



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2013
EMA/COMP/245993/2005 Rev.2
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate for the treatment of primary malignant bone tumours

Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in February 2013 on request of the Sponsor.

On 28 October 2005, orphan designation (EU/3/05/321) was granted by the European Commission to Orphix Consulting GmbH, Germany, for (1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34, 34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate (also known as “AP23573”) for the treatment of primary malignant bone tumours.

The sponsorship was transferred to Merck Sharp & Dohme Limited, United Kingdom, in January 2009.

What are primary malignant bone tumours?

Tumours that begin in the bone tissues are known as primary malignant bone tumours. Primary malignant bone tumours are classified by the type of tissue they originate, the most common being bone sarcomas. They can occur in any bone of the body and they spread almost exclusively through the blood. There are many types of primary malignant bone tumours, which tend to behave differently. Primary malignant bone tumours are a serious condition, potentially debilitating and life-threatening.



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

At the time of designation, primary malignant bone tumours affected approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 47,000 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?

Surgery is currently the main choice of therapy for primary malignant bone tumours usually combined with chemotherapy (using drugs to kill cancer cells) prior to or after surgery. Several products were authorised for the condition in some countries in the Community at the time of submission of the application for orphan drug designation.

Satisfactory argumentation has been submitted by the sponsor to justify the assumption that AP23573 might be of potential significant benefit for the treatment of primary malignant bone tumours mainly because it might improve the long-term outcome of the patients. 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?

Rapamycin is a kind of antibiotic (chemical substances which have the capacity to block the growth of or kill microorganisms, such as bacteria). AP23573 is similar to rapamycin (a so-called rapamycin analogue), but with a slightly different structure. Specific receptors (cell proteins that can only bind other substances having a specific shape, in order to activate, or block, certain biologic reactions of the cell), the so-called mammalian target of rapamycin (mTOR), can bind to the rapamycin and its analogues. mTOR plays a role in a cascade of molecular reactions to bring a certain signal from outside the cell into the cell thereby controlling the growth of the cells. Rapamycin and its analogues can block (inhibit) the mTOR. AP23573 might, by inhibition of this receptor, help in slowing down or stopping the further growth of the cancer cells.

What is the stage of development of this medicine?

The effects of AP23573 were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with primary malignant bone tumours were ongoing.

AP23573 was not authorised anywhere worldwide for primary malignant bone tumours or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

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.

*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. At the time of designation, this represented a population of 466,600,000 (Eurostat 2005).

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:

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
United Kingdom
Telephone: +44 19 92 45 22 06
Telefax: +44 19 92 50 72 06
E-mail: externalaffairs_UK@merck.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 languages¹, Norwegian and Icelandic

Language	Active Ingredient	Indication
English	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate	Treatment of primary malignant bone tumours
Bulgarian	(1R,2R,4S)-4- {(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate	Treatment of primary malignant bone tumours
Czech	1R, 2R, 4S)-4- {(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexametyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyklohentriakontin-3-yl]propyl}-2-metoxi-cyklohexyldimetyl-fosfinát	Léčba primárních kostních nádorů
Danish	(1R, 2R, 4S)-4- {(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexametyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyklohentriakontin-3-yl]propyl}-2-metoxi-cyklohexyldimetyl-fosfinat	Behandling af primære maligne knogletumorer
Dutch	(1R, 2R, 4S)-4- {(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-penta-oxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontine-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-fosfinaat	Behandeling van primair kwaadaardige bottumoren

¹ At the time of transfer of sponsorship

Language	Active Ingredient	Indication
Estonian	(1R, 2R, 4S)-4-{{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihüdoksiid-10,21-dimetoksiid-6,8,12,14,20,26-heksametüül-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahüdro-3H-23,27-epoksüprüido[2,1-c][1,4]oksazaküklohentriakontiin-3-yl]propüül}-2-metoksü-tsükloheksüüldimetüül-fosfinaat	Primaarse te pahaloomuliste luukasvajate ravi
Finnish	(1R, 2R, 4S)-4-{{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroksi-10,21-dimetoksi-6,8,12,14,20,26-heksametyyli-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahydro-3H-23,27-epoksipyrido[2,1-c][1,4]oksatsasyklohentriakontiini-3-yyli]propyyli}-2-metoksisykloheksyyldimetyylifosfinaatti	Primaarisen pahanlaatuisen luukasvaimen hoito
French	(1R, 2R, 4S)-4-{{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-diméthoxy-6,8,12,14,20,26-hexaméthyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-époxyprido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-méthoxy-cyclohexyldiméthyl-phosphinate	Traitement des tumeurs malignes osseuses primaires
German	(1R, 2R, 4S)-4-{{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxyprido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-Phosphinat	Behandlung von primär malignen Knochentumoren
Greek	(1R, 2R, 4S)-4-{{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-διϋδροξυ-10,21-διμεθοξυ-6,8,12,14,20,26-εξαμεθυλο-1,5,11,28,29-πενταοξο-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-τετραεικοσαϋδρο-3H-23,27-εποξυπυριδο[2,1-c][1,4]οξακυκλοεντριακοντιν-3-υλο]προπυλο}-2-μεθοξυ-κυκλοεξυλοδιμεθυλο-φωσφινικό	Θεραπεία πρωτοπαθών κακοήθων όγκων των οστών

Language	Active Ingredient	Indication
Hungarian	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihidroxī-10,21-dimetoxi-6,8,12,14,20,26-hexametil-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahidro-3H-23,27-epoxipirido[2,1-c][1,4]oxazaciclohentriacontin-3-il]propil}-2-metoxi-ciclohexildimetil-foszfīnat	Rosszindulatú primer csontdaganatok kezelése
Italian	Fosfinato di (1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-diidrossi-10,21-dimetossi-6,8,12,14,20,26-esametil-1,5,11,28,29-pentaosso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosaidro-23,27-epossi-3H-pirido[2,1-c][1,4]ossazacicloentriacontin-3-il]propil}-2-metossi-cicloesildimetile	Trattamento di tumori primari maligni ossei
Latvian	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihidroksi-10,21-dimetoksi-6,8,12,14,20,26-heksametil-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kozahidro-3H-23,27-epoksipirido[2,1-c][1,4]oksazaciclohentriakontīn-3-il]propil}-2-metoksi-cikloheksildimetil-fosfīnāts	Primāru ļaundabīgu kaulu audzēju ārstēšana
Lithuanian	(1R, 2R, 4S)-4-(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihidroksi-10,21-dimetoksi-6,8,12,14,20,26-heksametil-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahidro-3H-23,27-epoksipirido[2,1-c][1,4]oksazaciclohentriakontan-3-il]propil-2-metoksi-cikloheksildimetil-fosfīnatas	Pirminių piktybinių kaulų auglių gydymas
Maltese	(1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate	Kura ta' tumuri malinni primarji fl-għadam

Language	Active Ingredient	Indication
Polish	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimetoksy-6,8,12,14,20,26-heksametylo-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoksypirido[2,1-c][1,4]oksazacyklohentriakontyno-3-yl]propyl}-2-metoksy-cykloheksyldimetilofosfinian	Leczenie pierwotnych złośliwych guzów kości
Portuguese	Fosfinato de (1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihidroxi-10,21-dimetoxi-6,8,12,14,20,26-hexametil-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahidro-3H-23,27-epóxi-pirido[2,1-c][1,4]oxazaciclohentriacontin-3-il]propil}-2-metoxi-ciclohexildimetilo	Tratamento do tumor ósseo maligno primário
Romanian	(1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihidroxi-10,21-dimetoxi-6,8,12,14,20,26-hexametil-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahidro-3H-23,27-epoxipirido[2,1-c][1,4]oxazaciclohentriacontin-3-il]propil}-2-metoxi-ciclohexildimetil-fosfinat	Tratamentul tumorilor maligne osoase primare
Slovak	1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimetoxi-6,8,12,14,20,26-hexametyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyklohentriakontin-3-yl]propyl}-2-metoxi-cyklohexyldimetil-fosfinát	Liečba primárneho malígneho tumoru kostí
Slovenian	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihidroksi-10,21-dimetoksi-6,8,12,14,20,26-heksametil-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahidro-3H-23,27-epoksipirido[2,1-c][1,4]oksazaciclohentriakontin-3-yl]propil}-2-metoksi-cikloheksildimetil-fosfinat	Zdravljenje primarnih malignih kostnih tumorjev

Language	Active Ingredient	Indication
Spanish	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihidroxi-10,21-dimetoxi-6,8,12,14,20,26-hexametil-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahidro-3H-23,27-epoxipirido[2,1-c][1,4]oxazaciclohentriacontin-3-yl]propil}-2-methoxi-ciclohexildimetil-fosfinato	Tratamiento de los tumores malignos primarios de hueso
Swedish	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexametyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyklohentriacontin-3-yl]propyl}-2-metoxi-cyklohexyldimetyl-fosfinat	Behandling av primära maligna ben tumörer
Norwegian	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroksy-10,21-dimetoksy-6,8,12,14,20,26-heksametyl-1,5,11,28,29-pentaokso-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-kosahydro-3H-23,27-epoksypyrido[2,1-c][1,4]oksazacyklohentriakontin-3-yl]propyl}-2-metoksy-cykloheksyldimetyl-fosfinat	Behandling av primære maligne bentumorer
Icelandic	(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-tvíhýdroxý-10,21-tvímethoxý-6,8,12,14,20,26-hexamethýl-1,5,11,28,29-pentaoxó-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahýdró-3H-23,27-epoxýpýrídó[2,1-c][1,4]oxazacyklóhentríacontín-3-yl]própýl}-2-methoxý-cýklóhexýl tvímethýl-fosfínat	Meðferð við illkynja beinæxlum