EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Obiltoxaximab SFL (obiltoxaximab)
Treatment of anthrax
EU/3/18/2065
Sponsor: SFL Pharmaceuticals Deutschland GmbH

Note

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

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1. Product and administrative information

Product	
Designated active substance	Obiltoxaximab
International Non-Proprietary Name	Obiltoxaximab
Tradename	Obiltoxaximab SFL
Orphan condition	Treatment of anthrax
Sponsor's details:	SFL Pharmaceuticals Deutschland GmbH Marie-Curie-Strasse 8 79539 Loerrach Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	SFL Regulatory Services GmbH
COMP opinion	19 July 2018
EC decision	24 August 2018
EC registration number	EU/3/18/2065
Post-designation procedural history	
Transfer of sponsorship	Transfer from SFL Regulatory Services GmbH to SFL Pharmaceuticals Deutschland GmbH – EC decision of 13 Jul 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Filip Josephson
Applicant	SFL Pharmaceuticals Deutschland GmbH
Application submission	3 June 2019
Procedure start	20 June 2019
Procedure number	EMA/H/C/005169
Invented name	Obiltoxaximab SFL
Proposed therapeutic indication	Obiltoxaximab SFL is indicated in combination with appropriate antibacterial drugs in all age groups for treatment of inhalational anthrax due to Bacillus anthracis. Obiltoxaximab SFL is indicated in all age groups for post-exposure prophylaxis of inhalational anthrax when alternative therapies are not appropriate or are not available. Further information on Obiltoxaximab SFL can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/obiltoxaximab-sfl
CHMP opinion	17 September 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Eva Malikova / Nikolaos Sypsas
Sponsor's report submission	24 January 2020 (EMA/OD/0000025701) 17 June 2020 (EMA/OD/0000037218)
COMP discussion	8-10 September 2020

COMP opinion (adoption via written procedure)	21 September 2020

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 obiltoxaximab was considered justified based on non-clinical data showing increased survival with the proposed product in valid models of the condition;
- the condition is life-threatening due to development of pleural effusions, haemorrhagic mediastinitis and haemorrhagic meningitis, linked to a fatality rate of 45% up to 100%;
- the condition was estimated to be affecting less than 0.01 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 obiltoxaximab will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing improved survival when the product was used in addition to levofloxacin and ciprofloxacin, currently authorized for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the 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

Anthrax is an acute infectious disease caused by Bacillus anthracis, that may be infecting man via cutaneous (the most common naturally occurring form), pulmonary or gastrointestinal routes. Anthrax commonly affects hoofed animals such as sheep and goats, but humans can also be infected.

The main risk factor for getting anthrax is some type of contact with contaminated animal hides, hair, bone products, and wool. Inhalation anthrax was most commonly contracted when workers breathed in airborne anthrax spores, which can be released during industrial processes such as tanning hides and processing wool.

Breathing in spores means a person has been exposed to the disease, but it doesn't mean they'll get symptoms. The bacteria spores must "germinate," before the actual disease occurs. Once the spores germinate, they release several toxic substances, which cause internal bleeding, swelling, and tissue death.

Person to person transmission of inhalational disease does not occur. The incubation period for inhalation anthrax ranges from 1 to 60 days and patients have frequently complained over fever, chills, drenching sweats, profound fatigue, minimally productive cough, nausea or vomiting, and chest discomfort. Cutaneous anthrax would not be expected to be a major problem in case of deliberate release of anthrax spores, although it is not impossible that this might occur.

The approved therapeutic indication is:

"Obiltoxaximab SFL is indicated in combination with appropriate antibacterial drugs in all age groups for treatment of inhalational anthrax due to *Bacillus anthracis*.

Obiltoxaximab SFL is indicated in all age groups for post-exposure prophylaxis of inhalational anthrax when alternative therapies are not appropriate or are not available."

The proposed therapeutic indication falls within the scope of the designated orphan condition "Treatment of anthrax".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The life-threatening nature of inhalational anthrax disease remains unchanged since the submission of the ODD application on 18 May 2018; and no new therapies for inhalational anthrax have been approved in the EU in the meantime.

Inhalational anthrax, the most severe form of anthrax, has a fatality rate of approximately 50% even when managed with the best treatment options currently available and under circumstances of heightened awareness (Jernigan et al., 2002). Patients who are not appropriately diagnosed and treated during the prodromal phase of localised infection and progress to the fulminant stage of inhalational anthrax have a mortality rate of 97%, regardless of the treatment they receive (Holty et al., 2006).

Number of people affected or at risk

The sponsor performed a PubMed literature search to retrieve published articles on the epidemiology of anthrax. A total of 25 publications were identified, two of which represented case reports of inhalational anthrax occurring over the past approximately 50 years (Enticknap, Galbraith et al. 1968, Anaraki, Addiman et al. 2008).

Anthrax is subject to surveillance in the EU, with the ECDC as the repository of data collected across Europe. According to ECDC, total 58 confirmed cases of anthrax have been reported in the EU/EEA between 2010 and 2015, ranging from 1 to 31 confirmed cases per year (ECDC 2017). According to the sponsor, a limitation of the ECDC data is that there is no indication of the type of anthrax and many cases are assumed to be of cutaneous anthrax, which is usually more easily self-limiting than inhalation forms. In any case the prevalence (in fact incidence) of anthrax in the EU is very low, and can be approximated to 0.001 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

The main approach for treatment of suspected or confirmed clinical cases of inhalational anthrax, as well as for post-exposure prophylaxis is antibiotic therapy, usually with fluoroquinolones.

There are no studies in humans but data from guinea pigs and monkeys have indicated that doxycycline and ciprofloxacin are both efficacious in prophylaxis and in curative treatment (1). However, early treatment is essential. Because of the mortality associated with inhalational anthrax, two or more antimicrobial agents predicted to be effective are recommended; however, controlled studies to support a multiple drug approach are not available. Ciprofloxacin is the recommended first line treatment. Other quinolones such as Ofloxacin and Levofloxacin offer alternative treatment options but dose recommendations can presently only be given in adults. Doxycycline and penicillins are alternative therapies when susceptibility has been confirmed although penicillin is not bactericidal against Bacillus anthracis. Oral amoxicillin is also an option for late-stage therapy if the patient is improving and susceptibility has been confirmed. In this regard, preliminary data indicate that B. anthracis may produce penicillin-hydrolysing enzymes (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm).

Ciprofloxacin is licensed for the treatment of inhalation anthrax. In spite of prolonged combination antibiotic treatment with effective drugs the mortality rate of inhalation anthrax remains unacceptably high and there is certainly room for new therapeutic approaches to improve the prognosis of patients who have been exposed to anthrax spores.

Ciprofloxacin, doxycycline and penicillins are authorised for the condition in the Community.

Significant benefit

The sponsor supported the significant benefit with a battery on non-clinical studies, namely in rabbits and monkeys, the two most widely used species for anthrax development studies. Some of the studies investigated the pharmacological effects of obiltoxaximab and some pharmacodynamics parameters such as the anti-PA antibody response, while a number of other studies were proof of concept studies using obiltoxaximab as monotherapy or in combination (table 1) after bacterial challenge and established disease.

Table 1. Proof of concept studies in rabbits and monkeys

Type of study	**Test system**	**Dose range and route of admin.**	**Study No.**
Combination treatment (human-equivalent dose)	Rabbit/NZW	Obiltoxaximab i.v. + levo: 0 mg/kg + 0 mg/kg/day po x 3 days 8 mg/kg + 0 mg/kg/day po x 3 days 0 mg/kg + 50 mg/kg/day po x 3 days 8 mg/kg + 50 mg/kg/day po x 3 days	1030
Combination treatment (human-equivalent dose)	Rabbit/NZW	Obiltoxaximab *i.v.* + levo: 0 mg/kg + 0 mg/kg/day po x 3 days 8 mg/kg + 0 mg/kg/day po x 3 days 0 mg/kg + 50 mg/kg/day po x 3 days 8 mg/kg + 50 mg/kg/day po x 3 days	1045
Combination treatment (below human-equivalent dose)	Monkey/ cynomolgus	Obiltoxaximab + cipro: 0 mg/kg + 0 mg/kg/day po x 4 days 8 mg/kg + 0 mg/kg/day po x 4 days 0 mg/kg + 10 mg/kg/day po x 4 days 8 mg/kg + 10 mg/kg/day po x 4 days	1056
Combination treatment (below human-equivalent dose)	Monkey/ cynomolgus	Obiltoxaximab + cipro: 0 mg/kg + 0 mg/kg/day po x 4 days 0 mg/kg + 10 mg/kg/day po x 4 days 0 mg/kg + 26 mg/kg/day po x 4 days 8 mg/kg + 10 mg/kg/day po x 4 days	2469
Combination treatment (below human-equivalent dose)	Rabbit/NZW	Obiltoxaximab *i.v.* + levo: 0 mg/kg + 0 mg/kg/day po x 3 days 0 mg/kg + 6.5 mg/kg/day po x 3 days 16 mg/kg + 6.5 mg/kg/day po x 3 days	AR028
Combination treatment (below human-equivalent dose)	Rabbit/NZW	Obiltoxaximab *i.v.* + doxy *i.v.*: 0 mg/kg + 2 mg/kg bid x3 8 mg/kg + 2 mg/kg bid x3	AP-10-055
Monotherapy treatment	Rabbit/NZW	Obiltoxaximab *i.v.*: 0, 1, 4, 16 mg/kg Levo: 50 mg/kg/day x 3 days po	AR021
Monotherapy treatment	Rabbit/NZW	Obiltoxaximab *i.v.*: 0, 1, 4, 8, 16 mg/kg	AR033
Monotherapy treatment	Monkey/ cynomolgus	Obiltoxaximab *i.v.*: 0, 4, 8 mg/kg	AP201
Monotherapy treatment	Monkey/ cynomolgus	Obiltoxaximab *i.v.*: 0, 8, 32 mg/kg	AP203
Monotherapy treatment	Monkey/ cynomolgus	Obiltoxaximab *i.v.*: 0, 4, 16 mg/kg	AP204
Monotherapy treatment	Monkey/ cynomolgus	Obiltoxaximab *i.v.*: 0, 16 mg/kg	AP202

The studies performed by the sponsor showed overall superior efficacy than quinolones (levofloxacin or ciprofloxacin) when obiltoxaximab was used as monotherapy, and the best efficacy was achieved with combination treatment (see table 2).

Table 2. Survival data for anthrax treatment studies with obiltoxaximab in combination with antibiotics

Study No.	Test system	Obiltoxaximab i.v. + antibiotic	Survival at Day 28	Boschloo P-value[1]	95% CI[2]
1030	Rabbit/ NZW	Untreated	0% (0/6)	N/A	N/A
		8 mg/kg + levo 0 mg/kg/day	75% (12/16)	N/A	N/A
		0 mg/kg + levo 50 mg/kg/day po x 3 days	40% (2/5)	N/A	N/A
		8 mg/kg + levo 50 mg/kg/day po x 3 days	100% (4/4)	0.0458	(-0.089, 0.947)
1045	Rabbit/ NZW	Untreated	0% (0/6)	N/A	N/A
		8 mg/kg + levo 0 mg/kg/day	64% (7/11)	N/A	N/A
		0 mg/kg + levo 50 mg/kg/day po x 3 days	78% (7/9)	N/A	N/A
		8 mg/kg + levo 50 mg/kg/day po x 3 days	82% (9/11)	0.4682	(-0.341, 0.466)
1056	Monkey/ cynomolgus	Untreated	0% (0/8)	N/A	N/A
		8 mg/kg + cipro 0 mg/kg/day	50% (4/8)	N/A	N/A
		0 mg/kg + cipro 10 mg/kg/day po x 4 days	15% (2/13)	N/A	N/A
		8 mg/kg + cipro 10 mg/kg/day po x 4 days	62% (8/13)	0.0106*	(0.072, 0.757)

Cipro – Ciprofloxacin; CI - Confidence Interval; *i.v.* – Intravenous; Levo – Levofloxacin
[1]p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma=0.001) compared to fluoroquinolone alone. Includes all randomised untreated challenged animals and randomised to treatment animals that received treatment
[2]Exact 95% CI of difference in survival rates

The sponsor also tested the product in post-exposure prophylaxis, showing similar efficacy as in the treatment setting. Post-exposure prophylaxis is considered by the COMP as part of treatment and it is therefore covered by this application.

The significant benefit is adequately supported by the non-clinical studies in rabbits and monkeys performed by the sponsor, which show better efficacy of obiltoxaximab as single therapy compared to fluoroquinolones, and additionally increased efficacy when used in combination with fluoroquinolones.

4. COMP position adopted on 21 September 2020

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 anthrax (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.001 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 development of pleural effusions, haemorrhagic mediastinitis and haemorrhagic meningitis, linked to a fatality rate of 45% and up to 100%;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Obiltoxaximab SFL may be of potential significant benefit to those affected by the orphan condition is confirmed. Since clinical trials exposing humans to anthrax spores would neither be ethical nor feasible, the sponsor provided non-clinical data in established models of inhalational anthrax showing improved survival when the product was used in addition to levofloxacin and ciprofloxacin, which are still currently authorized for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the 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 Obiltoxaximab SFL, obiltoxaximab for treatment of anthrax (EU/3/18/2065) is not removed from the Community Register of Orphan Medicinal Products.