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SCIENCE MEDICINES HEALTH

11 July 2019  
EMA/397644/2019  
Committee for Orphan Medicinal Products

## Orphan designation withdrawal assessment report

Vitrakvi (larotrectinib)  
Sponsor: Bayer AG

### Note

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

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# 1. Introductory comment

The marketing authorisation application of Vitrakvi was associated with four orphan designations in the following conditions:

- “Treatment of soft tissue sarcoma” (EU/3/15/1606, EMA/OD/184/15),
- “Treatment of salivary gland cancer” (EU/3/18/1995, EMA/OD/213/17),
- “Treatment of glioma” (EU/3/18/2097, EMA/OD/116/18),
- “Treatment of papillary thyroid cancer” (EU/3/18/2098, EMA/OD/117/18).

The four orphan maintenance assessments are covered in this one document. Of note, the sponsor of the designations withdrew all four orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues.

## 2. (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate (larotrectinib) for treatment of soft tissue sarcoma EU/3/15/1606 (EMA/OD/184/15)

### 2.1. Product and administrative information

<b>Product</b>	
Active substance	(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate
International Non-Proprietary Name	Larotrectinib
Orphan indication	Treatment of soft tissue sarcoma
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L-onco
Sponsor's details:	Bayer AG 51368 Leverkusen Germany
<b>Orphan medicinal product designation procedural history</b>	
Sponsor/applicant	TMC Pharma Services Ltd
COMP opinion date	10 December 2015
EC decision date	11 January 2016
EC registration number	EU/3/15/1606
<b>Post-designation procedural history</b>	
Transfer of sponsorship	Transfer from TMC Pharma Services Ltd to Loxo Oncology Limited – EC decision of 30 November 2017  Transfer from Loxo Oncology Limited to Bayer AG – EC decision of 25 June 2018
<b>Marketing authorisation procedural history</b>	
Rapporteur / co-Rapporteur	F. Josephson / A. Moreau
Applicant	Bayer AG
Application submission date	24 August 2018
Procedure start date	13 September 2018
Procedure number	EMA/H/C/004919
Invented name	Vittrakvi

Approved therapeutic indication	<p>VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,</p> <ul style="list-style-type: none"> <li>- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and</li> <li>- who have no satisfactory treatment options (see sections 4.4 and 5.1).</li> </ul> <p>Further information on Vitrakvi can be found in the European public assessment report (EPAR) on the Agency's website <a href="https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi">https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi</a></p>
CHMP opinion date	25 July 2019
<b>COMP review of orphan medicinal product designation procedural history</b>	
COMP Co-ordinators	F. Naumann-Winter / E. Penninga
Sponsor's report submission date	30 August 2018
18-20 June 2019	18-20 June 2019
Withdrawal request	2 July 2019
Withdrawal from Register	11 July 2019

## **2.2. Grounds for the COMP opinion at the designation stage**

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate was considered justified based on pre-clinical in vivo data and preliminary clinical data showing a reduction in the number of metastasis;
- the condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%;
- the condition was estimated to be affecting not more than 3 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in the number of metastasis in patients with advanced disease. The Committee considered that this constitutes a clinically relevant advantage.

## **2.3. 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**

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP noted that the initially proposed therapeutic indication would not fall within the scope of the cluster of designated orphan conditions "Treatment of salivary gland cancer" (EU/3/18/1995, EMA/OD/213/17), "Treatment of glioma" (EU/3/18/2097, EMA/OD/116/18), "Treatment of papillary thyroid cancer" (EU/3/18/2098, EMA/OD/117/18), and "Treatment of soft tissue sarcoma" (EU/3/15/1606, EMA/OD/184/15). A tissue independent therapeutic indication cannot be considered to be within the scope of a limited number of orphan designations covering separate tumour types.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of soft tissue sarcoma.

#### **Intention to diagnose, prevent or treat**

At the time of this review, the COMP and CHMP assessments were still ongoing. The CHMP subsequently confirmed that the overall benefit/risk was positive (please see EPAR of Vitrakvi).

### **Chronically debilitating and/or life-threatening nature**

At the time of this review, the COMP and CHMP assessments were still ongoing.

For the purpose of this review, it is claimed that there has been no change in the chronically debilitating or life-threatening nature of soft tissue sarcoma since the initial designation. Soft tissue sarcoma has been described to remain life-threatening and chronically debilitating with a 5-year relative survival for soft tissue sarcoma of 58%. Reported survival for treated patients with metastatic disease is only 12 to 16 months, and the 2-year survival rate is approximately 30%.

The COMP noted that soft tissue sarcoma remains chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of soft tissue sarcoma.

### **Number of people affected or at risk**

At the time of this review, the COMP and CHMP assessments were still ongoing.

For this review the prevalence for salivary gland cancer has been estimated to be 1 per 10,000. A systematic literature search on prevalence of soft tissue sarcoma has been conducted. The final estimate was based on 5-year partial prevalence figures from different national cancer registries in the EU. A weighted average figure has been calculated taking into consideration the population size. The use of 5-year prevalence figures has not been adequately justified.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of soft tissue sarcoma.

**Table 1.** Summary of available evidence – soft tissue sarcoma

Source data	Calculations	Estimated 5-Year Prevalence per 10,000
The Netherlands Cancer Registry (2018) reported a 5-year prevalence in 2016 for soft tissue sarcoma of 1989. Prevalence divided by Dutch population estimate on 1/1/2017 (Eurostat, 2018) (17,081,507)	$(1989/17081507) * 10,000$	1.164
A report from the Italian Cancer Registry (AIRTUM, 2014) reported a 5-year prevalence in 2010 for soft tissue sarcoma of 6541. Prevalence divided by Italian population estimate on 1/1/2011 (Eurostat, 2018) (59,364,690)	$(6541/59364690) * 10,000$	1.102
NORDCAN (2018) 5-year prevalence of soft tissue sarcoma in Nordic countries in 2015 (3101) was applied to the Nordic population 2016 (Eurostat, 2018) (26,592,090)	$(3101/26592090) * 10,000$	1.166
The UK Cancer Prevalence Project (NCRAS, 2010) reported a 5-year prevalence in 2010 for soft tissue sarcoma of 5106. Prevalence applied to the 2011 UK population (Eurostat, 2018) (63,022,532)	$(5106/63022532) * 10,000$	0.810
Weighted Average	$(1989+6541+3101+5106)/ (17,081,507+59,364,690 +26,592,090+63,022,532) * 10,000$	1.008

**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**

There are medicinal products authorised in the EU for the treatment of soft tissue sarcoma: doxorubicin, ifosfamide, dacarbazine, trabectedin, pazopanib, eribulin. Most recently olaratumab (Lartruvo) was authorised in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin. The EMA published a recommendation to revoke the marketing authorisation of Lartruvo based on its assessment of the results of the ANNOUNCE study (please see press release 26/04/2019).



The COMP also takes into consideration the most current ESMO guideline (Ann Oncol (2014) 25 (suppl 3): iii102-iii112.) describing the best standard of care for treating patients affected by the condition.

### **Significant benefit**

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP did not conclude on significant benefit. The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of soft tissue sarcoma.

### 3. Larotrectinib for treatment of salivary gland cancer EU/3/18/1995 (EMA/OD/213/17)

#### 3.1. Product and administrative information

<b>Product</b>	
Active substance	Larotrectinib
International Non-Proprietary Name	Larotrectinib
Orphan indication	Treatment of salivary gland cancer
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L-onco
Sponsor's details:	Bayer AG 51368 Leverkusen Germany
<b>Orphan medicinal product designation procedural history</b>	
Sponsor/applicant	Loxo Oncology Limited
COMP opinion date	15 February 2018
EC decision date	21 March 2018
EC registration number	EU/3/18/1995
<b>Post-designation procedural history</b>	
Transfer of sponsorship	Transfer from Loxo Oncology Limited to Bayer AG – EC decision of 25 June 2018
<b>Marketing authorisation procedural history</b>	
Rapporteur / co-Rapporteur	F. Josephson / A. Moreau
Applicant	Bayer AG
Application submission date	24 August 2018
Procedure start date	13 September 2018
Procedure number	EMA/H/C/004919
Invented name	Vitrakvi
Therapeutic indication	<p>VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,</p> <ul style="list-style-type: none"> <li>- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and</li> <li>- who have no satisfactory treatment options (see sections 4.4 and 5.1).</li> </ul> <p>Further information on Vitrakvi can be found in the European public assessment report (EPAR) on the Agency's website <a href="https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi">https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi</a></p>
CHMP opinion date	25 July 2019
<b>COMP review of orphan medicinal product designation procedural history</b>	
COMP Co-ordinators	F. Naumann-Winter / E. Penninga

Sponsor's report submission date	30 August 2018
COMP discussion	18-20 June 2019
Withdrawal request	2 July 2019
Withdrawal from Register	11 July 2019

### **3.2. Grounds for the COMP opinion at the designation stage**

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2018 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing larotrectinib was considered justified based on preliminary clinical data showing partial and complete response in patients with the condition;
- the condition is life-threatening due to neoplasms with high-risk features which tend to have an aggressive clinical course and 5-year survival rates ranging from 30% to 40%;
- the condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made;
- the sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

### **3.3. 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**

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP noted that the initially proposed therapeutic indication would not fall within the scope of the cluster of designated orphan conditions "Treatment of salivary gland cancer" (EU/3/18/1995, EMA/OD/213/17), "Treatment of glioma" (EU/3/18/2097, EMA/OD/116/18), "Treatment of papillary thyroid cancer" (EU/3/18/2098, EMA/OD/117/18), and "Treatment of soft tissue sarcoma" (EU/3/15/1606, EMA/OD/184/15). A tissue independent therapeutic indication cannot be considered to be within the scope of a limited number of orphan designations covering separate tumour types.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of salivary gland cancer.

#### **Intention to diagnose, prevent or treat**

At the time of this review, the COMP and CHMP assessments were still ongoing. The CHMP subsequently confirmed that the overall benefit/risk was positive (please see EPAR of Vitrakvi).

#### **Chronically debilitating and/or life-threatening nature**

At the time of this review, the COMP and CHMP assessments were still ongoing.

For the purpose of this review, it is claimed that there has been no change in the chronically debilitating or life-threatening nature of salivary gland cancer since the initial designation. Salivary gland cancer has been characterised by slow growth, multiple local recurrences, and a prolonged clinical course, often with the delayed development of distant metastasis. The condition has been described to remain life threatening with 5-year survival for stage IV disease of 35-40% when local control has failed, or distant metastases are present.

The COMP noted that the that salivary gland cancer remains life-threatening due to neoplasms with high-risk features which tend to have an aggressive clinical course and 5-year survival rates ranging from 30% to 40%.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of salivary gland cancer.

**Number of people affected or at risk**

At the time of this review, the COMP and CHMP assessments were still ongoing.

For this review the prevalence of salivary gland cancer has been estimated to be 0.196 per 10,000. A systematic literature search on prevalence of salivary gland cancer has been conducted. The final estimate has been based on the 5-year prevalence figure for head and neck tumours as reported by GLOBOCAN/ECIS (2012) taking into consideration the proportion for salivary gland cancer. This estimate could be updated with 2018 ECIS data. Furthermore, the use of 5-year prevalence has not been sufficiently justified.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of salivary gland cancer.

**Table 2.** Summary of available evidence – salivary gland cancer

Source data	Calculations	Estimated 5-Year Prevalence per 10,000
<p>GLOBOCAN<sup>1</sup> does not publish data for salivary gland carcinoma specifically. To estimate all head and neck tumours, combine the 2012 5-year prevalence estimates for Lip + oral cavity tumours, Nasopharynx tumours, and Other Pharynx tumours (198506). Prevalence divided by EU28 population 2013 (505,166,839). Published literature was used to estimate the proportion of all head and neck cancers comprised by salivary gland cancers (&lt;5%, Bensadoun 2001<sup>2</sup> and Ata-Ali 2016<sup>3</sup>)</p>	<p>(198506/505166839) *10,000*0.05</p>	<p>0.196</p>

Source data	Calculations	Estimated 5-Year Prevalence per 10,000
Netherlands Cancer Registry <sup>4</sup> reported a 5-year prevalence in 2012 for salivary gland tumours of 617. Prevalence divided by Dutch population estimate on 1/1/2013 (from Eurostat) (16,779,575)	$(617/16779575) * 10,000$	0.368
A report from the Italian Cancer Registry <sup>5</sup> reported a 5-year prevalence in 2010 for salivary gland cancer of 2562. Prevalence divided by Italian population estimate on 1/1/2011 (from Eurostat) (59,364,690)	$(2562/59364690) * 10,000$	0.432
NORDCAN <sup>6</sup> 5-year prevalence of salivary gland carcinoma in Nordic countries in 2014 (1107) was applied to the Nordic population 2015 (26,374,416)	$(1107/26,374,416) * 10,000$	0.420
The UK Cancer Prevalence Project <sup>7</sup> reported a 5-year prevalence in 2010 for salivary gland cancer of 2305. Prevalence applied to the 2011 UK population (from Eurostat) (63,022,532)	$(2305/63022532) * 10,000$	0.366
Weighted Average	$(0.368 * 16,779,575) + (0.432 * 59,364,690) + (0.420 * 26374416) + (0.366 * 63022532) / (16,779,575 + 59,364,690 + 26374416 + 63022532)$	0.398

### 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

There are currently no authorised treatments in the EU for the treatment of salivary gland cancer. 5-Fluorouracil and Cisplatin have an indication for use in head and neck cancer, but are generally not considered for significant benefit by the COMP.

There is currently no consensus ESMO treatment guideline. The primary treatment for salivary gland cancer without metastases is surgical resection. The success of surgical resection depends on the location and extent of the tumor. Radiotherapy is used as an adjuvant to resection for patients who exhibit lymph node metastases, locally advanced disease, bone or nerve involvement, recurrent

disease, or any combination of other adverse features. Radiotherapy is also commonly used in the management of unresectable disease, although it is not always effective. For patients with advanced, recurrent or metastatic disease, chemotherapy is the typical primary therapy. The intent of treatment in this setting is generally palliative.

The non-pharmacological treatment options cannot be considered to be satisfactory in the metastatic setting and the COMP therefore concluded that no significant benefit needs to be demonstrated.

**Significant benefit**

Not applicable.

## 4. Larotrectinib for treatment of glioma EU/3/18/2097 (EMA/OD/116/18)

### 4.1. Product and administrative information

<b>Product</b>	
Active substance	Larotrectinib
International Non-Proprietary Name	Larotrectinib
Initial orphan condition	Treatment of glioma
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L-onco
Sponsor's details:	Bayer AG 51368 Leverkusen Germany
<b>Orphan medicinal product designation procedural history</b>	
Sponsor/sponsor	Bayer AG
COMP opinion date	18 October 2018
EC decision date	19 November 2018
EC registration number	EU/3/18/2097
<b>Marketing authorisation procedural history</b>	
Rapporteur / Co-rapporteur	F. Josephson / A. Moreau
Sponsor	Bayer AG
Application submission date	24 August 2018
Procedure start date	13 September 2018
Procedure number	EMA/H/C/004919
Invented name	Vitrakvi
Therapeutic indication	<p>VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,</p> <ul style="list-style-type: none"> <li>- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and</li> <li>- who have no satisfactory treatment options (see sections 4.4 and 5.1).</li> </ul> <p>Further information on Vitrakvi can be found in the European public assessment report (EPAR) on the Agency's website <a href="https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi">https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi</a></p>
CHMP opinion date	25 July 2019
<b>COMP review of orphan medicinal product designation procedural history</b>	
COMP rapporteur(s)	F. Naumann-Winter / E. Penninga
Sponsor's report submission date	21 November 2018
COMP discussion	18-20 June 2019
Withdrawal request	2 July 2019

Withdrawal from Register	11 July 2019
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## **4.2. Grounds for the COMP opinion**

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing larotrectinib was considered justified based on preliminary clinical data showing disease control in patients affected by the condition;
- 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 larotrectinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing disease control in patients affected by the condition, who have failed the current best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

## **4.3. 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***

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP noted that the initially proposed therapeutic indication would not fall within the scope of the cluster of designated orphan conditions "Treatment of salivary gland cancer" (EU/3/18/1995, EMA/OD/213/17), "Treatment of glioma" (EU/3/18/2097, EMA/OD/116/18), "Treatment of papillary thyroid cancer" (EU/3/18/2098, EMA/OD/117/18), and "Treatment of soft tissue sarcoma" (EU/3/15/1606, EMA/OD/184/15). A tissue independent therapeutic indication cannot be considered to be within the scope of a limited number of orphan designations covering separate tumour types.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of glioma.

### **Intention to diagnose, prevent or treat**

At the time of this review, the COMP and CHMP assessments were still ongoing. The CHMP subsequently confirmed that the overall benefit/risk was positive (please see EPAR of Vitrakvi).



### Chronically debilitating and/or life-threatening nature

At the time of this review, the COMP and CHMP assessments were still ongoing.

For the purpose of this review, it is claimed that there has been no change in the chronically debilitating or life-threatening nature of glioma since the initial designation. Glioma has been described to remain life-threatening and chronically debilitating with approximately 95% of patients with glioblastoma succumb to the disease within 5 years of diagnosis.

The COMP noted that glioma remains 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. Moreover, the COMP considered that glioma is life-threatening, with poor survival of less than 5% for glioblastoma multiforme patients.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of glioma.

### Number of people affected or at risk

At the time of this review, the COMP and CHMP assessments were still ongoing.

For this review the prevalence of glioma has been estimated to be 0.79 per 10,000. A systematic literature search on prevalence of glioma has been conducted. The final estimate has been established by using the average (table 1) of two observational 5-year prevalence figures reported by GLOBOCAN/ECIS (2018) and RARECARE (Crocetti et al, 2012). The COMP noted that the RARECARE project also reported on complete prevalence: 2.6 per 10,000.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of glioma.

**Table 3.** Summary of available evidence – glioma

Source data	Calculations	Estimated 5-Year Prevalence per 10,000
GLOBOCAN (2012) reported the 2012 5-year prevalence estimate for brain/CNS cancers in the EU28 as 44,240. According to a recent publication from the EURO CARE-5 study (Visser et al., 2015), gliomas represent 85.9% of all malignant brain tumours. Prevalence divided by EU28 population 2013 (from Eurostat, 2018) (505,166,839).	$((44240 * 0.859) / 505166839) * 10,000$	0.75
Crocetti et al., 2012 reported the 2003 5-year prevalence of glioma as 8.3 per 100,000.	$(8.3 / 100000) * 10000$	0.83
Average prevalence	$(0.75 + 0.83) / 2$	0.79

## 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**

There are medicinal products authorised in the EU for the treatment of glioma: temozolomide, 5-aminolevulinic acid hydrochloride, carmustine and lomustine.

The COMP also takes into consideration the most current ESMO guideline is from September 2014, (Stupp et al., Ann Oncol. 2014 Sep; 25 Suppl 3:iii93-101.), which describes the current treatment options and management of patients.

### **Significant benefit**

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP did not conclude on significant benefit. The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of glioma.

## 5. Larotrectinib for papillary thyroid cancer EU/3/18/2098 (EMA/OD/117/18)

### 5.1. Product and administrative information

<b>Product</b>	
Active substance	Larotrectinib
International Non-Proprietary Name	Larotrectinib
Initial orphan condition	Treatment of papillary thyroid cancer
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L-onco
Sponsor's details:	Bayer AG 51368 Leverkusen Germany
<b>Orphan medicinal product designation procedural history</b>	
Sponsor/applicant	Bayer AG
COMP opinion date	18 October 2018
EC decision date	19 November 2018
EC registration number	EU/3/18/2098
<b>Marketing authorisation procedural history</b>	
Rapporteur / Co-rapporteur	F. Josephson / A. Moreau
Applicant	Bayer AG
Application submission date	24 August 2018
Procedure start date	13 September 2018
Procedure number	EMA/H/C/004919
Invented name	Vitrakvi
Therapeutic indication	<p>VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,</p> <ul style="list-style-type: none"> <li>- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and</li> <li>- who have no satisfactory treatment options (see sections 4.4 and 5.1).</li> </ul> <p>Further information on Vitrakvi can be found in the European public assessment report (EPAR) on the Agency's website <a href="https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi">https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi</a></p>
CHMP opinion date	25 July 2019
<b>COMP review of orphan medicinal product designation procedural history</b>	
COMP rapporteur(s)	F. Naumann-Winter / E. Penninga
Sponsor's report submission date	23 November 2018
COMP discussion	18-20 June 2019
Withdrawal request	2 July 2019

Withdrawal from Register	11 July 2019
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## **5.2. Grounds for the COMP opinion**

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing larotrectinib was considered justified based on preliminary clinical data showing that patients respond to treatment;
- the condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment and in case of development of metastasis with wide spread of the tumour;
- the condition was estimated to be affecting approximately 3.3 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 larotrectinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients, who have failed the current best standard of care including authorised products, respond to treatment. The Committee considered that this constitutes a clinically relevant advantage.

## **5.3. 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**

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP noted that the initially proposed therapeutic indication would not fall within the scope of the cluster of designated orphan conditions "Treatment of salivary gland cancer" (EU/3/18/1995, EMA/OD/213/17), "Treatment of glioma" (EU/3/18/2097, EMA/OD/116/18), "Treatment of papillary thyroid cancer" (EU/3/18/2098, EMA/OD/117/18), and "Treatment of soft tissue sarcoma" (EU/3/15/1606, EMA/OD/184/15). A tissue independent therapeutic indication cannot be considered to be within the scope of a limited number of orphan designations covering separate tumour types.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of papillary thyroid cancer.

#### **Intention to diagnose, prevent or treat**

At the time of this review, the COMP and CHMP assessments were still ongoing. The CHMP subsequently confirmed that the overall benefit/risk was positive (please see EPAR of Vitrakvi).

### **Chronically debilitating and/or life-threatening nature**

At the time of this review, the COMP and CHMP assessments were still ongoing.

For the purpose of this review, it is claimed that there has been no change in the chronically debilitating or life-threatening nature of papillary thyroid cancer since the initial designation. Papillary thyroid cancer has been described to remain life-threatening and chronically debilitating. Most differentiated thyroid cancers including papillary thyroid cancer are treatable tumours with an excellent prognosis after surgical resection and radioiodine therapy. Unfortunately, 10% to 15% of thyroid cancers will exhibit aggressive behaviour. Approximately one-third of patients with differentiated thyroid cancers will have tumour recurrences. Distant metastases are present in about 20% of patients with recurrent cancer and indicate a terminal prognosis. Approximately half of patients with distant metastases die within 5 years.

The COMP noted that papillary thyroid cancer remains chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. Moreover, the COMP considered that the condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment and in case of development of metastasis with wide spread of the tumour.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of papillary thyroid cancer.

### **Number of people affected or at risk**

At the time of this review, the COMP and CHMP assessments were still ongoing.

For this review the prevalence of papillary thyroid cancer has been estimated to be 1 per 10,000. A systematic literature search on prevalence of papillary thyroid cancer has been conducted. The Netherlands Cancer Registry was found to be the only epidemiological source to provide an estimate for differentiated thyroid cancer (papillary and follicular thyroid cancer combined). Furthermore, thyroid cancer figures have been reported in the Italian, Nordic, and UK Cancer Registries. The proportion of papillary thyroid cancer was assumed and 20-year partial prevalence statistics were reported. The average weighted prevalence rate across all data sources was 3.29 per 10,000; however there is no adequate justification to use the underlying figures and assumptions.

The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of papillary thyroid cancer.

**Table 4.** Summary of available evidence - papillary thyroid cancer

Source Data	Proportion of thyroid cancer comprised by papillary subtype	Calculations	Estimated Prevalence per 10,000
The Netherlands Cancer Registry (2018) reported a 20-year prevalence in 2016 for <b>papillary and follicular</b> thyroid tumours of 6604. Prevalence divided by Dutch population estimate on 1/1/2017 (Eurostat, 2018) (17,081,507)	N/A (estimate is specific to papillary/follicular thyroid cancer)	$(6604/17081507) * 10,000$	3.87
A report from the Italian Cancer Registry (AIRTUM, 2014) reported the complete prevalence of thyroid cancer in 2010 of 116,485. Prevalence divided by Italian population estimate on 1/1/2011 (Eurostat, 2018) (59,364,690)	77% <sup>a</sup>	$((116485 * 0.77) / 59364690) * 10,000$	15.1
	80-85% <sup>b</sup>	$((116485 * 0.85) / 59364690) * 10,000$	16.7
	85-90% <sup>c</sup>	$((116485 * 0.90) / 59364690) * 10,000$	17.7
	90.86% <sup>d</sup>	$((116485 * 0.9086) / 59364690) * 10,000$	17.8
	<b>Average</b>	<b><math>(15.1 + 16.7 + 17.7 + 17.8) / 4</math></b>	<b>16.8</b>
NORDCAN (2018) complete prevalence of thyroid cancer in the Nordic countries in 2015 (27076) was applied to the Nordic population 2016 (Eurostat, 2018) (26,592,090)	77% <sup>a</sup>	$((27076 * 0.77) / 26592090) * 10,000$	7.84
	80-85% <sup>b</sup>	$((27076 * 0.85) / 26592090) * 10,000$	8.65
	85-90% <sup>c</sup>	$((27076 * 0.90) / 26592090) * 10,000$	9.16
	90.86% <sup>d</sup>	$((27076 * 0.9086) / 26592090) * 10,000$	9.25
	<b>Average</b>	<b><math>(7.84 + 8.65 + 9.16 + 9.25) / 4</math></b>	<b>8.73</b>
The UK Cancer Prevalence Project (NCRAS, 2010) reported a 20-year prevalence rate in 2010 for thyroid cancer of 3.65 per 10,000.	77% <sup>a</sup>	$(3.65 * 0.77)$	2.81
	80-85% <sup>b</sup>	$(3.65 * 0.85)$	3.10
	85-90% <sup>c</sup>	$(3.65 * 0.90)$	3.29
	90.86% <sup>d</sup>	$(3.65 * 0.9086)$	3.32
	<b>Average</b>	<b><math>(2.81 + 3.10 + 3.29 + 3.32) / 4</math></b>	<b>3.13</b>
<b>Weighted Average: 20-year Prevalence</b>	$(3.87 * 17081507) + (3.13 * 63,022,532) / (17081507 + 63,022,532)$	<b>3.29</b>	

## 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**

There are medicinal products in the EU, which are authorised for the treatment of papillary thyroid cancer: sorafenib, lenvatinib and doxorubicin.

Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Nexavar is indicated for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

The COMP also takes into consideration the most current ESMO Clinical Practice Guidelines for thyroid cancer (Pacini et al, Ann Oncol 2012; 23 (Suppl 7): vii110-vii119), which describe the current treatment options and management of patients. The more recently authorised products have not been described in this guideline.

### **Significant benefit**

At the time of this review, the COMP and CHMP assessments were still ongoing. The COMP did not conclude on significant benefit. The sponsor withdrew all orphan designations for Vitrakvi prior to a potential COMP adoption of a list of issues. This included the designation for the treatment of papillary thyroid cancer.