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Public summary of opinion on orphan designation

(R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride for the treatment of hereditary angioedema

On 27 June 2018, orphan designation (EU/3/18/2028) was granted by the European Commission to BioCryst UK Ltd, United Kingdom, for (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride (also known as BCX7353) for the treatment of hereditary angioedema.

What is hereditary angioedema?

Angioedema is a disease characterised by attacks of swelling beneath the skin that can occur anywhere in the body, such as in the face, limbs, gut and larynx (voice box), causing discomfort and pain.

Angioedema can be caused by low levels of 'C1 inhibitor', a protein in the blood involved in the control of the 'kallikrein-kinin' system. This system plays a role in causing the swelling and inflammation seen in angioedema. Patients with low levels of C1 inhibitor have excessive activity of this system, which leads to the symptoms of angioedema.

The C1 inhibitor deficiency can be 'hereditary' or 'acquired'. Hereditary angioedema is caused by abnormalities in the gene responsible for the production of C1 inhibitor. Acquired angioedema is caused by conditions that increase the breakdown of C1 inhibitor such as in some cancers and autoimmune diseases.

Hereditary angioedema is a long-term debilitating disease that may be life threatening because, when the swelling occurs in the larynx, it can obstruct the airways and impede breathing.

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

At the time of designation, hereditary angioedema affected approximately 0.5 in 10,000 people in the European Union (EU). This was equivalent to a total of around 26,000 people*, and is below the ceiling

*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 517,400,000 (Eurostat 2018).

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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?

At the time of designation, several medicines were authorised in the EU for the treatment of hereditary angioedema. These included medicines containing human C1 inhibitors (Cinryze and Berinert), conestat alfa (Ruconest) and icatibant (Firazyr).

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with hereditary angioedema. This is because early studies showed that it could help to prevent swelling attacks. In addition, the medicine is to be given by mouth, and thus is expected to be easier to use than currently available treatment given by injection.

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 activity of kallikrein proteins, which are part of the kallikrein-kinin system. As the system is overactive in patients with angioedema, resulting in the characteristic swelling and inflammation, blocking it is expected to reduce the number of angioedema attacks.

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 hereditary angioedema were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for hereditary angioedema. Orphan designation of the medicine had been granted in the United States for treatment of C1-inhibitor-dependent angioedema.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 24 May 2018 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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	(R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride	Treatment of hereditary angioedema
Bulgarian	(R)-1-(3-(аминометил) фенил)-N-(5-((3-цианофенил)(циклопропилметиламино)метил)-2-флуорофенил)-3-(трифлуорометил)-1H-пиразол-5-карбоксамид дихидрохлорид	Лечение на наследствен ангиоедем
Croatian	(R)-1-(3-(aminometil) fenil)-N-(5-((3-cijanofenil)(ciklopropilmetilamino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-karboksamid dihidroklorid	Liječenje hereditarnog angioedema
Czech	(R)-1-(3-(aminomethyl) fenyl)-N-(5-((3-cyanofenyl)(cyklopropylmethylamino)methyl)-2-fluorofenyl)-3-(trifluoromethyl)-1H-pyrazol-5-karboxamid dihydrochlorid	Léčba hereditárního angioedému.
Danish	(R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorphenyl)-3-(trifluormethyl)-1H-pyrazol-5-carboxamiddihydrochlorid	Behandling af hereditært angioødem
Dutch	(R)-1-(3-(aminomethyl) fenyl)-N-(5-((3-cyaanfenyl)(cyclopropylmethylamino)methyl)-2-fluorfenyl)-3-(trifluormethyl)-1H-pyrazool-5-carboxamidedihydrochloride	Behandeling van hereditair angioedema
Estonian	(R)-1-(3-(aminometüül) fenüül)-N-(5-((3-tsüanofenüül)(tsükloprpüülmetüülamino)metüül)-2-fluorofenüül)-3-(trifluorometüül)-1H-pürasool-5-karboksamiiddivesinikkloriid	Päriliku angioödeemi ravi
Finnish	(R)-1-(3-(aminometyyli) fenyyli)-N-(5-((3-syanofenyyli)(syklopropyylilmetyyliamino)metyyli)-2-fluorofenyyli)-3-(trifluorometyyli)-1H-pyratsoli-5-karboksamididihydrokloridi	Perinnöllisen angioödeeman hoito
French	(R)-1-(3-(aminométhyl) phényl)-N-(5-((3-cyanophényl)(cyclopropylméthylamino)méthyl)-2-fluorophényl)-3-(trifluorométhyl)-1H-pyrazole-5-carboxamide dichlorhydrate	Traitement de l'angioedème héréditaire

[1] At the time of designation

Language	Active ingredient	Indication
German	(R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorphenyl)-3-(trifluormethyl)-1H-pyrazol-5-carboxamiddihydrochlorid	Behandlung des hereditären Angioödems
Greek	(R)-1-(3-(αμινομεθυλο) φαινυλο)-N-(5-((3-κυανοφαινυλο)(κυκλοπροπυλομεθυλαμινο)μεθυλο)-2-φθοροφαινυλο)-3-(τριφθορομεθυλο)-1H-πυραζολο-5-διυδροχλωρικό καρβοξαμίδιο.	Θεραπεία του συγγενούς αγγειοοιδήματος
Hungarian	(R)-1-(3-(aminometil)-fenil)-N-(5-((3-cianofenil)(ciklopropil-metil-amin)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-karboxamid-dihidroklorid	Örökletes angioedema kezelése
Italian	(R)-1-(3-(amminometil) fenil)-N-(5-((3-cianofenil)(ciclopropilmetilammino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazolo-5-carbossammide dicloridrato	Trattamento dell'angioedema ereditario
Latvian	(R)-1-(3-(aminometil) fenil)-N-(5-((3-ciānfenil)(ciklopropilmetilamino)metil)-2-fluorfenil)-3-(trifluormetil)-1H-pirazol-5-karboksamīda dihidrohlorīds	Iedzimtas angioedēmas ārstēšana
Lithuanian	(R)-1-(3-(aminometil) fenil)-N-(5-((3-cianofenil)(ciklopropilmetilamino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-karboksamido dihidrochloridas	Paveldimos angioedemos gydymas
Maltese	(R)-1-(3-(amminometil) fenil)-N-(5-((3-ċjanofenil)(ċiklopropilmetilammino)metil)-2-fluworofenil)-3-(trifluworometil)-1H-pirażol-5-karboksamid diidroklorid	Kura ta' anġoedema ereditarja
Polish	Dichlorowodorek (R)-1-(3-(aminometylo) fenylo)-N-(5-((3-cyjanofenylo)(cyklopropylometyloamino)metylo)-2-fluorofenylo)-3-(trifluorometylo)-1H-pyrazolo-5-karboksyamidu	Leczenie dziedzicznego obrzęku naczynioruchowego
Portuguese	(R)-1-(3-(aminometil) fenil)-N-(5-((3-cianofenil)(ciclopropilmetilamino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-dicloridrato de carboxamida	Tratamento do angioedema hereditário
Romanian	Diclorhidrat de (R)-1-(3-(aminometil) fenil)-N-(5-((3-cianofenil)(ciclopropilmetilamino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-carboxamidă	Tratamentul angioedemului ereditar
Slovak	(R)-1-(3-(aminometyl) fenyl)-N-(5-((3-kyanofenyl)(cyklopropylmetylamino)metyl)-2-fluorofenyl)-3-(trifluorometyl)-1H-pyrazol-5-karboxamid dihydrochlorid	Liečba hereditárneho angioedému
Slovenian	(R)-1-(3-(aminometil) fenil)-N-(5-((3-cianofenil)(ciklopropilmetilamino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-karboksamid dihidroklorid	Zdravljenje hereditarnega angioedema

Language	Active ingredient	Indication
Spanish	(R)-1-(3-(aminometil) fenil)-N-(5-((3-cianofenil)(ciclopropilmetilamino)metil)-2-fluorofenil)-3-(trifluorometil)-1H-pirazol-5-carboxamida dihidrocloruro	Tratamiento del angioedema hereditario
Swedish	(R)-1-(3-(aminometyl) fenyl)-N-(5-((3-cyanofenyl)(cyklopropylmetylamino)metyl)-2-fluorofenyl)-3-(trifluorometyl)-1H-pyrazol-5-karboxamid-dihydroklorid	Behandling av hereditärt angioödem
Norwegian	(R)-1-(3-(aminometyl) fenyl)-N-(5-((3-cyanofenyl)(syklopropylmetylamin)metyl)-2-fluorfenyl)-3-(trifluormetyl)-1H-pyrazol-5-karboksamid dihydroklorid	Behandling av heriditært angioødem
Icelandic	(R)-1-(3-(amínómetýl) fenýl)-N-(5-((3-cýanófenýl)(cýklóprópýlmetýlamínó)metýl)-2-flúorfenýl)-3-(tríflúormetýl)-1H-pýrasól-5-karboxamíð díhýdróklóríð	Meðferð við arfgengum æðabjúg