



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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## Public summary of opinion on orphan designation

1-(((2S,4S)-2-((((S)-(4-Bromophenoxy)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride for the treatment of hepatocellular carcinoma

On 4 June 2020, orphan designation EU/3/20/2285 was granted by the European Commission to Medivir AB, Sweden, for 1-(((2S,4S)-2-((((S)-(4-bromophenoxy)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride (also known as MIV-818) for the treatment of hepatocellular carcinoma.

### What is hepatocellular carcinoma?

Hepatocellular carcinoma is a primary cancer of the liver (a cancer that starts in the liver, rather than one that has spread to the liver from elsewhere in the body). It is more common in men than in women, and occurs mostly in people who have liver scarring (cirrhosis), or after hepatitis B or C infection. Features of the disease include yellow skin, pain and swelling in the belly, easy bruising, weight loss, weakness, loss of appetite and nausea (feeling sick).

Hepatocellular carcinoma is a long-term debilitating and life-threatening condition, with most patients surviving from a few months to a few years after diagnosis, depending on the stage of the disease at diagnosis.

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

At the time of designation, hepatocellular carcinoma affected approximately 2.9 in 10,000 people in the European Union (EU). This was equivalent to a total of around 151,000 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).

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\*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, Iceland, Liechtenstein, Norway and the United Kingdom. This represents a population of 519,200,000 (Eurostat 2020).



## What treatments are available?

At the time of designation, some patients with early stage hepatocellular carcinoma were treated with surgery to remove part of the liver, liver transplantation or radiofrequency ablation (directing heat and electricity through a needle to destroy cancer cells). Chemotherapy (medicines to treat cancer) was used if surgery was not possible or the disease had spread to other parts of the body (metastatic disease). A number of medicines, including lenvatinib and sorafenib were authorised in the EU for use in hepatocellular carcinoma.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with hepatocellular carcinoma because laboratory studies suggest it may be better than sorafenib at slowing down the growth of hepatocellular carcinoma and effectiveness may further improve when it is combined with sorafenib. 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 is a prodrug that is converted inside liver cells to its active form, troxacitabine. Troxacitabine resembles natural substances called nucleosides, and like them can be incorporated into the genetic material (DNA) of the dividing cancer cells. This damages the DNA and results in the death of the cell. By acting in this way, the medicine is expected to control the growth of hepatocellular carcinoma.

## 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 hepatocellular carcinoma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of hepatocellular carcinoma or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 23 April 2020, recommending the granting of this designation.

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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](#).

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   | 1-((2S,4S)-2-((((S)-(4-bromophenoxy))((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride              | Treatment of hepatocellular carcinoma     |
| Bulgarian | 1-((2S,4S)-2-((((S)-(4-бромо фенокси))((S)-1-оксо-1-(((S)- пентан-2-ил)окси)пропан-2-ил)амино)фосфорил)окси)метил)-1,3-диоксолан-4-ил)-2-оксо-1,2- дихидро пиримидин-4-аминиум хлорид          | Лечение на хепатоцелуларен карцином       |
| Croatian  | 1-((2S,4S)-2-((((S)-(4-bromofenoksi))((S)-1-okso-1-(((S)-pentan-2-il)oksi)propan-2-il)amino)fosforil)oksi)metil)-1,3-dioksolan-4-il)-2-okso-1,2- dihidro pirimidin-4-aminiumklorid             | Liječenje hepatocelularnog karcinoma      |
| Czech     | 1-((2S,4S)-2-((((S)-(4-bromofenoxy))((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)fosforyl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chlorid                  | Léčba hepatocelulárního karcinomu         |
| Danish    | 1-((2S,4S)-2-((((S)-(4-bromophenoxy))((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium klorid                | Behandling af hepatocellulært karcinom    |
| Dutch     | 1-((2S,4S)-2-((((S)-(4-broomfenoxy))((S)-1-oxo-1-(((S)-pentaan-2-yl)oxy)propaan-2-yl)amino)fosforyl)oxy)methyl)-1,3-dioxolaan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride              | Behandeling van hepatocellulair carcinoom |
| Estonian  | 1-((2S,4S)-2-((((S)-(4-bromofenoksü))((S)-1-okso-1-(((S)-pentaan-2-üül)oksü)propaan-2-üül)amino)fosforüül)oksü)metüül)-1,3-dioksolaan-4-üül)-2-okso-1,2- dihüdro pürimidiin-4-amiinium-kloriid | Hepatotsellulaarse kartsinoomi ravi       |

<sup>1</sup> At the time of designation

| Language   | Active ingredient                                                                                                                                                                              | Indication                                |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Finnish    | 1-((2S,4S)-2-((((S)-(4-bromifenoksi)((S)-1-okso-1-(((S)-pentan-2-yyli)oksi)propan-2-yyli)amino)fosforyyli)oksi)metyyli)-1,3-dioksolaani-4-yyli)-2-okso-1,2-dihydropyrimidiini-4-aminiumkloridi | Hepatosellulaarisen karsinooman hoito     |
| French     | Chlorure de 1-((2S,4S)-2-((((S)-(4-bromophénoxy)((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propane-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidine-4-aminium          | Traitement du cancer hépatocellulaire     |
| German     | 1-((2S,4S)-2-((((S)-(4-Bromphenoxy)((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium-chlorid                 | Behandlung des Leberzellkarzinoms         |
| Greek      | Χλωριούχο 1-((2S,4S)-2-((((S)-(4-βρωμο φαινοξυ)((S)-1-οξο-1-(((S)- πεντανό-2-υλ)οξυ)προπανο-2-υλ)αμινο)φωσφορυλ)οξυ)μεθυλ)-1,3-διοξολαν-4-υλ)-2-οξο-1,2- διυδρο πυριμιδινό-4-αμμώνιο           | Θεραπεία του ηπατοκυτταρικού καρκινώματος |
| Hungarian  | 1-((2S,4S)-2-((((S)-(4-bromofenoxi)((S)-1-oxo-1-(((S)- pentán-2-il)oxi)propán-2-il)amino)foszforil)oxi)methyl)-1,3-dioxolán-4-il)-2-oxo-1,2- dihidropirimidin-4-aminium klorid                 | Hepatocelluláris carcinoma kezelése       |
| Italian    | 1-((2S,4S)-2-((((S)-(4-bromofenossi)((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)ammino)fosforil)oxy)metil)-1,3-dioxolan-4-yl)-2-oxo-1,2- diidropirimidina-4-amminium cloruro                | Trattamento del carcinoma epatocellulare  |
| Latvian    | 1-((2S,4S)-2-((((S)-(4-bromofenoksi)((S)-1-okso-1-(((S)- pentān-2-il)oksi)propān-2-il)amino)fosforil)oksi)metil)-1,3-dioksolān-4-il)-2-okso-1,2- dihidropirimidīn-4-amīnija hlorīds            | Hepatocellulāras karcinomas ārstēšana     |
| Lithuanian | 1-((2S,4S)-2-((((S)-(4-bromofenoksi)((S)-1-okso-1-(((S)-pentan-2-il)oksi)propan-2-il)amino)fosforil)oksi)metil)-1,3-dioksolan-4-il)-2-okso-1,2- dihidropirimidin-4-amonio chloridas            | Hepatoceliulinės karcinomos gydymas       |

| Language   | Active ingredient                                                                                                                                                                       | Indication                              |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Maltese    | 1-((2S,4S)-2-((((S)-(4-bromofenossi)(((S)-1-osso-1-(((S)-pentan-2-il)ossi)propan-2-il)amino)fosforil)ossi)metil)-1,3-dirossolan-4-il)-2-osso-1,2- diidropirimidina-4-klorur tal-aminju  | Kura tal-karċinoma epatoċellulari       |
| Polish     | Chlorek 1-((2S,4S)-2-((((S)-(4-bromofenoksy)(((S)-1-okso-1-(((S)-pentan-2-ilo)oksy)propan-2-ilo)amino)fosforyl)oksy)metyl)-1,3-dioksolano-4-ilo)-2-okso-1,2-dihidropirymidyno-4-aminium | Leczenie raka wątrobowokomórkowego      |
| Portuguese | Cloreto de 1-((2S,4S)-2-((((S)-(4-bromofenoxi)(((S)-1-oxo-1-(((S)-pentan-2-il)oxi)propan-2-il)amino)fosforil)oxi)metil)-1,3-dioxolan-4-il)-2-oxo-1,2-dihidropirimidin-4-aminio          | Tratamento do carcinoma hepatocelular   |
| Romanian   | Clorură de 1-((2S,4S)-2-((((S)-(4-bromofenoxi)(((S)-1-oxo-1-(((S)-pentan-2-il)oxi)propan-2-il)amino)fosforil)oxi)metil)-1,3-dioxolan-4-il)-2-oxo-1,2-dihidropirimidin-4-aminu           | Tratamentul carcinomului hepatocelular  |
| Slovak     | 1-((2S,4S)-2-((((S)-(4-bróm fenoxi)(((S)-1-oxo-1-(((S)- pentán-2-yl)oxy)propán-2-yl)amino)fosforyl)oxy)metyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidín-4-amínium chlorid           | Liečba hepatocelulárneho karcinómu      |
| Slovenian  | 1-((2S,4S)-2-((((S)-(4-bromofenoksi)(((S)-1-okso-1-(((S)-pentan-2-il)oksi)propan-2-il)amino)fosforil)oksi)metil)-1,3-dioksolan-4-il)-2-okso-1,2- dihidropirimidin-4-aminijev klorid     | Zdravljenje hepatocelularnega karcinoma |
| Spanish    | Cloruro de 1-((2S,4S)-2-((((S)-(4-bromofenoxi)(((S)-1-oxo-1-(((S)-pentano-2-il)oxi)propan-2-il)amino)fosforil)oxi)metil)-1,3-dioxolan-4-il)-2-oxo-1,2-dihidropirimidin-4-aminium        | Tratamiento del carcinoma hepatocelular |
| Swedish    | 1-((2S,4S)-2-((((S)-(4-bromofenoxi)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxi)propan-2-yl)amino)fosforyl)oxi)metyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminiumklorid              | Behandling av hepatocellulärt karcinom  |
| Norwegian  | 1-((2S,4S)-2-((((S)-(4-bromfenoksy)(((S)-1-okso-1-(((S)-pentan-2-yl)oksy)propan-2-yl)amino)fosforyl)oksy)metyl)-1,3-dioksolan-4-yl)-2-okso-1,2-dihydropyrimidin-4-aminiumklorid         | Behandling av hepatocellulært karsinom  |

| Language  | Active ingredient                                                                                                                                                             | Indication                         |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Icelandic | 1-((2S,4S)-2-((((S)-(4-brómó fenoxý))((S)-1-oxó-1-((S)-pentan-2-ýl)oxý)própan-2-ýl)amínó)fosfórýl)oxý)metýl)-1,3-díoxólan-4-ýl)-2- oxó-1,2- díhýdrópýrimídín-4-amíníum klóríð | Meðferð við lifrarfrumukrabbameini |