular and genotypic context (See PRECAUTIONS: Non-cutaneous malignancy).

Dabrafenib inhibits $BRAF^{V600}$ mutant melanoma cell growth *in vitro* and *in vivo*.

Pharmacodynamic Effects

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

In subjects with $BRAF^{V600}$ mutant melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Determination of BRAF mutation status

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) developed by Response Genetics Inc. (RGI). The RGI 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.

Pharmacokinetics

The pharmacokinetics of dabrafenib were determined in patients with BRAF mutation-positive metastatic melanoma after single dose and after repeat dosing at 150 mg twice daily with dosing approximately 12 hours apart.

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 75 and 150 mg following single-dose administration, but the increase was slightly less than dose-proportional after repeat twice daily dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios averaged 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, $AUC_{(0\text{-}t)}$ and predose concentration (Ct) at steady state 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.

Metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized 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 hours 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.

Excretion

Terminal half-life following IV microdose is 2.6 hours. Dabrafenib terminal half-life is 8 hours due to a prolonged terminal phase after oral administration. IV plasma clearance after single dose is 12 L/hr. Following repeat oral dose administration, the oral clearance (CL/F) is 35 L/hr.

Faecal excretion is the major route of elimination after oral dose, accounting for 71% of a radioactive dose while urinary excretion accounted for 23% of radioactivity as metabolites.

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 DOSAGE AND ADMINISTRATION*).*

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 DOSAGE AND ADMINISTRATION*).*

Age: 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: There are insufficient data to evaluate the potential effect of race on dabrafenib pharmacokinetics.

CLINICAL TRIALS

The efficacy of TAFINLAR in the treatment of adult patients with $BRAF^{V600}$ mutation positive unresectable or metastatic melanoma has been evaluated in 3 studies (BRF113683 [BREAK-3], BRF113710 [BREAK-2] and BRF113929 [BREAK-MB]). Included

in these studies were in total 402 subjects with BRAF V600E and 49 subjects with BRAF V600K mutation. Patients with evidence of active CNS disease (e.g. radiographically unstable or with symptomatic lesions) and those with disease progression in the brain in the last 3 months were excluded from the pivotal Phase III study.

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. Screening included central testing of BRAF mutation V600E using a BRAF mutation assay conducted on the most recent tumour sample available.

The trial enrolled 250 patients randomised 3:1 to receive either dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks. The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to progression-free survival (PFS) per investigator assessment for patients with $BRAF^{V600E}$ mutation positive metastatic melanoma. Patients on the DTIC arm were allowed to cross over and receive 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% CI 0.18, 0.51; p< 0.0001) was achieved. PFS from the primary analysis is shown in Figure 1. Efficacy results from a post-hoc analysis with 6-months additional follow-up are summarised in Table 1. Overall survival data from a further post-hoc analysis based on an 18 December 2012 data cut is provided in Table 2 and shown in Figure 2.

Table 1: Efficacy in previously untreated patients (BREAK-3 study, 25 June 2012)

	Intention-to-Treat Population	
Endpoints/ Assessment	**TAFINLAR N=187**	**DTIC N=63**
Progression-free survival		
Median, months (95% CI)	6.9 (5.2, 9.0)	2.7 (1.5, 3.2)
HR (95% CI)	0.37 (0.24, 0.58)	
	P<0.0001	
Overall response[a]		
% (95% CI)[b]	59 (51.4, 66.0)	24 (21.4, 36.2)
	P<0.0001	
Duration of response		
	N=110	N=15
Median, months (95% CI)	8.0 (6.6, 11.5)	7.6 (5.0, 9.7)

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR-not reached

a. Defined as complete response+partial response.
b. Confirmed response.

As of 25 June 2012, thirty-five subjects (55.6%) of the 63 randomised to DTIC crossed over to TAFINLAR. Median PFS after cross-over was 4.4 months.

Figure 1: Progression-Free Survival - previously untreated patients (BREAK 3 ITT population, 19 December 2011)

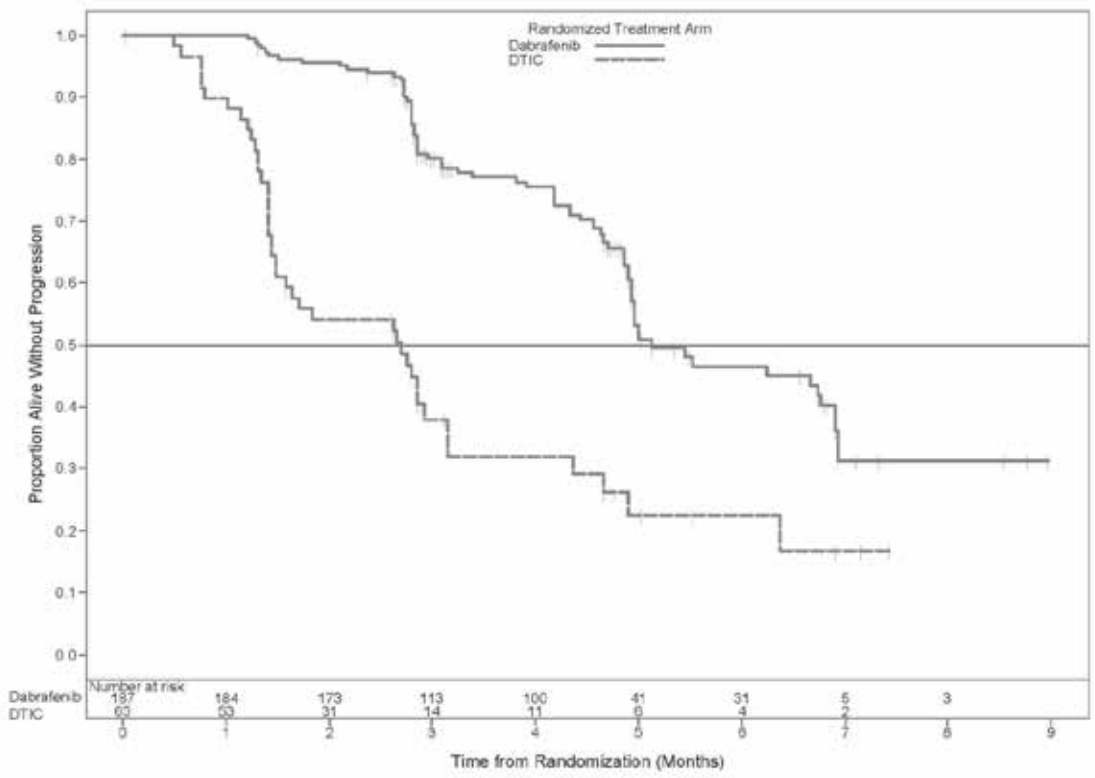
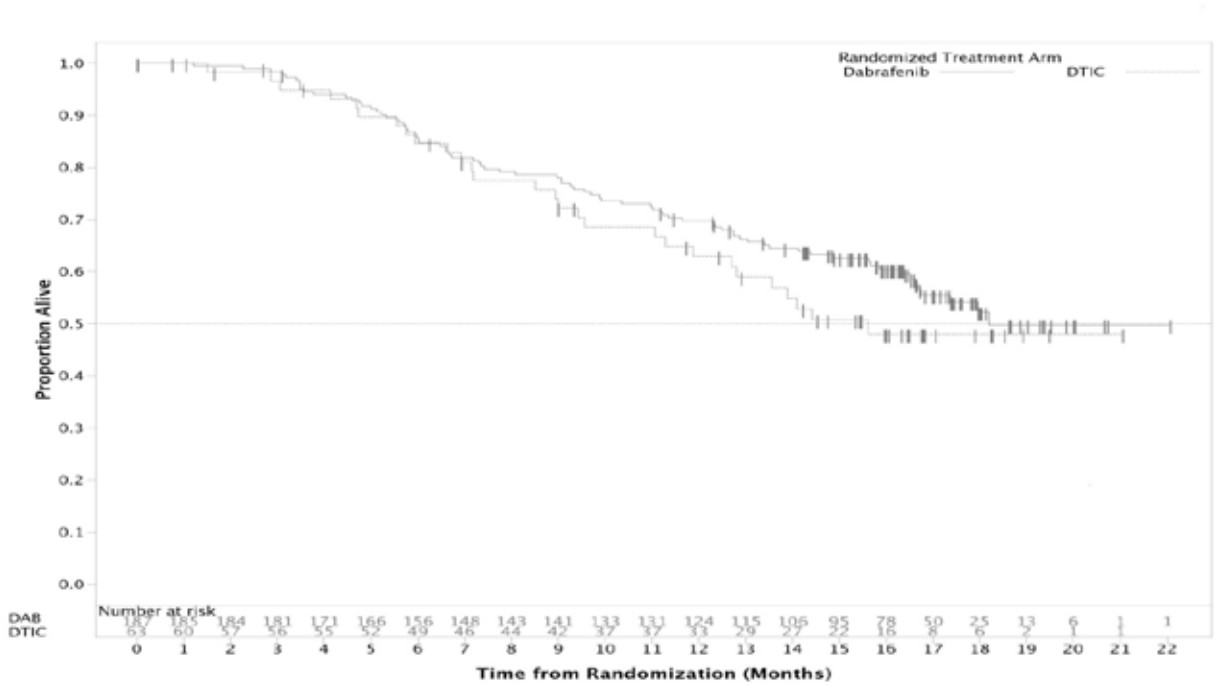


Table 2: Survival data from a post-hoc analysis (18 December 2012).

Treatment	Number of deaths (%)	12-month OS rate	Hazard Ratio (95% CI)
DTIC	28 (44%)	63%	0.76 (0.48, 1.21) [(a)]
dabrafenib	78 (42%)	70%	

Patients were not censored at the time of cross-over.

Figure 2: 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 multi-centre, 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), which is a measure of response (CR+PR) of intracranial lesions using modified RECIST criteria as assessed by investigators. The results are summarised in Table 3. Of note, the benefit risk, in terms of intracranial response, relative to surgery or stereotactic radio-surgery has not been studied directly however evidence from cohort B below suggests that prior local treatment does not preclude subsequent benefit from BRAF inhibition.

Table 3: Efficacy Data in Patients with Brain Metastases (BREAK-MB study)

	All Treated Subjects Population			
	$BRAF^{V600E}$ (Primary)		$BRAF^{V600K}$	
Endpoints/ Assessment	**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	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)				
	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 $BRAF^{V600E}$ positive subjects.

Patients who were previously untreated or failed at least one prior systemic therapy (Results from the phase II study BREAK-2)

BRF113710 (BREAK-2) was a multi-centre, global, open-label, single-arm, Phase II study that enrolled 92 subjects with histologically confirmed metastatic melanoma (Stage IV) with confirmed $BRAF^{V600E \text{ or } V600K}$ mutation-positive melanoma. Subjects were treatment-naïve (n=15) or received prior treatment (n=77) in the metastatic setting (i.e., chemotherapy, immunotherapy, prior targeted therapy, etc.).

The investigator assessed confirmed response rate in the primary efficacy population of patients with $BRAF^{V600E}$ metastatic melanoma (n=76) was 59% (95% CI: 48.2, 70.3) including 7% complete response. Median PFS was 6.3 months (95% CI: 4.6, 7.7) and the median duration of response was 5.2 months (95% CI: 3.9, not calculable). Prior systemic therapy did not appear to significantly impact response. The investigator assessed confirmed response rate in a secondary efficacy population of patients with $BRAF^{V600K}$ mutation positive metastatic melanoma (n=16) was 13% (95% CI: 0.0, 28.7) with a median duration of response of 5.3 months (95% CI: 3.7, 6.8). There were no complete responses in the V600K patient population. Although the evidence for the efficacy of dabrafenib is limited by the low number of patients, median OS appeared consistent with data in patients with BRAF V600E positive tumours.

INDICATIONS

TAFINLAR is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

CONTRAINDICATIONS

TAFINLAR is contraindicated in patients with hypersensitivity to the active substance dabrafenib mesilate or any of the excipients (see DESCRIPTION).

PRECAUTIONS

Before taking dabrafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma (see CLINICAL TRIALS). Further around 40% of BRAF wild-type metastatic melanomas have oncogenic NRAS mutations which may result in paradoxical activation of MAP-kinase signalling in the presence of BRAF inhibitors such as dabrafenib and may lead to accelerated tumour growth. Dabrafenib should not be used in patients with BRAF wild-type melanoma.

Pyrexia and serious non-infectious febrile events

Fever has been reported in clinical trials. In 1% of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency (See ADVERSE EFFECTS). 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.

Therapy with dabrafenib should be interrupted if the patient's temperature is ≥ 38.5ºC. Patients should be evaluated for signs and symptoms of infection. TAFINLAR can be restarted once the fever resolves with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. If fever is associated with other severe signs or symptoms, TAFINLAR should be restarted at a reduced dose once fever resolves and as clinically appropriate.

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with TAFINLAR (see ADVERSE EFFECTS). Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. It is recommended that skin examination be performed prior to initiation of TAFINLAR and every month throughout treatment with TAFINLAR and for up to 6 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 TAFINLAR treatment 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. These were identified within the first 5 months of therapy, were managed with excision and did not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancy

In vitro experiments have demonstrated paradoxical activation of 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 TAFINLAR exposure, when RAS mutations are present. Cases of RAS-associated malignancies have been reported, both with another BRAF inhibitor (Chronic myelomonocytic leukemia and non-cutaneous SCC of the head and neck) and with TAFINLAR when administered in combination with the MEK inhibitor trametinib (colorectal cancer, pancreatic cancer). Patients should be monitored as clinically appropriate for up to 6 months after discontinuation of TAFINLAR or until initiation of another anti-neoplastic therapy.

Uveitis

Ophthalmologic reactions, including uveitis and iritis have been reported.. Patients should be routinely monitored for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy.

Pancreatitis

Pancreatitis has been reported in < 1% of dabrafenib-treated subjects. 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.

Hyperglycaemia

Hyperglycaemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycaemic 68 agent therapy can occur with TAFINLAR. In the pivotal study, five of 12 patients with a history of diabetes required more intensive hypoglycaemic therapy while taking TAFINLAR. The incidence of Grade 3 hyperglycaemia based on laboratory values was 6% (12/187) in patients treated with TAFINLAR compared to none of the dacarbazine-treated patients. Monitor serum glucose levels as clinically appropriate during treatment with TAFINLAR in patients with pre-existing diabetes or hyperglycaemia. Advise patients to report symptoms of severe hyperglycaemia such as excessive thirst or any increase in the volume or frequency of urination.

Renal failure

Renal failure has been identified in <1% of patients treated with TAFINLAR. Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported. 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.

Effects on Fertility

There are no data in humans. Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

In combined female fertility, early embryonic and embryofetal 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 estrous cycle, mating or fertility.

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

Use in Pregnancy (Category D)

There are no adequate and well-controlled studies of TAFINLAR in pregnant women. Animal studies have shown embryofetal development toxicity, including teratogenic effects. In adult female rats dosed with dabrafenib before mating and during gestation embryofetal toxicities included embryo-lethality and fetal ventricular septal defects at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC) TAFINLAR 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 TAFINLAR, the patient should be informed of the potential hazard to the fetus.

Use in Lactation

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

Paediatric Use

The safety and efficacy of TAFINLAR has not been yet established in children and adolescents (< 18 years). 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), testicular toxicity (degeneration and tubular dilation) and earlier vaginal opening (with no associated effects on ovarian weights or morphologic changes in female reproductive tissues) were observed.

Use in the Elderly

No dose adjustment is required in patients over 65 years (see DOSAGE AND ADMINISTRATION and PHARMACOKINETICS). Compared with younger subjects (< 65), more subjects over 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.

Genotoxicity

Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Carcinogenicity

Carcinogenicity studies with dabrafenib have not been conducted. An increase in cutaneous malignancies has been observed with BRAF inhibitors with preliminary evidence suggesting this occurs in patients harbouring other MAPK pathway mutations, including RAS, in skin (see PRECAUTIONS for cuSCC, new primary melanoma and non-cutaneous malignancy).

Ability to perform tasks that require judgement, motor or cognitive skills

There have been no studies to investigate the effect of dabrafenib on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of dabrafenib. The clinical status of the patient and the adverse event profile of dabrafenib should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

INTERACTIONS WITH OTHER MEDICINES

Effect of Other Medicines on TAFINLAR

Dabrafenib is a substrate of CYP2C8 and CYP3A4, while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Co-administration of ketoconazole (CYP3A4 inhibitor) and gemfibrozil (CYP2C8 inhibitor) increased the AUC of dabrafenib by 71 and 47%, respectively. Pharmacokinetic data showed increases in hydroxy- and desmethyl-dabrafenib AUC with ketokonazole (increases of 82 and 68% respectively while a decrease in AUC was noted for carboxy-dabrafenib (decrease of 16%). No clinically relevant changes were noted in the AUC of the metabolites during co-administration with gemfibrozil. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are 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, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are coadministered with dabrafenib. Avoid coadministration of TAFINLAR with potent inducers of CYP2C8 or CYP3A4 (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, St. John's wort (Hypericum perforatum)).

Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Medicinal products such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

Effect of TAFINLAR on Other Medicines

Dabrafenib induces CYP3A4- and CYP2C9-mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters. The single dose AUC of midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate) was decreased by 74 and 37%, respectively with co-administration of dabrafenib. Co-administration of dabrafenib and medicinal products which are affected by the induction of these enzymes or transporters such as hormonal contraceptives (see PRECAUTIONS -PREGNANCY AND LACTATION*)*, dexamethasone, antiretroviral agents, or immunosuppressants may result in decreased concentrations and loss of efficacy. Concomitant use of dabrafenib with these medicinal products should generally be avoided if monitoring for efficacy and dose adjustment is not possible.

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Transient inhibition of CYP3A4 may be observed during the first few days of treatment. Upon discontinuation of dabrafenib, concentrations of sensitive CYP3A4 substrates may increase and subjects should be monitored for toxicity and dosage of these agents may need to be adjusted.

Exercise caution and consider additional INR (International Normalized Ratio) monitoring when dabrafenib is used concomitantly with warfarin.

Effects of dabrafenib on substance transport systems

Dabrafenib is an in vitro inhibitor of of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1) and OATP1B3 and clinical relevance cannot be excluded. Therefore caution is recommended at co-administration of dabrafenib and OATB1B1 or OATP1B3 substrates such as statins.

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, the risk of a drug-drug interaction is minimal based on clinical exposure.

Dabrafenib and desmethyl-dabrafenib were also shown to be moderate inhibitors of human breast cancer resistance protein (BCRP); however, based on clinical exposure, the risk of a drug-drug interaction is minimal.

Neither dabrafenib nor its 3 metabolites were demonstrated to be inhibitors of P-glycoprotein (Pgp) in vitro.

ADVERSE EFFECTS

Clinical Trial Data

Safety data were integrated from five clinical monotherapy studies and included 578 patients with melanoma. Approximately 30% of patients received treatment with dabrafenib for more than 6 months.

In the integrated dabrafenib safety population, the most common (³ 15%) adverse reactions were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, skin papilloma, alopecia, rash and vomiting.

Adverse reactions are listed below by MedDRA body system organ class.

The following convention has been utilised for the classification of frequency:

Very common	³ 1 in 10
Common	³ 1 in 100 to < 1 in 10
Uncommon	³ 1 in 1,000 to < 1 in 100
Rare	³ 1 in 10,000 to < 1 in 1,000
Very rare	< 1 in 10,000

Neoplasms benign and malignant (including cysts and polyps)

Very common	Papilloma
Common	Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrhoeic keratosis, basal cell carcinoma
Uncommon	New primary melanoma

Immune System Disorders

Uncommon	Hypersensitivity, panniculitis

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	Skin effects (rash, hyperkeratosis), alopecia, palmar-plantar erythrodysaesthesia syndrome
Common	Skin effects (actinic keratosis, skin lesion, dry skin, erythema)

Musculoskeletal and connective tissue disorders

Very common	Arthralgia, myalgia, pain in extremity

Renal disorders

Uncommon	Renal failure, acute renal failure, nephritis

General disorders and administration site conditions

Very common	Asthenia, chills, fatigue, pyrexia
Common	Influenza-like illness

Investigations

Common	LVEF decrease
Uncommon	QT prolongation

Table 4 lists the very common (³ 10% of subjects) adverse events reported in the Phase III randomised, open-label study [BREAK-3].

Table 4: Adverse events reported in at Least 10% of subjects receiving TAFINLAR or Placebo in BREAK-3 (Safety Population) by maximum grade.

Preferred term	Number (%) of Subjects					
	Dabrafenib (N=187)			DTIC (N=59)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any event	**185 (99)**	**55 (29)**	**7 (4)**	**54 (92)**	**16 (27)**	**8 (14)**
Hyperkeratosis	69 (37)	1 (<1)	1 (<1)	0	0	0
Headache	59 (32)	0	0	5 (8)	0	0
Pyrexia	52 (28)	6 (3)	0	6 (10)	0	0
Arthralgia	51 (27)	2 (1)	0	1 (2)	0	0
Skin papilloma	45 (24)	0	0	1 (2)	0	0
Alopecia	41 (22)	0	0	1 (2)	0	0
PPE syndrome	37 (20)	4 (2)	0	1 (2)	0	0
Fatigue	36 (19)	2 (1)	0	14 (24)	0	0
Nausea	35 (19)	0	1 (<1)	30 (51)	0	0
Asthenia	33 (18)	1 (<1)	0	9 (15)	1 (2)	0
Rash	31 (17)	0	0	0	0	0
Vomiting	23 (12)	1 (<1)	1 (<1)	15 (25)	0	0
Cough	23 (12)	0	0	3 (5)	0	0
Back pain	22 (12)	5 (3)	0	4 (7)	0	0
Constipation	21 (11)	2 (1)	1 (<1)	8 (14)	0	0
Diarrhoea	20 (11)	1 (<1)	0	7 (12)	0	0
Myalgia	20 (11)	0	0	0	0	0
Nasopharyngitis	19 (10)	0	0	2 (3)	0	0
Pain in extremity	16 (9)	1 (<1)	0	7 (12)	0	0
Abdominal pain	7 (4)	1 (<1)	0	8 (14)	0	1 (2)
Anaemia	7 (4)	1 (<1)	0	7 (12)	1 (2)	1 (2)
Neutropenia	2 (1)	1 (<1)	0	10 (17)	4 (7)	4 (7)
Leukopenia	1 (<1)	0	0	6 (10)	2 (3)	0

DTIC = dacarbazine, PPE = palmar-plantar erythrodysaesthesia

Table 5 Incidence of Laboratory Abnormalities Increased from Baseline Occurring at a Higher Incidence in Patients Treated with TAFINLAR in BRF113683 [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3 or 4)]

	Dabrafenib (n=187)		DTIC (n=59)	
	All Grades (%)	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
Hyperglycemia	**50**	**6**	**43**	0
Hypophosphatemia	**37**	**6***	**14**	2
Increased Alkaline phosphatase	**19**	**0**	**14**	2
Hyponatremia	**8**	**2**	**3**	0

*Grade 4 laboratory abnormality limited to hypophosphatemia (n=1).

Description of selected adverse reactions

Pyrexia

Fever has been reported in clinical trials. In 1% of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency. 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 DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 9% (52/578) of patients treated with TAFINLAR. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. Ninety-six percent of patients who developed cuSCC continued on treatment without dose modification.

New primary melanoma

New primary melanomas have been reported in clinical trials with TAFINLAR. Cases were managed with excision and did not require treatment modification (see PRECAUTIONS).

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 PRECAUTIONS).Cases of RAS-driven malignancies have been seen with TAFINLAR. Patients should be monitored as clinically appropriate.

Special populations

Elderly population

Of the total number of patients in clinical studies of dabrafenib (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 events that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse events compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these subjects and younger subjects.

DOSAGE AND ADMINISTRATION

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for TAFINLAR therapy.

The efficacy and safety of TAFINLAR have not been established in patients with wild-type BRAF melanoma (*see* CLINICAL TRIALS). TAFINLAR should not be used in patients with BRAF wild-type melanoma (see PRECAUTIONS).

Adults

The recommended dose is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg).

TAFINLAR should be taken either at least one hour before, or at least two hours after a meal, leaving an interval of approximately 12 hours between doses. TAFINLAR should be taken at similar times every day.

Treatment should continue until disease progression or the development of unacceptable toxicity (see Table 7).

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

Dose modifications

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 6 and Table 7).

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

Therapy should be interrupted if the patient's temperature is ≥ 38.5°C. Patients should be evaluated for signs and symptoms of infection (see PRECAUTIONS).

Recommended dose level reductions and recommendations for dose modifications are provided in Table 6 and Table 7, respectively. Dose adjustments resulting in a dose lower than 50 mg twice daily are not recommended.

Table 6: **Recommended TAFINLAR dose level reductions**

Dose Level	**Dose/Schedule**
Full dose	150 mg twice daily
First reduction	100 mg twice daily
Second reduction	75 mg twice daily
Third reduction	50 mg twice daily

Table 7: **TAFINLAR dose modification schedule**

Grade (CTC-AE)*	**Recommended TAFINLAR Dose Modifications**
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 – 1 and reduce

	by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until grade 0 – 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 dose should not exceed 150 mg twice daily.

Populations

Paediatric population

The safety and efficacy of TAFINLAR have not been established in children and adolescents (< 18 years). Studies in juvenile animals have shown effects of dabrafenib which had not been observed in adult animals (see PRECAUTIONS).

Elderly

No dose adjustment is required in patients over 65 years (see PHARMACOKINETICS).

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on dabrafenib oral clearance or on the concentrations of its metabolites (see PHARMACOKINETICS). There are no clinical data in subjects with severe renal impairment and the potential need for dose adjustment cannot be determined. TAFINLAR should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on dabrafenib oral clearance or on the concentrations of its metabolites (see PHARMACOKINETICS). There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. 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. TAFINLAR should be used with caution in patients with moderate or severe hepatic impairment.

OVERDOSAGE

Symptoms and Signs

There is currently very limited experience with overdosage with TAFINLAR. The maximum dose of TAFINLAR administered during clinical trials was 600 mg (300 mg twice daily).

Treatment

There is no specific antidote for overdosage of TAFINLAR. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, TAFINLAR should be withheld and supportive care instituted. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The TAFINLAR 50 mg capsules are, opaque, size 2 hard capsule composed of a dark red body and dark red cap containing a white to slightly coloured solid. The capsule shells are imprinted with GS TEW and 50 mg. The TAFINLAR 50 mg capsules are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 28 or 120 capsules.

The TAFINLAR 75 mg capsules are opaque, size 1 hard capsule composed of a dark pink body and dark pink cap containing a white to slightly coloured solid. The capsule shells are imprinted with GS LHF and 75 mg. The TAFINLAR 75 mg capsule are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 28 or 120 capsules.

Storage Conditions

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
21 August 2013

Date of most recent amendment: 21 August 2013

TAFINLAR is a registered trade mark of the GlaxoSmithKline group of companies.

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