

21 March 2014
EMA/COMP/5578/2014
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol for the treatment of acute myeloid leukaemia

On 16 January 2014, orphan designation (EU/3/13/1230) was granted by the European Commission to Voisin Consulting S.A.R.L., France, for (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol for the treatment of acute myeloid leukaemia.

What is acute myeloid leukaemia?

Acute myeloid leukaemia (AML) is a cancer of the white blood cells (cells that fight against infections). In patients with AML, the bone marrow (the spongy tissue inside the large bones, where blood cells are produced) produces large numbers of abnormal, immature white blood cells. These abnormal cells quickly build up in large numbers in the bone marrow and are found in the blood.

AML is a life-threatening disease because these abnormal immature cells take the place of the normal blood cells, causing bleeding episodes, blood clots and reducing the patient's ability to fight infections.

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

At the time of designation, AML affected approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 51,000 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).

What treatments are available?

Treatment for AML is complex and depends on a number of factors including the extent of the disease, whether it has been treated before, and the patient's age, symptoms and general state of health. At

*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 512,200,000 (Eurostat 2013).

the time of designation, the main treatments for AML were chemotherapy (medicines to treat cancer) and haematopoietic (blood) stem-cell transplantation (a complex procedure where the patient receives stem cells from a matched donor to help restore the bone marrow).

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for some patients with AML because early clinical studies show beneficial effects in patients whose leukaemia came back after previous treatments. These assumptions 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?

This medicine is expected to block the activity of an enzyme called DOT1L histone methyltransferase, which is involved in 'turning on' genes within cells. In AML, DOT1L is thought to work abnormally by 'turning on' certain genes that increase the division and growth of leukaemia cells. By blocking DOT1L, this medicine is expected to prevent abnormal activity of such genes, thus leading to a reduction in 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 AML were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for AML. Orphan designation of the medicine had been granted in the United States of America for treatment of AML and acute lymphoblastic leukaemia.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 12 December 2013 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:

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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 AMLiance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in AML official EU languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl amino)methyl)tetrahydrofuran-3,4-diol	Treatment of acute myeloid leukaemia
Bulgarian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-амино-9 <i>H</i> -пурин-9-ил)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>терт</i> -бутил)-1 <i>H</i> -бензо[<i>d</i>]имидазол-2-ил)етил)циклобутил)(изопропил)амино)метил)тетрахидрофуран-3,4-диол	Лечение на остра миелоидна левкемия
Czech	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)ethyl)cyklobutyl)(isopropyl amino)methyl)tetrahydrofuran-3,4-diol	Léčba akutní myeloidní leukémie
Croatian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciklobutil)(izopropil amino)metil)tetrahidrofuran-3,4-diol	Liječenje akutne mijeloične leukemije
Danish	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)ætyl)cyclobutyl)(isopropyl amino)metyl)tetrahydrofuran-3,4-diol	Behandling af akut myeloid leukæmi
Dutch	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purine-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazool-2-yl)ethyl)cyclobutyl)(isopropyl amino)methyl)tetrahydrofuraan-3,4-diol	Behandeling van acute myeloïde leukemie
Estonian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -puriin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butüül)-1 <i>H</i> -bensoo[<i>d</i>]imidasool-2-üül)etüül)cüklobutüül)(isopropüül)amino)metüül)tetrahüdrofuraan-3,4-diool	Akuutse müeloidse leukeemia ravi
Finnish	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -puriini-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tertiaalinenbutyyli</i>)-1 <i>H</i> -bentso[<i>d</i>]imidatsoli-2-yl)etyyli)syklobutyli)(isopropyli)amino)metyyli)tetrahydrofuraani-3,4-glykoli	Akuutin myelooisen leukemian hoito

¹ At the time of designation

Language	Active ingredient	Indication
French	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tétrahydrofuran-3,4-diol	Traitement de la leucémie aiguë myéloïde
German	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-Amino-9 <i>H</i> -Purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>Tert</i> -Butyl)-1 <i>H</i> -Benzo[<i>d</i>]Imidazol-2-yl)Ethyl)Cyclobutyl)(Isopropyl)Amino)Methyl)Tetrahydrofuran-3,4-diol	Behandlung der akuten myeloischen Leukämie
Greek	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-αμινό-9 <i>H</i> -πουρίνο-9-υλο)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>τετρα</i> βουτυλο)-1 <i>H</i> -βενζο[<i>d</i>]ιμιδαζολο-2-υλο)αιθυλο)κυκλοβουτυλο)(ισοπροπυλο)αμινο)μεθυλο)τετραϋδροφουρανική-3,4-διόλη	Θεραπεία της οξείας μυελοειδούς λευχαιμίας
Hungarian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>terc</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciklobutil)(izopropil)amino)metil)tetrahidrofurán-3,4-diol	Akut myeloid leukaemia kezelése
Italian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-ammino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>terz</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazolo-2-il)etil)ciclobutil)(isopropil)amino)metil)tetraidrofurano-3,4-diolo	Trattamento della leucemia mieloide acuta
Latvian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purīn-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>terc</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciklobutil)(izopropil)amino)metil)tetrahidrofurān-3,4-diols	Akūtas mieloleikozes ārstēšana
Lithuanian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciklobutil)(izopropil)amino)metil)tetrahidrofuran-3,4-diolis	Ūmios mieloleukozės gydymas
Maltese	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol	Kura tal-lewkimja mjelojda akuta
Polish	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -puryn-9-ylo)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butylo)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-ylo)etylo)cyklobutylo)(izopropylo)amino)metylo)tetrahydrofurano-3,4-diol	Leczenie ostrej białaczki szpikowej

Language	Active ingredient	Indication
Portuguese	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purina-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)etil)ciclobutil)(isopropil)amino)metil)tetrahidrofurano-3,4-diol	Tratamento da leucémia mielóide aguda
Romanian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>terț</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciclobutil)(izopropil)amino)metil)tetrahidrofuran-3,4-diol	Tratamentul leucemiei mieloide acute
Slovak	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purín-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)etyl)cyklobutyl)(izopropyl)amino)metyl)tetrahydrofurán-3,4-diol	Liečba akútnej myeloickej leukémie
Slovenian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciklobutil)(izopropil)amino)metil)tetrahidrofuran-3,4-diol	Zdravljenje akutne mieloične levkemije
Spanish	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-il)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>ter</i> butil)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-il)etil)ciclobutil)(isopropil)amino)metil)tetrahidrofurano-3,4-diol	Tratamiento de la leucemia mieloide aguda
Swedish	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)etyl)cyklobutyl)(isopropyl)amino)metyl)tetrahydrofuran-3,4-diol	Behandling av akut myeloisk leukemi
Norwegian	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amino-9 <i>H</i> -purin-9-yl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -butyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)etyl)syklobutyl)(isopropyl)amino)metyl)tetrahydrofuran-3,4-diol	Behandling av akutt myelogen leukemi
Icelandic	(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(6-amínó-9 <i>H</i> -púrín-9-ýl)-5-(((1 <i>r</i> ,3 <i>S</i>)-3-(2-(5-(<i>tert</i> -bútýl)-1 <i>H</i> -bensó[<i>d</i>]ímídasól-2-ýl)etýl)sýklóbútýl)(ísóprópýl)amínó)metyl) tetrahýdrófúran-3,4-díól	Meðferð við bráðu kyrningahvítblæði