

20 April 2015  
EMA/COMP/635488/2011 Rev.2  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid for the treatment of multiple myeloma

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| First publication                                                                                                                                                                                                                                                                                                       | 13 October 2011  |
| Rev.1: sponsor's name change                                                                                                                                                                                                                                                                                            | 20 November 2013 |
| Rev.2: transfer of sponsorship                                                                                                                                                                                                                                                                                          | 20 April 2015    |
| <b>Disclaimer</b><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. |                  |

On 27 September 2011, orphan designation (EU/3/11/899) was granted by the European Commission to Takeda Global Research and Development Centre (Europe) Ltd., United Kingdom, for 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid (also known as ixazomib citrate) for the treatment of multiple myeloma.

In November 2013, Takeda Global Research and Development Centre (Europe) Ltd changed name to Takeda Development Centre Europe Ltd.

The sponsorship was transferred to Takeda Pharma A/S, Denmark, in March 2015.

### What is multiple myeloma?

Multiple myeloma is a cancer of a type of white blood cell called plasma cells. Plasma cells are found in the bone marrow, the spongy tissue inside the large bones in the body. In multiple myeloma, the division of plasma cells becomes out of control, resulting in abnormal, immature plasma cells multiplying and filling up the bone marrow. This interferes with production of normal white blood cells, red blood cells and platelets (components that help the blood to clot), leading to complications such as anaemia (low red blood cell counts), bone pain and fractures, raised blood calcium levels and kidney disease.

Multiple myeloma is a debilitating and life-threatening disease that is associated with poor long-term survival.

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

At the time of designation, multiple myeloma affected approximately 2.4 in 10,000 people in the European Union (EU). This was equivalent to a total of around 122,000 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).

### **What treatments are available?**

At the time of designation, several medicines were authorised for multiple myeloma in the EU. The main treatment for multiple myeloma was chemotherapy (medicines to treat cancer) usually combined with steroids to reduce the activity of the immune system, the body's natural defences. Where chemotherapy did not work, some patients received an allogenic stem-cell transplant (a complex procedure where the patient receives stem cells from a matched donor to help restore the bone marrow). Radiotherapy (treatment with radiation) was used in treating pain and weakened bones. Interferon alfa, a protein normally produced by the body during viral infections, was sometimes used in combination with chemotherapy.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with multiple myeloma because it may improve the outcome of patients, particularly if used in combination with other treatments in patients whose cancer is otherwise not responsive to treatment or has come back. 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 proteasome inhibitor. It blocks the proteasome, which is an enzyme complex within the cells that breaks down proteins when they are no longer needed. When the proteins in the cancer cells are not broken down, including the proteins that control cell growth, the cancer cells are damaged and to eventually die. The medicine is expected to be taken by mouth.

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

The effects of this medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with this medicine in patients with multiple myeloma were ongoing.

At the time of submission, this medicine was not authorised anywhere in the EU for multiple myeloma. Orphan designation had been granted in the United States for the treatment of multiple myeloma.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 8 July 2011 recommending the granting of this designation.

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\*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 507,700,000 (Eurostat 2011).

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:

Takeda Pharma A/S  
Dybendal Alle 10  
2630 Taastrup  
Denmark  
Tel. +45 4677 1111  
Fax +45 4675 6640  
<http://www.takeda.dk/kontakt/>

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   | 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl} diacetic acid              | Treatment of multiple myeloma    |
| Bulgarian | 2,2'-{2-[(1R)-1-({[(2,5-дихлоробензоил)амино]ацетил}амино)-3-метилбутил]-5-оксо-1,3,2-диоксaborолан-4,4-дил}диоцетна киселина             | Лечение на мултиплен миелом      |
| Croatian  | 2,2'-{2-[(1R)-1-({[(2,5-diklorobenzoil)amino]acetil}amino)-3-metilbutil]-5-okso-1,3,2-dioksaborolan-4,4-diil} diacetatna kiselina         | Liječenje multiplog mijeloma     |
| Czech     | 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolan-4,4-diyl} dioctová kyselina           | Léčba mnohočetného myelomu       |
| Danish    | 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolan-4,4-diyl} dieddikesyre                | Behandling af multipelt myelom   |
| Dutch     | 2,2'-{2-[(1R)-1-({[(2,5-dichloorbenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolan-4,4-diyl} diacetisch zuur             | Behandeling van multipel myeloom |
| Estonian  | 2,2'-{2-[(1R)-1-({[(2,5-diklorobensüül)amino]atsetüül}amino)-3-metüülbutüül]-5-okso-1,3,2-dioksaborolaan-4,4-diüül} atsetoäädikhape       | Multiibelse müeloomi ravi        |
| Finnish   | 2,2'-{2-[(1R)-1-({[(2,5-diklooribentsoyyli)amino]asetyyli}amino)-3-metyylibutyyli]-5-okso-1,3,2-dioksaborolaani-4,4-diyyli} dietikkahappo | Multippeli myelooman hoito       |
| French    | 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acétyl}amino)-3-méthylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl} diacétique                 | Traitement du myélome multiple   |
| German    | 2,2'-{2-[(1R)-1-({[(2,5-Dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolan-4,4-diyl} Acetessigsäure              | Behandlung des multiplen Myeloms |

<sup>1</sup> At the time of transfer of sponsorship

| Language   | Active ingredient                                                                                                                 | Indication                             |
|------------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Greek      | 2,2'-{2-[(1R)-1-({[(2,5-δichλωροβενζουyl)αμινο]ακετυl}αμινο)-3-μεθυλβοϋτυl]-5-οξo-1,3,2,-διοξαβορολανη-4,4-διυl} ακετοξικό οξύ    | Θεραπευτική αγωγή πολλαπλού μυελώματος |
| Hungarian  | 2,2'-{2-[(1R)-1-({[(2,5-diklórbenzoil)amino]acetil}amino)-3-metilbutil]-5-oxo-1,3,2-dioxaborolán-4,4-diil} diacetát               | Myeloma multiplex kezelése             |
| Italian    | 2,2'-{2-[(1R)-1-({[(2,5-diclorobenzoil)amino]acetil}amino)-3-metilbutil]-5-oxo-1,3,2-dioxaborolano-4,4-diyl} diacetato            | Trattamento del mieloma multiplo       |
| Latvian    | 2,2'-{2-[(1R)-1-({[(2,5-dihlorbenzoil)amino]acetil}amino)-3-metilbutil]-5-okso-1,3,2-dioksaborolān-4,4-diil} dietikskābe          | Multiplās mielomas ārstēšana           |
| Lithuanian | 2,2'-{2-[(1R)-1-({[(2,5-dichlorbenzoil)amino]acetil}amino)-3-metilbutil]-5-okso-1,3,2-dioksaborolan-4,4-diil} diacto rūgštis      | Dauginės mielomos gydymas              |
| Maltese    | 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl} diacetic acid      | Kura tal-mjeloma multipla              |
| Polish     | Kwas 2,2'-{2-[(1R)-1-({[(2,5-dichlorobenzoilo)amino]acetylo}amino)-3-metylobutylo]-5-okso-1,3,2-dioksaborolano-4,4-diyl} dioctowy | Leczenie szpiczaka mnogiego            |
| Portuguese | 2,2'-{2-[(1R)-1-({[(2,5-diclorobenzoil)amino]acetil}amino)-3-metilbutil]-5-oxo-1,3,2-dioxaborolano-4,4-diil} diacético            | Tratamento do mieloma múltiplo         |
| Romanian   | Acid 2,2'-{2-[(1R)-1-({[(2,5-diclorobenzoil)amino]acetil}amino)-3-metil-butil]-5-oxo-1,3,2-dioxaborolan-4,4-diil} diacetic        | Tratamentul mielomului multiplu        |
| Slovak     | kyselina 2,2'-{2-[(1R)-1-({[(2,5-dichlórbenzoyl)amino]acetyl}amino)-3-metylbutyl]-5-oxo-1,3,2-dioxaborolán-4,4-diyl} dioctová     | Liečba mnohopočetného myelómu          |
| Slovenian  | 2,2'-{2-[(1R)-1-({[(2,5-diklorobenzoil)amino]acetil}amino)-3-metilbutil]-5-okso-1,3,2-dioksaborolan-4,4-diil} diacetatna kislina  | Zdravljenje multiplega mieloma         |
| Spanish    | Ácido 2,2'-{2-[(1R)-1-({[(2,5-diclorobenzoil)amino]acetil}amino)-3-metilbutil]-5-oxo-1,3,2-dioxaborolano-4,4-diil} diacético      | Tratamiento del mieloma múltiple       |
| Swedish    | 2,2'-{2-[(1R)-1-({[(2,5-diklorobensoyl)amino]acetyl}amino)-3-metylbutyl]-5-oxo-1,3,2-dioxaborolan-4,4-diyl} diättiksyra           | Behandling av multipelt myelom         |
| Norwegian  | 2,2'-{2-[(1R)-1-({[(2,5-diklorobenzoyl)amino]acetyl}amino)-3-metylbutyl]-5-okso-1,3,2-dioksaborolan-4,4-diyl} dieddiksyre         | Behandling av myelomatose              |

| Language  | Active ingredient                                                                                                        | Indication                |
|-----------|--------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Icelandic | 2,2'-{2-[(1R)-1-({[(2,5-díklórbensóyl)amínó]asetýl}amínó)-3-metýlbútýl]-5-oxó-1,3,2-díoxabórólan-4,4-díyl}asetóedikssýra | Meðferð við mergfrumuæxli |