Norwegian Medical Products Agency

Single technology assessment of medicinal products for very small patient groups with extremely severe conditions

Supplement to Submission Guidelines for Single Technology Assessment of Medicinal Products

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Foreword

It is a requirement that all new medicinal products are subject to single technology assessment (STA) before any decision is made about public funding. This also applies to medicinal products aimed at *very small patient groups with extremely severe conditions*. A comprehensive submission guideline for STA of medicinal products details principles and methodological requirements for submission of documentation for technology assessments of medicinal products and is available on the Norwegian Medicines Agencys (NoMAs) website. The overall principles also apply to medicinal products for *very small patient groups with extremely severe conditions*.

As of 01.01.2018, arrangements of STA for medicinal products in very small patient groups with extremely severe conditions came into effect based on guidance from the Norwegian Regulations on Medicinal Products chapter 14 (dated 1.1.2018), the preparatory work for chapter 14 of the said Regulations, including the consultation paper [1] and the White Paper St. 34 (2015-2016) [2, 3], “Principles for priority setting in health care” known as the “Priority-setting White Paper”.

In the consultation paper for the Norwegian Regulations on Medicinal Products, the Ministry of Health and Care Services (“Helse- og omsorgsdepartementet”) briefly outlined the practical application of the arrangements. Parts of the consultation paper were based on cross-departmental evaluation. On behalf of the Ministry of Health and Care Services, NoMA led in 2016 a working group with representatives from the Norwegian Institute of Public Health, the Norwegian Directorate of Health and the four regional health authorities. The working group developed the concepts and the operationalisation of the principles for prioritisation and, in particular, the proposed arrangements for very small patient groups with extremely serious conditions, in accordance with the Priority-setting White Paper.

Table of contents

1. Introduction

The Norwegian Regulations on Medicinal Products (“legemiddelforskriften”) §14-5 second and third paragraph states:

> «Pre-approved reimbursement can only be granted if the use of resources is reasonable in relation to the benefit of the medicine, taking into account the severity of the condition. For extremely severe conditions, a higher level of resource use in relation to the benefit will be accepted than for less severe conditions.
>
> Medicinal products which do not satisfy the requirements of the second paragraph can, nonetheless, in particular cases be granted pre-approved reimbursement if the medicine is aimed at very small patient groups with extremely severe conditions where the expected benefit of the medicine is considerable. The use of resources must, however, be acceptable in relation to the benefit».

Interventions for public funding in the health services will be evaluated according to three prioritisation criteria namely benefit, resource and severity, and evaluated together and weighed against each other as outlined in the Priority-setting White Paper [2, 3]. A rare disease in itself is not a prioritisation criterion [2]. The Priority-setting White Paper emphasises that it is not the rarity of a condition itself, but rather the circumstances typically associated with conditions that are of relevance when making such assessment. The Priority-setting White Paper highlights two factors relevant for the assessment of medicinal products for very small patient groups with extremely severe conditions:

- *A lower evidence level can be accepted:* It may be relevant to set different requirements for documentation of benefit than for other interventions as the relevant patient group can in many cases be too small for conducting a randomised controlled trial to assess efficacy and safety.

- *A higher level of resource use can be accepted for specific interventions compared to other interventions:* The industry may have weaker incentive to develop medications when the patient group for absorbing development costs is small. The use of resources must, nonetheless, be acceptable in relation to the benefit.

Two assumptions must be fulfilled for a lower level of documentation and a higher level of resource use to be accepted. The Priority-setting White Paper states the following [3]:

> «First, a less stringent requirement for documentation of the benefit of the interventions means there must be greater focus on monitoring to document the benefit of the treatment. Methods and technologies funded under such a scheme must be required to implement procedures to further document efficacy and any associated risk, among other things. (…)
>
> Second, to retain its legitimacy, a scheme such as this must truly be limited to what is actually defined as a very small patient group with a very severe condition. If this group is defined too broadly, it will undermine the objectives of equitable and fair priority setting. This delimitation must be distinguished from the definition of rare diseases, which has been designated for other purposes.»

The two prioritisation criteria, benefit and resource, are calculated in the cost-effectiveness ratio and evaluated against the third prioritisation criterion, severity. For more severe conditions, a higher cost-effectiveness ratio can be accepted. Specific discretionary assessments can be considered in the overall evaluation of an intervention specifically related to evaluations of the quality or level of uncertainty in the evidence, as well as the overall budget implications.

2. Guiding criteria/principles

In the consultation paper for the Norwegian Regulations on Medicinal Products a set of guiding principles are described for defining which medicinal products are covered by this arrangement (the text is translated by NoMA, and hence not an official translated version):

> «In the Ministry's opinion, it is not useful to set absolute conditions for evaluating whether the requirements for "very small patient groups ", "extremely severe conditions " or "considerable expected benefit ", cf. the suggestion for § 14-5 third paragraph is fulfilled. There should, however, be guiding criteria for decision-making.»

NoMA must, in single technology assessments, consider whether the medicinal product qualifies for this scheme according to the guiding criteria very small patient group, extremely severe condition, and considerable expected benefit. In addition, the medicinal product must be evaluated against the three prioritisation criteria: benefit, resource use and severity. If the medicinal product qualifies for the scheme according to the guidance criteria, a lower level of documentation and a higher level of resource use may be considered acceptable, cf. the Priority-setting White Paper (Prioriteringsmeldingen) [2] and the Norwegian Regulations on Medicinal Products ("legemiddelforskriften") §14-5 third paragraph.

The three guiding criteria for deciding whether a medicinal product is intended for treating a very small patient group with an extremely severe condition are describes in the following sections, cf. consultation paper for the Norwegian Regulations on Medicinal Products [1].

All three of these indicative criteria should be fulfilled in order for a medicinal product to be considered under this part of the Norwegian Regulations on Medicinal Products (legemiddelforskriften § 14-5 third paragraph). The criteria are indicative in nature and must be assessed in accordance with an overall assessment in each specific case and might also be subject to re-evaluation on a later date to assess whether the criteria have been fulfilled.

2.1 Very small patient group

The patient alliance EURORDIS and the European Medicine Agency (EMA) define a rare disease as a condition with an incidence of fewer than five per 10 000 inhabitants. In Norway, a condition is considered rare if fewer than 1 in 10 000 are affected. This means less than 500 people have the condition in total in Norway [4]. In former circulars about the National Insurance act §5-14, the Norwegian Directorate of Health has applied this definition [5]. In 2004, NICE established the term *Ultra orphan drugs*. They suggested that this term applies to medicinal products for diseases which affect fewer than 1 in 50 000, i.e. around 100 patients in Norway [6]. Today, NICE uses the term *Highly specialised technology* about medicinal products for small patient groups [7].

Rarity is not a prioritisation criterion in the Norwegian health service [2]. This arrangement for very small patient groups with extremely severe conditions is not a scheme for medicinal products treating rare diagnoses, cf. the definitions above.

In the Priority-setting White Paper an acceptance of higher resource use per quality-adjusted life year for medicinal products with indications for very small patient groups with extremely severe conditions, is justified by weaker incentive for the pharmaceutical industry to develop medications when the patient group for absorbing development costs is small. In this context, it is therefore relevant to consider the number of patients, both nationally and globally, and therewith also the share of the global sales any potential Norwegian patients will represent.

Many medicinal products have multiple indications which can include treatment of rare diseases, in addition to more prevalent diseases affecting a higher number of patients. It is therefore relevant to

consider the total number of patients per medicinal product on a global basis and in Norway, rather than the number of new patients per year and per indication.

The following criteria apply for very small patient groups:

a) Fewer than approx. 1 patient per 100 000 inhabitants affected on a global basis per medicine (prevalence on a global basis)
b) Fewer than approx. 50 patients in Norway per medicine (steady state prevalence in Norway).

Criteria a) and b) must be viewed together when considering whether a medicinal product qualifies for this scheme.

There are several circumstances which should be considered when comparing the number of patients relevant for treatment in Norway with the number of relevant patients in other countries. Norway constitutes a small proportion of the global pharmaceutical market. Rare genetic conditions can have different prevalence in different countries, and low prevalence in Norway, does not necessarily reflect the global prevalence.

Global patient numbers can be presented either as a birth prevalence, yearly incidence or prevalence [8]. Because these data can be very uncertain, any evaluation of the number of patients on a global basis should also be assessed discretionally.

Very rare diseases can be difficult to diagnose. When a new intervention is available to treat a disease, increased awareness including subsequent diagnostics opens for more extensive and precise diagnoses. Diseases which appear very rare can therefore increase in prevalence once a treatment has been introduced and eventually stabilise (steady state prevalence). How long it takes for a steady state to be reached must be evaluated in each case. In budget calculations used in single technology assessments it is assumed for simplicity that the market, i.e., the use of the new intervention, is stabilised after five years.

2.2 Extremely severe condition

The severity of a condition is measured using the concept of absolute shortfall, i.e., how many quality-adjusted life years patients in the relevant group will lose on average by the absence of the medicinal product under evaluation, cf. Norwegian Regulations on Medicinal Products §14-3. See Submission *Guidelines for Single Technology Assessments* for a more detailed description of absolute shortfall.

The Priority-setting White Paper mentions children with congenital genetic diseases as an example of conditions where a higher use of resources can be justified using the argument of greater absolute shortfall.

For a condition to be considered extremely severe, an absolute shortfall should be equivalent to a minimum loss of around 30 quality-adjusted life years.

2.3 Considerable expected benefit

In addition to the criteria about the size of the patient group and the severity of the disease, there is an indicative criterion of considerable expected benefit from treatment [1]. Benefit is measured by how many quality-adjusted life years on average the intervention potentially can provide for patients in the relevant patient group compared with relevant current treatment practice.

The following indicative criterion applies to considerable expected benefit: The expected benefit of the treatment in question is considerable and leads to a gain of at least 2 quality-adjusted life years compared to standard treatment.

3. Documentation requirements

The Submission Guidelines for Single Technology Assessments also apply for submissions under the scheme for very small patient groups with extremely severe conditions. Even though the Norwegian Medicines Agency can accept a lower requirement for documentation in the evaluation, the submission should, to the greatest degree possible, adhere to the guidelines. Pre-meetings with the NoMA are highly recommended in advance of submission to clarify documentation requirements for such cases. It can also be expedient for companies applying for a marketing authorisation for medicinal products for small patient groups to request parallel EMA/EUnetHTA 21 Joint Scientific Consultation.

In accordance with the Priority-setting White Paper considerable uncertainty in the documentation or calculation methods will lead to lower prioritisation in decisions on new interventions. For medicinal products aimed at very small patient groups with extremely severe conditions, however, a lower requirement for documentation may be accepted.

The submitted documentation is required to be the best reasonably expected, given the very small patient group with extremely severe conditions. The association between outcome measures used in clinical studies and effects of future morbidity, or death, must be sufficiently substantiated. NoMA involves Norwegian clinical experts in these evaluations.

Even if a new intervention qualifies for consideration under this arrangement, the decision-maker can conclude that the medicinal product will not to be publicly funded if the documentation is inadequate.

4. Procedures and processes

The procedures for STA of medicinal products follow the established process for all new interventions, cf. Norwegian Regulations on Medicinal Products chapter 14 and Nye Metoder [10].

NoMA can, in exceptional cases, carry out STA of an intervention without submitted documentation/information from the Health Technology Developer, cf. Norwegian Regulations on Medicinal Products §14-4 fifth paragraph.

5. Monitoring

Methods and technologies funded under this scheme are required to implement procedures to further document efficacy, safety, and patient numbers relevant for treatment. This documentation may also, where relevant, form the basis for re-evaluation of the specific agreement after a given time period.

Monitoring can occur at two levels:

- Single patient level involves collection of relevant data on use of the medicinal product in clinical practice. This can, for example, be efficacy or safety data, or data on resource use. The regional health authorities are responsible for treatment and therefore collecting these data.

  In addition, it may be appropriate to develop relevant start and stop criteria for the treatment. Start criteria define which patients can receive treatment. This could be requirements on the patients` symptoms level, level of function, or results from diagnostic tests. Stop criteria ensure that treatment ceases if the patient does not respond sufficiently, or if the condition has changed making it no longer reasonable to continue treatment. Clinical experts and user representatives are involved in the development of start and stop criteria.

- Collection of group level data through new studies, follow-up studies and/or real-world data. The health technology developer must commit to share this information with NoMA.

6. Involvement of patient representatives and clinicians

When relevant NoMA approaches user representatives and clinical experts to obtain information relevant to complement the documentation submitted by the health technology developer.

References

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