5 February 2015
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Committee for Orphan Medicinal Products

# Public summary of opinion on orphan designation

Recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class for the treatment of cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA))

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| Rev.1: information about Marketing Authorisation | 17 November 2009 |
| Rev.2: withdrawal from the Community Register | 23 March 2011 |
| Rev.3: sponsor's change of address | 5 February 2015 |
| Disclaimer<br>Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication. | |

***Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in December 2010 on request of the Sponsor.***

On 20 March 2007, orphan designation EU/3/07/439 was granted by the European Commission to Novartis Europharm Limited, United Kingdom, for recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class for the treatment of cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA).

## What are cryopirin-associated periodic syndromes?

Cryopirin associated syndromes is a group of syndromes that all share the presence of alterations in the same gene and are characterized by a number of similar symptoms. The fact that the syndromes have alterations in the gene that contains the genetic information of a protein called cryopirin indicates

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that the expression of the alteration, even if slightly different, shares a common pathway. The syndromes are characterised by the presence of recurrent episodes of urticarial rash, fever and joint pain (arthralgia). The group includes Familial Cold Urticaria syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA). Cryopirin associated syndromes are chronically debilitating due to the recurrent episodes of the disease (fever, urticaria, arthralgia) and the development of long-term complications.

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

At the time of designation, cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)) affected approximately 0.05 in 10,000 people in the European Union (EU). This was equivalent to a total of around 2,500 people[*], and is below the threshold 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?

No satisfactory methods of treatment existed that were authorised at the time of application.

Several products with anti-inflammatory activity and others to control symptoms are not authorised for the indication but were used to treat the symptoms.

## How is this medicine expected to work?

Interleukin 1 (IL-1) has been identified as one of the substances responsible for rise in body temperature and systemic inflammation. A subtype of interleukin 1 (IL1-beta) is spontaneously secreted by some blood cells (monocytes) in patients with MWS and FACS. The activity of this type of interleukin seems to be regulated by cryopirin, which is the protein that seems altered in this condition. Therefore the inhibition of IL1-beta has been proposed for treatment of the condition.

Antibodies are proteins in the body that target and bind specific structures that can be either circulating in the blood stream or on the surface of cells. The product is an antibody able to bind to IL-1 and to block its activity in the body.

## What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, clinical trials in patients with systemic-onset juvenile idiopathic arthritis were initiated.

Recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class was not authorised anywhere worldwide for cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)) or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

[*]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 27), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 500,300,000 (Eurostat 2007).

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 7 February 2007 recommending the granting of this designation.

Update: Recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class (Ilaris) has been authorised in the EU since 23 October 2009 for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg, including:

- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

More information on Ilaris can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

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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:

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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 languages[1], Norwegian and Icelandic

| Language | Active Ingredient | Indication |
|---|---|---|
| English | Recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class | Treatment of cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA) |
| Bulgarian | Рекомбинантно човешко моноклонално антитяло от клас lgG1/K срещу човешки IL-1бета | Лечение на периодични синдроми,свързани с криопирин (синдром на фамилна студова уртикария (FCAS), синдром на Muckle-Wells (MWS) и мултисистемно възпалително заболяване с начало в неонаталния период (NOMID), известно също като хроничен инфантилен неврологично-кожно-ставен синдром (CINCA) |
| Czech | Rekombinantní lidská monoklonální protilátka třídy IgG1/K proti humánnímu IL-1 beta | Léčba kryopirin- asociovaného syndromu ( Familiárního chladového autozánětlivého syndromu, FCAS) Muckle-Wellsova syndromu (MWS), , multisystémového zánětlivého onemocnění se začátkem v novorozeneckém věku (NOMID) / chronického infantilního neurologického kožního a kloubního syndromu (CINCA) |
| Danish | Recombinant humant monoklonalt antistof mod human IL-1beta af IgG1/K klasse | Behandling af kryopyrin-associerede periodiske syndromer (familiært kulde-urticaria syndrom (FCUS), Muckle-Wells syndrom (MWS), og systemisk inflammatorisk sygdom med neonatal debut (NOMID)også kendt som kronisk infantil neurologisk hud- og ledsyndrom (CINCA) |
| Dutch | Recombinant humaan monoclonaal antilichaam tegen humaan IL-1 beta van de klasse IgG1/K | Behandeling van cryopirine geassocieerde periodieke syndromen (familiaal koude-geïnduceerd auto-inflammatoir syndroom [FCAS],Muckle-Wells syndroom [MWS], en neonatale multisystemische inflammatoire aandoening [NOMID],ook omschreven als chronisch infantiel neurologisch cutaan en articulair [CINCA] syndroom). |
| Estonian | Inimese IgG1/K klassi IL-1 beeta vastane rekombinantne inimese monoklonaalne antikeha | Krüopiriiniga seotud perioodiliste sündroomide (perekondliku külmast tingitud urtikaaria sündroomi (FCUS), Muckle-Wells sündroomi (MWS), ja neonataalse algusega multisüsteemse põletikulise haiguse (NOMID), tuntud ka kui kroonilise infantiilse neuroloogis-kutaanse-artikulaarse sündroomi (CINCA)) raviks |

[1] At the time of designation

| Language | Active Ingredient | Indication |
|---|---|---|
| Finnish | DNA-yhdistelmätekniikalla tuotettu humaani monoklonaalinen IgG1/K luokan IL1-beeta vasta-aine | Kryopiriiniin liittyvien periodisten oireyhtymien hoito (familiaalinen kylmäurtikaria (FCUS), Muckle-Wellsin oireyhtymä (MWS), imeväisiässä alkava multisysteeminen inflammatorinen tauti (NOMID), joka tunnetaan myös nimellä imeväisiän krooninen neurologinen kutaaninen artikulaarinen oireyhtymä (CINCA) |
| French | Anticorps monoclonal recombinant humain anti-IL1 bêta de la classe des IgG1/K | Traitement des syndromes périodiaques associés à la cryopyrine (urticaire familial au froid (FCAS), syndrome de Muckle-Wells (MWS), , maladie systémique inflammatoire à début néo-natal (NOMID) aussi appelé syndrome chronique infantile neurologique cutané et articulaire (CINCA) |
| German | Rekombinanter humaner monoklonaler Antikörper gegen humanes IL-1 beta der IgG1/K Klasse | Behandlung von Cryopirin-assoziiertem Syndrom (familiäres autoinflammatorisches Kälte-Syndroms (FACS), Muckle-Wells-Syndroms (MWS) und der multisystemischen entzündlichen Erkrankung mit Beginn im Neugeborenenalter (NOMID), auch bekannt als chronisch infantiles neuro-dermo-artikuläres Syndrom (CINCA) |
| Greek | Ανασυνδυασμένο ανθρώπινο μονοκλωνικό αντίσωμα τύπου IgG1/K κατά της ανθρώπειας IL-1 β | Θεραπεία των περιοδικών συνδρόμων που συσχετίζονται με την κρυοπυρίνη (του οικογενούς συνδρόμου κνησμού μετά από έκθεση στο ψύχος (FCUS), του συνδρόμου Muckle-Wells (MWS), και της πολυσυστηματικής νόσου νεογνικής έναρξης (NOMID) επίσης γνωστή ως χρόνιο βρεφικό φλεγμονώδες νευρολογικό δερματικό αρθρικό σύνδρομο (CINCA) |
| Hungarian | Az IgG1/K osztályba tartozó humán IL 1béta elleni rekombináns humán monoklonális antitest | Cryopirin függő periodikus szindrómák (Familiáris hideg urticaria szindróma), Muckle-Wells szindróma (MWS), újszülöttkori multiszisztémás gyulladásos betegség, más néven krónikus gyermekkori neuro-dermo-artikuláris szindróma kezelése |
| Italian | Anticorpo monoclonale umano ricombinante della classe IgG1/K, anti Interleuchina-1beta | Trattamento delle sindromi periodiche associate a criopirinopatia (sindrome di Muckle-Wells (MWS), orticaria da freddo (FCAS), malattia infiammatoria multisistemica ad insorgenza neonatale (NOMID)/sindrome cronica infantile neurologica cutanea ed articolare (CINCA) |
| Latvian | Rekombinanta IgG1/K klases monoklonāla antiviela pret cilvēka IL-1 beta | Ar kriopirīnu saistītu periodisku sindromu Makla un Velsa sindroma (MWS-*Muckle-Wells Syndrome*), ģimenes aukstuma nātrenes sindroma (FCUS- *Familial Cold Urticaria Syndrome*) un jaundzimušo multisistēmiskās iekaisuma slimības (NOMID- *Neonatal Onset Multisystem Inlammatory Disease*) un hroniska zīdaiņu neiroloģiskā ādas un locītavu sindroma (CINCA- *Chronic Infantile Neurological Cutaneous Articular Syndrome)* ārstēšanai |

| Language | Active Ingredient | Indication |
|---|---|---|
| Lithuanian | Rekombinantinis žmogaus monokloninis antikūnis prieš žmogaus IL – 1 beta, IgG1/K klasės | Periodinių sindromų, asocijuotų kriopirino (Šeiminio šalčio urtikarijos sindromo – ŠŠUS/ angl. FCUS - Familial Cold Urticaria Syndrome; Muckle-Wells sindromo (MWS) ir Daugiasisteminės uždegiminės ligos naujagimystės pradžioje – DULNP/angl. NOMID - Neonatal Onset Multisystem Inflammatory Disease, taip pat žinomos kaip Lėtinio kūdikių neurologinio, odos ir sąnarių sindromo – LKNOSS/angl. CINCA -Chronic Infantile Neurological Cutaneous Articular Syndrome) gydymas |
| Maltese | Anti-korp monoklonali uman rikombinanti għall-IL-1beta uman tal-klassi IgG1/K | Kura tas-sindromi perjodiċi assoċjati mal-cryopyrin (sindrome ta' l-urtikarja tal-kesħa (FCAS), sindrome ta' Muckle-Wells (MWS), u l-marda ta' infjammazzjoni multisistemika li tibda mat-twelid (NOMID), magħrufa ukoll bħala sindrome kronika infantili newroloġika, tal-ġilda u artikulari (CINCA) |
| Polish | Ludzkie rekombinowane przeciwciało monoklonalne klasy IgG1/K przeciwko ludzkiej interleukinie 1 beta (IL-1beta) | Leczenie okresowego zespołu zależnego od kriopiryny (rodzinna zimna pokrzywka – ang. familial cold autoinflammatory syndrome – FCAS), zespołu Muckle-Wells'a (ang. Muckle-Wells Syndrome - MWS) i noworodkowej zapalnej choroby wieloukładowej (ang. neonatal-onset multisystem inflammatory disease – NOMID) znanej również jako przewlekły niemowlęcy zespół neurologiczno-skórno-stawowy (ang. chronic infantile neurological cutaneous and articular syndrome - CINCA) |
| Portuguese | Anticorpo monoclonal humano recombinante da classe IgG1/K para a IL-1beta humana | Tratamento dos síndromes periódicos associados à criopirina (Síndrome de urticária ao frio familiar [FCUS], Sindrome de Muckle-Wells [MWS], e Doença inflamatória multissistémica de início neonatal (NOMID), também conhecida por Síndrome neuro-cutâneo-articular crónico do lactente(CINCA) |
| Romanian | Anticorp monoclonal uman recombinant anti-interleukină-1beta umană din clasa IgG1/K | Tratamentul sindroamelor periodice asociate criopirinei (sindromul familial al urticariei la rece=FCUS, sindromul Muckle-Wells=MWS) şi a bolii inflamatorii multisistemice cu debut neonatal, cunoscută şi ca sindromul cronic infantil neurologic articular şi cutanat (CINCA). |
| Slovak | Rekombinantná humánna monoklonálna protilátka triedy IgG1/K proti humánnemu IL-1beta | Liečba periodického syndrómu spojeného s kryopirínom (syndróm familiárnej chladovej žihľavky (FCUS), Muckleovho-Wellsovho syndrómu (MWS) a multisystémovej zápalovej choroby s nástupom v novorodeneckom veku (NOMID)/chronického neurologického, kožného a kĺbového syndrómu detí (CINCA) |
| Slovenian | rekombinantno humano monoklonsko protitelo proti humanemu IL-1beta iz podrazreda IgG1/K | Zdravljenje s kriopirinom povezanih sindromov (sindrom familiarne urtikarije na mraz (FCUS), sindrom Muckle-Wells (MWS) in multisistemska vnetna bolezen novorojenčkov (NOMID) znana tudi kot kronični infantilni nevrološki kožni in sklepni sindrom (CINCA) |

| Language | Active Ingredient | Indication |
|---|---|---|
| Spanish | Anticuerpo monoclonal recombinante humano anti IL-1beta humana de la clase IgG1/K | Tratamiento del los síndrome periódicos asociados a la criopirina (síndrome de Muckle-Wells (MWS), síndrome autoinflamatorio familiar inducido por frío (FCAS), y enfermedad neonatal multisistémica inflamatoria (NOMID), también denominada síndrome articular y cutáneo neurológico infantil crónico (CINCA)) |
| Swedish | Human rekombinant monoklonal antikropp mot humant IL-1 beta i IgG1/K klassen | Behandling av cryopirin-förbindade periodiska syndrom (familjärt autoinflammatoriskt köldsyndrom (FCAS), Muckle-Wells syndrom (MWS), och systemisk inflammatorisk sjukdom med neonatal debut (NOMID)/kroniskt neurologiskt, hud och ledsyndrom hos barn (CINCA) ), |
| Norwegian | Rekombinant humant monoklonalt antistoff av type IgG1/K mot human IL-1beta | Behandling av cryopyrin-assosierte periodiske syndromer (familiært kuldeurticaria-syndrom (FCUS), Muckle-Wells syndrom (MWS), og neonatal multisystem inflammatorisk sykdom (NOMID)/kronisk infantilt nevrologisk hud- og leddsyndrom (CINCA) |
| Icelandic | Raðbrigða manna einstofna mótefni gegn manna IL-1 beta í IgG1/K flokkinum | Til meðferðar á crýópírín-tengdum lotubundnum heilkennum,Muckle-Wells heilkenni (MWS), og fjölkerfabólgusjúkdómi hjá nýburum (NOMID), einnig þekkt sem langvarandi taugarænu húð- og liðaheilkenni hjá ungbörnum (CINCA) |