



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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EMA/COMP/317921/2005 Rev.3  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

(*E*)-(1*S*,4*S*,10*S*,21*R*)-7-[(*Z*)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone for the for the treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated)

On 28 October 2005, orphan designation (EU/3/05/328) was granted by the European Commission to The Matthews Consultancy Ltd, United Kingdom, for (*E*)-(1*S*,4*S*,10*S*,21*R*)-7-[(*Z*)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone (also known as "*depsipeptide*") for the for the treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated).

The sponsorship was transferred to Gloucester Pharmaceuticals Limited, United Kingdom, in October 2008 and to Celgene Europe Limited, United Kingdom, in September 2010.

### **What is peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated)?**

Peripheral T-cell lymphoma belongs to the group of non-Hodgkin's lymphoma, which is a type of cancer that originates from the lymphatic system. The lymphatic system is part of the body's immune system and helps fighting infections. It is a complex system made up of organs such as the bone marrow, the thymus (a gland behind the breast bone), the spleen (an organ in the abdomen, near the stomach), and the lymph nodes (or lymph glands, located throughout the body), which are connected by a network of tiny lymphatic vessels. There are two main types of cells, which make up the lymphatic tissue. These cells are called lymphocytes and belong to the group of white blood cells. The two types are called B lymphocytes (B cells) and T lymphocytes (T cells). Most lymphocytes start growing in the bone marrow. The T cells go from the bone marrow to the thymus where they continue to mature. Normally, the lymphatic cells grow in a controlled manner. Peripheral T-cell lymphoma is caused by the uncontrolled growth of T-lymphocytes originating from the thymus in different stages of maturity. Different types of peripheral T-cell lymphoma have been identified and categorised (nodal, other extranodal and leukaemic/disseminated). Patients most often present with generalised lymph node enlargement, liver enlargement and bone marrow involvement. Peripheral T-cell lymphoma is a serious and life-threatening condition.



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

At the time of designation, peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated) affected less than 1 in 10,000 people in the European Union (EU)\*. This is equivalent to a total of fewer than 46,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

## **What treatments are available?**

There are currently several medicinal products authorised in the Community for treatment of non-Hodgkin lymphoma. The choice of treatment depends in particular on the extension of the disease as well as on the responses to therapies previously prescribed. Although chemotherapy (using medicines to kill cancer cells) is the current standard of care for peripheral T-cell lymphoma, most tumours will come back and then more intensive regimens of several chemotherapeutic agents are given.

Depsipeptide might be of potential significant benefit for the treatment of peripheral T-cell lymphoma because it is expected to act in a different way than other available medicines. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

## **How is this medicine expected to work?**

Enzymes are proteins produced by the cells of the body that speed up the conversion of certain substances into other substances. Depsipeptide appears to inhibit or reduce the activity of an enzyme, called histone deacetylase, which is necessary for cell growth and multiplication. As these enzymes are no more available to help the formation of new genetic material, this might lead to the arrest of cell growth. Since peripheral T-cell lymphoma is caused by the uncontrolled growth of the T-lymphocytes, depsipeptide might help in slowing down or stopping this uncontrolled cell growth.

## **What is the stage of development of this medicine?**

The effects of depsipeptide were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with peripheral T cell lymphoma were ongoing.

Depsipeptide was not authorised anywhere worldwide for the treatment of peripheral T-cell lymphoma, at the time of submission. Orphan designation of depsipeptide was granted in Europe and in the United States for the treatment of cutaneous T-cell lymphoma.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 9 September 2005 recommending the granting of this designation.

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\* 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 25), Norway, Iceland and Liechtenstein. This represents a population of 459,700,000 (Eurostat 2004).

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:

Celgene Europe Limited  
1 Longwalk Road  
Stockley Park  
Uxbridge  
Middlesex UB11 1DB  
United Kingdom  
Telephone: +44 208 831 83 00  
Telefax: +44 208 831 83 01  
E-mail: [medinfo.uk.ire@celgene.com](mailto:medinfo.uk.ire@celgene.com)

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<sup>1</sup>, Norwegian and Icelandic

Language	Active Ingredient	Indication
English	(E)-(1S,4S,10S,21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone	Treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated)
Bulgarian	(E)-(1S,4S,10S,21R)-7-[(Z)-етилиден]-4,21-диизопропил-2-окса-12,13-дитиа-5,8,20,23-тетраазабицикло[8.7.6] трикос-16-ен-3,6,9,19,22-пентон	Лечение на периферен Т-клетъчен лимфом (нодален, екстранодален и левкемизирал/дисеминиран)
Czech	(E)-(1S,4S,10S,21R)-7-[(Z)-etylidén]-4,21-diizopropyl-2-oxo-12,13-ditio-5,8,20,23-tetraazabicyklo[8.7.6]tricos-16-én-3,6,9,19,22-pentone	Léčba periferních T-lymfomů (nodální, extranodální a leukemické/disseminované)
Danish	(E)-(1S,4S,10S,21R)-7-[(Z)-ethyliden]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-en-3,6,9,19,22-penton	Behandling af perifer T-celle lymfom (nodal, andre extranodale og leukæiske/desseminerede)
Dutch	(E)-(1S,4S,10S,21R)-7-[(Z)-ethylideen]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-een-3,6,9,19,22-pentone	Behandeling van perifere T-cel lymfomen (nodale, andere extranodale en leukemische/uitgezaaide)
Estonian	(E)-(1S,4S,10S,21R)-7-[(Z)-etülideen]-4,21-diisopropüül-2-oksa-12,13-ditia-5,8,20,23-tetraasabitsüklo[8.7.6]trikos-16-een-3,6,9,19,22-pentoon	Perifeerse T-rakulise lümfoomi (nodulaarne, teised ekstranodulaarsed ja leukeemilised/dissemineerunud) ravi
Finnish	(E)-(1S,4S,10S,21R)-7-[(Z)-etyylideeni]-4,21-diisopropyli-2-oksa-12,13-ditia-5,8,20,23-tetraatsabisyklo[8.7.6]trikos-16-eeni-3,6,9,19,22-pentoni	Perifeerisen T-solulymfooman hoito (nodaalinen, muu ekstranodaalinen ja leukeeminen/ disseminoitunut)
French	(E)-(1S,4S,10S,21R)-7-[(Z)-éthylidène]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tétrazabicyclo[8.7.6]tricos-16-ène-3,6,9,19,22-pentone	Traitement du lymphome périphérique à cellules T (nodulaire, autre extra nodulaire et leucémique/disséminé)
German	(E)-(1S,4S,10S,21R)-7-[(Z)-ethyliden]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-en-3,6,9,19,22-penton	Behandlung des peripheren T-Zell-Lymphoms (nodulär, extranodulär und leukämisch/disseminiert)
Greek	(E)-(1S,4S,10S,21R)-7-[(Z)-αιθυλιδενo]-4,21-διισοπροπουλ-2-οξα-12,13-διθια-5,8,20,23-τετρααζαδικυκλο[8.7.6]τρικοσ-16-ενε-3,6,9,19,22-πεντόνη	Θεραπεία του λεμφώματος περιφερικών κυττάρων T (λεμφαδενικό, άλλο εκτός λεμφαδένων και λευχαιμικό/ διάσπαρτο)

<sup>1</sup> At the time of transfer of sponsorship

Language	Active Ingredient	Indication
Hungarian	(E)-(1S,4S,10S,21R)-7-[(Z)-etilidén]-4,21-diizopropil-2-oxa-12,13-ditia-5,8,20,23-tetraazabicyklo[8.7.6]trikoz-16-én-3,6,9,19,22-penton	Perifériás T-sejtes lymphoma (nodalis, egyéb extranodalis és leukémiás/disszeminált) kezelése
Italian	(E)-(1S,4S,10S,21R)-7-[(Z)-etilidene]-4,21-diisopropil-2-ossa-12,13-ditia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone	Trattamento del linfoma periferico a cellule T (nodale, altre forme extranodali e leucemico/disseminato)
Latvian	(E)-(1S,4S,10S,21R)-7-[(Z)-etilidēn]-4,21-diizopropil-2-oksa-12,13-ditia-5,8,20,23-tetraazabicyklo[8.7.6]trikoz-16-ēn-3,6,9,19,22-pentons	Perifēriskās T-šūnu limfomas (nodālas, citas ekstranodālas un leukēmiskas / izsētas) ārstēšana
Lithuanian	(E)-(1S,4S,10S,21R)-7-[(Z)-etilideno]-4,21-diizopropil-2-oksa-12,13-ditia-5,8,20,23-tetraazabicyklo[8.7.6]trikoz-16-en-3,6,9,19,22-pentonas	Periferinės T ląstelių limfomas (mazgų, kitos ne mazgų ir leukeminės/diseminuotos) gydymas
Maltese	(E)-(1S,4S,10S,21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone	Kura tal-linfoma periferali taċ-ċelluli tat-tip T (fin-nodi, oħrajn barra n-nodi u lewkimiċi/mxerrda)
Polish	(E)-(1S,4S,10S,21R)-7-[(Z)-etylideno]-4,21-diizopropyl-2-oksa-12,13-ditia-5,8,20,23-tetraazobicyklo[8.7.6]trikoz-16-eno-3,6,9,19,22-penton	Leczenie obwodowego chłoniaka T-komórkowego (węzłowy, inny pozawęzłowy i białaczkopodobny/rozsiany)
Portuguese	(E)-(1S,4S,10S,21R)-7-[(Z)-etilideno]-4,21-diisopropil-2-oxa-12,13-ditia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-eno-3,6,9,19,22-pentona	Tratamento do linfoma periférico das células T (nodulares, outros extra nodulares e leucémicos/dessiminados)
Romanian	(E)-(1S,4S,10S,21R)-7-[(Z)-etilidenă]-4,21-diisopropil-2-oxa-12,13-ditia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentonă	Tratamentul limfomului periferic cu celule T (ganglionar, extraganglionar și leucemic/diseminat)
Slovak	(E)-(1S,4S,10S,21R)-7-[(Z)-etylidén]-4,21-diizopropyl-2-oxo-12,13-ditio-5,8,20,23-tetraazabicyklo[8.7.6]tricos-16-én-3,6,9,19,22-penton	Liečba periférneho T-bunkového lymfómu (nodálneho, iného extranodálneho a leukemického/diseminovaného)
Slovenian	(E)-(1S,4S,10S,21R)-7-[(Z)-etiliden]-4,21-diizopropil-2-oksa-12,13-ditia-5,8,20,23-tetraazabicyklo[8.7.6]trikoz-16-en-3,6,9,19,22-penton	Zdravljenje perifernega limfoma celic T (nodalni, ekstranodalni, levkemični/diseminirani)
Spanish	(E)-(1S,4S,10S,21R)-7-[(Z)-etiliden]-4,21-diisopropil-2-oxa-12,13-ditia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-eno-3,6,9,19,22-pentona	Tratamiento del linfoma de células T periféricas (ganglionar, otros extraganglionares, leucémico/disseminado)

Language	Active Ingredient	Indication
Swedish	( <i>E</i> )-(1 <i>S</i> ,4 <i>S</i> ,10 <i>S</i> ,21 <i>R</i> )-7-[( <i>Z</i> )-etyliden]-4,21-diisopropyl-2-oxa-12,13-ditia-5,8,20,23-tetraazabicyklo[8.7.6]trikos-16-ene-3,6,9,19,22-penton	Behandling av perifert T-cellslymfom (nodal, andra extranodala och leukemisk/spridd)
Norwegian	( <i>E</i> )-(1 <i>S</i> ,4 <i>S</i> ,10 <i>S</i> ,21 <i>R</i> )-7-[( <i>Z</i> )-etyliden]-4,21-diisopropyl-2-oksa-12,13-ditia-5,8,20,23-tetraazabisyklo[8.7.6]trikos-16-en-3,6,9,19,22-penton	Behandling av perifert T-cellelymfom (nodalt, annet ekstranodalt og leukemisk/disseminert)
Icelandic	( <i>E</i> )-(1 <i>S</i> ,4 <i>S</i> ,10 <i>S</i> ,21 <i>R</i> )-7-[( <i>Z</i> )-etýlíden]-4,21-tvíísóprópýl-2-oxa-12,13-tvítía-5,8,20,23-tetraazatvícykló[8.7.6]tríkós-16-ene-3,6,9,19,22-pentón	Meðferð við útlægu T-eitilfrumukrabbameini (í eitlum, utan þeirra og hvítblæðis/dreift)