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REVIEW

The European Medicines Agency review of entrectinib for the treatment of adult or paediatric patients with solid tumours who have a neurotrophic tyrosine receptor kinase gene fusions and adult patients with non-small-cell lung cancer harbouring ROS1 rearrangements

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Entrectinib is an inhibitor of the tyrosine kinases TRKA, TRKB, TRKC [all together known as neurotrophic tyrosine receptor kinases (NTRKs)], ROS1 and anaplastic lymphoma kinase (ALK). On 31 July 2020, a conditional marketing authorisation valid through the European Union (EU) was issued for entrectinib for the treatment of adult and paediatric patients 12 years of age and older with NTRK fusion-positive solid tumours that are locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor and have no satisfactory therapy; and also for adult patients with ROS1-positive non-small-cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors. The submission was based on three open-label, multicentre, phase I studies (ALKA, STARTRK-1 and STARTRK-NG) and one phase II study (STARTRK-2). In patients with NTRK-positive solid tumours, the objective response rate (ORR) was 63.5% [95% confidence interval (CI) 51.5% to 74.4%] and the median duration of response (DOR) was 12.9 months (95% CI 9.3-not estimable). In patients with ROS1-positive NSCLC, the ORR was 67.1% (95% CI 59.25% to 74.27%) and the median DOR was 15.7 months (95% CI 13.9-28.6 months). The most frequent adverse events were dysgeusia, fatigue, dizziness, constipation, diarrhoea, nausea, increased weight, paraesthesia, increased creatinine, myalgia, peripheral oedema, vomiting, arthralgia, anaemia and increased AST. The aim of this manuscript is to summarise the scientific review of the application leading to regulatory approval of entrectinib in the EU.

Key words: entrectinib, NTRK, ROS1, NSCLC, EMA

BACKGROUND

Neurotrophic tyrosine receptor kinase (NTRK) gene fusions arise from intra- or inter-chromosomal rearrangements juxtaposing the 3′ NTRK gene with various 5′ partner genes. NTRK fusions are rare events in common adult cancers [e.g. <1% in non-small-cell lung cancer (NSCLC) and 1%-2% in colorectal carcinoma], but more frequently observed in some rare cancers, such as 90%-100% of mammary analogue secretory carcinoma, a rare form of salivary gland cancer, and secretory breast cancer, for which the NTRK fusion ETV6-NTRK3 is pathognomonic.[1] NTRK fusions have also been described in several paediatric tumours, being characteristic of infantile fibrosarcoma and congenital mesoblastic nephroma and very frequent in high-grade glioma.[2] The overall prevalence of NTRK fusions in all cancer patients is estimated to be 0.25%-1%.[3]

The prognosis for patients with NTRK fusion-positive locally advanced or metastatic solid tumours who have progressed following prior therapy or with no acceptable standard therapy is poor, particularly in case of central nervous system (CNS) involvement. Expected objective response rates (ORRs) to later lines of treatment are typically <30%, with a median duration of response (DOR) <10 months, and patients who have exhausted all therapeutic options are generally offered palliative care.[4] In September 2019, the NTRK inhibitor larotrectinib was granted conditional marketing authorisation (CMA) in the European

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Union (EU) for the treatment of adult and paediatric patients with solid tumours displaying NTRK gene fusions, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options. This was based on a pooled analysis comprising 93 patients with TRK fusion-positive tumours enrolled across three open-label single-arm studies.[5–7] The ORR in the pooled dataset was 72% [95% confidence interval (CI) 62% to 81%] with 88% sustained responses at 12 months.

Lung cancer is the leading cause of cancer-associated death in men and women.[8] NSCLC represents >80% of all cases, including nonsquamous (i.e. adenocarcinoma, large-cell carcinoma and other cell types) and squamous cell carcinoma. In Europe, adenocarcinoma represents nearly half of all lung malignancies and its incidence has been increasing over the last decades.[9] Lately, a number of actionable molecular alterations have been identified in NSCLC, leading to the development and approval of targeted therapies such as erlotinib, afatinib, gefitinib, osimertinib and dacomitinib for epidermal growth factor receptor mutations; crizotinib, ceritinib, alectinib, brigatinib and lorlatinib for anaplastic lymphoma kinase (ALK) gene fusions; crizotinib for ROS1 gene fusions and dabrafenib in combination with trametinib for BRAF V600 mutation.[10,11] ROS1 rearrangements have been documented in 1%-2% of patients with NSCLC. ROS1 can rearrange with a myriad of partner genes, with CD74-ROS1 fusion being the most common. Patients with ROS1 fusion-positive NSCLC are more frequently female, of younger age and typically have no prior history of smoking.[12] Crizotinib was the only drug authorised in the EU for ROS1-rearranged NSCLC. The approval was based on a phase I/II study whose updated results revealed an ORR of 72% (95% CI 58% to 83%), median DOR of 24.7 months (95% CI 15.2-45.3), median progression-free survival (PFS) of 19.3 months (95% CI 15.2-39.1) and median overall survival (OS) of 51.4 months (95% CI 29.3-not reached).[13] According to European Society for Medical Oncology (ESMO) guidelines,[11] single-agent crizotinib is recommended as frontline or salvage therapy for patients with ROS1-rearranged stage IV NSCLC. If the patient already received crizotinib, he/she may be offered platinum-based salvage therapy. The development of resistance to crizotinib represents a major hurdle and causes the vast majority of patients to eventually progress on therapy.[12]

On 7 January 2019, Roche GmbH, Germany, applied for a CMA via the European Medicines Agency (EMA) centralised procedure for entrectinib (trade name Rozlytrek). CMA is an EMA regulatory tool that facilitates early access to medicines that fulfil an unmet medical need. This type of approval allows the EMA to recommend a medicine for marketing authorisation with less complete data than normally expected, if the benefit of a medicine's immediate availability to patients outweighs the risk inherent to the fact that not all the data are yet available. Comprehensive data are still being generated after authorisation in agreed timelines. The review was conducted by the Committee for Medicinal Products for Human Use (CHMP) and the positive opinion was issued on 28 May 2020. The marketing authorisation holder applied for the following indications: 'Rozlytrek is indicated for the treatment of adult and paediatric patients with NTRK fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies. Rozlytrek as monotherapy is indicated for the treatment of patients with ROS1-positive, advanced NSCLC.

NONCLINICAL ASPECTS

Entrectinib is an inhibitor of the tyrosine kinases TRKA, TRKB and TRKC (encoded by the genes *NTRK1*, *NTRK2* and *NTRK3*, respectively), ROS1 receptor tyrosine kinase (encoded by the gene *ROS1*) and ALK (encoded by the gene *ALK*). Inhibition of TRK, ROS1 and ALK leads to inhibition of downstream signalling pathways, including phospholipase C gamma, mitogen-activated protein kinase and phosphoinositide 3 kinase/protein kinase B, which in turn leads to inhibition of cell proliferation and induction of tumour cell apoptosis.[14] Of note, entrectinib could penetrate the blood–brain barrier and showed antitumour activity in multiple intracranial tumours models. Entrectinib-related effects in repeat-dose toxicity studies were either fully reversible (e.g. QT prolongation) or showed a trend towards reversibility (e.g. skin, liver and hematopoietic toxic effects) upon entrectinib discontinuation. Effects on growth and development were present in the 13-week rat juvenile toxicology study and, therefore, a relevant warning addressed to pregnant women and women of childbearing potential was included in the summary of product characteristics. The proposed posology was 600 mg once daily for adults, and 300 mg/m^2 for children aged 12 years or older, until disease progression or unacceptable toxicity. The simulations of the exposure to entrectinib and its metabolites in individuals aged ≥12 years were comparable to those obtained in adults. The applicant claimed that the proposed posology of 300 mg/m^2 (i.e. 400 mg in patients with a body surface area ≥1.1 to <1.5 m^2) was safer, and the risk for overexposure was lower compared with the U.S. Food and Drug Administration (FDA) approved posology of 500 mg for this body surface area group.

TRIAL DESIGN

The submission was based on three open-label, multicentre, phase I studies (ALKA, STARTRK-1 and STARTRK-NG) and one phase II study (STARTRK-2) of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours harbouring NTRK1/2/3, ROS1 or ALK gene rearrangements (Table 1).[15,16] The primary endpoints of the ALKA, STARTRK-1 and STARTRK-NG trials were first cycle dose-limiting toxicity, maximum tolerated dose and recommended phase II dose. The primary endpoint of the STARTRK-2 trial was ORR as per blinded independent central review (BICR) and secondary endpoints were, among others, DOR, time to response, adverse events (AEs), PFS

Table 1. Summary of entrectinib clinical trials

Protocol	Study design	Study objectives	Entrectinib dose and regimen	Patient population
ALKA	First-in-human, phase I, multicentre, open-label, dose escalation study	First-cycle DLTs and MTD. Safety, tolerability, PK and antitumour activity	Schedule A: 100, 200, 400, 800, 1200 or 1600 mg/m^2/day OD 4-day on, 3-day off schedule for 3 weeks followed by 1-week rest Schedule B: 200 or 400 mg/m^2/day or 600 mg/day OD in 4-week cycles Schedule C: 400 or 800 mg/m^2/day OD in a continuous 4-day on, 3-day off schedule	Adult patients with advanced/ metastatic solid tumours, including patients with NTRK, ROS1 or ALK molecular alterations
STARTRK-1	Phase I, single-arm, multicentre, open-label, dose escalation and expansion study	Dose escalation: First-cycle DLTs, MTD, RP2D and antitumour activity Dose expansion: ORR, safety, tolerability, PK and PD	Entrectinib OD in a continuous daily dosing regimen in 4-week cycles Doses: 100, 200, 400 mg/m^2/day; 800 mg/day; 600 mg/day if BSA $\leq$ 1.85 m^2 or 800 mg/day if BSA $>$ 1.85 m^2	Adult patients with solid tumours harbouring NTRK, ROS1 or ALK molecular alterations (mandatory for the dose-expansion phase)
STARTRK-2	Phase II, global, single-arm, open-label, multicentre, basket study	Efficacy (CNS separately), safety, tolerability, PK, ventricular repolarisation and patient-reported outcomes	Entrectinib 600 mg OD in a continuous daily dosing regimen in 4-week cycles	Adult patients with solid tumours with NTRK, ROS1 or ALK gene fusions (excluding ALK-positive NSCLC)
STARTRK-NG	Phase I/Ib, single-arm, multicentre, open-label, five-part, dose escalation and expansion study	MTD or RP2D in children and adolescents, safety profile, PK, efficacy parameters, intracranial tumour response in CNS patients	Entrectinib OD in a continuous daily dosing regimen with 4-week cycles. Dosing as per nomogram ranging from 250 to 750 mg/m^2/day	Children and young adults (2-22 years) with recurrent or refractory solid tumours and primary CNS tumours, with or without NTRK, ROS1 or ALK molecular alterations

ALK, anaplastic lymphoma kinase; BSA, body surface area; CNS, central nervous system; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; OD, once daily; ORR, objective response rate; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase II dose.

and OS. The number of patients enrolled in these trials was as follows:

- ALKA: The planned sample size was 70 patients. Overall, 58 patients were enrolled and 57 received study drug. Of those, 1 patient with an NTRK fusion-positive solid tumour and 9 patients with ROS1-rearranged NSCLC were included in the pooled efficacy datasets.
- *STARTRK-1*: No power calculations were done, but the dose escalation segment included 76 patients overall, of whom 2 patients with NTRK fusion-positive solid tumours and 7 patients with ROS1-positive NSCLC were included in the pooled efficacy datasets.
- *STARTRK-2*: A basket trial with a two-stage sequential testing design, incorporating up to 62 patients per basket. Most patients included in the pooled efficacy dataset were enrolled in this study.

The paediatric study STARTRK-NG was not included in the integrated efficacy analysis and was presented separately to support the activity of entrectinib in paediatric patients. In October 2018 a total of 29 patients had been enrolled, of whom 7 harboured NTRK fusion-positive tumours. Most patients had NTRK and ROS1 gene fusions detected by next-generation sequencing.

CLINICAL EFFICACY

NTRK positive solid tumours

An integrated efficacy analysis was presented comprising 54 adult patients who received at least one entrectinib dose (600 mg or above) across all three studies (ALKA, STARTRK-1 and STARTRK-2), had not received prior therapy with an NTRK inhibitor and had extracranial tumours. A larger dataset including 74 patients with a minimum follow-up of 6 months [cut-off date (COD): 31 October 2018] was provided upon request from the CHMP.

The median follow-up of the large dataset ($n = 74$) was 14.2 months. The ORR as per BICR was 63.5% (95% CI 51.5% to 74.4%), including a complete response rate of 6.8%. The median DOR and PFS were 12.9 months (95% CI 9.3-not estimable) and 11.2 months (95% CI 8.0-15.7 months), respectively. Median OS was 23.9 months (95% CI 16.0-not estimable), but these results were still immature (only 32.4% of OS events). In the extended dataset, 16 patients had secondary CNS disease at baseline (ORR 50.0%, 95% CI 24.7-75.4), which was measurable in 8 of them (ORR 62.5%, 95% CI 24.5% to 91.5%). Response rates according to the most common tumour types were 56.3% in sarcoma ($n = 16$), 69.2% in NSCLC ($n = 13$), 92.3% in mammary analogue secretory carcinoma ($n = 13$), 100% in secretory breast cancer ($n = 4$), 42.9% in thyroid cancer ($n = 7$), 28.6% in colorectal carcinoma ($n = 7$) and 50% in neuroendocrine tumours ($n = 4$). Patients with primary CNS tumours were evaluated separately, and only 1 of 7 (12.5%) achieved an objective response.

ROS1-positive NSCLC

An integrated efficacy analysis was presented comprising 94 adult patients treated with at least one dose of entrectinib (600 mg or above) across all three studies (ALKA, STARTRK-1 and STARTRK-2) who had not received prior therapy with an ROS1 inhibitor having at least 12 months of follow-up. A larger dataset including 161 patients with >6 months of

follow-up (COD: 1 May 2019) was provided upon request from the CHMP.

The median follow-up of the large dataset ($n = 161$) was 15.8 months (95% CI 14.49-18.23). The ORR as per BICR for the entire population was 67.1% (95% CI 59.25% to 74.27%), including 8.7% of complete responses. The median DOR and PFS were 15.7 (95% CI 13.9-28.6) and 15.7 months (95% CI 11-21.1), respectively. Data on OS were still immature, with only 23.6% of events. CNS disease was present at baseline in 46 patients, in whom the ORR was 52.2% (95% CI 36.95% to 67.1%). The intracranial ORR and median intracranial DOR for the 24 patients with measurable CNS disease were 79.2% (95% CI 57.85% to 92.9%) and 12.9 months (95% CI 6.8-22.1), respectively. Of 27 patients who received entrectinib after crizotinib (not part of the integrated efficacy dataset), 19 had experienced CNS-only progression and 8 systemic progression before entrectinib therapy. A total of 2/19 (10.5%) responses were observed among the former and 1/8 (12.5%) among the latter.

Paediatric patients were enrolled in the STARTRK-NG trial. Among seven patients with confirmed NTRK-positive tumours, only six were evaluable for efficacy and all achieved an objective response, with a DOR ranging from 1.8 to 9.3 months.

CLINICAL SAFETY

The safety data from all four studies was pooled to include 504 patients, 475 adults and 29 children (integrated safety population; COD: October 2018). Most patients received all planned therapy, with a median number of one missed dose (range 0-50), and a median duration of drug exposure of 5.5 months (range 0-42.1) corresponding to a median of 7.0 courses (range 1-92) and a median dose intensity of 96.4%. Almost all patients (99.4%) experienced at least one treatment-emergent AE. Most patients (91.5%) had at least one treatment-related AE, with the most frequent being dysgeusia (41.4%), fatigue (27.9%), dizziness (25.4%), constipation (23.7%), diarrhoea (22.8%), nausea (20.8%), increased weight (19.4%), paraesthesia (18.9%), increased creatinine (15.2%), myalgia (15.2%), peripheral oedema (14.1%), vomiting (13.5%), arthralgia (12.4%), anaemia (12.1%) and increased aspartate aminotransferase (11.0%). At least one serious AE was documented in 39.9% (9.7% treatment related), while AEs of grade 3 or higher were observed in 61.1% of patients (32.1% treatment related). AEs leading to treatment discontinuation occurred in 9.1% of patients, and AEs leading to patients' death were observed in 5.6%, although none was considered related to the study drug by the investigators.

AEs of special interest were not predefined, but some AEs were selected based on previous clinical experience, mechanism of action and safety profile from drugs with similar targets. Neurological AEs were reported in 88.7% of patients, but most of them were of grade 1 (45.4%) or 2 (26.5%). Cognitive AEs were documented in 24.2% of patients, with only 4.4% being of grade $\geq$3. Peripheral neuropathy was reported in 15.7% of patients, while ataxia and related disorders were also observed in 15.7%. Syncope and seizures were documented in 4.6% and 2.2% of patients, respectively.

Increased creatinine and other renal AEs were reported in 40.5% of patients, but most were grade 1-2, and haematologic toxicity was reported in 37.1% of patients (anaemia: 28.2%, neutropenia: 11.3%). Liver abnormalities were documented in 22.6% of patients, but most were grade 1-2 and resolved without any intervention. Weight gains were observed in 26.4% of patients (grade 3: 7.9%) and were more frequent in the paediatric population. Other selected AEs were congestive heart failure (3.2%), pneumonitis (2.0%), QT interval prolongation (4.0%) and bone fractures (6.2%). This last AE was more common in children (20.7%) than adults (5.3%).

BENEFIT–RISK ASSESSMENT

The proposed indications were (i) adult and paediatric patients aged 12 years and older with solid tumours harbouring NTRK gene fusions who have locally advanced or metastatic disease, or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options; and (ii) adult patients with ROS1-positive, advanced NSCLC not previously treated with ROS1 inhibitors. Data were pooled and derived from single-arm studies, which limited the interpretation of time-to-event endpoints. A fundamental problem of using pooled data from the entire development programme was the lack of confirmatory results.

For the first indication, the data initially submitted comprised 54 adult patients who had received at least one dose of entrectinib and no other NTRK inhibitor. A larger dataset including 74 patients was subsequently provided (Table 2). Entrectinib induced clinically meaningful and durable objective responses in patients with NTRK-fusion positive solid tumours for whom non-NTRK-targeted therapeutic options are either not available or have been exhausted. There was, however, uncertainty about the precise magnitude of the effect due to the single-arm trial design and incomplete understanding of the importance of histology and concomitant genomic aberrations. In order to confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the applicant was asked to submit a pooled analysis from ongoing and proposed clinical trials as specific obligations for the CMA. The applicant was also asked to submit these results according to tumour histology and genomic profiling. The CHMP also felt it was important to determine lack of efficacy in specific tumour subtypes. To that effect, the applicant accepted to inform the EMA in case of $<$4 responders in a group of sequentially enrolled 13 patients evaluable for efficacy (i.e. ORR $<$30%). An indication in adolescents aged 12-18 years was considered possible based on allometric scaling due to the low number of adolescents with tumours harbouring NTRK 1/2/3 gene fusions.

Regarding the ROS1-rearranged NSCLC indication, entrectinib showed antitumour activity by inducing a

Table 2. Key favourable and unfavourable effects of entrectinib for patients with ROS1-positive NSCLC or NTRK-positive solid tumours (pooled analysis, COD: 31 October 2018)

Effect	Unit	Result	Uncertainties/strength of evidence
Favourable effects			
Indication: patients with ROS1-positive, advanced NSCLC ($n = 161$) (COD: 1 May 2019)			
ORR by BICR	% 95% CI	67.1% (59.25-74.27)	Post hoc definition of the SAP
DOR by BICR	Median (months) 95% CI	15.7 (13.9-28.6)	Half of the patients still on treatment at the COD
Indication: adult and paediatric patients with *NTRK* fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies. Pooled study population (n = 74) (COD: 31 October 2018)			
ORR by BICR	% 95% CI	63.5 (51.5-74.4)	Different ORRs across tumour types. Primary CNS tumours not included.
DOR by BICR	Median (months) 95% CI	12.9 (9.3-NE)	31% of patients on treatment at the COD
Unfavourable effects (COD: 31 October 2018)			
Safety population ($n = 504$)			
Total AEs	%	99	Interpretation of safety hampered by:
Grade ≥3 AEs	%	61.1	Single-arm study
SAEs	%	39.9	Differences across the safety subsets in exposure,
AEs leading to discontinuation	%	9.1	dose, administration regimen, formulation,
AEs leading to death	%	5.6	underlying malignancy, genetics and sample size
			Highest uncertainty in the paediatric subset.
			Only two grade 5 events assessed as related to entrectinib by investigator, all occurred in adults.
AEs by SOC	%		
Nervous system		82.5	
Gastrointestinal		81.5	
General		73.4	
Respiratory		~60	
Musculoskeletal		~55	
Grade 3-4 AEs (≥5%)	%		
Anaemia		9.7	
Weight increased		7.3	
Dyspnoea		5.4	
Fatigue		~5	
SAEs by SOC (≥5%)	%		
Respiratory		11.9	
Infections		11	
Nervous system		8.5	
AEs of special interest			
Neurological AEs (nervous system and/or psychiatric)	%	88.7	
Renal AEs		40.5	
Haematologic AEs		37.1	
Eye disorders AEs		26	
Increased weight		26.4	
Hepatic AEs		22.6	
Bone fractures		6.2	
ECG QT prolonged		4	
Congestive heart failure		3.2	
Pneumonitis		2	

AEs, adverse events; BICR, blinded independent central review; CNS, central nervous system; COD, cut-off date; DOR, duration of response; ECG, electrocardiogram; NE, not evaluable; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; SAEs, severe adverse events; SAP, statistical analysis plan; SOC, system organ class.

relevant ORR of some durability, confirmed with longer follow-up and a larger dataset. The magnitude of this effect was considered clinically meaningful and likely to translate into a clinically relevant impact on PFS. Although ORR and DOR appeared similar to what was achieved by the EMA-approved agent crizotinib, uncertainties remained due to the lack of direct controls. The achievement of intracranial responses in patients with no prior radiotherapy suggested activity of entrectinib in CNS disease, although estimates should be interpreted with caution given the small number of patients. To address the uncertainties in the subgroup of patients with brain metastases and to generate comparative data, the CHMP imposed a postauthorisation efficacy study: an open label randomised clinical trial of entrectinib versus crizotinib in previously untreated patients with ROS1-positive NSCLC, with and without CNS disease. The applicant planned to enrol 220 patients, of whom at least 30% will have baseline CNS disease.

The safety database included 504 patients across four clinical studies (Table 2). Overall, the safety database in the claimed indications was relatively limited, although acceptable in the context of the rare biomarker-positive indications. In addition, the uncontrolled design did not allow to separate signs/symptoms of the underlying malignancy from entrectinib-related AEs. The safety population was also characterised by a significant heterogeneity in terms of age, type of underlying malignancy, dose, drug regimen and formulation. Such heterogeneity limited the

precise evaluation of the drug's safety profile. The paediatric safety database was very limited and heterogeneous. However, the safety profile of entrectinib did not raise concerns that the benefit seen in either NTRK fusion-positive solid tumours or ROS1-rearranged NSCLC would be offset by toxicity. In conclusion, the balance of benefits and risks could be established as positive based on the outstanding activity and a reasonable characterisation of the safety profile.

As comprehensive data were not yet available, a CMA was requested. CMA is reserved for medicinal products that treat, prevent or diagnose seriously debilitating diseases; or life-threatening diseases or rare diseases (orphan medicinal products); or drugs to be used in emergency situations in response to threats. For a CMA, a major therapeutic advantage over authorised products needs to be justified. Although on 19 September 2019, the European Commission granted a CMA to VITRAKVI (larotrectinib), another NTRK inhibitor, for a similar indication, it was possible to approve a second product under CMA (EMA/CHMP/509951/2006, Rev.1) because confirmatory evidence for larotrectinib is still awaited and entrectinib could address the unmet medical need in this indication to a similar extent. With this approval, the applicant is obliged to submit additional data (specific obligations) to confirm that the benefit—risk balance is positive. The CMA is only valid for 1 year but can be renewed. If supportive data are provided or are no longer required, a CMA can be converted to full marketing authorisation, but it can also be suspended or revoked if at any time the benefit—risk is considered negative.

CONCLUSIONS

Based on the review of data on quality, safety and efficacy, the CHMP concluded by majority decision that the risk—benefit balance of entrectinib was favourable in the following indications:

- Treatment of adult and paediatric patients aged 12 years and older, with solid tumours harbouring a *NTRK* gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, have not received a prior *NTRK* inhibitor and have no satisfactory treatment options.
- Treatment of adult patients with *ROS1*-positive NSCLC not previously treated with ROS1 inhibitors.

The CHMP therefore recommended the granting of a conditional marketing authorisation subject to the following conditions:

- A pooled analysis of an increased sample size of NTRK fusion-positive patients to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, including adolescents, due in March 2027.
- A study of tumour genomic profiling in plasma and/or tissue at baseline and progression to further investigate the impact of the presence/absence of other molecular aberrations on the efficacy of entrectinib together with clinical evaluation according to tumour histology, due in March 2027.
- A postauthorisation efficacy study to further characterise the efficacy of entrectinib in patients with ROS1-positive NSCLC and baseline CNS metastases, due in December 2027.
- A risk management plan, which must be updated at the request of the EMA or whenever new information leading to a significant change in the benefit—risk profile is obtained.

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DISCLOSURE

There are no conflicts of interest to disclose.

DISCLAIMER

This publication is a summary of the European Public Assessment Report, the Summary of Product Characteristics and other product data as published on the EMA website (https://www.ema.europa.eu/en/medicines). For the most current information on this marketing authorisation, please refer to the EMA website. The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the author(s) is/are employed/affiliated.

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