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Rare diseases, orphan medicines

Getting the facts straight

EMA is eager for European citizens with rare diseases to have access to specific and effective medicines. The European Union's orphan legislation has been designed to help overcome the extra hurdles these medicines face to get on the market.

Broadly speaking, the orphan legislation foresees giving orphan designation for substances that could be used for treating, preventing or diagnosing a rare and serious condition. Orphan designation can help the medicine's developer advance the medicine to the stage where it can be authorised to be put on the market. Formal approval (marketing authorisation) is needed before a medicine can legally be marketed.

Misunderstandings often arise about orphan medicines and how orphan designation is given. The following questions and answers address some common ones.

1. Can I be treated with a medicine for my rare disease as soon as it is given orphan designation?

No. Orphan designation does not itself permit the use of a medicine.

Orphan designation simply signals that the medicine looks promising. There might be little or no proof that it works in patients. Only when the medicine is given its marketing authorisation can you be sure that the medicine has EMA's confidence that it works and is acceptably safe.

Generally, the application for orphan designation comes quite early in the medicine's development – the medicine is considered for marketing authorisation only when enough evidence of its effects has built up.

Exceptionally, a doctor might consider using the medicine before it has its marketing authorisation, for example through a compassionate use program. When contemplating use of a medicine that does not have marketing authorisation, the patient and the doctor need to be fully convinced that there is no other suitable treatment option (including leaving the condition untreated).

In some cases, it might be possible to enrol on a clinical trial set up to test the medicine's effects on patients. Clinical studies, including ongoing ones, are listed in: EU Clinical Trials Register and ClinicalTrials.gov.

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2. Does orphan designation speed up development time and marketing authorisation?

Not necessarily. Giving orphan designation helps ensure that medicines for rare diseases are developed at all, and not necessarily to speed up such development. We have no evidence that having orphan designation leads to shorter development time or quicker evaluation for marketing authorisation.

3. Does the same committee consider orphan designation and marketing authorisation?

Two separate EMA committees are involved with orphan designation and marketing authorisation.

The Committee for Orphan Medicinal Products (COMP) evaluates applications for orphan designation and it also considers if medicines previously granted orphan designation can continue to be classified as orphan medicines at the time of marketing authorisation. Applications for marketing authorisation go before the Committee for Medicinal Products for Human Use (CHMP).

Both committees' recommendations are sent to the European Commission which makes the final decision – on granting orphan designation on the one hand or marketing authorisation on the other. EMA publishes its recommendations on its website either under 'rare disease (orphan) designations' or under 'European public assessment reports'.

4. Does orphan designation granted outside the EU count in the EU?

No, because orphan designations are granted by different authorities and the rules for designation vary. So, a medicine may be classified an orphan in the EU but not necessarily so elsewhere, and the other way round. For example the definition of what is considered rare ('prevalence threshold') is different in the United States (US) from that used in the EU. And in the EU the developer might have to show that the medicine brings significant benefit but this does not apply in the US.

5. What is 'significant benefit'?

Significant benefit means that a medicine produces a clinically relevant advantage or makes a major contribution to patients' care, compared with existing methods to treat the condition. Thus orphan designation is given to a product that will improve patients' current treatment, having considered what else is available (see also Q. 6).

6. How is the assessment for 'significant benefit' different from that for 'benefit–risk'?

When other treatments already exist for the condition, the application for orphan designation has to show that the candidate medicine brings significant benefit compared with those treatments. For example, an orphan medicine may be suitable for patients for whom current treatments do not work, or by adding it to current treatment it is likely to improve patients' outcome. A medicine can also be said to show significant benefit if it works as well as other treatments but is significantly easier or more convenient to use.

By contrast, for a benefit–risk assessment in a marketing authorisation, the application has to show that the candidate medicine's benefit (how well it works) outstrips its risks (its known and possible side effects). A medicine's benefit–risk assessment often involves comparison with other treatment but there is no obligation to show that the candidate medicine is more beneficial than all other methods for treating the condition.

7. For authorised medicines, why is the medical condition in the orphan designation not always the same as that in the marketing authorisation?

The medical condition specified in the orphan designation is often broader than the use ('indication') for which the medicine eventually gets marketing authorisation. This is because the marketing authorisation indication is based on the evidence that the company gives in its application. Generally, the authorised indication is based on the characteristics of patients in the clinical trials and might exclude certain groups like the very young or pregnant women, or it might include patients with only one variant of the condition. For example, a medicine originally designated orphan for cystic fibrosis might subsequently be authorised for use only in those aged over 12 years with a specific mutation (change) in the CFTR gene (reflecting studies showing positive outcome in this group), rather than for all patients with cystic fibrosis.

8. Who secures availability of an orphan medicine in the EU and sets prices?

National authorities in individual EU countries, together with the company, make arrangements for the local availability of all medicines (including orphan medicines) as well as their pricing. EMA is not involved in the supply and reimbursement of medicines.

EMA's principal remit is to ensure that authorised medicines work, they are acceptably safe and are of good quality. And in the case of orphan medicines, EMA assesses the application to ensure that the medicine benefits patients with rare diseases. EMA evaluations are based on a scientific assessment of all available evidence on medicines but do not consider their costs.

9. Despite EMA assessing significant benefit for an orphan medicine, why do national authorities sometimes reject use of the medicine?

EU countries make their own decisions on providing a medicine within the country's health service. In many cases, they use health technology assessment (HTA) to compare the medicine with other health technologies. National requirements and priorities can lead to differences in how a medicine's value is judged against the standard treatment in that country.

Moreover, national decisions may also consider value-for-money; medicines may be provided through the country's health service only if its cost in relation to its benefit meets set thresholds. EMA's assessment does not take costs into account.

10. Why is there a 10-year exclusivity period for orphan medicines once they are marketed?

Orphan designation offers incentives to encourage development of orphan medicines and their availability. Once an orphan medicine is authorised it qualifies for 10-year market exclusivity (see also Q. 11). This is because, with limited usage of the medicine in the orphan disease, it can take longer to recoup the medicine's research and development costs.

11. Does market exclusivity that results from orphan designation prevent marketing of other medicines?

Market exclusivity is an incentive offered by orphan designation. This arrangement, which operates once the medicine has received marketing authorisation, blocks similar competitor medicines from entering the market for 10 years. However, this market exclusivity does not necessarily block medicines which are used for the same rare disease but differ from the first medicine on the basis of

their molecular make up, the way they work and the way they are used. And even a similar medicine could be marketed in some circumstances, for example if it is made in such a way that it works better than the orphan product for treating the disease.

12. Will all diseases become orphan now that we have personalised medicine?

No. Orphan conditions are defined broadly to cover a range of disease variants (see Q. 7). Personalised medicines require the use of biomarkers to identify the specific variant of the disease that the patient suffers from. However, the use of biomarkers to identify a subset of patients for whom the medicine can be used is generally not accepted for orphan designation.

13. Why do so many products have orphan designation?

It is important to distinguish between the designation for development support and the later authorisation for marketing. The designation step early in development opens the gate to encourage development in rare diseases. However, a great many do not go on to gain marketing authorisation. So far, 66% of applicants successfully gained orphan designation for their medicines and have been able to take advantage of incentives to develop them further. Despite this, only 8% of medicines have actually reached the market as orphan medicines.

14. What information does EMA publish on orphan medicines?

Once a medicine receives orphan designation from the European Commission, we publish a summary of the COMP assessment in plain language. Once the medicine receives marketing authorisation, the CHMP assessment report of the marketing authorisation application is published together with the COMP scientific assessment of the review of the orphan designation. The COMP scientific assessment is published both when the COMP concludes that the orphan designation should be maintained and when it should be removed, as well as when the applicant withdraws the orphan designation at the time of the COMP review. Finally, the Agency publishes the meeting documents of the COMP (agenda and minutes).

15. Any more questions?

You can find out more on the EMA website, especially how orphan designation is given.

If you have any questions that we haven't answered, please get in touch by using the EMA's 'send a question' facility.