15 November 2023
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Finlee (dabrafenib mesylate)
Treatment of glioma
EU/3/20/2372

Sponsor: Novartis Europharm Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Dabrafenib mesylate
Other name(s)	Dabrafenib mesylate, GSK2118436
International Non-Proprietary Name	Dabrafenib
Tradename	Finlee
Orphan condition	Treatment of glioma
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion	5 November 2020
EC decision	9 December 2020
EC registration number	EU/3/20/2372
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson/Eva Skovlund
Applicant	Novartis Europharm Limited
Application submission	9 September 2022
Procedure start	29 September 2022
Procedure number	EMA/H/C/005885/0000
Invented name	Finlee

Proposed therapeutic indication	*Low-grade glioma* Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. *High-grade glioma* Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment. In combination with trametinib for the treatment of paediatric patients with BRAF V600 mutation-positive low-grade glioma or relapsed/refractory high-grade glioma Further information on Finlee can be found in the European public assessment report (EPAR) on the Agency's website www.ema.europa.eu/en/human/EPAR/Finlee
CHMP opinion	14 September 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter/ Bozenna Dembowska-Baginska
Sponsor's report submission	27 March 2023
COMP discussion	3-5 October 2023
COMP opinion	5 October 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing dabrafenib mesylate was considered justified based on preliminary clinical data showing a response in patients with glioma BRAF V600+ advanced solid tumours;
- the condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor survival of less than 5% for glioblastoma multiforme patients;
- the condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made;

- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing dabrafenib mesylate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete response in a subset of patients who have glioma BRAF V600+ advanced solid tumours. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Gliomas are tumours that originate in the glial cells of the central nervous system (CNS), such as astrocytes, oligodendrocytes and ependymal cells, and are therefore located in the brain or the spinal cord. This heterogeneous group of tumours makes up about 30% of all brain and CNS tumours, and 80% of all malignant brain tumours. The three most common types of glioma are ependymomas, oligodendrogliomas, and astrocytomas, classified based on their phenotypic cell characteristics and molecular markers. Glioblastoma multiforme (grade 4 astrocytomas) is the most common and aggressive subtype of glioma, accounting for up to 50% of all primary brain gliomas (Zhang et al., 2012).

The aetiology of gliomas remains largely unknown. Several occupations, environmental carcinogens, dietary factors, and viruses have been reported to be associated with an elevated glioma risk. However, the only environmental factor that is unequivocally associated with an increased risk of brain tumours, including gliomas, is X-irradiation of the brain in the context of treatment for another disease. The majority of gliomas occur sporadically: familial gliomas account for approximately 5% of malignant gliomas, and less than 1% of gliomas are associated with inherited mutations of highly penetrant genes related with rare syndromes.

The fifth edition of WHO CNS classifies 'Gliomas', 'Glioneuronal Tumours', and 'Neuronal Tumours' into 6 different families: (1) 'Adult-type diffuse gliomas' (the majority of primary brain tumours in adults); (2) 'Paediatric-type diffuse low-grade gliomas' (expected to have good prognoses); (3) 'Paediatric-type diffuse high-grade gliomas' (expected to behave aggressively); (4) 'Circumscribed astrocytic gliomas' ("circumscribed" referring to their more solid growth pattern, as opposed to the inherently "diffuse" tumours in groups 1, 2, and 3); (5) 'Glioneuronal and neuronal tumours' (a diverse group of tumours, featuring neuronal differentiation); and (6) 'Ependymomas' (Louis et al., 2021).

The approved therapeutic indication "*Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. Finlee in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment*." falls within the scope of the designated orphan condition "Treatment of Glioma".

Trametinib is subject to a separate marketing authorisation and the orphan criteria will therefore be assessed separately.

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

Glioma is chronically debilitating in nature for both paediatric and adult forms as it is associated with tumour related symptoms including seizures, headaches, fatigue, memory changes, cognitive decline, or other neurocognitive dysfunctions depending on the tumour location (Dietrich, 2020; van den Bent, 2022a). These symptoms also progress over time due to the diffuse infiltrative glioma growth or because of complications or adverse effects with multimodal treatments (Dietrich, 2020; van den Bent, 2022a).

Paediatric low-grade gliomas or glioneuronal tumours (WHO grade 1 or 2) are highly heterogeneous entities. The most common single entity is pilocytic astrocytoma (0.91/100.000 patients aged 0 to 19 years), followed by ganglioglioma, dysembryoplastic neuroepithelial tumour (DNET), and Grade 2 diffuse gliomas.

Paediatric high grade gliomas (pHGGs) consist of Grade 3 tumours like anaplastic astrocytomas (0.1/100.000 patients age 0 to 19 years) and anaplastic gangliogliomas, and Grade 4 tumours include glioblastomas (0.18/100.000 patients age 0 to 19 years), diffuse intrinsic pontine glioma (DIPG) (80% of brain stem tumours, which accounts for 15% of all CNS tumours), and gliomatosis cerebri, which is a highly infiltrative, special manifestation of HGG affecting multiple brain regions (*Hauser, P. Classification and Treatment of Pediatric Gliomas in the Molecular Era. Children 2021, 8,739).* Overall survival is dependent on the type of paediatric glioma.

In the case of adult gliomas the condition is life-threatening with an estimated median overall survival (OS) for grade 2/3 gliomas ranging from 3 years to 14 years despite extensive treatment with surgery, radiation and/or chemotherapy (Van den bent et al, 2021; Lassman et al 2022 and Buckner et al, 2016), while median OS drops to almost 14 months for Grade 4 gliomas even with aggressive therapy (Stupp et al, 2005).

The condition is considered to be both chronically debilitating and life threatening.

Number of people affected or at risk

As part of the orphan designation in 2020 the sponsor provided a detailed epidemiological report in support of the prevalence estimate of glioma in the EEA/EU. The same report was used for this maintenance procedure.

A targeted literature search was performed on 27 March 2020, using the MEDLINE (PubMed) and Elsevier Embase databases. The aim of this literature search was to identify relevant articles on the epidemiology of malignant glioma in Europe with a specific focus on prevalence data, as well as a focus on tumours with BRAF V600 mutations. Two different search strategies were used:

1. Focusing the disease definition to glioma and using standard descriptive epidemiology terms;
2. Focusing the disease definition to glioma and adding terms related to BRAF mutations with the aim of identifying any publication reporting the occurrence of BRAF mutations among the population of patients diagnosed with glioma.

They have accessed the RARECARENet (www.rarecarenet.eu) which is built on work done for the Surveillance of Rare Cancers in Europe (RARECARE) project in collaboration with Rare Cancers Europe.

Several other cancer databases and projects compile data from European cancer registries, such as Cancer Incidence in Five Continents (CI5), the European Cancer Information System (ECIS), the Global Cancer Observatory (GLOBOCAN), and NORDCAN (specific to Nordic countries). However, these sources use the ICD-O-3 primary site codes to define cancer categories, as opposed to ICD-O-3 histology codes, and therefore provide data only for all brain and CNS tumours combined (C70-72). Data for specific glioma histology codes are not available in these sources. Cancer registry data from national, regional, and glioma-specific databases included in relevant publications are included in this report.

Eleven studies were identified that reported incidence estimates for all gliomas or for specific subtypes such as glioblastoma (range 2012 -2019). The following results are from the combined European incidence data:

- A total of 43,037 gliomas diagnosed in 1995-2002 and recorded by 64 cancer registries in the EU-27 were included. The crude annual incidence rate for all glial tumours combined was 0.54 per 10,000 persons, with most of the cases being astrocytic tumours (0.48 per 10,000).
- Males had a higher incidence than females, 0.63 versus 0.45 per 10,000, for all glial tumours combined.
- Incidence increased with age, with the lowest rate among patients aged 0-19 years (0.12 per 10,000) and the highest among patients aged 60 years or more (1.21 per 10,000) for all glial tumours combined.
- Standardised to the European standard population, the incidence rate for all glial tumours combined was 0.50 per 10,000 persons.

A total of 12 studies were identified that estimated survival of patients diagnosed with malignant glioma (range 2010 to 2018). Only one study provided a combined European survival rate, with a total of 46 European cancer registries participating in RARECARE providing data (Crocetti et al., 2012).

- A total of 13,667 glial tumours were included in the analysis. The 1-year relative survival estimate was 44%, and the 5-year estimate was 20%.
- Astrocytic tumours had the lowest 5-year relative survival rate (15%), while the 5-year survival rate for oligodendroglial tumours was 55%, and the 5-year survival rate for ependymal tumours was 74%.
- Five-year relative survival for all glial tumours combined decreased with increasing age: 58.1% for those aged 0-19 years; 52.8% for those aged 20-39 years; 19.1% for those aged 40-59 years, and 4.4% for those aged 60 years or more.

In the present application, the sponsor also shortly refers to the prevalence of paediatric glioma and on BRAF V600E mutated glioma, which are noted, but not considered relevant for the prevalence of the overarching orphan condition.

The sponsor states that since the initial OD in 2020, glioma prevalence has not changed and continues to be approximately 2.6 in 10,000. In view of the reference to RARECARE data, the data set is quite old (predating 2008) but is still acceptable by the COMP in view of the lack of newly introduced efficacious products.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Surgery is common in the initial therapeutic approach for tumour debulking and obtaining tissue for diagnosis.

Two thirds of paediatric gliomas are classified as low-grade (LGG), while in adults this is around 20%. Gross total excision is the primary treatment strategy for low grade gliomas. Most patients eventually experience tumour progression and require post-surgical therapy, such as carboplatin and vincristine (both used off-label for paediatric glioma).

Table 1. Comparison of the characteristics between paediatric and adult low-grade gliomas.

	pLGG	aLGG
Anatomical Location	Supra- and infratentorial each 30%	Supratentorial (eloquent regions) 80%
Most common histopathology	WHO I: 74% WHO II: 26% Pilocytic astrocytoma 65%	WHO I: 10–15% WHO II: 85–90% Diffuse LGG 60%
Primary treatment	Surgery, GTR increases OS	Surgery, GTR increases OS
Indication for adjuvant therapy	Radiographic progression (>25% of volume) or recurrence not amenable to re-resection	Radiographic progression or recurrence not amenable to re-resection
Chemotherapy	carboplatin and vincristine (CV)	Temozolomide (TMZ) often preferred to procarbazine, lomustine, and vincristine (PCV)
Radiotherapy	Salvage therapy, 45–50.4 Gy in 1.8 Gy fractionsConsider proton beam therapy if feasible	Concomitant with chemotherapy with 50.4–54 Gy in 1.8Gy fractions
Novel therapies	BRAF/MEK inhibitors (trametinib, selumetinib), ongoing trials	-
10-year OS (%)	>90%	~60%
Molecular alterations	BRAF600 17%	IDH mutant 70%
Malignant transformation	Extremely rare (2.9–6.7%), after Chemo or RT might be higher	Common, up to 86%
Associated syndromes	NF-1, TSC NF-1 associated OPG highly sensitive to chemotherapy but more side effects with RT TSC associated SEGA mTOR therapy	-
Prognostic factors	Location (optic pathway, brainstem worse prognosis, OPG with NF-1 very good prognosis), GTR (better prognosis), young age (worse prognosis)	Location (eloquent worse prognosis), GTR (better prognosis), diffuse LGG WHO II (worse prognosis), age <40 years (better prognosis)

Abbreviations: OS = overall survival, NF-1 = neurofibromatosis, TSC = tuberous sclerosis complex, GTR = gross total resection, MEK inhibitor = mitogen-activated protein kinase, IDH = isocitrate dehydrogenase, RT = radiotherapy, LGG = low grade glioma, OPG = optic pathway glioma.

Table from Greuter et al. 2021 Children 2021, 8, 1075. https://doi.org/10.3390/children8111075

The molecular genetics of paediatric HGG (pHGG) are distinct from those in adults, and therefore, adult clinical trial data cannot be extrapolated to children (Rallis et al Cancer Genomics & Proteomics 19: 390-414 (2022). Treatment for paediatric HGG also includes surgery, radiotherapy and chemotherapy. Due to potential risk for long-term neurocognitive effects of radiotherapy, post-surgical chemotherapy is preferred over radiotherapy for children younger than 3 years. The lack of authorised standard of care for recurrent paediatric HGG is illustrated by the publication of Perwein et al, 2023 (How I treat recurrent pediatric high-grade glioma (pHGG): a Europe-wide survey study J Neurooncol. 2023 Feb;161(3):525-538. doi: 10.1007/s11060-023-04241-6.). Survival outcomes for recurrent HGG remains poor (Kline et al 2018 Survival outcomes in pediatric recurrent high-grade glioma: results of a 20-year systematic review and meta-analysis. J Neurooncol. 2018 Mar;137(1):103-110. doi: 10.1007/s11060-017-2701-8.)

The most current ESMO guideline is from September 2014 and describes the current treatment options and management of in adult patients, only (Stupp et al., Ann Oncol. 2014 Sep; 25 Suppl 3:iii 93-101.):

The EANO guideline by Weller et al. (2014) (EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma), describes the treatment of adult and paediatric HGG.

NHS (UK) Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma (extrapolated from current SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low-Grade Glioma: Klin Padiatr. 2019;231(3):107-135).'

Temozolomide (TMZ), a chemotherapy drug that provides additional benefit when used with radiation therapy is authorised for adults and children over the age of three for newly diagnosed disease, and for adolescents and adults for the treatment of recurrent or progressive disease. In view that the proposed therapeutic indication for dabrafenib concerns children from one year of age, temozolomide is not considered a satisfactory method for the entirety of the patient population targeted by dabrafenib.

For the management of recurrent high-grade glioma (grade III or IV), procarbazine, lomustine, vincristine (PCV) or single agent lomustine chemotherapy is considered as an alternative to TMZ. Procarbazine, carboplatin and vincristine are used off-label. Only the well-known chemotherapeutic lomustine is broadly authorised nationally in an age-independent manner for the palliative treatment of intracranial tumours and its use is mostly restricted to multidrug combination therapy. Lomustine has also been used as an alternative in paediatric patients who have toxicity reactions to carboplatin. It has been studied in use as an alternative in the combination thioguanine/procarbazine/CCNU/vincristine (TPCV), (J Clin Oncol 30:2641-2647, 2012 by American Society of Clinical Oncology).

Carmustine intravenous is contraindicated for children in many member states of the European Union and carmustine wafers are only authorised for adults.

In conclusion, only the broadly authorised lomustine may be considered a satisfactory method from the regulatory perspective.

Significant benefit

Dabrafenib is a RAF kinase inhibitor, that targets the BRAF V600 mutant form over the wild-type form of the BRAF enzyme. This inhibits cell proliferation via cell cycle arrest in G1 which is followed by cell death. Dabrafenib is intended to be used in combination with trametinib.

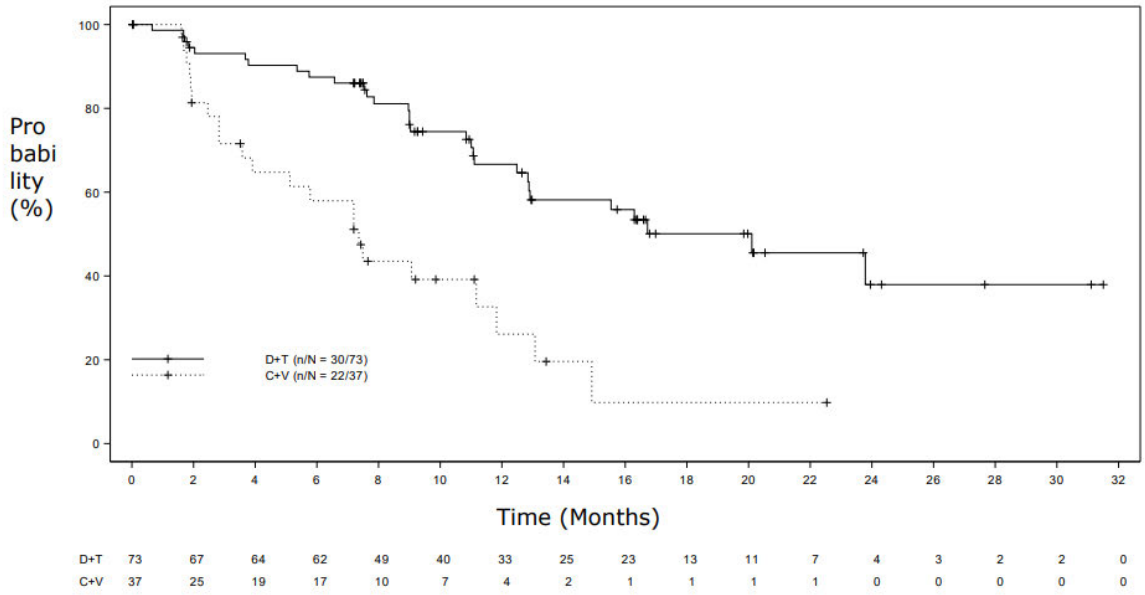
No protocol assistance (PA) was requested discussing the acceptability of the data for significant benefit.

The sponsor has submitted data from their pivotal Phase II open-label global study CDRB436G2201 which was designed to evaluate the effect of dabrafenib in combination with trametinib in children ≥ 1 year of age and adolescent patients with BRAF V600 mutation positive Low-Grade Glioma (LGG) or relapsed or refractory High-Grade Glioma (HGG).

The LGG cohort of the pivotal study CDRB436G2201 was designed as a randomized comparison of dabrafenib and trametinib combination with standard chemotherapy (carboplatin and vincristine, both used off-label) in patients with BRAF V600 mutant LGG requiring first systemic therapy.

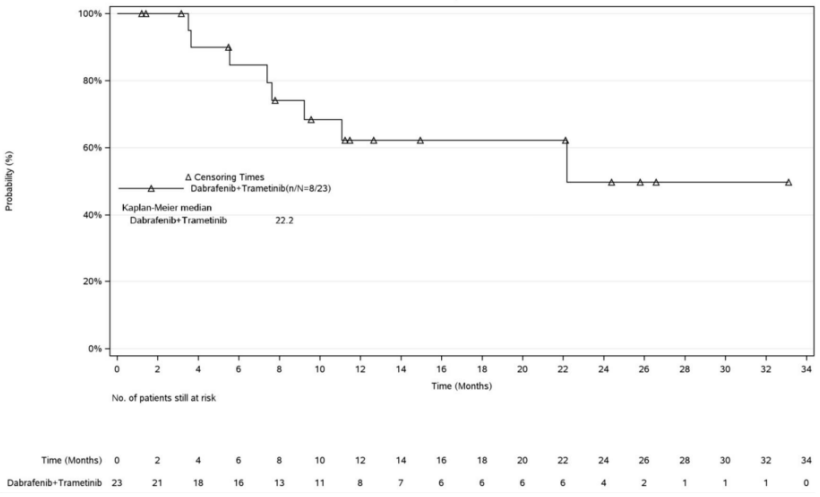
The subsequent hierarchical testing also demonstrated a clinically meaningful benefit in progression-free survival (PFS) over chemotherapy, with an estimated 69% risk reduction in progression/death.

Figure 1. Kaplan-Meier curves for progression-free survival in Study G2201 (LGG cohort, primary analysis) BRAF mutation-positive paediatric high-grade glioma (WHO Grades 3 and 4)



In the single-arm high-grade glioma cohort, 41 patients with relapsed or refractory HGG were enrolled and treated with dabrafenib plus trametinib for a median duration of 72.7 weeks. The ORR in this cohort was 56.1% (23/41), 95% CI (39.7%, 71.5%): CR in 12 patients (29.3%) and PR in 11 patients (26.8%). The median duration of response (DOR) was 22.2 months (95% CI: 7.6 – NE), with 15 patients (65.2%) censored at the time of the primary analysis. The Kaplan-Meier estimate for DOR at 12 months was 62.2% (95% CI: 36.3 – 80.0) To put into perspective the difficulties in treating this paediatric patient population a recent publication by Kline et al indicated that, "Across decade subgroups, PFS was 3.6 months (95% CI 2.1, 5.0; p-value < 0.001) for the first decade (1996–2006) and 3.3 months (95% CI −2.6, 9.2; p-value = 0.269) for the second decade (2007–2016; Supplemental figure 2). OS was 4.2 months (95% CI 2.1, 6.2; p-value < 0.001) for the first decade and 8.5 months (95% CI 5.6, 11; p-value < 0.001) for the second decade (Survival outcomes in paediatric recurrent high-grade glioma: results of a 20-year systematic review and meta-analysis J Neurooncol. 2018 March; 137(1): 103–110.)

Figure 2. Kaplan- Meier plot of DOR per Independent review based on RANO criteria (FASH)



The product is targeting a paediatric patient population with either LGG or recurrent HGG. The data submitted (accepted by the CHMP) shows an improvement in ORR and PFS compared to available currently recommended first-line treatment in paediatric LGG. Furthermore, ORR and DoR in relapsed HGG compare favourably to published results of available treatments. Many medicinal products for the treatment of paediatric glioma options in children are off-label or cannot be defined as satisfactory methods as described above. Only because of its very broad and unspecific label, lomustine is considered as satisfactory method.

Dabrafenib is intended for use in combination with trametinib as an alternative to currently recommended first line treatment with vincristine and carboplatin in patients with LGG with BRAF V600E mutation.

The use of lomustine in paediatric LGG is restricted to multidrug combination therapy in a third- or fourth line setting after failure of other preferred off-label options (such as vinblastine or bevacizumab) (Gnekov et al, 2019). The claim of significant benefit is therefore supported by the documented efficacy in an earlier line setting for LGG.

For paediatric recurrent HGG, there is no recognised standard of care and historical rates of ORR for patients with molecularly unselected relapsed refractory pHGG treated with the best available therapy are 5-12% (reviewed Zhang D, Liu X, Fan C, et al: Novel drugs in paediatric gliomas. Oncol Lett 13:2881-2885, 2017).

Therefore, the significant benefit of the combination of dabrafenib and trametinib is based on a clinically relevant advantage of improved efficacy in both LGG and HGG.

4. COMP position adopted on 5 October 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of glioma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 2.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality change and cognitive impairment. The condition is life-threatening, with poor survival of less than 5% for glioblastoma multiforme patients;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Finlee, the assumption that Finlee may be of potential significant benefit to those affected by the orphan condition still holds. In low grade glioma patients Finlee showed an improvement in progression free survival when compared to the standard of care. In relapsed and refractory high grade glioma patients Finlee showed a higher rate of durable response compared to another authorised treatment option. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Finlee, dabrafenib mesylate for treatment of glioma (EU/3/20/2372) is not removed from the Community Register of Orphan Medicinal Products.