

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

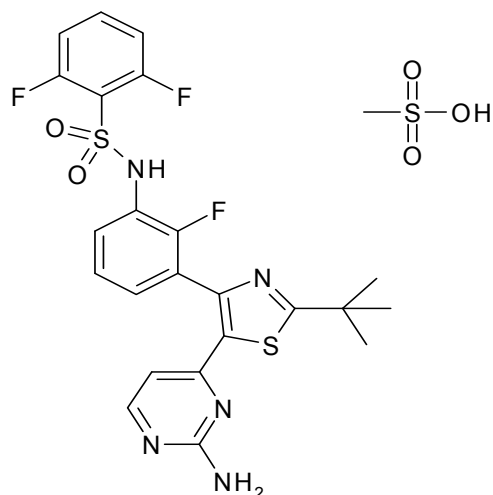
Tafinlar 50mg hard capsules

Tafinlar 75mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: dabrafenib mesilate

Chemical name: N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulphonamide, methane sulphonate salt



Molecular formula:  $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$

Molecular weight: 615.68

CAS Registry Number: 1195768-06-9

### Active Substance

#### Hard Capsules

- **50mg:** Each hard capsule contains 50mg of dabrafenib (as mesilate).
- **75mg:** Each hard capsule contains 75mg of dabrafenib (as mesilate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsules.

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

### **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.

### **TAFINLAR 75 mg**

# NEW ZEALAND DATA SHEET

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.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

### 4.2 Dose and method of administration

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for TAFINLAR therapy and in combination with trametinib (see section 5.1). The efficacy and safety of TAFINLAR have not been established in patients with wild-type BRAF melanoma (see section 5.1). TAFINLAR should not be used in patients with BRAF wild-type melanoma (see section 4.4).

When dabrafenib is used in combination with trametinib, please refer to the full trametinib Data Sheet: Dosage and administration, for trametinib dosing instructions.

### Dosage

#### **Adults**

The recommended dose of Tafinlar either 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). Treatment should continue until disease progression or the development of unacceptable toxicity (see Table 1).

When dabrafenib and trametinib are taken in combination, take the once-daily dose of trametinib at the same time each day with either the morning dose or the evening dose of dabrafenib.

### Dose modifications

#### *Monotherapy and in combination with dabrafenib*

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1 and Table 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).

Therapy should be interrupted if the patient's temperature is  $\geq 38.5^{\circ}\text{C}$ . Patients should be evaluated for signs and symptoms of infection (see section 4.4).

Recommended dose level reductions and recommendations for dose modifications are provided in Table 1 and Table 2, respectively. Dose adjustments resulting in a dose lower than 50 mg twice daily are not recommended.

**Table 1 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 2 TAFINLAR dose modification schedule for haemorrhagic events**

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

## NEW ZEALAND DATA SHEET

	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.

If treatment related toxicities occur when dabrafenib is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below.

Exceptions where dose modifications are necessary for only dabrafenib:

- Pyrexia
- Uveitis

Refer to the full data sheet of trametinib for dose modification guidelines.

### Detailed dosing modifications for selected adverse reactions

#### *New Primary Malignancies:*

For New Primary Cutaneous Malignancies no dose modifications are required. For New Primary Non-Cutaneous Malignancies, permanently discontinue Tafinlar in patients who develop RAS mutation-positive non-cutaneous malignancies.

#### *Haemorrhagic events:*

Permanently discontinue Tafinlar, and also permanently discontinue trametinib if administered in combination, for all Grade 4 haemorrhagic events and for any Grade 3 haemorrhagic events that do not improve.

Withhold Tafinlar for up to 3 weeks for Grade 3 haemorrhagic events; if improved resume at a lower dose level.

If used in combination, withhold trametinib for Grade 3 haemorrhagic events; if improved resume at a lower dose level.

#### *Pyrexia Management*

If the patient's temperature is  $\geq 38.5^{\circ}\text{C}$ , therapy with Tafinlar should be interrupted when dabrafenib is used as monotherapy or in combination with trametinib; trametinib should be continued at the same dose. Initiate treatment with anti-pyretics such as ibuprofen or paracetamol. Patients should be evaluated for signs and symptoms of infection (see section 4.4)

The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

<b>Patient's temperature</b>	<b>MEKINIST monotherapy</b>	<b>MEKINIST combination therapy with dabrafenib</b>
38.5°C - 40°C	Do not modify the MEKINIST dose	Do not modify the MEKINIST dose. Withhold dabrafenib.  Upon resolution of pyrexia, resume dabrafenib with appropriate anti-pyretic prophylaxis either at the same dose level, or reduce dabrafenib one dose level, if pyrexia is recurrent.
> 40°C or if fever is complicated	Withhold MEKINIST until fever resolves.  Upon resolution of pyrexia,	Withhold MEKINIST and dabrafenib. Initiate treatment with anti-pyretics such as ibuprofen (preferred) or paracetamol.

## NEW ZEALAND DATA SHEET

Patient's temperature	MEKINIST monotherapy	MEKINIST combination therapy with dabrafenib
by rigors, hypotension, dehydration, or renal failure	resume MEKINIST at same or lower dose level.	Upon resolution of pyrexia, resume therapy with appropriate anti-pyretic prophylaxis with: <ul style="list-style-type: none"> <li>• MEKINIST at the same or at a lower dose level and</li> <li>• dabrafenib at either a lower dose level or permanently discontinue dabrafenib</li> </ul>

Upon resolution of pyrexia, therapy can be restarted with appropriate anti-pyretic prophylaxis either:

- Tafinlar at a lower dose level, and if being used in combination with trametinib: trametinib at the same or lower dose level
- Or permanently discontinue Tafinlar

### *Uveitis Management*

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.

### **Special populations**

#### *Paediatric patients (< 18 years of age)*

The safety and efficacy of TAFINLAR have not been established in children and adolescents (< 18 years). Tafinlar is not recommended in this age group.

Studies in juvenile animals have shown effects of dabrafenib which had not been observed in adult animals (see section 4.4).

*Patients > 65 years of age* No dose adjustment is required in patients over 65 years (see section 5.2).

#### *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 section 5.2). 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 section 5.2) 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.

### **Administration**

Swallow the capsules whole with a full glass of water.

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.

## NEW ZEALAND DATA SHEET

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

### 4.3 Contraindications

TAFINLAR is contraindicated in patients with hypersensitivity to the active substance dabrafenib mesilate or any of the excipients (see section 6.1).

### 4.4 Special warnings and precautions for use

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 section 5.1). 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

Pyrexia was reported in clinical trials with dabrafenib monotherapy and in combination with trametinib (see section 4.8). In a Phase III clinical trial in patients with melanoma, the incidence and severity of pyrexia were increased when Tafinlar was used in combination with trametinib (57% [119/209], 7% Grade 3) as compared to dabrafenib monotherapy (33% [69/211], 2% Grade 3). In patients with melanoma who received the combination dose of Tafinlar 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had three or more events. Pyrexia may be accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency (See sections 4.4 and 4.8). Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

For management of pyrexia, see Dosage and Administration, Dose Modification Guidelines and the full data sheet for trametinib.

#### 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 section 4.8). In a Phase III study in patients with melanoma, 10 % (22/211) of patients receiving dabrafenib monotherapy developed cuSCC with a median time to the first occurrence of approximately 8 weeks. In patients who received the combination dose of TAFINLAR in combination with trametinib, 3 % (6/209) of patients developed cuSCC and, events occurred later, with the median time to onset of the first occurrence of 20 to 32 weeks. More than 90 % of patients on TAFINLAR who developed cuSCC continued on treatment without dose modification.

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 ZEALAND DATA SHEET

New primary melanomas have been reported in patients treated with dabrafenib. In clinical trials in melanoma, 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 secondary/recurrent 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, which may lead to increased risk of non-cutaneous malignancies in patients treated with TAFINLAR. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. Consider the benefits and risks before continuing treatment with TAFINLAR in patients with a non-cutaneous malignancy that has a RAS mutation.

Following discontinuation of TAFINLAR, monitoring for non-cutaneous secondary/ recurrent malignancies should continue for up to 6 months 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 in melanoma clinical trials. One of the events occurred on the first day of dosing of a melanoma patient and recurred following re-challenge at a reduced dose. 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.

### TAFINLAR in combination with trametinib

See the data sheet for trametinib Special Warnings and Precautions for Use.

### Haemorrhage

## NEW ZEALAND DATA SHEET

Haemorrhagic events, including major haemorrhagic events have occurred in patients taking trametinib in combination with TAFINLAR (see section 4.8). Out of the 559 patients treated with TAFINLAR in combination with trametinib, there were six fatal intracranial haemorrhagic events (1 %). If patients develop symptoms of haemorrhage they should immediately seek medical care.

### 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) and testicular toxicity (degeneration and tubular dilation) were observed.

### Use in the Elderly

No dose adjustment is required in patients over 65 years (see sections 4.2 and 5.2). 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. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

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 section 4.4).

### 4.5 Interaction with other medicines and other forms of interaction

Dabrafenib induces CYP3A4- and CYP2C9-mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters.

Dabrafenib and may also induce transporters (e.g. P-glycoprotein (P-gp)). In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels.

Co-administration of dabrafenib and medicinal products which are affected by the induction of these enzymes or transporters such as hormonal contraceptives (see sections 4.4 and 4.6), 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. If co-administration of these medications is necessary, monitor subjects for loss of efficacy or consider substitutions of these medicinal products.

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.

### Midazolam

## NEW ZEALAND DATA SHEET

In a clinical study in 12 subjects using a single dose of midazolam (a CYP3A4 substrate),  $C_{max}$  and AUC were decreased by 61 % and 74 % respectively with co-administration of repeat dose Tafinlar 150 mg BID.

### Warfarin

In a separate trial in 14 subjects, repeat-dosed Tafinlar decreased the single-dose AUC of S-warfarin (a CYP2C9 substrate) and of R-warfarin (a substrate of CYP3A4/CYP1A2) by 37 % and 33 % respectively, with a small increase in  $C_{max}$  (18 % and 19 % respectively). 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 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 OATP1B1 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 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 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 (P-gp) *in vitro*.

### Combination of dabrafenib with trametinib

Co-administration of repeat dosing dabrafenib 150 mg twice daily and trametinib 2 mg once daily resulted in a 16% increase in dabrafenib  $C_{max}$  and a 23% increase in dabrafenib AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when TAFINLAR is administered in combination with Mekinist using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib  $C_{max}$  and AUC are considered not clinically relevant. See the full data sheet for Mekinist for guidelines on drug interactions associated with Mekinist monotherapy.

## 4.6 Fertility, pregnancy and lactation

### **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 oestrous cycle, mating or fertility. 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  $\geq 20$  mg/kg/day ( $\geq 0.5$  times human clinical exposure based on AUC).



## NEW ZEALAND DATA SHEET

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 ( $\geq 0.2$  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)**

Tafinlar can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of TAFINLAR in pregnant women. Reproductive studies in animals have demonstrated TAFINLAR induced embryofetal development toxicity, including teratogenic effects. In adult female rats dosed with dabrafenib before mating and during gestation, embryofetal toxicities included embryo-lethality and foetal ventricular septal defects and variation in thymic shape were observed at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at  $\geq 20$  mg/kg/day ( $\geq 0.5$  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 foetus.

### Women of childbearing potential

Women of childbearing potential should be advised that animal studies have been performed showing Tafinlar to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective methods of contraception (methods that result in less than 1% pregnancy rates) during therapy and for 4 weeks following discontinuation of dabrafenib. Dabrafenib may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as barrier methods, should be used (see section 4.5).

### **Use in Lactation**

There are no data on the effect of Tafinlar on the breast-fed child, or the effect of TAFINLAR on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in a suckling child from TAFINLAR, a nursing mother should be advised of the potential risks to the child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Tafinlar and any potential adverse effects on the breast-fed child from Tafinlar or from the underlying maternal condition.

### **4.7 Effects on ability to drive and use machines**

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.

### **4.8 Undesirable effects**

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

### Clinical Trial Data

## NEW ZEALAND DATA SHEET

Safety data were integrated from five clinical monotherapy studies and included 578 patients with BRAF V600 mutant unresectable or metastatic melanoma. Approximately 30% of patients received treatment with dabrafenib for more than 6 months.

In the integrated dabrafenib safety population, the most common ( $\geq 15\%$ ) 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	$\geq 1$ in 10
Common	$\geq 1$ in 100 to $< 1$ in 10
Uncommon	$\geq 1$ in 1,000 to $< 1$ in 100

**Table 3 Adverse reactions with Tafinlar monotherapy**

<b><i>Neoplasms benign and malignant (including cysts and polyps)</i></b>	
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, seborrheic keratosis, basal cell carcinoma
Uncommon	New primary melanoma
<b><i>Immune System Disorders</i></b>	
Uncommon	Hypersensitivity, panniculitis
<b><i>Infections and infestations</i></b>	
Common	Nasopharyngitis
<b><i>Metabolism and nutrition disorders</i></b>	
Very common	Decreased appetite
Common	Hypophosphataemia, hyperglycaemia
<b><i>Nervous system disorders</i></b>	
Very common	Headache
<b><i>Eye disorders</i></b>	
Uncommon	Uveitis
<b><i>Respiratory, thoracic and mediastinal disorders</i></b>	
Very common	Cough
<b><i>Gastrointestinal disorders</i></b>	
Very common	Nausea, vomiting, diarrhoea
Common	Constipation
Uncommon	Pancreatitis
<b><i>Skin and subcutaneous tissue disorders</i></b>	
Very common	Skin effects (rash, hyperkeratosis), alopecia, palmar-plantar erythrodysesthesia syndrome
Common	Skin effects (actinic keratosis, skin lesion, dry skin, erythema), pruritus, photosensitivity reaction <sup>1)</sup>
Uncommon	Panniculitis
<b><i>Musculoskeletal and connective tissue disorders</i></b>	
Very common	Arthralgia, myalgia, pain in extremity
<b><i>Renal disorders</i></b>	
Uncommon	Renal failure, acute renal failure, nephritis
<b><i>General disorders and administration site conditions</i></b>	
Very common	Asthenia, chills, fatigue, pyrexia
Common	Influenza-like illness
<b><i>Investigations</i></b>	
Common	LVEF decrease

# NEW ZEALAND DATA SHEET

Uncommon                      QT prolongation

<sup>1)</sup> Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials were Grade 1 and no dose modification was required.

## Tafinlar and trametinib Combination Therapy

The safety of dabrafenib and trametinib combination therapy has been evaluated in two randomized Phase III studies of patients with BRAF mutant unresectable or metastatic melanoma treated with dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily (see section 5.1). The most common adverse reactions ( $\geq 20\%$ ) for Tafinlar and trametinib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral oedema, and cough.

Table 4 lists adverse reactions when trametinib was used in combination with dabrafenib from the randomized double-blind Phase III study MEK115306 (n = 209, COMBI-d), and integrated safety data from MEK115306 (n = 209) and from the randomized open-label Phase III study MEK 116513 (n = 350, COMBI-v).

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

Very common:	$\geq 1$ in 10
Common:	$\geq 1$ in 100 and $< 1$ in 10
Uncommon	$\geq 1$ in 1,000 and $< 1$ in 100

**Table 4 Adverse reactions for trametinib in combination with dabrafenib from the randomized double-blind phase III combination study MEK115306 (COMBI-d), and integrated safety data from two randomized phase III combination studies, MEK115306 and MEK116513 (COMBI-d and COMBI-v)**

	Frequency classification	
	COMBI-d n=209	COMBI-d and COMBI-v Integrated Data n=559
<b>Infections and Infestations</b>		
Urinary tract infection	Very common	Common
Nasopharyngitis	Very common	Very common
Cellulitis	Common	Common
Folliculitis	Common	Common
Paronychia	Common	Common
Rash pustular	Common	Common
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>		
Cutaneous squamous cell carcinoma(SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma	Common	Common
Papilloma including skin papilloma	Common	Common
Seborrhoeic keratosis	Common	Common
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
<b>Blood and lymphatic system disorders</b>		
Neutropenia	Very Common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
<b>Immune system disorders</b>		
Hypersensitivity	Uncommon	Uncommon
<b>Metabolic and nutrition disorders</b>		

## NEW ZEALAND DATA SHEET

	Frequency classification	
	COMBI-d n=209	COMBI-d and COMBI-v Integrated Data n=559
Decreased appetite	Very common	Very common
Dehydration	Common	Common
Hyperglycaemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
<b>Nervous system disorders</b>		
Headache	Very common	Very common
Dizziness	Very common	Very common
<b>Eye disorders</b>		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
<b>Cardiac disorders</b>		
Ejection fraction decreased	Common	Common
Left ventricular dysfunction	NR	Uncommon
Cardiac failure	NR	Uncommon
Bradycardia	Common	Common
<b>Vascular disorders</b>		
Cardiac failure	NR	Uncommon
Hypertension	Very common	Very common
Haemorrhage <sup>1</sup>	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	NR	Uncommon
<b>Gastrointestinal disorders</b>		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
<b>Investigations</b>		
Alanine aminotransferase increased	Very common	Very common
Aspartate aminotransferase increased	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Gamma-glutamyltransferase increased	Common	Common
<b>Skin and subcutaneous tissue disorders</b>		

## NEW ZEALAND DATA SHEET

	Frequency classification	
	COMBI-d n=209	COMBI-d and COMBI-v Integrated Data n=559
Dry skin	Very common	Very common
Pruritus	Very common	Very common
Rash	Very common	Very common
Dermatitis acneiform	Very common	Common
Erythema	Common	Common
Actinic keratosis	Common	Common
Night sweats	Common	Common
Hyperkeratosis	Common	Common
Alopecia	Common	Common
Palmar-plantar erythrodysesthesia syndrome	Common	Common
Skin lesion	Common	Common
Hyperhidrosis	Common	Common
Skin fissures	Common	Common
Panniculitis	Common	Common
Photosensitivity reaction <sup>1)</sup>	Common	Common
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	NR	Uncommon
<b>Renal disorders</b>		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	NR	Uncommon
<b>General disorders and administration site disorders</b>		
Fatigue	Very common	Very common
Oedema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face oedema	Common	Common

NR= Not reported

<sup>1)</sup> Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials were Grade 1 and no dose modification was required.

### 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 sections 4.2 and 4.4).

## NEW ZEALAND DATA SHEET

### 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 section 4.4).

### 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). 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.

## 4.9 Overdose

### **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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# NEW ZEALAND DATA SHEET

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors ATC Code: L01XE23

#### **Mechanism of action**

##### ***TAFINLAR monotherapy***

Dabrafenib is an ATP-competitive inhibitor of RAF kinases with IC<sub>50</sub> 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<sub>50</sub> values of 3.2 and 5.0nM, respectively. Oncologic 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 section 4.4).

Dabrafenib inhibits BRAF V600 mutant melanoma cell growth *in vitro* and *in vivo*.

##### ***TAFINLAR in 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. Dabrafenib and trametinib inhibit two critical kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib is synergistic 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.

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.

#### **Cardiac electrophysiology**

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

#### **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.

# NEW ZEALAND DATA SHEET

## Clinical Efficacy and Safety

### **Tafinlar monotherapy**

The efficacy and safety 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.

### *BREAK-3: Study in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma*

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<sup>2</sup> 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 had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and 97 % of patients had metastatic disease.

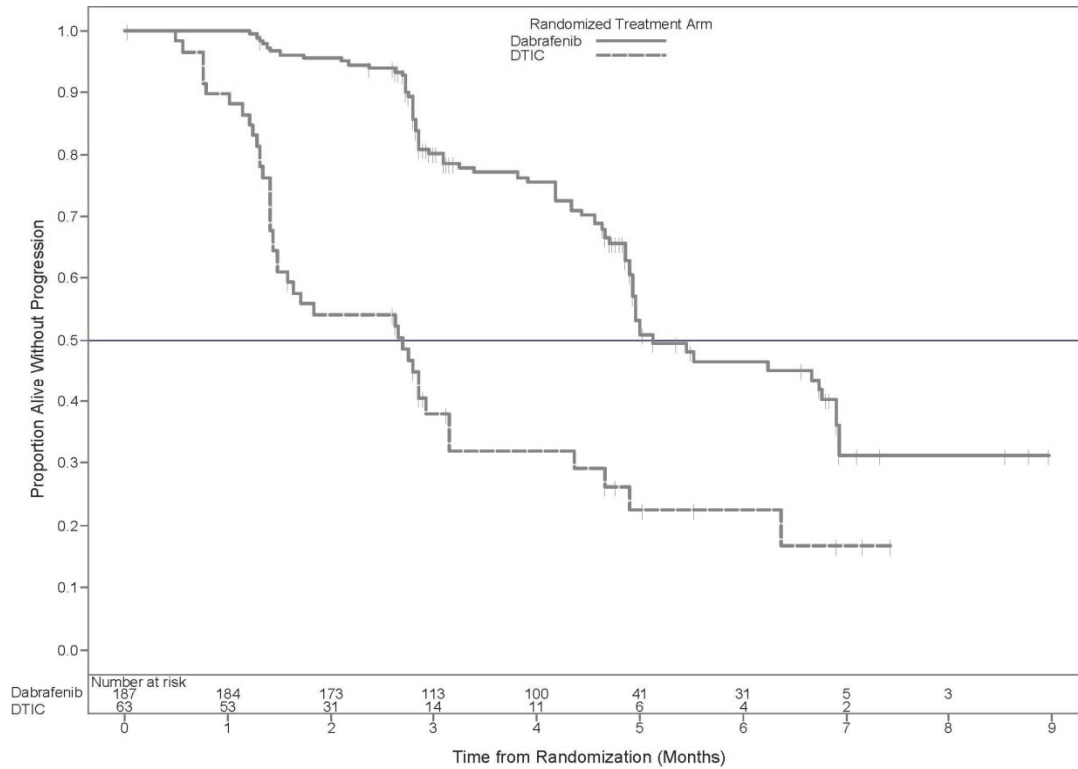
At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR = 0.30; 95% CI 0.18, 0.51; p< 0.0001) was achieved. PFS from the primary analysis is shown in Figure 1. Efficacy results from a post-hoc analysis with 6-months additional follow-up are summarised in Table 5.

Overall survival data from a further post-hoc analysis based on an 18 December 2012 data cut is provided in Table 6 and shown in Figure 2.



# NEW ZEALAND DATA SHEET

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



**Table 5 Monotherapy efficacy data by Investigator Assessment in previously untreated patients (BREAK-3 study, 25 June 2012)**

	Intention-to-Treat Population	
Endpoints/ Assessment	TAFINLAR N=187	DTIC N=63
<b>Progression-free survival</b>		
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	
<b>Overall response<sup>a</sup></b>		
% (95 % CI) <sup>b</sup>	59 (51.4, 66.0)	24 (21.4, 36.2)
	P<0.0001	
<b>Duration of response</b>		
	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

# NEW ZEALAND DATA SHEET

b. Confirmed response

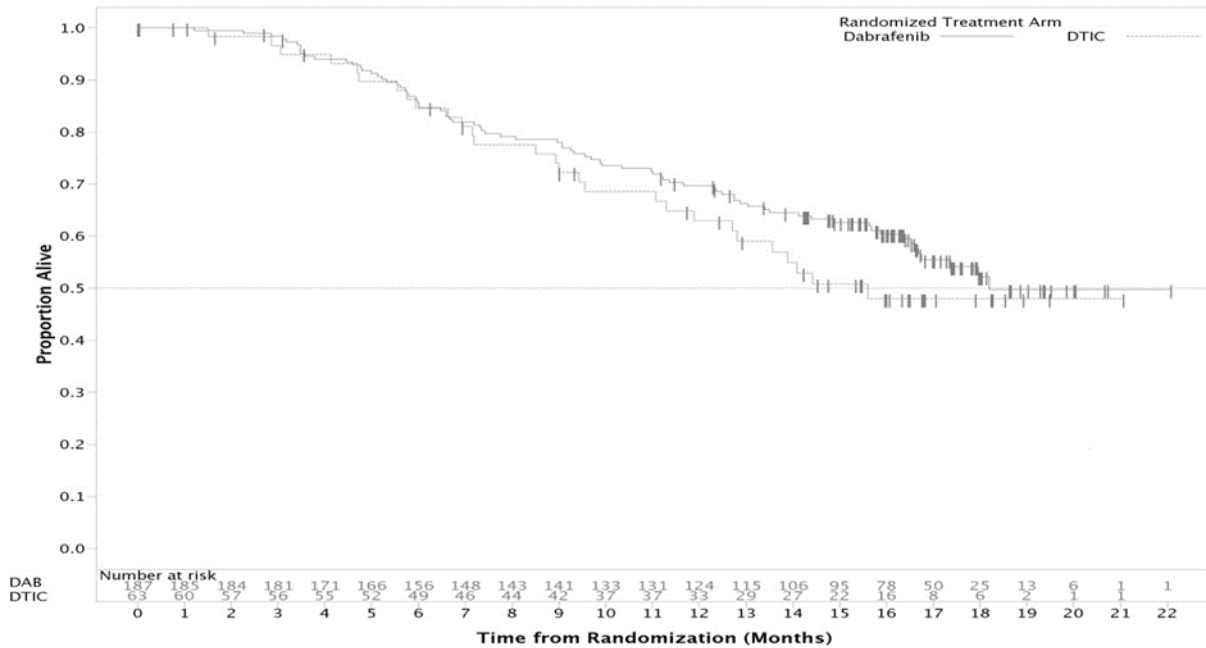
As of 25 June 2012, thirty-five subjects (55.6%) of the 63 randomised to DTIC crossed over to TAFINLAR. Median PFS after cross-over was 4.4 months.

**Table 6 Survival data from a post-hoc analysis (18 December 2012)**

Treatment	Number of deaths (%)	12-month OS rate	Hazard Ratio
DTIC	28 (44%)	63%	0.76 (0.48, 1.21) <sup>(a)</sup>
Tafinlar	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)**



**BREAK-MB: Patients with Stage IV BRAF-mutation positive (V600E or V600K) brain metastases**

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 7. 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.

## NEW ZEALAND DATA SHEET

**Table 7 Efficacy Data in Patients with Brain Metastases (BREAK-MB study)**

Endpoints/ Assessment	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
<b>Overall intracranial response rate, % (95% CI)<sup>a</sup></b>	39% (28.0, 51.2) P<0.001	31% (19.9, 43.4) P<0.001 <sup>b</sup>	7% (0.2, 31.9)	22% (6.4, 47.6)
<b>Duration of intracranial response, median months (95% CI)</b>	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)
<b>Overall response, % (95% CI)<sup>a</sup></b>	38% (26.8, 49.9)	31% (19.9, 43.4)	0 (0, 21.8)	28% (9.7, 53.5)
<b>Duration of response, median months (95% CI)</b>	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
<b>Progression-free survival, median months (95% CI)</b>	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
<b>Overall survival, median months (95% CI)</b>	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<sup>V600E</sup> positive subjects.

**BREAK-2: Study in Stage IV metastatic patients who were previously untreated or failed at least one prior systemic therapy (Results from the phase II study)**

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 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

## NEW ZEALAND DATA SHEET

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.

### **TAFINLAR in combination with trametinib**

The efficacy and safety of the recommended dose of dabrafenib (150 mg twice daily) in combination with trametinib (2 mg once daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two pivotal Phase III studies.

#### MEK115306 (COMBI-d)

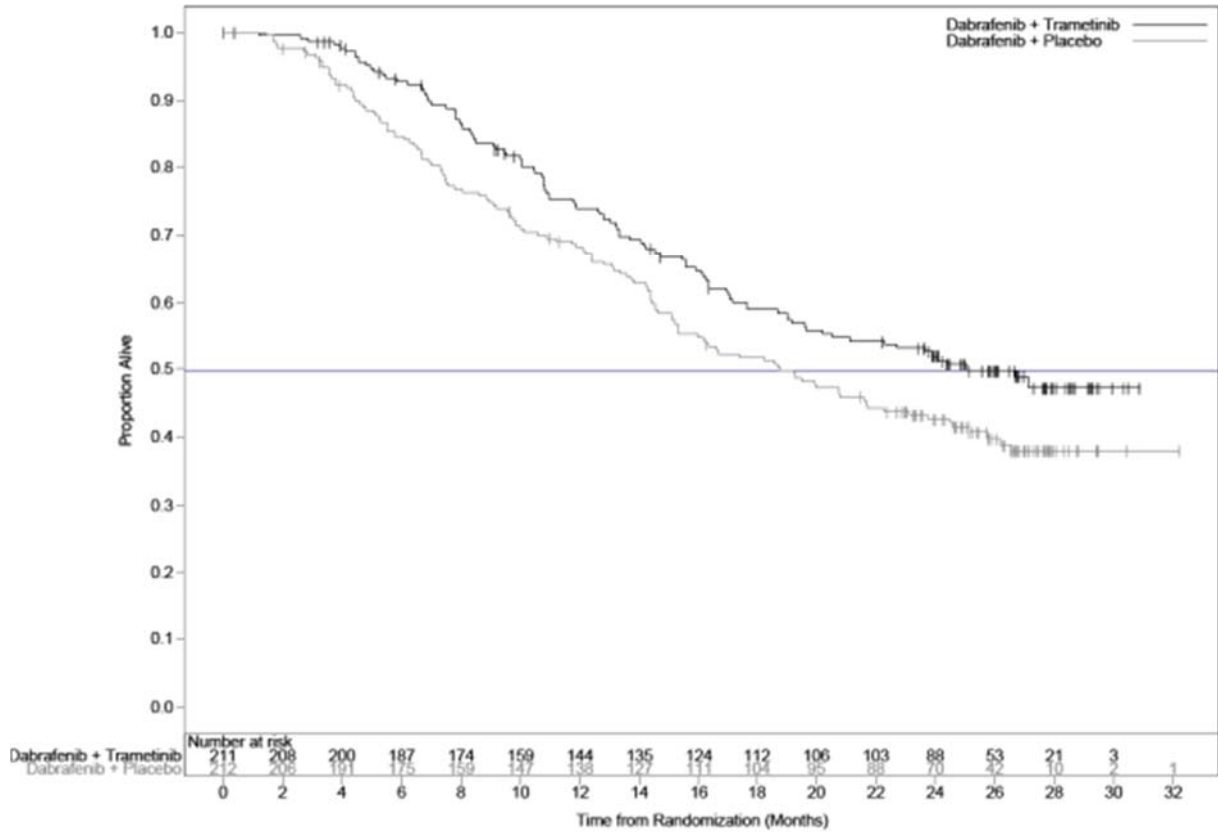
MEK115306 (COMBI-d) was a Phase III, randomized, double-blind study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo as first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was investigator assessed 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 randomized 1:1 to either the combination therapy arm (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) (N = 211) or dabrafenib monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Males constituted 53 % of patients and the median age was 56 years; Majority of patients had an ECOG performance score of 0 (72 %) and had Stage IVM1c disease (66 %). Most patients had the BRAF V600E mutation (85 %); the remaining 15 % of patients had the BRAF V600K mutation.

At the time of final OS analysis, a total of 222 deaths (52.5%) [combination 99 deaths (47 %) and dabrafenib 123 deaths (58 %)] out of the randomized (or ITT) population were reported. The median follow up time on study treatment was 20 months in the combination therapy arm and 16 months in the dabrafenib monotherapy arm. Study MEK115306 showed a statistically significant 29 % reduction in the risk of death for the combination therapy arm compared with the dabrafenib monotherapy arm (HR=0.71, 95 % CI: 0.55, 0.92; p=0.011). The median OS was 25.1 months for the combination therapy arm and 18.7 months for the dabrafenib monotherapy arm. The 12-month (74 %) and 24-month (51.4 %) OS estimates for the combination were also greater than those for dabrafenib monotherapy (67.6 % and 42.1%, respectively).

# NEW ZEALAND DATA SHEET

**Figure 3: Kaplan-Meier Overall Survival Curves (ITT Population)**



Efficacy Results of PFS, ORR and Duration of Response are summarized in Table 8.

**Table 8 Investigator-Assessed Efficacy Results for MEK115306 (COMBI-d) study (Primary Data Cut and Final Data Cut)**

Endpoints	Primary analysis*		Final analysis*	
	Tafinlar plus trametinib	Tafinlar	Tafinlar plus trametinib	Tafinlar
<b>Investigator Assessed PFS</b>	<b>(N=211)</b>	<b>(N=212)</b>	<b>(N=211)</b>	<b>(N=212)</b>
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)
Median, months (95% CI <sup>a</sup> )	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 5.9 (9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 ( 0.53, 0.84)	
p value (log-rank test)	0.035		< 0.001	
	<b>(N=210)</b>	<b>(N=210)</b>	<b>(N=210)</b>	<b>(N=210)</b>
Overall Response Rate <sup>b</sup> % (95% CI)	67 (59.5, 73.0)	51 (44.5, 58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)
% Difference in response rate	15 <sup>d</sup>		15 <sup>d</sup>	

## NEW ZEALAND DATA SHEET

Endpoints	Primary analysis*		Final analysis*	
	Tafinlar plus trametinib	Tafinlar	Tafinlar plus trametinib	Tafinlar
<b>Investigator Assessed PFS</b>	<b>(N=211)</b>	<b>(N=212)</b>	<b>(N=211)</b>	<b>(N=212)</b>
(CR <sup>c</sup> +PR <sup>c</sup> )				
95% CI for difference	(5.9, 24.5)		(6.0, 24.5)	
p value	0.0014		0.0014	
Median duration of response (months) (95 % CI)	9.2 <sup>e</sup> (7.4, NR)	10.2 <sup>e</sup> (7.5, NR)	12.9 (9.4, 19.5)	10.6 (9.1,13.8)

\*Primary data cut: 26 August 2013, Final data cut: 12 January 2015

<sup>a</sup> Confidence interval

<sup>b</sup> Overall Response Rate = Complete Response + Partial Response

<sup>c</sup> CR: Complete Response, PR: Partial Response

<sup>d</sup> ORR difference calculated based on the ORR result not rounded

<sup>e</sup> At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing

NR = Not reached

### MEK116513 (COMBI-v)

Study MEK116513 was a 2-arm, randomized, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma. The primary endpoint of the study was overall survival. 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 randomized 1:1 to either the combination therapy arm (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most subjects were White (> 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 %). 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 a BRAF V600E mutation (89 %).

The OS analysis was conducted when 222 total deaths (77% of the required events for the final analysis) occurred. The Independent Data Monitoring Committee (IDMC) recommended stopping the study since the OS results crossed the pre-specified efficacy boundary. As a consequence the interim OS summary was considered the final comparative OS analysis.

The OS analysis for Study MEK116513 was based on 222 deaths (32 %) [combination: 100 deaths (28 %) and vemurafenib 122 deaths (35 %)]. The median follow up time on study treatment was 11 months for the combination arm and 9 months in the vemurafenib arm. Study MEK116513 showed a statistically significant 31% reduction in the risk of death for the combination therapy compared with vemurafenib (HR = 0.69, 95 % CI: 0.53, 0.89; p = 0.005). The median OS was not yet reached for the combination arm, and was 17.2 months for vemurafenib monotherapy. Results of the endpoints for PFS, ORR and Duration of response are summarized in Table 9.

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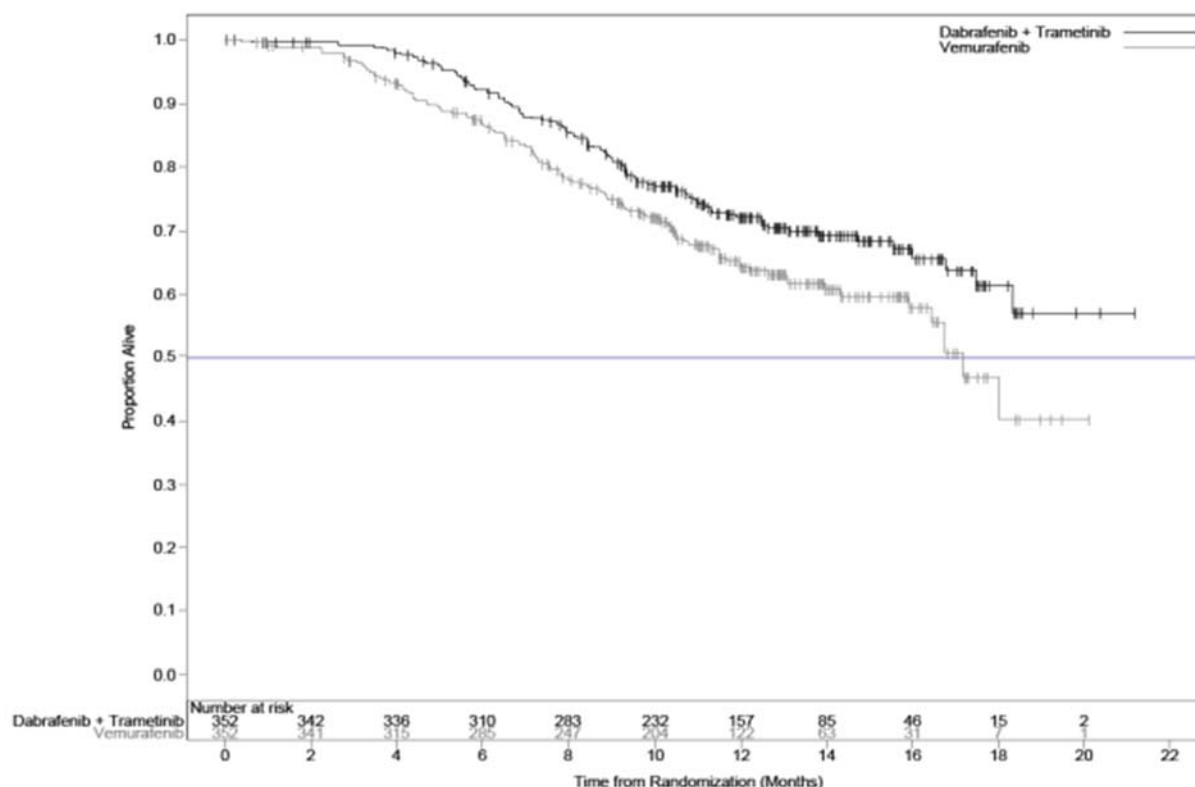
**Table 9 Investigator-Assessed Efficacy Results for MEK116513 (COMBI-v) study**

Endpoint	TAFINLAR + Trametinib (N=352)	Vemurafenib (N=352)
<b>Investigator Assessed PFS</b>		
Progressive disease or death, n (%)	166 (47)	217 (62)
Median, months	11.4	7.3
95 % CI	(9.9, 14.9)	(5.8, 7.8)
Hazard Ratio		0.56
95 % CI		(0.46, 0.69)
p value		< 0.001
Overall Response Rate, n (%)	226 (64)	180 (51)
95 % CI	(59.1, 69.4)	(46.1, 56.8)
Difference in response rate (CR+PR), %		13
95% CI for difference		(5.7, 20.2)
p value		0.005
<b>Duration of Response (months)</b>		
Median	13.8	7.5
95% CI	(11.0, NR)	(7.3, 9.3)

PFS= Progression Free Survival; NR= Not reached

# NEW ZEALAND DATA SHEET

Figure 4 Kaplan-Meier Overall Survival Curves (ITT Population)



## 5.2 Pharmacokinetic properties

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 12 mg and 300 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  $C_{max}$ ,  $AUC_{(0-\tau)}$  and predose concentration ( $C_{\tau}$ ) at steady state were 1478 ng/mL, 4341 ng\*hour/mL and 26 ng/mL, respectively.

### **Effect of food**

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/ metabolism**



## NEW ZEALAND DATA SHEET

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.

### ***Elimination***

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/hour. Following repeat oral dose administration, the oral clearance (CL/F) is 35 L/hour. 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 populations***

#### *Hepatic Impairment*

A population pharmacokinetic analysis in 65 patients with mild hepatic impairment indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) does 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*

The pharmacokinetics of TAFINLAR were characterised in 233 patients with mild renal impairment (GFR 60-89 mL/min/1.73 m<sup>2</sup>) and 30 patients with moderate renal impairment (GFR 30-59 mL/min/1.73 m<sup>2</sup>) enrolled in clinical trials, using a population analysis. The effect of mild to moderate renal impairment on TAFINLAR clearance was small (< 6 % for both categories) and was not clinically relevant. No data are available in subjects with severe renal impairment (see section 4.2).

#### *Paediatric patients (< 18 years of age)*

No studies have been conducted to investigate the pharmacokinetics of TAFINLAR in pediatric patients.

#### *Patients ≥ 65 years of 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*

# NEW ZEALAND DATA SHEET

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/ethnicity

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.

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

## 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 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 oestrous cycle, mating or fertility. 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  $\geq 20$  mg/kg/day ( $\geq 0.5$  times human clinical exposure based on AUC).

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

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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.

# NEW ZEALAND DATA SHEET

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Store below 30°C.

## 6.5 Nature and contents of container <and special equipment for use, administration or implantation>

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 capsule are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 28 or 120 capsules\*.

\*Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal <and other handling>

Special precautions for disposal

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

## 7. MEDICINE SCHEDULE

Prescription medicine.

## 8. SPONSOR

Novartis New Zealand Limited

109 Carlton Gore Road

Newmarket

Auckland 1023

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## 9. DATE OF FIRST APPROVAL

19<sup>th</sup> June 2014

## 10. DATE OF REVISION OF THE TEXT

31st July 2017

(Ref: taf040817iNZ based on Novartis CDS dated 1 June 2017)