EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation

Bifunctional fusion protein composed of two extracellular domains of transforming growth factor beta receptor II fused with a human immunoglobulin G1 monoclonal antibody against programmed death ligand 1 for the treatment of biliary tract cancer

On 14 December 2018, orphan designation (EU/3/18/2112) was granted by the European Commission to Merck Europe B.V., the Netherlands, for bifunctional fusion protein composed of two extracellular domains of transforming growth factor beta receptor II fused with a human immunoglobulin G1 monoclonal antibody against programmed death ligand 1 (also known as M7824) for the treatment of biliary tract cancer.

What is biliary tract cancer?

Biliary tract cancer is cancer of the bile ducts and gallbladder. These are parts of the digestive system that transport and store bile, a fluid which is produced by the liver and released into the intestines after a meal to help digest fats. The cancer is characterised by various features such as abnormal liver function tests, pain in the belly, yellowish discoloration of the skin and weight loss.

Biliary tract cancer is a long-term debilitating and life-threatening disease due to liver failure and problems caused when the cancer blocks the bile ducts.

What is the estimated number of patients affected by the condition?

At the time of designation, biliary tract cancer affected approximately 1.5 in 10,000 people in the European Union (EU). This was equivalent to a total of around 78,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 517,400,000 (Eurostat 2018).

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What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU for the treatment of biliary tract cancer. Some patients with early disease could undergo surgery to remove the cancer. Other treatments included chemotherapy (medicines to treat cancer).

How is this medicine expected to work?

This medicine is made of a monoclonal antibody (a type of protein) linked to part of another protein called TGFβRII.

The TGFβRII part of the medicine attaches to and blocks TGFβ, a protein involved in the growth, progression, and spreading of many types of cancer, as well as in the suppression of the immune system.

The monoclonal antibody attaches to and blocks PD-L1, a protein present on the surface of many cancer cells. PD-L1 usually attaches to cells of the immune (defence) system called T cells, preventing the T cells from attacking the cancer cells.

By attaching to and blocking both PD-L1 and TGFβ, the medicine is expected to allow the immune system to recognise and kill the cancer cells, and also slow down the growth of the cancer.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with the medicine in patients with biliary tract cancer were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for biliary tract cancer or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 8 November 2018 recommending the granting of this designation.

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Contact details of the current sponsor for this orphan designation can be found on the EMA website.

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases, which includes a directory of patients' organisations registered in Europe;
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Bifunctional fusion protein composed of two extracellular domains of transforming growth factor beta receptor II fused with a human immunoglobulin G1 monoclonal antibody against programmed death ligand 1	Treatment of biliary tract cancer
Bulgarian	Двуфункционален фузионен протеин, състоящ се от два екстрацелуларни домейна на рецептор II за трансформиращия растежния фактор бета, свързан с човешки имуноглобулин G1 моноклонално антитяло срещу лиганд 1 на рецептора на програмирана клетъчна смърт	Лечение на рак на жлъчните пътища
Croatian	Bifunkcijski fuzijski protein sastavljen od dviju izvanstaničnih domena receptora II za transformirajući faktor rasta beta koje su fuzionirane s humanim monoklonskim protutijelom imunoglobulinom G1 protiv liganda 1 za programiranu smrt stanice	Liječenje raka bilijarnog trakta
Czech	Bifunkční fúzní protein složený ze dvou extracelulárních domén transformujícího se receptoru pro růstový faktor beta II fúzovaný s monoklonální protilátkou humánního imunoglobulinu G1 proti ligandu 1 programové smrti	Léčba karcinomu žlučových cest
Danish	Bifunktionelt fusionsprotein bestående af to ekstracellulære domæner af transformerende vækstfaktor beta-receptor II, fusioneret med et humant immunoglobulin G1 monoklonalt antistof mod programmeret celledødsligand-1	Behandling af galdegangscancer
Dutch	Bifunctioneel fusie-eiwit samengesteld uit twee extracellulaire domeinen van 'transforming-growth factor beta'-receptor II, gefuseerd met een humaan monoklonaal immunoglobuline G1-antilichaam tegen geprogrammeerde-celdood-ligand 1	Behandeling van galweg kanker
Estonian	Kahest transformeeriva kasvufaktor beeta tüüp 2 retseptori rakuvälisest domeenist ja programmeeritud rakusurma ligandi 1 vastasest inimese monoklonaalsest IgG1 antikehast koosnev kahetoimeline liitvalk	Sapiteede kasvaja ravi

[1] At the time of designation

Language	Active ingredient	Indication
Finnish	Kaksitoiminen fuusioproteiini, joka muodostuu kahdesta ekstrasellulaarisesta kasvainkasvutekijä beetan reseptori II:n domeenista, jotka ovat yhteensulautuneet ohjelmoitua solukuoleman ligandi 1:ä vastaan suunnatun ihmisen immunoglobuliini G1:n monoklonaalisen vasta-aineen kanssa	Sappiteiden syövän hoito
French	Protéine de fusion bifonctionnelle constituée de deux domaines extracellulaires des récepteurs II du facteur de croissance transformant bêta fusionnés avec un anticorps monoclonal humain de type immunoglobuline G1 dirigé contre le ligand de mort cellulaire programmée de type 1	Traitement du cancer des voies biliaires
German	Bifunktionales Fusionsprotein, bestehend aus zwei extrazellulären Domänen vom Typ-II-Rezeptor des transformierenden Wachstumsfaktors beta, fusioniert mit einem humanen monoklonalen Immunglobulin-G1-Antikörper gegen den programmierten Zelltodliganden 1	Behandlung von Tumoren der Gallenwege
Greek	Διλειτουργική πρωτεΐνη σύντηξης αποτελούμενη από δύο εξωκυτταρικές περιοχές υποδοχέα αυξητικού παράγοντα μετασχηματισμού βήτα τύπου II συντηγμένων με μονοκλωνικό αντίσωμα ανθρώπινης ανοσοσφαιρίνης G1 έναντι του συνδέτη προγραμματισμένου θανάτου 1	Θεραπεία του καρκίνου της χοληφόρου οδού
Hungarian	A transzformáló növekedési faktor bétareceptor II kettő extracelluláris doménjéből, valamint az ehhez fúzionált, 1-es programozott halálligand elleni humán G1 immunoglobulin monoklonális antitestből álló kétfunkciós fúziós fehérje	Epeúti rák kezelése
Italian	Proteina di fusione bifunzionale composta da due domini extracellulari del recettore del fattore di crescita trasformante-beta 2 fusi con un anticorpo monoclonale umanizzato del tipo immunoglobulina G1 diretto contro il ligando della morte programmata 1	Trattamento del carcinoma delle viebiliari
Latvian	Bifunkcionāls sapludināts proteīns, kas sastāv no diviem transformējošā augšanas faktora-bēta II tipa receptora ekstracelulārajiem domēniem, kas sapludināti ar cilvēka imūnglobulīna G1 monoklonālo antivielu pret programmētās bojāejas ligandu-1	Žultsvadu sistēmas vēža ārstēšana
Lithuanian	Dvifunkcinis susiliejimo baltymas, sudarytas iš dviejųekstraląstelinių transformuojančio augimo faktoriaus beta receptoriaus II domenų, sulietų su žmogaus imunoglobulino G1 monokloniniu antikūnu prieš programuotos ląstelių žūties ligandą 1	Tulžies latakų vėžio gydymas

Language	Active ingredient	Indication
Maltese	Proteina tal-fużjoni b'żewġ funzjonijiet magħmula minn żewġ dominji extraċellulari tar-riċettur beta II tal-fattur tat-tkabbir tat-trasformazzjoni imwaħħal ma' antikorp monoklonali G1 tal-immunoglobulina umana kontra l-ligand 1 ta' mewt ipprogrammata	Kura tal-kanċer tal-apparat tal-bili
Polish	Dwufunkcyjne białko fuzyjne składające się z dwóch domen pozakomórkowych receptora transformującego czynnika wzrostu beta typu II zespolonych z ludzkim przeciwciałem monoklonalnym klasy G1 przeciwko ligandowi receptora programowanej śmierci komórki typu 1	Leczenie raka dróg żółciowych
Portuguese	Proteína de fusão bifuncional composta por dois domínios extracelulares do recetor II do fator transformador de crescimento beta–fundido com um anticorpo monoclonal humano de tipo imunoglobulina G1 contra o ligando 1 da morte celular programada	Tratamento da neoplasia das vias biliares
Romanian	Proteină de fuziune bifuncțională compusă din două domenii extracelulare ale receptorului II al factorului de creștere și transformare beta fuzionat cu un anticorp monoclonal de tip imunoglobulină umană G1 împotriva ligandului 1 implicat în moartea celulară programată	Tratamentul cancerului de căi biliare
Slovak	Bifunkčný fúzny proteín zložený z dvoch extracelulárnych domén transformujúceho rastového faktora beta receptora II fúzovaného s ľudským imunoglobulínom G1 monoklonálnej protilátky proti programovanému smrtiacemu ligandu 1	Liečba karcinómu žlčových ciest
Slovenian	Dvofunkcijska fuzijska beljakovina, sestavljena iz dveh zunajceličnih domen za transformacijo beta receptorjev II rastnega faktorja, spojena s človeškim monoklonskim protitelesom tipa immunoglobulin G1 proti ligandu za programirano celično smrt 1	Zdravljenje raka žolčnih vodov
Spanish	Proteína de fusión bifuncional compuesta por dos dominios extracelulares del receptor 2 del factor de crecimiento transformante-beta fusionada con un anticuerpo monoclonal de la inmunoglobulina humana G1 dirigido contra el ligando 1 de muerte programada	Tratamiento del cáncer del árbol biliar
Swedish	Bifunktionellt fusionsprotein bestående av två extracellulära domäner från transformerande tillväxtfaktor beta receptor II fusionerade med en human monoklonal IgG1-antikropp mot programmerad celldöd ligand 1	Behandling av gallvägscancer

Language	Active ingredient	Indication
Norwegian	Bifunksjonelt fusjonsprotein sammensatt av to ekstracellulære domener av transformerende vekstfaktor beta-reseptor II fusjonert med et humant immunoglobulin G1 monoklonalt antistoff mot programmert død ligand 1	Behandling av gallegangskreft
Icelandic	Samrunaprótein með tvíþætta virkni sem felur í sér tvö utanfrumuhneppi ummyndandi vaxtarþáttarviðtaka beta II tengt einstofna ónæmisglóbúlín G1 mótefni út mönnum gegn bindingu PD-L1 sameindarinnar	Meðferð við krabbameini í gallvegum