EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 January 2023
EMADOC-628903358-34665
European Medicines Agency

Statement on the amended policy on orphan designations for inherited retinal dystrophies

The Committee on Orphan Medicinal Products (COMP) has adopted a statement explaining its amended policy on orphan designations (OD) for inherited retinal dystrophies (IRD), the scientific and regulatory rationale for this change, and potential next steps for developers of orphan medicinal products.

Amended policy on orphan designations for inherited retinal dystrophies

Based on a thorough review, supported by a consultation of IRD clinical experts and patients, the COMP has adopted a new approach for designating conditions in IRDs. The COMP has decided that three options will be available for orphan conditions in an IRD OD application.

The three options are:

- For therapies that are relatively broadly applicable in IRDs, terms (e.g. *Rod-dominant phenotype)* can be selected from table 1 for orphan designated conditions. If a particular broad therapy could target more than one group, multiple orphan designations may be needed.
- For targeted gene therapies, the OD condition can be constructed from the term "inherited retinal dystrophy due to dysfunction in the target-gene.
- Finally, for some IRDs which may not fit the table 1 scheme, an occasional singular orphan designation outside the table 1 structure may still be necessary for non-gene therapy product(s).

Table 1 Grouping for inherited retinal diseases for the purpose of orphan designation

1. Non-syndromic IRD
    - *1.1. Cone-dominant phenotype**
    - *1.2. Rod-dominant phenotype*
    - *1.3. Macular dystrophy*
2. Syndromic IRD
    - *2.1. Cone-dominant phenotype*
    - *2.2. Rod-dominant phenotype*
    - *2.3. Macular dystrophy*
3. Inherited choroidal dystrophies
4. Hereditary vitreoretinopathies

* Phenotypes include inherited pathological dysfunction as well as inherited progressive degenerations

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Scientific and regulatory rationale

Inherited retinal dystrophies are a group of diseases affecting retinal structure and function. The classical names of IRDs (e.g. retinitis pigmentosa, Leber congenital amaurosis) were developed when the underlying genetics were not known or not well understood, and were based on clinical appearance, and other signs and symptoms. The genetics of IRDs are very complex.[1,2,3,4,5,6,7,8] It is now understood that one abnormal gene can have different clinical appearances (phenotypes) e.g. abnormalities in the *RDH12* gene has been associated with early-onset severe retinal dystrophy/Leber congenital amaurosis (EOSRD/LCA), (mild) retinitis pigmentosa, cone-rod dystrophy, and macular dystrophy. It is also understood that one phenotype (e.g. autosomal recessive retinitis pigmentosa) can be associated with variants in more than 60 different genes such as the *ABCA4* gene, *AGBL5* gene, *AHR* gene and others.

Upon request by sponsors, the COMP has the mandate to consider the submitted application and designate an orphan condition if all criteria are satisfied. *The Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another*, and *Commission notice 2016/C 424/03* provides information on what constitutes a *valid condition,* and what may be an acceptable subset of a disease for the purpose of the orphan designation.

Previously, COMP has used classical IRD terms as OD conditions. Given the complexity of IRDs, defining the OD condition in IRD is not straight forward. In addition, using classically derived IRD names for the orphan condition may mean that some otherwise treatable patients may be out of scope of an approved treatment if these patients show different signs and symptoms to the classical group. According to scientific literature, the identification of the genetic cause of the disease represents a hallmark for the patients IRD.[9,10,11] With the approval a targeted gene-therapy, it is also timely to consider the OD policy in the light of such a licensed indication.

Therefore, the COMP undertook a review to ascertain the *state of the art* in IRDs to assess what would be the best set of terms for orphan designation in this therapeutic setting. The review included a literature review, overview of 64 active OD in IRDs in the EU including the nature of the product, possible alternative grouping systems of IRDs [12,13,14,15,1], and a consultation of IRD clinical experts and patients. This consultation included perspectives from patients and clinicians on several aspects such as prevalence, [16,9,17] on current clinical practice, the most up to date sources of information, and optimal clinical groupings. Finally, COMP considered of the pros and cons of different possible approaches to setting the OD for IRDs.

Based on these in-depth considerations, supported by the outcome of the consultation, the COMP has adopted a new approach for designating conditions in IRDS. The COMP has decided that three options as identified above will be available for orphan designated condition in an IRD OD application.

Impact on sponsors

Sponsors with existing ODs in IRD may consider amending their OD before filing a marketing authorisation application (MAA) or protocol assistance in the event that the existing designation would not cover the intended target patient population, and hence a potential therapeutic indication in the case of MAA.

For new OD submissions, sponsors should specify the orphan condition applied for and fully justify the chosen approach in line with the recommendations in this document and the orphan legislation and guidance as these will be considered by the COMP when deciding on the OD application.

Information sources

Information on genetics of IRDs:

https://web.sph.uth.edu/RetNet/disease.htm

https://www.omim.org/

Information on orphan designations in the EU:

- Active orphan designations in the EU: the Community Registry of Orphan medicinal Products

  https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a

- Guidance

  Orphan designation: Overview | European Medicines Agency (europa.eu)

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