



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2013
EMA/COMP/246033/2005 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 soft tissue sarcoma

Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in February 2013 on request of the Sponsor.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 26 August 2005, orphan designation (EU/3/05/312) 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 (AP23573) for the treatment of soft tissue sarcoma.

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

What is soft tissue sarcoma?

Soft tissue sarcomas are cancers of the supporting tissues of the body. They can occur in muscle, fat, blood vessels or in any of the other tissues that support, surround and protect the organs of the body. There are many types of soft tissue sarcoma. The cause of soft tissue sarcoma is largely unknown. Soft tissue sarcoma is a serious condition, potentially debilitating and life-threatening.



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

At the time of designation, soft tissue sarcoma affected approximately 2 in 10,000 people in the European Union (EU). This was equivalent to a total of around 93,000 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 early stage soft tissue sarcomas. For larger sarcomas, and where it is thought there is a possibility of cancer cells being left behind, after a surgical intervention, radiotherapy (using high-dose x-rays or other high-energy rays to kill cancer cells) and chemotherapy (using drugs to kill cancer cells) are usually used. Several products for treatment of soft tissue sarcoma 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 soft tissue sarcoma 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?

AP23573 is structurally similar to a kind of antibiotic (chemical substances which have the capacity to block the growth of or to kill microorganisms, such as bacteria) called rapamycin (and is therefore a so-called rapamycin analogue). 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 soft tissue sarcoma were ongoing.

AP23573 was not authorised anywhere worldwide for soft tissue sarcoma 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 13 July 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:

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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 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-epoxyprido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate	Treatment of soft tissue sarcoma
Bulgarian	(1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-дихидрокси-10,21-диметокси-6,8,12,14,20,26-хексаметил-1,5,11,28,29-пентаоксо-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34а-тетра-козахидро-3Н-23,27-епоксипиридо[2,1-с][1,4]оксазациклохентриако́нтин-3-yl]пропил}-2-метокси-циклохексилдиметил-фосфинат	Лечение на сарком на меките тъкани
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-dimetoxy-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-epoxyprido[2,1-c][1,4]oxazacyklohentriakontin-3-yl]propyl}-2-metoxy-cyklohexyldimetyl-fosfinát	Léčba sarkomu měkkých tkání
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-dimetoxy-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-epoxyprido[2,1-c][1,4]oxazacyklohentriakontin-3-yl]propyl}-2-metoxy-cyklohexyldimetyl-fosfinat	Behandling af bløddelssarkom

¹ At the time of transfer of sponsorship

Language	Active Ingredient	Indication
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 weke delen sarcoom
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-epoksüpürido[2,1-c][1,4]oksazaküklohentriakontiin-3-yl]propüül}-2-metoksü-tsükloheksüüldimetüül-fosfinaat	Pehmele kudede sarkoomi 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-metoksisykloheksyylidimetyylifosfinaatti	Pehmytkudossarkooman 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-époxy pyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-méthoxy-cyclohexyldiméthyl-phosphinate	Traitement des sarcomes des tissus mous

Language	Active Ingredient	Indication
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-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-Phosphinat	Behandlung des Weichteilsarkoms
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 του σαρκώματος των μαλακών ιστών
Hungarian	(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]oxazacyclohentriacontin-3-il]propil}-2-metoxi-ciclohexildimetil-foszfinat	Lágy szöveti sarcoma kezelésére
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-eossi-3H-pirido[2,1-c][1,4]ossazacicloentriacontin-3-il]propil}-2-metossi-cicloesildimetile	Trattamento dei sarcomi dei tessuti molli

Language	Active Ingredient	Indication
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]oksazaciklohentriakontin-3-il]propil}-2-metoksi-cikloheksildimetil-fosfināts	Mīksto audu sarkomas 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]oksazaciklohentriakontan-3-il]propil-2-metoksi-cikloheksildimetil-fosfinatas	Minkštųjų audinių sarkomos 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-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	Kura tas-sarkoma tat-tessuti rotob
Polish	(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-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]propylo}-2-metoksy-cykloheksylodimetylofosfinian	Leczenie mięsaków tkanek miękkich

Language	Active Ingredient	Indication
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 sarcoma dos tecidos moles
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 sarcomului țesuturilor moi
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-cyklohexyldimetyl-fosfinát	Liečba sarkómu mäkkých tkanív
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 sarkoma mehkih tkiv

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 del sarcoma de tejidos blandos
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-epoxyprido[2,1-c][1,4]oxazacyklohentriacontin-3-yl]propyl]-2-metoxi-cyklohexyldimetyl-fosfinat	Behandling av mjukdelssarkom
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-cosahydro-3H-23,27-epoksypyrido[2,1-c][1,4]oksazacyklohentriakontin-3-yl]propyl]-2-metoksy-cykloheksyldimetyl-fosfinat	Behandling av bløtvevssarkom
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-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-cosahýdró-3H-23,27-epoxýpýrídó[2,1-c][1,4]oxazacíclóhentríacontín-3-yl]própýl]-2-methoxý-cýclóhexýldímethýl-fosfínat	Meðferð við mjúkvefjasarkmeini