NOVARTIS

MEQSEL (Trametinib)

0.5 and 2 mg tablets

Professional Information

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SCHEDULING STATUS: **S4**

1. NAME OF THE MEDICINE

MEQSEL® 0.5 mg film-coated tablets

MEQSEL® 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MEQSEL 0,5 mg film-coated tablets contains trametinib dimethyl sulfoxide equivalent to 0,5 mg of free base.

MEQSEL 2 mg film-coated tablets contains trametinib dimethyl sulfoxide equivalent to 2 mg of free base.

MEQSEL contains sugar (mannitol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

MEQSEL 0.5 mg tablets

Yellow, ovaloid, biconvex, film-coated tablet with beveled edges, unscored with Novartis logo on one side, “TT” on the other side.

MEQSEL 2 mg film-coated tablets

Pink, round, biconvex, film-coated tablet with beveled edges, unscored with Novartis logo on one side, “LL” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic melanoma

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

MEQSEL as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Adjuvant treatment of melanoma

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

Advanced non-small cell cancer (NSCLC)

MEQSEL in combination with dabrafenib is indicated for the treatment of patients with advanced non-small cell cancer (NSCLC) with BRAF V600 mutation.

Low-grade glioma

MEQSEL in combination with dabrafenib is indicated for the treatment of paediatric patients 6 years of age and older and weighing at least 26 kg with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

Unresectable or metastatic solid tumours

MEQSEL in combination with dabrafenib is indicated for the treatment of adult and paediatric patients 6 years of age and older with unresectable or metastatic solid tumours with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

4.2 Posology and method of administration

Treatment with MEQSEL should be initiated by a medical practitioner experienced in the use of anticancer therapies.

Confirmation of BRAF V600 mutation using an approved/validated test is required for the selection of patients appropriate for MEQSEL monotherapy and in combination with dabrafenib.

When MEQSEL is used in combination with dabrafenib, please refer to the full dabrafenib prescribing information, Posology and method of administration, for dabrafenib dosing instructions.

Posology

Adult patients

The recommended dose of MEQSEL in combination with dabrafenib is 2 mg given orally once daily with a full glass of water.

MEQSEL should be taken without food, at least 1 hour before or 2 hours after a meal.

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

Missed doses

If a dose of MEQSEL is missed, only take the dose if it is more than 12 hours until the next scheduled dose.

Dose adjustments

The management of adverse events may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1-1, Table 1-2, Table 1-3 and Table 2).

Table 1-1 Recommended dose level reductions for MEQSEL

Dose Level Reductions	**Recommended Starting Dosage**
Starting dose	2 mg orally once daily
1st dose reduction	1.5 mg orally once daily

2nd dose reduction	1 mg orally once daily
Permanently discontinue if unable to tolerate MEQSEL 1 mg orally once daily	

Refer to full dabrafenib prescribing information, section 4.2.

Dose adjustment for MEQSEL, in combination with dabrafenib, below 1 mg once daily, is not recommended.

Paediatric patients

The recommended dosage for MEQSEL tablets in paediatric patients who weigh at least 26 kg, is based on body weight (Table 1-2). A recommended dose for patients who weigh less than 26 kg has not been established.

Table 1-1 Recommended weight-based dosing for MEQSEL tablets in paediatric patients

Body weight	**Recommended starting dosage**
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

Recommended dose level reductions for MEQSEL tablets in paediatric patients are provided in Table 1-3.

Table 1-2 Recommended dose level reductions for MEQSEL tablets in paediatric patients

Dose level reduction	**Recommended starting dosage**		
	1 mg orally once daily	**1.5 mg orally once daily**	**2 mg orally once daily**
First dose reduction	0.5 mg orally once daily	1 mg orally once daily	1.5 mg orally once daily
Second dose reduction	-	0.5 mg orally once daily	1 mg orally once daily
Permanently discontinue if unable to tolerate a maximum of two dose reductions			

Duration of treatment

The recommended duration of treatment for patients with unresectable or metastatic melanoma or solid tumours or NSCLC is until disease progression or unacceptable toxicity.

In the adjuvant melanoma setting, the treatment duration is limited to a maximum of 1 year.

The recommended duration of treatment for paediatric patients with LGG is until loss of clinical benefit or until unacceptable toxicity. There are limited data in patients older than 18 years of age with LGG who require first systemic therapy. Therefore, continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

Table 2: MEQSEL dose modification schedule (excluding pyrexia)

Grade (CTC-AE*)	**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 0-1and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

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

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 MEQSEL dose should not exceed 2 mg once daily.

Pyrexia management:

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

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

Exceptions where dose modifications are necessary for MEQSEL only:

- Left ventricular ejection fraction (LVEF) reduction.
- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED).
- Pneumonitis and Interstitial Lung Disease (ILD)

LVEF reduction/left ventricular dysfunction management:

MEQSEL should be interrupted in patients who have an asymptomatic, absolute decrease of > 10 % in LVEF compared to baseline and the ejection fraction below the institution's lower limit of normal (LLN) (see section 4.4). If MEQSEL is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with MEQSEL may be restarted, but reduce the dose by one dose level with careful monitoring.

MEQSEL should be permanently discontinued with Grade 3 or 4 left ventricular cardiac dysfunction or if repeat LVEF-reduction does not recover.

Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED) management:

If RPED is diagnosed, follow the dose modification schedule (intolerable) in Table 2 above for MEQSEL and, if MEQSEL is being used in combination with dabrafenib, continue dabrafenib at the same dose (see section 4.4).

Pneumonitis and Interstitial Lung Disease (ILD) management:

For events of pneumonitis, follow dose modification guidelines in Table 2 for MEQSEL only; no modification of dabrafenib is required when taken in combination with MEQSEL.

Special populations

Children

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

Elderly

No dose adjustment is required in patients over 65 years (see section 5.2).

Renal impairment

No dosage adjustment required in patients with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of MEQSEL (see section 5.2). There are no clinical data with trametinib in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. MEQSEL should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment. In a population pharmacokinetic analysis, MEQSEL oral clearance and thus exposure was not significantly different in patients with mild hepatic impairment compared to patients with normal hepatic function (see section 5.2).

MEQSEL should be used with caution in patients with moderate or severe hepatic impairment.

4.3 Contraindications

- Hypersensitivity to the active substance, trametinib or to any of the excipients of MEQSEL
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

LVEF Reduction/Left Ventricular Dysfunction

MEQSEL has been reported to decrease LVEF (see section 4.8). In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease in patients treated with trametinib as monotherapy or in combination with dabrafenib was between two to five months. MEQSEL should be used with caution in patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with MEQSEL with a recommendation of periodic follow-up within eight weeks of initiating therapy, as clinically appropriate. LVEF should continue to be evaluated during treatment with MEQSEL as clinically appropriate (see section 4.2).

Haemorrhage

Haemorrhagic events, including major haemorrhagic events have occurred in patients taking MEQSEL as monotherapy and in combination with dabrafenib (see section 4.8). Out of the 559 metastatic melanoma patients treated with MEQSEL in combination with dabrafenib, there were six fatal intracranial haemorrhagic cases (1 %). Two out of 82 patients (2 %) receiving MEQSEL in combination with dabrafenib in a Phase II non-small cell adenocarcinoma trial had fatal intracranial haemorrhagic events.

If patients develop symptoms of haemorrhage, they should immediately seek medical care.

Visual Impairment

Disorders associated with visual disturbances, including chorioretinopathy or retinal pigment epithelial detachment (RPED) and Retinal Vein Occlusion (RVO) have been observed with MEQSEL. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with MEQSEL (see section 4.8). MEQSEL is not recommended in patients with a history of RVO.

A thorough ophthalmological evaluation should be performed at baseline and during treatment with MEQSEL, if clinically warranted. If patients report visual disturbances at any time while on MEQSEL therapy, additional ophthalmological evaluation should be undertaken. If a retinal abnormality is noted, treatment with MEQSEL should be interrupted immediately and referral to a retinal specialist should be considered. If RPED is diagnosed, follow the dose modification schedule (intolerable) in Table 2 (see section 4.2). In patients who experience RVO, treatment with MEQSEL should be permanently discontinued.

Skin toxicity

Rash

In clinical studies with MEQSEL, rash has been observed in about 60 % of patients as monotherapy and 20 to 30 % in combination with dabrafenib (see section 4.8). The majority of these cases was Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Severe cutaneous adverse reactions

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

Venous thromboembolism (VTE)

VTE**,** including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur on MEQSEL monotherapy and when MEQSEL is used in combination with dabrafenib. If patients develop symptoms of VTE they should immediately seek medical care.

Pyrexia

Pyrexia was reported in the clinical trials with MEQSEL**.** The incidence and severity of pyrexia are increased when MEQSEL is used in combination with dabrafenib. In patients with melanoma who received the combination dose of dabrafenib 150 mg twice daily and MEQSEL 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, and hypotension which in some cases can lead to acute renal insufficiency. Serum creatinine and other evidence of renal function should be monitored 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**.**

A cross-study comparison in 1,810 patients treated with combination therapy demonstrated a reduction in the incidence of high-grade pyrexia and other pyrexia-related adverse outcomes when both MEQSEL and dabrafenib were interrupted, compared to when only dabrafenib was interrupted. Therefore, interruption of both MEQSEL and dabrafenib is recommended if the patient's temperature is ≥ 38 ˚C, and in case of recurrence, therapy can also be interrupted at the first symptom of pyrexia (see section 4.2 and 5.1).

Colitis and gastrointestinal perforation

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking MEQSEL as monotherapy and in combination with dabrafenib. Treatment with MEQSEL monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal

perforation, including a history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognised risk of gastrointestinal perforation.

If patients develop symptoms of colitis and gastrointestinal perforation, they should immediately seek medical care**.**

Haemophagocytic lymphohistiocytosis (HLH)

In post-marketing experience, HLH has been observed with MEQSEL in combination with dabrafenib. If HLH is suspected, treatment should be interrupted. If HLH is confirmed, treatment should be discontinued and appropriate management of HLH should be initiated.

Tumour Lysis Syndrome (TLS)

Cases of TLS, including fatal cases, have been reported in patients treated with MEQSEL in combination with dabrafenib (see section 4.8). Risk factors for TLS include rapidly growing tumours, a high tumour burden, renal dysfunction and dehydration. Patients with risk factors for TLS should be closely monitored, prophylaxis should be considered (e.g. intravenous hydration and treatment of high uric acid levels prior to initiating treatment) and treated as clinically indicated.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicines on MEQSEL:

In vitro and *in vivo* data suggest that the pharmacokinetics (PK) of trametinib is unlikely to be affected by other medicines. MEQSEL is deacetylated via carboxylesterases and possibly other hydrolytic enzymes. There is little evidence from clinical studies for interactions mediated by carboxylesterases. CYP enzymes play a minor role in the elimination of trametinib and the compound is not a substrate of CYP enzymes or of the following transporters: breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2, and the multidrug and toxin extrusion protein (MATE) 1. MEQSEL is an *in vitro* substrate of the efflux

transporter P-glycoprotein (Pgp) but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability.

As MEQSEL is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (including carboxylesterases), its pharmacokinetics are unlikely to be affected by other medicines through metabolic interactions. MEQSEL repeat-dose exposure was not affected by co-administration with a cytochrome P450 (CYP) 3A4 inducer (see section 5.2).

Based on *in vitro* and *in vivo* data, MEQSEL is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters (see section 5.2).

Repeat dose administration of MEQSEL 2 mg once daily had no clinically relevant effect on the single dose C_{max} and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate.

Combination with dabrafenib

Co-administration of repeat dosing of dabrafenib 150 mg twice daily and MEQSEL 2 mg once daily resulted in a 16 % increase in dabrafenib C_{max} and a 23 % increase in dabrafenib AUC. A small decrease in MEQSEL bioavailability, corresponding to a decrease in AUC of 12 %, was estimated when dabrafenib is administered in combination with MEQSEL using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib C_{max} and AUC are considered not clinically relevant**.**

See prescribing information for dabrafenib for guidelines on interactions associated with dabrafenib monotherapy.

4.6 Fertility, pregnancy and lactation

MEQSEL is contraindicated during pregnancy or in woman who may become pregnant (see section 4.3).

Animal studies have been performed showing MEQSEL to be harmful to the developing foetus and adverse effects were seen on female reproductive organs. Trametinib may impair fertility in humans.

Women of childbearing potential/Contraception in males and females

Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) when using MEQSEL during treatment and for four months after stopping treatment with MEQSEL.

Females of reproductive potential receiving MEQSEL in combination with dabrafenib should be advised that dabrafenib may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as barrier methods, should be used.

Male patients must use a condom during intercourse and not to father a child during therapy and for 4 months following discontinuation of trametinib to avoid unnecessary exposure of trametinib to the foetus.

Breastfeeding

Women should not breastfeed their infant if on treatment with MEQSEL (see section 4.3).

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of MEQSEL should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills. Driving may be impaired by such adverse events.

4.8 Undesirable effects

Summary of the safety profile

Unresectable or metastatic melanoma

MEQSEL monotherapy

The safety of trametinib monotherapy has been evaluated in an integrated population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with trametinib 2 mg orally once daily. Of these patients, 211 patients were treated with MEQSEL for BRAF mutant melanoma in a randomised open label study. The most common adverse reactions (≥ 20 %) for trametinib include rash, diarrhoea, fatigue,

oedema peripheral, nausea, and dermatitis acneiform. In clinical trials with MEQSEL, adverse reactions of diarrhoea and rash were managed with appropriate supportive care (see section 4.2).

Adverse drug reactions are ranked by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Categories have been assigned based on absolute frequencies in the clinical trial data.

Table 3: Adverse events for MEQSEL monotherapy in melanoma

Infections and Infestations	
Common	Folliculitis, paronychia, cellulitis, rash pustular
Blood and lymphatic system disorders	
Common	Anaemia
Immune system disorders	
Common	Hypersensitivity[1]
Metabolism and Nutrition Disorders	
Common	Dehydration
Eye disorders	
Common	Vision blurred, periorbital oedema, visual impairment
Uncommon	Chorioretinopathy, retinal vein occlusion, papilloedema, retinal detachment

Cardiac disorders	
Common	Left ventricular dysfunction, ejection fraction decreased, bradycardia
Uncommon	Cardiac failure
Vascular Disorders	
Very common	Hypertension, haemorrhage[2]
Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, pneumonitis
Uncommon	Interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth
Common	Stomatitis
Uncommon	Gastrointestinal perforation, colitis
Hepatobiliary disorders	
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased

Skin and Subcutaneous Tissue Disorders	
Very common	Rash, dermatitis acneiform, dry skin, pruritus, alopecia
Common	Skin chapped, erythema, palmar-plantar erythrodysaesthesia syndrome, skin fissures
Musculoskeletal and connective tissue disorder	
Common	Blood creatine phosphokinase increased
Uncommon	Rhabdomyolysis
General disorders	
Very common	Fatigue, oedema peripheral, pyrexia
Common	Face oedema, mucosal inflammation, asthenia

[1]*May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.*

[2] *The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.*

MEQSEL and dabrafenib combination therapy:

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

Table 4 lists adverse reactions when MEQSEL was used in combination with dabrafenib from one randomised double-blind Phase III study (N=209), and integrated safety data from two randomised open-label Phase III studies (N= 559).

Table 4 Adverse events for MEQSEL in combination with dabrafenib in melanoma

	Frequency category	
	Double blind study n=209	**Open-label studies Integrated Data n=559**
Infections and Infestations		
Urinary tract infection	Very common	Common
Nasopharyngitis	Very common	Very common
Cellulitis	Common	Common
Folliculitis	Common	Common
Paronychia	Common	Common
Rash pustular	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
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
Seborrheic keratosis	Common	Common
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
Blood and lymphatic system disorders		

Neutropenia	Very Common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
Immune system disorders		
Hypersensitivity	Uncommon	Uncommon
Metabolic and nutrition disorders		
Decreased appetite	Very common	Very common
Dehydration	Common	Common
Hyperglycaemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Very common
Eye disorders		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
Cardiac disorders		
Ejection fraction decreased	Common	Common
Bradycardia	Common	Common

Left ventricular dysfunction	Not reported	Uncommon
Cardiac failure	Not reported	Uncommon
Vascular disorders		
Hypertension	Very common	Very common
Haemorrhage[1]	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	Not reported	Uncommon
Gastrointestinal disorders		
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
Gastrointestinal perforation	Not reported	Uncommon
Colitis	Uncommon	Uncommon
Hepatobiliary disorder		

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
Skin and subcutaneous tissue disorders		
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 erythrodysaesthesia syndrome	Common	Common
Skin lesion	Common	Common
Hyperhidrosis	Common	Common
Skin fissures	Common	Common
Panniculitis	Common	Common
Photosensitivity[2]	Common	Common

Musculoskeletal and connective tissue disorders		
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	Not reported	Uncommon
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure	Not reported	Uncommon
General disorders and administration site disorders		
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

[1]The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.

[2]Photosensitivity cases were also observed in post-marketing experience. All cases reported in the COMBI-d and COMBI-v clinical trials were Grade 1 and no dose modification was required.

Adjuvant treatment of melanoma

MEQSEL in combination with dabrafenib

The safety of MEQSEL in combination with dabrafenib was evaluated in a Phase III, randomised, double-blind study of MEQSEL in combination with dabrafenib versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection.

In the MEQSEL 2 mg once daily and dabrafenib 150 mg twice daily arm, the most common adverse reactions (≥ 20 %) were pyrexia, fatigue, nausea, headache, rash, chills, diarrhoea, vomiting, arthralgia, and myalgia.

Table 5 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥10 % for all grade adverse reactions or at an incidence ≥ 2 % for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the MEQSEL in combination with dabrafenib arm.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 5 Adjuvant treatment of melanoma – adverse drug reactions for MEQSEL in combination with dabrafenib vs. placebo

Adverse drug reactions	MEQSEL in combination with Dabrafenib N=435 %		Placebo N=432 %		Frequency category (combination arm, all grades)
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Infections and infestations					
Nasopharyngitis[1)]	12	<1	12	NR	Very common
Blood and lymphatic system disorders					
Neutropenia[2)]	10	5	<1	NR	Very common
Metabolism and nutrition disorders					
Decreased appetite	11	<1	6	NR	Very common
Nervous system disorders					
Headache[3)]	39	1	24	NR	Very common
Dizziness[4)]	11	<1	10	NR	Very common
Eye disorders					
Uveitis	1	<1	<1	NR	Common
Chorioretinopathy[5)]	1	<1	<1	NR	Common
Retinal detachment[6)]	1	<1	<1	NR	Common
Vascular disorders					
Haemorrhage[7)]	15	<1	4	<1	Very common
Hypertension[8)]	11	6	8	2	Very common
Respiratory, thoracic, and mediastinal disorders					

Cough[9)]	17	NR	8	NR	Very common
Gastrointestinal disorders					
Nausea	40	<1	20	NR	Very common
Diarrhoea	33	<1	15	<1	Very common
Vomiting	28	<1	10	NR	Very common
Abdominal pain[10)]	16	<1	11	<1	Very common
Constipation	12	NR	6	NR	Very common
Skin and subcutaneous tissue disorders					
Rash[11)]	37	<1	16	<1	Very common
Dry skin[12)]	14	NR	9	NR	Very common
Dermatitis acneiform	12	<1	2	NR	Very common
Erythema[13)]	12	NR	3	NR	Very common
Pruritus[14)]	11	<1	10	NR	Very common
Palmar-plantar erythrodysaesthesia syndrome	6	<1	1	<1	Common
Musculoskeletal and connective tissue disorders					
Arthralgia	28	<1	14	NR	Very common
Myalgia[15)]	20	<1	14	NR	Very common
Pain in extremity	14	<1	9	NR	Very common
Muscle spasms[16)]	11	NR	4	NR	Very common
Rhabdomyolysis	<1	<1	NR	NR	Uncommon
Renal and urinary disorders					
Renal failure	<1	NR	NR	NR	Uncommon

General disorders and administration site conditions					
Pyrexia[17)]	63	5	11	<1	Very common
Fatigue[18)]	59	5	37	<1	Very common
Chills	37	1	4	NR	Very common
Oedema peripheral[19)]	16	<1	6	NR	Very common
Influenza-like illness	15	<1	7	NR	Very common
Investigations					
Alanine aminotransferase increased[20)]	17	4	2	<1	Very common
Aspartate aminotransferase increased[21)]	16	4	2	<1	Very common
Alkaline phosphatase increased	7	<1	<1	<1	Common
Ejection fraction decreased	5	NR	2	<1	Common

1) Nasopharyngitis also includes pharyngitis.

2) Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia.

3) Headache also includes tension headache.

4) Dizziness also includes vertigo.

5) Chorioretinopathy also includes chorioretinal disorder.

6) Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.

[7] Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.

[8] Hypertension also includes hypertensive crisis.

[9] Cough also includes productive cough.

[10] Abdominal pain also includes abdominal pain upper and abdominal pain lower.

[11] Rash also includes rash maculo-papular, rash macular, rash generalised, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.

[12] Dry skin also includes xerosis and xeroderma.

[13] Erythema also includes generalised erythema.

[14] Pruritus also includes pruritus generalised and pruritus genital.

[15] Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.

[16] Muscle spasms also includes musculoskeletal stiffness.

[17] Pyrexia also includes hyperpyrexia.

[18] Fatigue also includes asthenia and malaise.

[19] Oedema peripheral also includes peripheral swelling.

[20] Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

[21] Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

NR: not reported

Advanced non-small cell cancer

MEQSEL in combination with dabrafenib:

The safety of MEQSEL in combination with dabrafenib has been evaluated in a multicentre, multi-cohort, non-randomised, open label study of patients with BRAF V600E mutation positive metastatic NSCLC.

With MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily arms the most common adverse drug reactions (≥ 20 %) for MEQSEL and dabrafenib combination therapy were pyrexia, nausea, vomiting, diarrhoea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash, dyspnoea and peripheral oedema.

Table 6 lists the adverse drug reactions for MEQSEL in combination with dabrafenib occurring at an incidence ≥ 10 % for all adverse drug reactions or at an incidence ≥ 2 % for Grade 3 and Grade 4 adverse drug reactions.

Adverse drug reactions are ranked by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Categories have been assigned based on absolute frequencies in the clinical trial data.

Table 6 Advanced NSCLC – adverse drug reactions for MEQSEL in combination with dabrafenib

Adverse drug reaction[1]	**MEQSEL in combination with dabrafenib**		**Frequency category**
	All grades n = 93 (%)	**Grades 3/4 n = 93 (%)**	
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Cutaneous squamous cell carcinoma of skin	3	2	Common
Blood and lymphatic system disorders			
Neutropenia[1]	15	8	Very common
Leukopenia	6	2	Common

Metabolism and nutrition disorders			
Hyponatraemia	14	9	Very Common
Dehydration	8	3	Common
Eye disorders			
Detachment of retina/retinal pigment epithelium	2	NR	Common
Nervous system disorders			
Headache	16	NR	Very common
Dizziness	14	NR	Very common
Cardiac disorders			
Ejection fraction decreased	9	4	Common
Vascular disorders			
Haemorrhage[2]	26	3	Very common
Hypotension	15	2	Very common
Pulmonary embolism	4	2	Common
Hypertension	8	6	Common
Gastrointestinal disorders			
Nausea	46	NR	Very common
Vomiting	37	1	Very common
Diarrhoea	33	1	Very common

Decreased appetite	28	NR	Very common
Constipation	16	NR	Very common
Pancreatitis acute	1	NR	Common
Skin and subcutaneous tissue disorders			
Erythema		NR	Very common
Dry skin	32	1	Very common
Rash[3]	31	3	Very common
Pruritus[4]	15	2	Very common
Hyperkeratosis[5]	13	1	Very common
Musculoskeletal and connective tissue disorders			
Muscle spasms	10	NR	Very common
Arthralgia	16	NR	Very common
Myalgia	13	NR	Very common
Renal and urinary disorders			
Renal failure	3	1	Common
Tubulointerstitial nephritis	2	2	Common
General disorders and administration site disorders			
Pyrexia	55	5	Very common
Asthenia[6]	47	6	Very common
Oedema [7]	35	NR	Very common
Chills	18	1	Very common

Investigations			
Blood alkaline phosphatase increased	12	NR	Very common
Aspartate aminotransferase increased	11	2	Very common
Alanine aminotransferase increased	10	4	Very common

[1] Neutropenia includes neutropenia and neutrophil count decreased. Neutrophil count decreased qualified as neutropenia event.

[2.] Haemorrhage includes cases of haemoptysis, haematoma, epistaxis, purpura, haematuria, subarachnoid haemorrhage, gastric haemorrhage, urinary bladder haemorrhage, contusion, haemtochezia, injection site haemorrhage, melaena, pulmonary and retroperitoneal haemorrhage.

NR: Not Reported.

[3] Rash includes rash, rash generalised, rash papular, rash macular, rash maculo-papular, and rash pustular.

[4] Pruritis includes pruritis, pruritis generalised and eye pruritus.

[5] Hyperkeratosis includes hyperkeratosis, actinic keratosis, seborrhoeic keratosis and keratosis pilaris.

[6] Asthenia also includes fatigue and malaise.

[7] Oedema includes generalised oedema and peripheral oedema.

Unresectable or metastatic tumours

MEQSEL in combination with dabrafenib

Further safety of MEQSEL in combination with dabrafenib was evaluated, as part of Study BRF117019, a multi-cohort, multi-centre, non-randomised, open-label study in adult patients with cancers with the BRAF V600E mutation. A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 in solid tumour cohorts, and 65 in haematological malignancy cohorts. Patients received MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity.

Among these 206 patients, 101 (49 %) were exposed to MEQSEL for ≥ 1 year and 103 (50 %) were exposed to dabrafenib for ≥ 1 year. The median age was 60 years (range: 18 to 89); 56 % were male; 79 % were white; and 34 % had baseline ECOG performance status 0 and 60 % had ECOG performance status 1. The adverse reaction profile among all patients was similar to that observed in other approved indications.

Adverse drug reactions (ADRs) from post-marketing experience and pooled clinical trials

The following ADRs have been derived from post-marketing experience including spontaneous case reports with MEQSEL in combination with dabrafenib. Because post-marketing ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these ADR frequencies have been calculated from the pooled clinical trials across indications. ADRs are listed according to system organ classes in MedDRA. Within each system organ class. ADRs are presented in order of decreasing seriousness.

Special populations

Paediatric patients

MEQSEL in combination with dabrafenib

The safety of *MEQSEL* in combination with dabrafenib was studied in 171 paediatric patients across two studies (G2201 and X2101) with BRAF V600E mutation-positive advanced solid tumours, of which 4 (2.3 %)

patients were 1 to < 2 years of age, 39 (22.8 %) patients were 2 to < 6 years of age, 54 (31.6 %) patients were 6 to < 12 years of age, and 74 (43.3 %) patients were 12 to < 18 years of age.

The overall safety profile in the paediatric population was similar to the safety profile observed in adults. The most frequently reported adverse drug reactions (≥ 20 %) were pyrexia, rash, headache, vomiting, dry skin, fatigue, diarrhoea, haemorrhage, neutropenia, nausea, dermatitis acneiform, abdominal pain, and cough.

An adverse drug reaction of weight increased was identified in the paediatric safety pool with a frequency of 15.2 % (very common). Fifty-one out of 171 patients (29.8 %) had an increase from baseline of ≥ 2 BMI-for-age-percentile categories.

Adverse drug reactions occurring at a higher frequency category in paediatric patients compared to adult patients were neutropenia, dermatitis acneiform, paronychia, anaemia, leukopenia (very common); bradycardia, dermatitis exfoliative generalised, hypersensitivity and pancreatitis (common).

Table 7 Most frequent Grade 3/4 Adverse drug reactions (≥ 2 %) for MEQSEL in combination with dabrafenib in paediatric patients

Adverse drug reactions	**MEQSEL in combination with dabrafenib** **N=171**
	Grade 3/4 **n (%)**
Neutropenia[1]	25 (15)
Pyrexia	15 (9)
Alanine aminotransferase increased[2]	10 (6)
Aspartate aminotransferase increased[3]	6 (4)
Weight Increased	7 (4)
Headache	5 (3)
Vomiting	5 (3)

Hypotension	4 (2)
Rash[4]	4 (2)
Blood alkaline phosphatase increased	4 (2)

1. *Neutropenia includes neutropenia, neutrophil count decreased, and febrile neutropenia.*
2. *ALT includes alanine aminotransferase increased and transaminases increased.*
3. *AST includes aspartate aminotransferase increased and transaminases increased.*
4. *Rash includes rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, and rash macular.*

Table 8 ADR from post-marketing experience and pooled clinical trials across indications

Adverse drug reaction	Combination frequency category	Monotherapy frequency category
Cardiac disorders		
Atrioventricular block[1]	Uncommon	Not known
Bundle branch block[2]	Rare	Not known
Immune system disorders		
Sarcoidosis	Uncommon	-
Haemophagocytic lymphohistiocytosis	Not known	-
Vascular disorders		
Venous thrombo-embolism (VTE)[3]		Common
Metabolism and nutrition disorders		
Tumour lysis syndrome	Not known	-
Nervous system disorders		
Peripheral neuropathy	Common	Common

1) Atrioventricular block includes atrioventricular block, atrioventricular block first degree, atrioventricular block second degree and atrioventricular block complete.

2) Bundle branch block includes bundle branch block, bundle branch block right, bundle branch block left and bundle branch block bilateral.

3) VTE includes, pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis.

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. Health care providers are requested to report any

suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no specific treatment for an overdose of trametinib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Haemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mitogen-activated protein kinase (MEK) inhibitors, ATC code: L01EE01.

Clinical efficacy and safety

MEQSEL in combination with dabrafenib

BRF117277/DRB436B2204 (COMBI-MB)-Metastatic melanoma patients with brain metastases

The efficacy and safety of MEQSEL in combination with dabrafenib in patients with BRAF mutant positive melanoma that has metastasised to the brain was studied in a non-randomised open-label, multi-centre Phase II study (COMBI-MB study).

A total of 125 patients were enrolled into four cohorts:

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

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Efficacy results are summarised in Table 9. Secondary endpoints were duration of intracranial response, ORR, PFS and OS.

Table 9 – COMBI-MB- Efficacy data by investigator assessment

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

CI = Confidence Interval

NR = Not Reported

Other studies

Pyrexia Management Analysis

Pyrexia is observed in patients treated with MEQSEL and dabrafenib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia. In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-A plus, N=552), interruption of both MEQSEL and dabrafenib when the patient's temperature was ≥ 38 °C (COMBI-A plus) or at the first symptom of pyrexia (COMBI-i; COMBI-A plus for recurrent pyrexia), resulted in improved pyrexia-related outcomes without impacting efficacy:

Unresectable or metastatic melanoma setting (COMBI-d/v vs COMBI-i):

- grade 3/4 pyrexia reduced from 6.6 % to 3.4 %
- hospitalisation due to pyrexia reduced from 12.3 % to 6.1 %
- pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.4 % to 1.9 %
- treatment discontinuation rates due to pyrexia were comparable, 1.1 % versus 1.9 %.

Adjuvant melanoma setting (COMBI-AD vs COMBI-A plus):

- grade 3/4 pyrexia reduced from 5.7 % to 4.3 %
- hospitalisation due to pyrexia reduced from 11.0 % to 5.1 %
- pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.0 % to 2.2 %
- treatment discontinuation due to pyrexia reduced from 6.2 % to 2.5 %.

5.2 Pharmacokinetic properties:

Absorption:

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72 % relative to an intravenous (IV) microdose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, geometric mean C_{max}, $AUC_{(0-t)}$ and pre dose concentration were 22.2 ng/mL, 370 ng*hr/mL and 12.1 ng/mL, respectively with a low peak: trough ratio (1.8). Inter-subject variability was low (< 28 %). Administration of a single dose of trametinib with a high-fat, high-calorie meal resulted in a 70 % and 10 % decrease in C_{max} and AUC, respectively compared to fasted conditions (see section 4.2). Trametinib tablets are immediate-release formulations that are expected to have similar food effects on PK.

Distribution

Binding of trametinib to human plasma proteins is 97.4 %. Trametinib has a volume of distribution of 1060 L determined following administration of a 5 µg IV microdose.

Biotransformation/metabolism

In vitro and *in vivo* studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolised by glucuronidation. The deacetylation is mediated by the carboxyl-esterases 1b, 1c and 2, and may also be mediated by other hydrolytic enzymes.

Elimination

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 127 hours (5.3 days) after single dose administration. Steady-state was achieved by Day 15. Trametinib plasma IV clearance is 3.21 L/hr.

Total dose recovery is low after a 10-day collection period (< 50 %) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long half-life. Drug-related material was excreted predominantly in the faeces (≥ 81 % of recovered radioactivity) and to a small extent in urine (≤ 19 %). Less than 0.1 % of excreted dose was recovered as parent urine.

SPECIAL POPULATIONS:

Hepatic Impairment

Population pharmacokinetic analyses and data from a clinical pharmacology study in patients with normal hepatic function or with mild bilirubin and/or AST elevations (based on National Cancer Institute [NCI] classification) indicate that hepatic function does not significantly affect trametinib oral clearance (see section 4.2).

Renal Impairment

Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib. The pharmacokinetics of trametinib was characterised in 223 patients enrolled in clinical trials with trametinib who had mild renal impairment and 35 patients with moderate renal impairment using a population pharmacokinetic analysis. Mild and moderate renal impairment had no effect on trametinib exposure (< 6 % for either group). No data are available in patients with severe renal impairment (see section 4.2).

Elderly

Based on the population pharmacokinetics analysis, age had no relevant clinical effect on trametinib pharmacokinetics.

Paediatric population (below 18 years)

The pharmacokinetics of trametinib in glioma and other solid tumours were evaluated in 244 paediatric patients (1 to < 18 years old) following single or repeat weight-adjusted dosing. Pharmacokinetic

characteristics (drug absorption rate and drug clearance) of trametinib in paediatric patients are comparable to those of adults. Weight was found to influence trametinib oral clearance. The pharmacokinetic exposures of trametinib at the recommended weight-adjusted dosage in paediatric patients were within range of those observed in adults.

Gender

Based on the adult population pharmacokinetic analysis, gender and weight were found to influence trametinib oral clearance. Although smaller female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dosage adjustment is warranted**.**

6 PHARMACUETICAL PARTICULARS

6.1 List of excipients

Mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal silicon dioxide.

Excipients of film-coating: Hypromellose, titanium dioxide, polyethylene glycol,

For 0.5 mg tablets: Opadry yellow (contains hypromellose, titanium dioxide, macrogol, iron oxide yellow). For 2 mg tablets: Opadry pink (contains hypromellose, titanium dioxide, macrogol, polysorbate 80, iron oxide red).

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package to protect from light and moisture. Keep the bottle tightly closed. Contains desiccant, do not remove or eat.

6.5 Nature and contents of the container

MEQSEL 0.5 and 2 mg tablets are packed in opaque white HDPE bottles with opaque white child resistant polypropylene closures inside an outer carton. This product is packaged with a silica gel desiccant.

Pack sizes: 7 or 30 tablets per bottle.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

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8. REGISTRATION NUMBERS:

MEQSEL® 0.5 mg: 51/32.2/0819

MEQSEL® 2 mg: 51/32.2/0820

9. DATE OF FIRST AUTHORISATION

20 March 2019

10. DATE OF REVISION OF THE TEXT

20 August 2026

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2022-PSB/GLC-1333-e

2021-PSB/GLC-1210-s

2020-PSB/GLC-1131-s