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EMA/140581/2017
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate for the treatment of soft tissue sarcoma

On 20 March 2017, orphan designation (EU/3/17/1847) was granted by the European Commission to Daiichi Sankyo Europe GmbH, Germany, for (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate (also known as DS-3032b) for the treatment of soft tissue sarcoma.

What is soft tissue sarcoma?

Soft tissue sarcoma is a type of cancer that affects the soft, supportive tissues of the body. It can occur in muscles, blood vessels, fat tissue or in other tissues that support, surround and protect organs. Patients with soft tissue sarcoma do not usually have symptoms in the early stages of the disease. First symptoms appear when the tumour grows large enough to cause swelling and pain.

Soft tissue sarcoma is a long-term debilitating and life-threatening disease, particularly when the cancer has spread to other parts of the body.

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

At the time of designation, soft tissue sarcoma affected approximately 3.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 170,000 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 515,700,000 (Eurostat 2017).

What treatments are available?

At the time of designation, the main treatment for early-stage soft tissue sarcoma was surgery. For large sarcomas, surgery was usually followed by radiotherapy (treatment with radiation) and chemotherapy (medicines to treat cancer) to kill any cancer cells that were left behind. Several medicines were authorised in the EU for the treatment of soft tissue sarcoma.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with soft tissue sarcoma. Patients with a type of soft tissue sarcoma called liposarcoma that did not respond to previous treatment or whose disease came back after previous treatment showed improved progression-free survival (how long patients lived without their disease getting worse) in early studies with the medicine. 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?

This medicine works by blocking the action of a protein known as MDM2. MDM2 normally regulates the action of a cancer-suppressing protein called p53. p53 prevents cancer by promoting repair of cells with damaged DNA and, if the damage cannot be repaired, inducing cell death.

In many cancers MDM2 is overactive, leading to reduced p53 activity. By attaching to MDM2 and blocking its action, this medicine is expected to increase the activity of p53 and restore the body's ability to prevent the growth of the cancer cells.

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 including patients with soft tissue sarcoma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for soft tissue sarcoma 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 16 February 2017 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:

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 languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate	Treatment of soft tissue sarcoma
Bulgarian	(3'R,4'S,5'R)-N-[(3R,6S)-6-карбамоилтетрахидро-2Н-пиран-3-ил]-6''-хлоро-4'-(2-хлоро-3-флуоропиридин-4-ил)-4,4-диметил-2''-оксо-1'',2''-дихидродиспиرو[циклохексан-1,2'-пирролидин-3',3''-индол]-5'-карбоксамин моно(4-метилбензенсулфонат) монохидрат	Лечение на сарком на меките тъкани
Croatian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoiltetrahidro-2H-piran-3-yl]-6''-kloro-4'-(2-kloro-3-fluoropiridin-4-yl)-4,4-dimetil-2''-okso-1'',2''-dihidrodispiro[cikloheksan-1,2'-pirrolidin-3',3''-indol]-5'-karboksamid mono(4-metilbenzensulfonat) monohidrat	Liječenje sarkoma mekih tkiva
Czech	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoiltetrahydro-2H-pyran-3-yl]-6''-chlor-4'-(2-chlor-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyklohexan-1,2'-pyrrolidin-3',3''-indol]-5'-karboxamid mono(4-methylbenzensulfonát) monohydrát	Léčba sarkomu měkkých tkání
Danish	(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexan-1,2'-pyrrolidin-3',3''-indol]-5'-carboxamid mono(4-methylbenzenesulfonat) monohydrat	Behandling af bløddelssarkom
Dutch	(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridine-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydraat	Behandeling weke delen sarcoom
Estonian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoüültetrahüdro-2H-püraan-3-üül]-6''-kloro-4'-(2-kloro-3-fluoropüridiin-4-üül)-4,4-dimetüül-2''-okso-1'',2''-dihüdrodispiro[tsükloheksaan-1,2'-pürrolidiin-3',3''-indool]-5'-karboksamiid mono(4-metüülbenseensulfonaat) monohüdraat	Pehmele kudede sarkoomi ravi
Finnish	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoyllitetrahydro-2H-pyran-3-yyli]-6''-kloori-4'-(2-kloori-3-fluoropyridin-4-yyli)-4,4-dimetyyli-2''-okso-1'',2''-dihydrodispiro[sykloheksaani-1,2'-pyrrolidiini-3',3''-indoli]-5'-karboksamidi mono(4-metyyliibentseenisulfonaatti) monohydraatti	Pehmytkudossarkooman hoito

¹ At the time of designation

Language	Active ingredient	Indication
French	Monohydrate de (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltétrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridine-4-yl)-4,4-diméthyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-méthylbenzène sulfonate)	Traitement des sarcomes des tissus mous
German	(3'R,4'S,5'R)-N-[(3R,6S)-6-Carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexan-1,2'-pyrrolidin-3',3''-indol]-5'-carboxamid mono(4-methylbenzenesulfonat)-monohydrat	Behandlung des Weichteilsarkoms
Greek	Μονοένυδρο μονο(4-μεθυλοβενζοσουλφονικό) (3'R,4'S,5'R)-N-[(3R,6S)-6-Καρβαμοϋλ-τετραϋδρο-2H-πυραν-3-υλ]-6''-χλωρο-4'-(2-χλωρο-3-φθοριοπυριδιν-4-υλ)-4,4-διμεθυλ-2''-οξο-1'',2''-διυδροδισπειρο[κυκλοεξανο-1,2'-πυρρολιδινο-3',3''-ινδολ]-5'-καρβοξαμίδιο	Θεραπεία του σαρκώματος των μαλακών ιστών
Hungarian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoiltetrahydro-2H-pirán-3-yl]-6''-klór-4'-(2-klór-3-fluoropiridin-4-yl)-4,4-dimetil-2''-oxo-1'',2''-dihidrodiszpiro[ciklohexán-1,2'-pirrolidin-3',3''-indol]-5'-karboxamid mono(4-metilbenzénszulfonát) monohidrát	Lágy szöveti sarcoma kezelése
Italian	(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoiltetraidro-2H-piran-3-il]-6''-cloro-4'-(2-cloro-3-fluoropiridin-4-il)-4,4-dimetil-2''-osso-1'',2''-diidrodispiro[cycloesano-1,2'-pirrolidina-3',3''-indolo]-5'-carbossamide mono (4-metilbenzenesolfonato) monoidrato	Trattamento dei sarcomi dei tessuti molli
Latvian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoiltetrahydro-2H-pirān-3-il]-6''-hloro-4'-(2-hloro-3-fluoropiridīn-4-il)-4,4-dimetil-2''-okso-1'',2''-dihidrodispiro[cikloheksān-1,2'-pirolidīn-3',3''-indola]-5'-karbohamīda mono(4-metilbenzolsulfonāta) monohidrāts	Mīksto audu sarkomas ārstēšana
Lithuanian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoiltetrahydro-2H-piran-3-il]-6''-chloro-4'-(2-chloro-3-fluoropiridin-4-il)-4,4-dimetil-2''-okso-1'',2''-dihidrodispiro[cicloheksano-1,2'-pirolidino-3',3''-indolo]-5'-karboksamido mono(4-metilbenzenosulfonato) monohidratas	Minkštųjų audinių sarkomos gydymas
Maltese	(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate	Kura tas-sarkoma tat-tessuti rotob
Polish	Monowodzian mono(4-metylobenzenesulfonianu) (3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoilotetrahydro-2H-piran-3-ylo]-6''-chloro-4'-(2-chloro-3-fluoropirydyn-4-ylo)-4,4-dimethlo-2''-okso-1'',2''-dihydrodispiro[cykloheksano-1,2'-pirolidyno-3',3''-indolo]-5'-karboksamidu	Leczenie mięsaków tkanek miękkich

Language	Active ingredient	Indication
Portuguese	Mono(4-metilbenzenossulfonato) de (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoiiltetra-hidro-2H-piran-3-il]-6"-cloro-4'-(2-cloro-3-fluoropiridin-4-il)-4,4-dimetil-2"-oxo-1",2"-dihidrodispiro[ciclo-hexano-1,2'-pirrolidin-3',3''-indole]-5'-carboxamida mono-hidratada	Tratamento do sarcoma dos tecidos moles
Romanian	Monohidrat de (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoiiltetrahidro-2H-piran-3-il]-6"-cloro-4'-(2-cloro-3-fluoropiridin-4-il)-4,4-dimetil-2"-oxo-1",2"-dihidrodispiro[ciclohexan-1,2'-pirolidin-3',3''-indol]-5'-carboxamid mono(4-metilbenzensulfonat)	Tratamentul sarcomului țesuturilor moi
Slovak	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoyltetrahydro-2H-pyrán-3-yl]-6"-chlór-4'-(2-chlór-3-fluórpyridín-4-yl)-4,4-dimetyl-2"-oxo-1",2"-dihydrodispiro[cyklohexán-1,2'-pyrolidín-3',3''-indol]-5'-karboxamid mono(4-metylbenzénsulfonát) monohydrát	Liečba sarkómu mäkkých tkanív
Slovenian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoiltetrahidro-2H-piran-3-il]-6"-kloro-4'-(2-kloro-3-fluoropiridin-4-il)-4,4-dimetil-2"-okso-1",2"-dihidrodispiro[cikloheksan-1,2'-pirolidin-3',3''-indol]-5'-karboksamid mono(4-metilbenzensulfonat) monohidrat	Zdravljenje sarkoma mehkih tkiv
Spanish	Monohidrato de (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoiiltetrahidro-2H-piran-3-yl]-6"-cloro-4'-(2-cloro-3-fluoropiridin-4-il)-4,4-dimetil-2"-oxo-1",2"-dihidrodispiro[ciclohexano-1,2'-pirrolidina-3',3''-indol]-5'-carboxamida mono(4-metilbencenosulfonato)	Tratamiento del sarcoma de tejidos blandos
Swedish	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamyltetraväte-2H-pyran-3-yl]-6"-klor-4'-(2-klor-3-fluoropyridin-4-yl)-4,4-dimetyl-2"-oxo-1",2"-divätedispiro[cyklohexan-1,2'-pyrrolidin-3',3''-indol]-5'-karboxamid mono(4-metylbenzenesulfonat) monohydrat	Behandling av mjukdelssarkom
Norwegian	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamoyltetrahydro-2H-pyran-3-yl]-6"-kloro-4'-(2-kloro-3-fluoropyridin-4-yl)-4,4-dimetyl-2"-okso-1",2"-dihydrodispiro[sykloheksan-1,2'-pyrrolidin-3',3''-indol]-5'-karboksamid mono(4-metylbenzensulfonat) monohydrat	Behandling av bløtvevssarkom
Icelandic	(3'R,4'S,5'R)-N-[(3R,6S)-6-karbamóýltetraýdró-2H-pýran-3-ýl]-6"-klóró-4'-(2-klóró-3-flúórópýridín-4-ýl)-4,4-dímetýl-2"-oxó-1",2"-díhýdróíspíró[sýklóhexan-1,2'-pýrrólídín-3',3''-indól]-5'-karboxamíð mónó(4-metýlbensensúlfónat) einhýdrat	Meðferð við mjúkvefjasarkmeini