



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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## Public summary of opinion on orphan designation

3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile for the treatment of von Hippel-Lindau disease

On 21 August 2020, orphan designation EU/3/20/2324 was granted by the European Commission to Merck Sharp & Dohme B.V, Netherlands, for 3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile (also known MK-6482) for the treatment of von Hippel-Lindau disease.

### What is von Hippel-Lindau disease?

Von Hippel-Lindau disease is a genetic disease characterised by growth of mostly benign but also cancerous tumours in many organs of the body, including in the kidneys, pancreas, adrenal glands and inner ear, as well as abnormal growth of blood vessels in the eye, brain and spinal cord.

The disease is caused by a defect in the *VHL* gene which is responsible for the production of a protein that prevents tumour formation. In patients with von Hippel-Lindau disease, the defective gene cannot produce sufficient protein that works properly, leading to the development of tumours.

Von Hippel-Lindau disease is a long-term debilitating and life-threatening disease due to the complications caused by the various tumours that can have wide-ranging effects on the body.

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

At the time of designation, von Hippel-Lindau disease affected approximately 0.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 16,000 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, no satisfactory methods were authorised in the EU for treating von Hippel-Lindau disease. Patients were mainly treated with surgery to remove tumours in the affected organs and with laser therapy to treat eye symptoms.

## How is this medicine expected to work?

The medicine blocks the activity of a protein called HIF-2 $\alpha$ , which accumulates when the oxygen levels in cells are low. HIF-2 $\alpha$  promotes cell survival, cell growth and formation of new blood vessels. HIF-2 $\alpha$  levels are raised in patients with von Hippel-Lindau disease (even when oxygen levels are normal). Therefore, by blocking the activity of HIF-2 $\alpha$ , it is expected that the medicine will slow down worsening of the disease and improve symptoms.

## 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 von Hippel-Lindau disease were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of von Hippel-Lindau disease 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 16 July 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

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	3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile	Treatment of von Hippel-Lindau disease
Bulgarian	3-(((1S,2S,3R)-2,3-дифлуоро-1-хидрокси-7-(метилсулфонил)-2,3-дихидро-1H-инден-4-ил)окси)-5-флуоробензонитрил	Лечение на болестта на von Hippel-Lindau
Croatian	3-(((1S,2S,3R)-2,3-difluor-1-hidroksi-7-(metilsulfonyl)-2,3-dihidro-1H-inden-4-il)oksi)-5-fluorobenzonitril	Liječenje von Hippel-Lindauove bolesti
Czech	3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorbenzonitril	Léčba von Hippel-Lindau choroby
Danish	3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitril	Behandling af von Hippel-Lindaus sygdom
Dutch	3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitril	Behandeling van de ziekte von Hippel-Lindau
Estonian	3-(((1S,2S,3R)-2,3-difluoro-1-hüdrosü-7-(metüülsulfonüül)-2,3-dihüdro-1H-indeen-4-üül)oksü)-5-fluorobensonitriil	Von Hippel-Lindau haiguse ravi
Finnish	3-(((1S,2S,3R)-2,3-difluori-1-hydroksi-7-(metyylisulfonyyli)-2,3-dihydro-1H-inden-4-yyli)oksi)-5-fluoribentsonitriili	Von Hippel-Lindaun oireyhtymän hoito
French	3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(méthylsulfonyl)-2,3-dihydro-1H-indén-4-yl)oxy)-5-fluorobenzonitrile	Traitement de la maladie de von Hippel-Lindau
German	3-(((1S,2S,3R)-2,3-Difluor-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorbenzonitril	Behandlung des von-Hippel-Lindau-Syndroms
Greek	3-(((1S,2S,3R)-2,3-διφθορο-1-υδροξυ-7-(μεθυλσουλφονυλ)-2,3-διυδρο-1H-ινδεν-4-υλ)οξυ)-5-φθοροβενζονιτριλιο	Θεραπεία της νόσου von Hippel-Lindau
Hungarian	3-(((1S,2S,3R)-2,3-difluoro-1-hidroxi-7-(metilszulfonil)-2,3-dihidro-1H-inden-4-il)oxi)-5-fluorobenzonitril	Von Hippel-Lindau betegség kezelése
Italian	3-(((1S,2S,3R)-2,3-difluoro-1-idrossi-7-(metilsulfonyl)-2,3-diidro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile	Trattamento della sindrome di von Hippel-Lindau

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

Language	Active ingredient	Indication
Latvian	3-(((1S,2S,3R)-2,3-difluoro-1-hidroksi-7-(metilsulfonil)-2,3-dihidro-1H-inden-4-il)oksi)-5-fluorobenzonitrils	Hipela un Lindava (Von Hippel-Lindau) slimības ārstēšana
Lithuanian	3-(((1S,2S,3R)-2,3-difluoro-1-hidroksi-7-(metilsulfonil)-2,3-dihidro-1H-inden-4-il)oksi)-5-fluorobenzonitrilas	Von Hippel-Lindau ligos gydymas
Maltese	3-(((1S,2S,3R)-2,3-difluoro-1-idrossi-7-(metilsulfonil)-2,3-diidro-1H-inden-4-il)ossi)-5-fluorobenzonitril	Kura tal-marda von Hippel-Lindau
Polish	3-(((1S,2S,3R)-2,3-difluoro-1-hydroksy-7-(metylosulfonylo)-2,3-dihydro-1H-inden-4-ylo)oksy)-5-fluorobenzonitryl	Leczenie choroby von Hippel-Lindau'a
Portuguese	3-(((1S,2S,3R)-2,3-difluoro-1-hidroxi-7-(metilsulfonil)-2,3-di-hidro-1H-inden-4-il)oxi)-5-fluorobenzonitrilo	Tratamento da doença de von Hippel-Lindau
Romanian	3-(((1S,2S,3R)-2,3-difluoro-1-hidroxi-7-(metilsulfonil)-2,3-dihidro-1H-inden-4-il)oxi)-5-fluorobenzonitril	Tratamentul sindromului von Hippel-Lindau
Slovak	3-(((1S,2S,3R)-2,3-difluór-1-hydroxy-7-(metylsulfonyl)-2,3-dihydro-1H-indén-4-yl)oxy)-5-fluórbenzonitril	Liečba Von Hippel-Lindau choroba
Slovenian	3-(((1S,2S,3R)-2,3-difluoro-1-hidroksi-7-(metilsulfonil)-2,3-dihidro-1H-inden-4-il)oksi)-5-fluorobenzonitril	Zdravljenje bolezni von Hippel-Lindau
Spanish	3-(((1S,2S,3R)-2,3-difluoro-1-hidroxi-7-(metilsulfonil)-2,3-dihidro-1H-inden-4-il)oxi)-5-fluorobenzonitrilo	Tratamiento del síndrome de von Hippel-Lindau
Swedish	3-((1S,2S,3R)-2,3-difluor-1-hydroxi-7-(metylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxi)-5-fluorbenzonitril	Behandling av von Hippel-Lindaus sjukdom
Norwegian	3-(((1S,2S,3R)-2,3-difluor-1-hydroksy-7-(metylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oksy)-5-fluorbenzonitril	Behandling av von Hippel-Lindaus sykdom
Icelandic	3-(((1S,2S,3R)-2,3-dífluór-1-hýdroxý-7-(metýlsulfonýl)-2,3-díhýdró-1H-inden-4-ýl)oxý)-5-flúoróbenzónítríl	Meðferð von Hippel-Lindau sjúkdóms