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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Koselugo (selumetinib)
Treatment of neurofibromatosis type 1
EU/3/18/2050

Sponsor: AstraZeneca AB

Note

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

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Selumetinib
Other name	Selumetinib
International Non-Proprietary Name	-
Tradename	Koselugo
Orphan condition	Treatment of neurofibromatosis type 1
Sponsor's details:	AstraZeneca AB 151 85 Södertälje Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	AstraZeneca AB
COMP opinion	21 June 2018
EC decision	31 July 2018
EC registration number	EU/3/18/2050
Marketing authorisation	
Rapporteur / Co-rapporteur	Alexandre Moreau/ Paula Boudewina van Hennik
Applicant	AstraZeneca AB
Application submission	6 March 2020
Procedure start	26 March 2020
Procedure number	EMA/H/C/005244
Invented name	Koselugo
Proposed therapeutic indication	Treatment of neurofibromatosis type 1 Further information on Koselugo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/koselugo
CHMP opinion	22 April 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Bozenna Dembowska-Baginska / Elisabeth Johanne Rook
Sponsor's report submission	22 April 2020
COMP discussion	13-15 April
COMP opinion via written procedure	26 April 2021

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

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 selumetinib was considered justified based on clinical data showing tumour response in neurofibromatosis type 1 patients with plexiform neurofibromas;
- the condition is life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms;
- the condition was estimated to be affecting approximately 3 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. 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

Neurofibromatosis type 1 (NF1) is an autosomal dominant clinically heterogeneous neurocutaneous genetic disorder. It is caused by germline mutations in the NF1 tumour suppressor gene (17q11.2) and rarely by 17q11 microdeletion (only 5%), which encodes the tumour suppressor protein neurofibromin 1. Several thousand distinct pathogenic NF1 mutations have been identified in affected individuals. Neurofibromin 1 is a guanosine 5' triphosphate (GTP)ase activating protein that promotes the conversion of active Ras GTP to inactive Ras guanosine 5'diphosphate. NF1 therefore functions as a negative regulator of the Ras proto oncogene, which is a key signalling molecule in the control of cell growth. NF1 mutation that leads to loss of function results in a failure to inactivate RAS, and can result in various tumour types, such as malignant or benign tumours. Approximately half of NF1 cases are familial, with complete penetrance, and the remainder are the result of de novo mutations.

NF1 is characterized by diverse and progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and the associated morbidities can be severe. Neurofibromas are histologically benign nerve sheath tumours, which can be broadly grouped into dermal neurofibroma or plexiform neurofibromas (PN). While the dermal neurofibromas originate from terminal nerve branches in the skin and rarely develop before puberty, PNs typically grow deeper in the body along large nerves and plexuses and are present at birth. PNs grow the fastest during the first decade of life, and can cause pain, motor impairment and obstruction.

Clinical manifestations also include cognitive deficits, learning disabilities, headaches, and seizures, café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules, and osseous dysplasias.

The approved therapeutic indication "Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above" falls within the scope of the designated orphan condition "Treatment of neurofibromatosis type 1".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review, treatment of neurofibromatosis type 1 is presented to the COMP to remain chronically debilitating and life-threatening disease. The clinical course can be debilitating due to pain, neurological and motor dysfunction, airway compromise, visual impairment, and/or disfigurement. The skin manifestations can be a psychological burden. In addition, individuals with NF1 are prone to develop benign or malignant tumours, such as sarcoma and gastrointestinal stromal tumours (GISTs). Optic pathway gliomas may cause delayed puberty and a short stature by pressuring on the hypothalamic region. NF1 is associated with an 8- to 15-year reduction in average life expectancy in both men and women, primarily due to malignant neoplasms and cardiovascular causes.

The COMP concluded that the condition remains life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms.

Number of people affected or at risk

At the time of designation, the prevalence (P) was agreed to be approximately 3 per 10,000.

For this review the prevalence was proposed to the COMP to remain less than 5 per 10,000 and was estimated to be 3 per 10,000. Following a literature search, 7 relevant studies from 1980 to present were identified with epidemiology data from Finland, Germany, Sweden and the UK with prevalence estimates ranging from 1.76 to 3.34 per 10000 (table 1). Based on a review of the published literature and the 2018 ORPHANET report on rare diseases in Europe the estimated prevalence of NF1 in the European Community ranges between 2 to 3 per 10,000 inhabitants. The estimated prevalence is not affected by the data from the UK.

Table 1 Prevalence of neurofibromatosis type 1 in Europe

Reference	Country	Study Years	Case Ascertainment	Population size	Prevalence ratio (prevalence per 10,000)
Publications identified in the period from February 2018 to December 2019					
None					
Publications identified in the search conducted in February 2018					
Kallionpää et al 2017	Finland	1987–2011	Identified from hospital records at tertiary and secondary referral centres	5,400,000	1:4,088 (2.45)
Evans et al 2010	Northwest England	1953-2008	Identified from a genetic register in Manchester	4,100,000	1:4,560 (2.19)
McKeever et al 2008	Northern Ireland	1997–2002	Children aged <16 years referred to Department of Medical Genetics in Belfast City Hospital who met clinical criteria	425,250	1:5,681 (1.76)
Lammert et al 2005	Germany	1999-2001	6-year olds screened at required medical exam for kindergarten	152,819	1:2,996 (3.34)
Poyhonen et al 2000	Northern Finland	1989-1996	Hospital records, genetic counselling clinics, contacting physicians and pathology laboratories	733,037	1:4,436 (2.25) 1: 2,983 (3.35) 10-19 yr. olds (peak)
Huson et al 1989	Southeast Wales, UK	1983–1986	Contacting physicians, medical/hospital records, genetic counselling records, neuropathology registers	668,100	1:4,950 (2.02)
Samuelsson and Axelsson 1981	Gothenburg, Sweden	1978	Identified residents with neurofibromatosis through medical records and physician requests.	440,082	1:4,600 (2.17)

The sponsor did not provide any further discussion regarding the calculation of the prevalence which was based on the published literature. To be conservative and account for the data provided, the COMP agreed on the prevalence to be 3 in 10,000.

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 no pharmacological treatments authorised for the treatment of NF1 in general, or plexiform neurofibromas associated with NF1 specifically, in the EU.

Symptomatic treatments are pain analgesics including opioids and antiepileptics.

There are 2 national disease management guidelines for NF1 available in Europe: from the UK (Neuro Foundation (UK) Guidelines 2016) and France (French National Protocol for NF1 2016). There is

currently no single therapy available for the treatment of NF1 and a multi-disciplinary approach to the management of NF1-related conditions is the mainstay of current treatment. Surgical removal is the primary treatment for neurofibromas and surgically amenable plexiform neurofibromas. However, most PNs are not amenable to complete resection due to encasement of, or close proximity to, vital structures. Permanent surgical complications (such as speech abnormalities, nerve palsies, and pain) following subtotal or partial PN resection have been reported in 18% of patients, with regrowth occurring in up to 55% of patients. Regrowth is most common in patients under age 10 years.

Although these guidelines do suggest several off-label strategies for the treatment of some NF1-related malignancies, these are based on incomplete evidence (such as carboplatin and vincristine, vinblastine, irinotecan, and bevacizumab for optic pathway glioma, ifosamide for MPNST (Malignant Peripheral Neve Sheath Tumour), or imatinib for GIST.

Significant benefit

Not applicable, since there are no satisfactory methods currently authorised in the EU for treatment of patients with neurofibromatosis type 1.

4. COMP List of questions

Not applicable.

5. COMP position adopted on 26 April 2021

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 neurofibromatosis type 1 (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia, developments of dermal and plexiform neurofibroma and increased risk of malignant neoplasms;
- there is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

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 Koselugo, selumetinib, for treatment of neurofibromatosis type 1 (EU/3/18/2050) is not removed from the Community Register of Orphan Medicinal Products.