Statens legemiddelverk

Arrangements for single technology assessment of pharmaceuticals for very small patient groups with extremely severe conditions

Valid from 01.01.2018

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Introduction

This memorandum describes the arrangements for single technology assessments of pharmaceuticals for very small patient groups with extremely severe conditions. The arrangements came into force on 01.01.2018. The arrangements are 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". The guidance is set out below. 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[1]. This memorandum gives more detail. For information about submitting documentation, see Guidelines for the submission of documentation for single technology assessment of pharmaceuticals[4, 5].

The Priority-setting White Paper
The fact that a disease is rare is not, in itself, a prioritisation criterion. There is, therefore, no grounds for prioritising the treatment of patients with rare diseases [2] . The Priority-setting White Paper emphasises that it is not the rarity of a condition itself, but rather certain factors that are typically associated with various conditions affecting only a small number of patients that are of relevance when making this assessment. The Priority-setting White Paper highlights two such situations relevant to the evaluation of pharmaceuticals for very small patient groups with extremely severe conditions:

- *A lower level of documentation can be accepted.*
  There may be situations linked to the treatment of small patient groups with severe conditions which mean it may be relevant to set different requirements for documentation of benefit than for other interventions. The patient group can often be too small for traditional controlled trials of effect to be carried out.
- *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.

There are two central preconditions which 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]:

[1] Parts of the consultation paper were based on cross-departmental evaluation.
On behalf of the Ministry of Health and Care Services, the Norwegian Medicines Agency, in the autumn 2016, led 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 concrete 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.

> « 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.»

Norwegian Regulations on Medicinal Products
The Norwegian Regulations on Medicinal Products §14-5 second and third paragraphs (NoMA translation):

> Reimbursement can only be pre-approved if the use of resource is in a reasonable proportion to the benefit of the pharmaceutical, taking into account the severity of the condition. In cases of great severity, a higher use of resource in relation to benefit will be accepted than in cases of lesser severity.
>
> A pharmaceutical which cannot satisfy the requirements of the second paragraph can, nonetheless, in particular circumstances, be pre-approved for reimbursement if it is aimed at very small patient groups with extremely severe conditions where the expected benefit of the medicine is large. The use of resource must, nonetheless, be acceptable in relation to the benefit.

Health technology assessments
It is a requirement that all new pharmaceuticals must be subject to a health technology assessment before a decision can be made to fund it publicly. This also applies to pharmaceuticals for *very small patient groups with extremely severe conditions*. The guidelines for documentation for single technology assessments [4, 5] also apply for submission of documentation for these pharmaceuticals. There are no specific guidelines for single technology assessments of pharmaceuticals for very small patient groups with extremely severe conditions.

Even though the Norwegian Medicines Agency can accept a lower requirement for documentation, the submission should, to the greatest degree possible, follow the recommendations in the guidelines for documentation for single technology assessments. We recommend pre-meetings with the Norwegian Medicines Agency before the preparation of documentation in order to clarify what sort of documentation is possible and appropriate in the individual case. It can also be expedient for companies applying for a marketing authorisation for pharmaceuticals for small patient groups to carry out an EMA-EUnetHTA Parallel Consultation.

The principles for prioritisation, which are described in the Priority-setting White Paper and which parliament has agreed in Recommendation 57 S (2016-2017), form the basis for the Norwegian Regulations on Medicinal Products chapter 14 [1]. The same principles will apply to the introduction of pharmaceuticals in the specialist health services, cf. consultation paper for the Norwegian Regulations on Medicinal Products[1].

Interventions in the health service will be evaluated according to the three prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion. The prioritisation criteria will be

evaluated together and weighed against each other. A cost/benefit ratio must be calculated which shows the use of resources in relation to the benefits. This is to be done in a health economic analysis, usually using a health economic model. The cost/benefit ratio will be evaluated against the severity of the relevant condition or disease. The more severe the condition is, the higher the cost/benefit ratio that can be accepted.

In a single technology assessment, specific discretionary assesments can be taken into account in the overall evaluation of the intervention. This is, in particular, linked to evaluations of the quality or level of uncertainty in the documentation, as well as the overall budget implications.

Norwegian Medicine Agency 01.01.2018.

Contents

1 Guideing criteria – which pharmaceuticals are covered by this arrangement?

In the Norwegian Regulations on Medicinal Products ("legemiddelforskriften") §14-5 second and third paragraphs, it 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 lesser severe condtions.
>
> A pharmaceutical which does not satisfy the requirements of the second section 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.»

Guiding principles to qualify for this arrangement
In the consultation paper for the Norwegian Regulations on Medicinal Products a set of guiding principles are described for defining which pharmaceuticals are covered by this arrangement (the text is translated by Norwegian Medicines Agency, 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 indicative criteria for decision-making.»

The Norwegian Medicines Agency must, in the health technology assessment, consider whether the pharmaceutical qualifies for this arrangement according to these indicative criteria, and must, in addition, evaluate the pharmaceutical against the three main prioritisation criteria: benefit, use of resources and severity. If the medicine qualifies for the arrangement according to the indicative criteria, then a lower level of documentation and a higher level of resource use than normal may be considered acceptable, cf. the Priority-setting White Paper (Prioriteringsmeldingen) [2] and the Norwegian Regulations on Medicinal Products ("legemiddelforskriften") §14-5 third paragraph. Tandvårds- och läkemedelsförmånsverket (TLV) in Sweden and the National Institute for Health and Care Excellence (NICE) in England have comparable criteria for evaluating and deciding on public financing of medicines for very small patient groups with severe conditions [6, 7].

The three guiding criteria for deciding whether a pharmaceutical is intended for treating a very small patient group with an extremely severe condition are as follows, cf. consultation paper for the Norwegian Regulations on Medicinal Products[1]:

1. Very small patient group:
   a) *Fewer than approx. 1 patient per 100 000 inhabitants on a global basis per pharmaceutical (prevalence on a global basis).*
   b) *Fewer than approx. 50 patients in Norway per pharmaceutical (steady state prevalence in Norway).*

2. Extremely severe condition: *Level of severity measured using absolute shortfall corresponding to at least 30 lost good life years*[2].
3. Considerable expected benefit from the pharmaceutical: *Expected benefit from the specific treatment is considerable and a minimum of two gained good life years compared to standard treatment*[2].

All three of these indicative criteria should be fulfilled in order for a medicine 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 every specific case. In some cases, it may, at a later date, be relevant to re-evaluate how far the indicative criteria have been fulfilled, cf. Chapter 4. Pharmaceuticals which do not qualify for this arrangement will be subject to a single technology assessment as for other pharmaceuticals which fall outside this arrangement. In such cases, the Norwegian Medicines Agency will not recommend acceptance of a higher level of resource use in relation to benefit than what is normally accepted.

1.1 Very small patient group

The patient alliance EURORDIS and the EU define a rare disease as a condition with an incidence of fewer than five per 10 000 inhabitants. In Norway, a diagnosis is considered rare if fewer than 1 in 10 000 people have the diagnosis. This means that there are fewer than around 500 people with the diagnosis in the whole country [8]. In former circulars about the National Insurance act §5-14, the Norwegian Directorate of Health has followed this definition [9]. In 2004, NICE established the term *Ultra orphan drugs*. They suggested that this term applies to pharmaceuticals for diseases which affect fewer than 1 person in 50 000, ie. around 100 patients in Norway[10]. Today NICE uses the term *Highly specialised technology* about pharmaceuticals for small patient groups [11].

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* an arrangement for pharmaceuticals for treating rare diagnoses, cf. the definitions above.

In the Priority-setting White Paper an acceptance of higher use of resources per good life year for *pharmaceuticals* 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 potential* Norwegian patients will represent. Pharmaceuticals for small patient groups often have studies with fewer patients. This will, in most cases, imply lower development costs.

It may be cheaper for a pharmaceutical company to get a new therapeutic indication approved, rather than to develop a new active substance. Many pharmaceuticals do not have disease-specific active mechanisms, but are, for example, directed towards specific mutations or immune responses. Such pharmaceuticals can, in many cases, have an effect in several different diagnoses. It is therefore most relevant to consider the total number of patients *per pharmaceutical* on a global basis and in Norway, rather than the number of new patients per year and per indication.

[2] To evaluate the number of good life years, the Norwegian Medicines Agency uses quality adjusted life years (QALYs), cf Priority-setting White Paper.

The following indicative criteria apply for *very small patient groups*:

a) *Fewer than approx. 1 patient per 100 000 inhabitants 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).*

The criteria a) and b) must be viewed together when considering whether a pharmaceutical qualifies for this arrangement.

There are several conditions which should be taken into account when comparing the number of patients relevant to treatment in Norway with the number of relevant patients in other countries. Norway will form a small proportion of the global market. Even if there are few patients in Norway, there may not be few patients worldwide. Rare genetic conditions can have different prevalence in different countries.

The United Kingdom and Sweden also have requirements for the size of the patient group in order to be able to accept a higher use of resource than for other pharmaceuticals [6, 7]. For a new medicine to be accepted into the programme for Highly specialised technologies in the United Kingdom, an assessment is used which corresponds to the indicative criteria above [12].

Data for the numbers of patients on a global basis will often be very uncertain. Different sources can give different estimates of the total number of patients on a global basis, and the number can be presented either as a birth prevalence, an incidence or a prevalence [13]. 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 treatment arises for a disease, this will often lead to increased knowledge about the diagnosis and in some cases it will establish new diagnostic tests. This can allow for clinicians', to a greater degree, being able to determine a diagnosis in patients where this has previously been unclear. Diseases which appear very rare today can, therefore, become less rare once a treatment has been introduced. It can therefore be difficult to estimate how many new patients there will be each year. The criterion must be seen in the light of the number of patients after the number of new cases each year has stabilised. This is called *steady state prevalence.* How long it will take for a steady state to be reached must be evaluated in each case. In budget calculations which are used in single technology assessments it is assumed for simplicity that the market, i.e., the use of the new pharmaceutical, will have stabilised after five years.

1.2 Extremely severe condition

This arrangement will apply for extremely severe conditions. The severity must be measured using the concept of absolute shortfall, i.e., how many good life years patients in the relevant group will lose on average by the absence of the pharmaceutical being evaluated, cf Norwegian Regulations on Medicinal Products §14-3. See *Guidelines for the documentation required for single technology assessments* [4, 5] 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 shortfall.

The Norwegian Medicines Agency has, since 2014, calculated the level of severity in technology assessments. Of 19 cases with calculations, only two indications had an absolute shortfall of more than twenty good life years [14]. To qualify for a separate arrangement, for example for children with genetic diseases, where a higher use of resources can be accepted, the absolute shortfall would have to be considerably higher than this.

The following indicative criterion applies for *extremely severe condition*:

A level of severity where the absolute shortfall equivalates to a minimum loss of around thirty good life years.

1.3 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 must be measured by how many good life years on average the intervention gives patients in the relevant patient group compared with relevant current treatment practice. In both England/Wales and Sweden there is an equivalent prerequisite for acceptance of a higher cost/benefit relation [6, 7].

In an article from 2014, Wisløff et al found that the median gain in 370 cost/effect analyses from 2010 was 0.06 good life years (QALYs)[15]. This corresponds to around 3 weeks of good health. Even low levels of improvement can be of value to patients, for example, by facilitating an easier everyday life. This, however, does not form the basis for increased priority over and above the normal prioritisation criteria.

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 approx. 2 good life years compared to standard treatment.

2 Procedures and processes

It is a requirement that all new pharmaceuticals are subject to a health technology assessment before any decision is made about whether they can be used with public funding. This also applies to pharmaceuticals aimed at *very small patient groups with extremely severe conditions*. The procedures for single technology assessments of these pharmaceuticals follows the established process for all new pharmaceuticals, cf. Norwegian Regulations on Medicinal Products chapter 14 and Nye Metoder [16].

a) For a single technology assessment the company has responsibility for sending in the necessary documentation [4, 5].

b) The Norwegian Medicines Agency assesses whether all three guiding criteria for the pharmaceutical to qualify for this arrangement are satisfied in the health technology assessment report. The Medicines Agency must maintain a close dialogue with the company about the evaluation of the indicative criteria for qualifying for this arrangement.

c) The Norwegian Hospital Procurement Trust, Division drug procurements (Sykehusinnkjøp HF Divisjon legemidler LIS) has responsibility for price negotiations and tendering processes.

d) The decision-maker[3] decides whether the pharmaceutical qualifies for this arrangement. On the basis of the single technology assessment, the decision-maker will also decide whether the pharmaceutical will be taken into use with public funding.

The Norwegian Medicines Agency can, in exceptional cases, carry out a health technology assessment of a pharmaceutical without documentation/information being sent in from the company, cf. Norwegian Regulations on Medicinal Products §14-4 fifth paragraph.

3 Lower requirement for documentation

The guidelines for submission of documentation for single technology assessments [4, 5] also apply for submissions of documentation for pharmaceuticals 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* of documentation should, to the greatest degree possible, follow the recommendations in the guidelines. We recommend pre-meetings with the Norwegian Medicines Agency before preparation of documentation in order to clarify what sort of documentation is possible or appropriate in the individual case.

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

There is, however, a requirement that the documentation presented is the best that can reasonably be expected, given that it is a very small patient group with extremely severe conditions. The link between outcome measures used in studies and effects of future morbidity, or death, must be sufficiently substantiated. The Norwegian Medicines Agency can involve Norwegian clinical experts in such evaluations.

Even if a pharmaceutical qualifies for consideration under this arrangement, the decision-maker can conclude that the pharmaceutical is not to be introduced on the grounds of documentation that is *too* poor or inadequate.

4 Monitoring

For pharmaceuticals which come under the arrangements for very small patient groups with extremely severe conditions, a lower requirement for documentation can be accepted than for other pharmaceuticals. This entails a higher requirement for follow-up after a decision is made. Methods and technologies funded under such a scheme must be required to implement procedures to further document effect, safety, as well as the number of patients who are relevant for treatment with the medicine. This documentation may be used as a basis for re-evaluating the medicines funded under the scheme once a certain amount of time has passed.

Monitoring of use can be split into two levels:

- Clinical level, ie, for each individual patient who is treated with the pharmaceutical.

[3] For hospital drugs the decision maker is the Decision Forum on behalf of Norwegian hospitals. For drugs reimbursed by the National Insurance Scheme the decision maker is the Norwegian Medicines Agency.

This involves collection of relevant data about the use of the pharmaceutical in clinical practice. This can, for example, be effect or safety data, or data on resource use. The regional health authorities are reponsible for treatment and therefore for collecting such data.

In addition, it may be appropriate to work out start and stop criteria: start criteria define which patients can receive the medicine. This may be a requirement about the level of symptoms in the patient, their level of function or results from diagnostic tests. Stop criteria are to ensure that the treatment with the medicine ceases if the patient does not respond sufficiently, or if the condition of the patient has changed so it is no longer reasonable to continue treatment. Relevant clinicians and user representatives are involved in the preparation of start and stop criteria.

- Collection of data at a group level

For pharmaceuticals which have gained a conditional marketing authorisation with requirements for further data on effect and safety, the company must obtain new documentation. This may, for example, be through new trials, follow-up studies or so-called *real world data*. Companies must commit themselves to sharing information from these studies with the Norwegian Medicines Agency.

5 Involvement of patient representatives and clinicians

The Norwegian Medicines Agency will obtain information from user representatives and clinicians to complement the documentation which is sent in by the company for the health technology assessment.

References

1. Helse- og omsorgsdepartementet, *Endringer i legemiddelforskriften og blåreseptforskriften mv - høringsnotat*. 2017: regjeringen.no.
2. Helse- og omsorgsdepartementet, *Meld. St. 34 (2015-2016) Verdier i pasientens helsetjeneste - melding om prioritering*. 2016.
3. Norwegian Ministry of Health and Care Services, *Principles for priority setting in health care*. 2017.
4. Statens legemiddelverk, *Retningslinjer for dokumentasjonsgrunnlag for hurtige metodevurderinger*. 2018: legemiddelverket.no.
5. Norwegian Medicines Agency, *Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals*. 2017.
6. TLV. *Cerezyme och Vpriv kvarstår i högkostnadsskyddet till sänkt pris*. 2017; Available from: https://www.tlv.se/lakemedel/omprovning-av-lakemedel/avslutade-omprovningar/Cerezyme-och-Vpriv-kvarstar-i-hogkostnadsskyddet-till-sankt-pris/.
7. NICE. *Topic selection*. 2017; Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/topic-selection.
8. Helsenorge.no. *Hva er en sjelden diagnose?* 2017; Available from: helsenorge.no.
9. Helsedirektoratet, *Rundskriv: § 5-14 - Legemidler, næringsmidler og medisinsk forbruksmateriell*. 2017.
10. NICE, *Citizens Council Report on Ultra Orphan Drugs*. 2004: London.
11. NICE, *Highly specialised technologies guidance*. 2017: London.
12. Barham, L., *NICE and Highly Specialised Technologies: three years on*, in *Pharmaphorum*. 2016.
13. Rath, A., *Prevalence and incidence of rare diseases: Bibliographic data Prevalence, incidence or number of published cases listed by diseases (in alphabetical order).* Orphanet Report Series, Rare Diseases collection, 2015: p. 1-55.
14. Helse- og omsorgsdepartementet, *På ramme alvor*. 2016: regjeringen.no.
15. Wisløff, T., et al., *Estimating QALY gains in applied studies: a review of cost-utility analyses published in 2010.* Pharmacoeconomics, 2014. **32**(4): p. 367-375.
16. *nyemetoder.no*. Available from: nyemetoder.no.