26 March 2021
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Pemazyre (Pemigatinib)
Treatment of biliary tract cancer
EU/3/18/2066
Sponsor: Incyte Biosciences Distribution B.V.

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Pemigatinib
Other name(s)	Pemazyre, Pemigatinib, Pemigatinib
International Non-Proprietary Name	Pemigatinib
Tradename	Pemazyre
Orphan condition	Treatment of biliary tract cancer
Sponsor's details:	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Incyte Biosciences Distribution B.V.
COMP opinion	19 July 2018
EC decision	24 August 2018
EC registration number	EU/3/18/2066
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau/Janet Koenig
Applicant	Incyte Biosciences Distribution B.V.
Application submission	21 November 2019
Procedure start	02 January 2020
Procedure number	EMA/H/C/005266/0000
Invented name	Pemazyre
Proposed therapeutic indication	Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy. Further information on Pemazyre can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/pemazyre
CHMP opinion	28 January 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Maria Elisabeth Kalland
Sponsor's report submission	16 July 2020
COMP discussion and adoption of list of questions	03-05 November 2020
COMP opinion (adoption via written procedure)	01 February 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 diagnose/prevent/treat the condition with the medicinal product containing pemigatinib was considered justified based on in vivo data in a model of the condition supporting inhibition of tumour growth, and preliminary clinical observations reporting responses in affected patients;
- the condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6 and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction;
- the condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

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

Biliary tract cancer (BTC) comprises a heterogeneous group of invasive carcinomas that arise from the epithelial lining of the gallbladder and bile ducts, with most being adenocarcinomas (over 90%). They are sub classified into anatomical subtypes with specific characteristics. Intrahepatic cholangiocarcinoma (iCCA), originates from the biliary tree within the liver, and extrahepatic cholangiocarcinoma (eCCA) originates outside of the liver parenchyma; the latter is further subdivided into perihilar cholangiocarcinoma (pCCA or Klatskin tumour) and distal cholangiocarcinoma (dCCA). Gallbladder carcinoma (GBC) arises from the mucosa cells of the gallbladder and is also classified as an extrahepatic biliary cancer. BTC is mostly sporadic with genetic, environmental and/or cultural risk factors are discussed in the literature.

The therapeutic indication "Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy" falls within the scope of the designated orphan condition "Treatment of biliary tract cancer".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed with a positive benefit/risk assessment of the CHMP. Please refer to the European Public Assessment Report.

Chronically debilitating and/or life-threatening nature

Prognosis of biliary tract cancer, especially when metastatic, is dismal. The 5-year survival rate varies by stage: 50% for stage I, 30% for stage II, 10% for stage III, and 0% for stage IV (Valle et al 2017. Cancer Discov. 2017;7(9): 943–962).

The COMP acknowledged that the condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6- and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

Number of people affected or at risk

The sponsor reviewed literature and registries and approached the issue of prevalence as a sum of the patients with cholangiocarcinoma (CCA) and number of patients with gallbladder cancer (GBC). The COMP acknowledged that appropriate data for estimating the prevalence of the condition would be available in the European Cancer Information System (ECIS).

The following incidence data were first retrieved as a first step of the estimation and reporting of prevalence.

- GBC: According to the ECIS, there were 7,764 estimated incident cases of GBC in 2020 in the 27 countries in the EU (EU27).
- CCA: According to the ECIS, there were also 60,934 estimated incident cases of liver cancer in 2020 in the EU27, and the sponsor also referred to a publication by Banales and colleagues reporting that CCA comprises approximately 15% of all primary liver tumours (Banales et al. Nature reviews Gastroenterology and hepatology, vol 17, September 17, 2020). Based on this, an estimate of 9,140 incident cases (60,934*0.15) of CCA in 2020 in the EU27 was estimated.

As a second step, the duration of the disease was considered on the basis of survival, and the sponsor made particular reference to the survival statistics in a publication by Alabraba and co-workers form a UK tertiary centre (Alabraba et al, 2019, European Journal of Surgical Oncology, 45, 1660-7). Based on that paper, a total number of 12,395 prevalent cases for GBC and 15,413 cases of CCA were estimated, yielding a total of 0.62 prevalent cases of BTC per 10,000.

The COMP considered that in the absence of sensitivity analysis of the used assumptions regarding survival and representation of all anatomic subtypes, a more conservative approach would be appropriate. It was considered therefore that the ECIS registry would support an incidence of all BTC of approximately 1 per 10,000 and the duration of the condition would be approximately 1.5 year for the purpose of this exercise. This was also in line with previous procedures of the Committee on the same indication.

It was therefore concluded that the prevalence would be approximately 1.5 per 10,000 at the time of maintenance of designation.

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

Several products are used off-label in the proposed condition: gemcitabine, cisplatin, oxaliplatin, 5-Fluorouracil (5-FU), carboplatin, mitomycin C, doxorubicin, interferon-alfa 2b, epirubicin, capecitabine, irinotecan, docetaxel.

It is acknowledged that these treatments are not specifically authorised for this condition and that the current methods of treatment cannot be considered satisfactory.

There is an ESMO clinical practice guideline for biliary cancer (Valle et al, Ann Oncol (2016) 27 (suppl 5): v28-v37).

- Surgery: radical surgery (with lymphadenectomy) is the only curative treatment of BTC. Evidence base is weak for adjuvant therapy (radiotherapy, chemoradiotherapy or chemotherapy alone).
- First line systemic chemotherapy: the treatment of choice for patients with locally advanced or inoperable disease: Cisplatin/gemcitabine is the reference chemotherapy regimen for patients with good performance status (PS; 0-1); oxaliplatin may be substituted for cisplatin where there is a concern about renal function, gemcitabine monotherapy may be considered for patients with PS 2.
- Second line: no established second-line chemotherapy regimen; patients should be encouraged to participate in clinical trials. Radiotherapy may be considered in patients with localised disease, after first-line chemotherapy. Radioembolisation may be considered in patients with inoperable iCCA, usually after first-line chemotherapy.

Significant benefit

Not applicable, since there are no satisfactory methods currently authorised in the EU for treatment of patients with biliary tract cancer.

4. COMP position adopted on 01 February 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 biliary tract cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6- and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction;

- 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 Pemazyre, pemigatinib, for Treatment of biliary tract cancer (EU/3/18/2066) is not removed from the Community Register of Orphan Medicinal Products.