7 November 2016
EMA/623833/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt for the treatment of osteomyelitis

On 14 October 2016, orphan designation (EU/3/16/1737) was granted by the European Commission to Voisin Consulting S.A.R.L., France, for (E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt (also known as Debio 1450 bis ethanolamine salt) for the treatment of osteomyelitis.

What is osteomyelitis?

Osteomyelitis is inflammation of bone or of bone marrow (the spongy tissue inside large bones). It is usually caused by the spread of infection to the bone from nearby tissue from an operation such as joint replacement surgery, or from open wounds and fractures. More than half of the cases are caused by bacteria called *Staphylococcus aureus*. Symptoms of osteomyelitis include pain, swelling, redness and warmth around the affected area and the patient may have fever or chills. Long-term osteomyelitis can block the blood supply to the bone, causing permanent damage (osteonecrosis).

Osteomyelitis is life-threatening because the bacteria can enter the circulation and damage other organs and it is debilitating in the long term because destruction of the bone can lead to disability.

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

At the time of designation, osteomyelitis affected approximately 2.5 in 10,000 people in the European Union (EU). This was equivalent to a total of around 128,000 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 513,700,000 (Eurostat 2016).

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What treatments are available?

At the time of designation, several antibiotics were authorised in the EU for treating infectious osteomyelitis. Vancomycin was one of the antibiotics used to treat serious infections due to Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). Surgery and other medical procedures were used to remove pus and damaged tissue and to improve circulation to the affected area.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with osteomyelitis because laboratory studies show that the medicine blocks the growth of resistant bacteria and is more effective than an authorised medicine against MRSA. This assumption will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

The medicine blocks an enzyme called FabI, which bacteria of the *Staphylococcus* family need to make fatty acids. Fatty acids are vital for the bacteria to make the wall that surrounds them and for other processes that allow bacteria to survive and grow. By blocking FabI, the medicine is expected to stop *Staphylococcus aureus* from spreading and thereby treat osteomyelitis caused by these bacteria.

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, no clinical trials with the medicine in patients with osteomyelitis had started.

At the time of submission, the medicine was not authorised anywhere in the EU for osteomyelitis 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 September 2016 recommending the granting of this designation.

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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 EMA website, on the medicine's rare disease designations page.

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	(E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt	Treatment of osteomyelitis
Bulgarian	(E)-(6-((N-метил-((3-метилбензофуран-2-ил) метил)амино)-3-оксопроп-1-ен-1-ил)-2-оксо-3,4-дихидро- 1,8-нафтиридин-1(2H)-ил)метил фосфат, бис етаноламинова сол	Лечение на остеомиелит
Croatian	(E)-(6-((N-metil-((3-metilbenzofuran-2-il)metil)amino)-3-oksoprop-1-en-1-il)-2-okso-3,4-dihidro-1,8-naftiridin-1(2H)-il)metilfosfat, bis-etanolaminska sol	Liječenje osteomijelitisa
Czech	(E)-(6-((N-methyl-((3-methylbenzofuran-2-yl) methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-nafthyridin-1(2H)-yl)methyl-fosfát bis-ethanolaminová sůl	Léčba osteomyelitidy
Danish	(E)-(6-((N-methyl-((3-methylbenzofuran-2-yl) methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methylphosphat, bis-ethanolaminsalt	Behandling af osteomyelitis
Dutch	(E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naftyridin-1(2H)-yl)methylfosfaat, bis-ethanolaminezout	Behandeling van osteomyelitis
Estonian	(E)-(6-((N-metüül-((3-metüülbensofuraan-2-üül) metüül)amino)-3-oksoprop-1-een-1-üül)-2-okso-3,4-dihüdro-1,8-naftüridiin-1(2H)-üül)metüülfosfaat bis-etanoolamiinsool	Osteomüeliidi ravi
Finnish	(E)-(6-((N-metyyli-((3-metyylibentsofuran-2-yyli)metyyli)amino)-3-oksoprop-1-en-1-yyli)-2-okso-3,4-dihydro-1,8-naftyridin-1(2H)-yyli)metyylifosfaatti, bisetanoliamiinisuola	Osteomyeliitin hoito
French	Sel de (E)-(6-((N-méthyl-((3-méthylbenzofurane-2-yl) méthyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridine-1(2H)-yl)méthyl phosphate, bis éthanolamine	Traitement de l'ostéomyélite
German	(E)-(6-((N-Methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methylphosphat, bis-Ethanolaminsalz	Behandlung der Osteomyelitis

[1] At the time of designation

Language	Active ingredient	Indication
Greek	(E)-(6-((N-μεθυλ-((3-μεθυλβενζοφουραν-2-υλ) μεθυλ)αμινο)-3-οξοπροπ-1-εν-1-υλ)-2-οξο-3,4-διυδρο-1,8-*ναφθυριδιν*-1(2H)-υλ)μεθυλ φωσφορικό, άλας δις-αιθανολαμίνης	Θεραπεία της οστεομυελίτιδας
Hungarian	(E)-(6-((N-metil-((3-metilbenzofurán-2-il) metil)amino)-3-oxoprop-1-én-1-il)-2-oxo-3,4-dihidro-1,8-naftiridin-1(2H)-il)metilfoszfát bisz-etanolamin sója	Osteomyelitis kezelése
Italian	(E)-(6-((N-metil-((3-metilbenzofurano-2-il) metil)ammino)-3-ossoprop-1-en-1-il)-2-osso-3,4-diidro-1,8-naftiridina-1(2H)-il)metilfosfato, sale di bis-etanolammina	Trattamento dell'osteomielite
Latvian	(E)-(6-((N-metil-((3-metilbenzofurān-2-il) metil)amino)-3-oksoprop-1-en-1-il)-2-okso-3,4-dihidro- 1,8-naftiridīn-1(2H)-il)metilfosfāta, bis etanolamīna sāls	Osteomielīta ārstēšana
Lithuanian	(E)-(6-((N-metil-((3-metilbenzofuran-2-il) metil)amino)-3-oksoprop-1-en-1-il)-2-okso-3,4-dihidro- 1,8-naftiridin-1(2H)-il)metilfosfatas, bis etanolamino druska	Osteomielito gydymas
Maltese	(E)-(6-((N-methyl-((3-methylbenzofuran-2-yl) methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro- 1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt	Kura tal-osteomjelite
Polish	metylofosforan (E)-(6-((N-metylo-((3-metylobenzofuran-2-yl) metylo)amino)-3-oksoprop-1-en-1-yl)-2-okso-3,4-dihydro- 1,8-naftyrydyn-1(2H)-yl), sól bis etanoloaminy	Leczenie zapalenia kości i szpiku kostnego
Portuguese	Sal bis etanolamina do fosfato de (E)-(6-((N-metil-((3-metilbenzofuran-2-il) metil)amino)-3-oxoprop-1-en-1-il)-2-oxo-3,4-di-hidro-1,8-naftiridin-1(2H)-il) metilo	Tratamento da osteomielite
Romanian	Sare de (E)-(6-((N-metil-((3-metilbenzofuran-2-il) metil)amino)-3-oxoprop-1-en-1-il)-2-oxo-3,4-dihidro-1,8-naftiridin-1(2H)-il)metil fosfat, bis etanolamină	Tratamentul osteomielitei
Slovak	(E)-(6-((N-metyl-((3-metylbenzofuran-2-yl) metyl)amino)-3-oxoprop-1-én-1-yl)-2-oxo-3,4-dihydro-1,8-naftyridín-1(2H)-yl)metyl fosfát bis etanolamínová soľ	Liečba osteomyelitídy
Slovenian	(E)-(6-((N-metil-((3-metilbenzofuran-2-il) metil)amino)-3-oksoprop-1-en-1-il)-2-okso-3,4-dihidro- 1,8-naftiridin-1(2H)-il)metil fosfat, bis etanolaminska sol	Zdravljenje osteomielitisa
Spanish	Sal de bis-etanolamina de (E)-(6-((N-metil-((3-metilbenzofuran-2-il) metil)amino)-3-oxoprop-1-en-1-il)-2-oxo-3,4-dihidro-1,8-naftiridin-1(2H)-il)metil fosfato	Tratamiento de la osteomielitis
Swedish	(E)-(6-((N-metyl-((3-metylbenzofuran-2-yl) metyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naftyridin-1(2H)-yl)metylfosfat, bis-etanolaminsalt	Behandling av osteomyelit

Language	Active ingredient	Indication
Norwegian	(E)-(6-((N-metyl-((3-metylbenzofuran-2-yl)-metyl)amino)-3-oksoprop-1-en-1-yl)-2-okso-3,4-dihydro-1,8-naftyridin-1(2H)-yl)-metylfosfat, bis-etanolaminsalt	Behandling av osteomyelitt
Icelandic	(E)-(6-((N-metýl-((3-metýlbensófúran-2-ýl) metýl)amínó)-3-oxópróp-1-en-1-ýl)-2-oxó-3,4-tvívetnis-1,8-nafþtridín-1 (2H)-ýl)metýlfosfat, bis etanólamínsalt	Meðferð við beinsýkingu