

## Appendix 1: Examples of Scenarios Where There Could be Significant Unmet Need and Contributing Factors for Uncertainty of Clinical Benefit<sup>25</sup>

Source: *Recommendation Framework for CADTH Common Drug Review and pan-Canadian Oncology Drug Review Programs: Guidance for CADTH's Drug Expert Committees.*<sup>25</sup>

**Table 6: Considerations for “Significant Unmet Need”**

Consideration	Description
Rarity of Condition	<p>The drug under review is approved by Health Canada for the treatment of a rare disease. Specifically, the condition for which the drug is indicated has the following characteristics:</p> <ul style="list-style-type: none"> <li>• is life-threatening, seriously debilitating or both serious and chronic in nature</li> <li>• affects a relatively small number of patients (incidence of fewer than 5 in 10,000, but typically closer to 1 in 100,000)</li> <li>• is often genetically based, onset at birth or early childhood, and leads to a shortened life-span</li> <li>• places a heavy burden on caregivers and the health care system</li> <li>• is difficult to study because of the small patient population.</li> </ul>
Population	<ul style="list-style-type: none"> <li>• Need is identified on a population or subpopulation basis (i.e., not on an individual basis)</li> </ul>
Absence of alternatives	<ul style="list-style-type: none"> <li>• There is an absence of clinically effective drug or non-drug alternative treatments.</li> <li>• Substantial morbidity and mortality exist despite the available drug or non-drug alternative treatments.</li> </ul>

**Table 7: Factors That Contribute to Uncertainty of Clinical Benefit**

Consideration	Description
Clinical data	<ul style="list-style-type: none"> <li>• Limited number of clinical studies</li> <li>• Small sample sizes (e.g., due to rare disease that affects a relatively small number of patients (incidence of fewer than 5 in 10,000 but typically closer to 1 in 100,000)</li> <li>• Absence of comparator groups</li> <li>• Alternative or adaptive trial designs for rare diseases</li> <li>• Short study durations or follow-up</li> <li>• Inability to distinguish disease severity in heterogeneous manifested rare diseases</li> <li>• Limited to surrogate end points</li> <li>• Insufficient evidence on meaningful clinical end points</li> <li>• Greater uncertainty in statistical analyses</li> </ul>

The above-noted scenario examples are intended to serve as illustrations, only, to help guide the reader to better understand some of the factors that CADTH's drug committees will assess as part of their deliberations in formulating a reimbursement recommendation. They are by no means exhaustive or impose any procedural obligations that would constitute grounds for a procedural review.

In these situations, although there is uncertainty with the clinical evidence, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease.

Significant, unmet clinical need is identified on a population or subpopulation basis (i.e., not on an individual basis) through the CADTH CDR and pCODR processes.

The rarity of the condition will not be the sole consideration for defining significant unmet need. In addition, the condition must be identifiable with reasonable diagnostic precision.

## Appendix 2: PBAC – Basis for Any Claim for the “Rule of Rescue”<sup>47</sup>

Source: *Pharmaceutical Benefits Scheme. 5.4 basis for any claim for the 'rule of rescue'. In: The Pharmaceutical Benefits Advisory Committee guidelines [Internet]. Canberra (AU): Australian Government, Department of Health; 2016 [cited 2018 Mar 7]. Available from: <https://pbac.pbs.gov.au/section-5/5-4-basis-for-any-claim-for-the-rule-of-rescue.html>*

### 5.4 Basis for any claim for the ‘rule of rescue’

The four factors described below apply in exceptional circumstances and are particularly influential in favour of listing. When all four factors apply concurrently, this is called the ‘rule of rescue’:

- No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients.
- The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the PBAC’s consideration.
- The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the PBAC’s consideration. However, the PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.
- The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the PBAC’s consideration.

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## Appendix 3: Australia – Life Saving Drugs Program (LSDP) Criteria and Conditions<sup>48</sup>

Source: *Life saving drugs program criteria and conditions* [Internet]. Canberra (ACT): Australian Government, Department of Health; 2016 Aug 17. [cited 2018 Feb 20]. Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/lstdp-criteria><sup>48</sup>

### Criteria for the Funding of a Drug

The following issues must be addressed in considering a submission to fund a drug through the Life Saving Drugs Program, and in formulating a recommendation to the Minister for Health.

- A) The drug must be found to meet each of the following criteria:
1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration.
  2. The disease is identifiable with reasonable diagnostic precision.
  3. Epidemiological and other studies provide evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease.
  4. There is evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug.
  5. The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost effectiveness criteria.
  6. There is no alternative drug listed on the PBS or available for public hospital in-patients, which can be used as lifesaving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP.
  7. There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition.
  8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.
- B) Consideration and advice will also be sought, if applicable, on:
1. The proposed price of the drug compared with the effective price of the drug in comparable overseas markets.
  2. The proposed cost of the drug compared with the cost of comparable drugs, if any, that are already funded through the LSDP.

### Pricing Issues

1. Only the cost of the drug will be funded through the LSDP. This may include a factor for importation and transportation of the drug by the manufacturer direct to the place of administration to the patient. No other transport, storage, administration, or any other hospital or medical expenses associated with the use of the drug, or management of the disease or condition, will be funded through the LSDP.

## **Patient Conditions for Initial and Ongoing Subsidy Through the LSDP**

- A) Following an Australian Government decision to fund a drug, a patient must meet the following conditions to receive subsidised drugs through the LSDP:
1. Satisfy the relevant criteria for treatment with the drug, as detailed in the relevant drug/condition LSDP Guidelines.
  2. Participate in the evaluation of effectiveness of the drug by periodic assessment, as directed by the relevant LSDP drug/condition Guidelines, or have an acceptable reason not to participate.
  3. Not be suffering from any other medical condition, including complications or sequelae of the primary condition, that might compromise the effectiveness of the drug treatment.
  4. Be a permanent Australian resident who qualifies for Medicare.
- B) Patient eligibility will be reviewed in accordance with the frequency set out in the relevant drug/condition LSDP Guidelines, but generally 12 months after commencing therapy and every 12 months thereafter.

Continued eligibility will be subject to the assessment of evidence, as outlined in the relevant drug/condition LSDP Guidelines, which demonstrates:

1. clinical improvement in the patient, or
2. stabilisation of the patient's condition.

The assessment of eligibility will be made with regard to the natural course and stage of the disease, as described in the relevant drug/condition LSDP Guidelines, and any exceptional circumstances that may apply.

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## Appendix 4: SMC – Ultra Orphan Drug Decision-Making Framework

Source: *Guidance to manufacturers for completion of New Product Assessment Form (NPAF): supplement on medicines for end of life and very rare conditions. November 2015. Glasgow (GB): Scottish Medicines Consortium; 2016. [cited 2018 Feb 15]. <https://www.scottishmedicines.org.uk/making-a-submission/>*

**Table 8: Factors to Consider When Completing the New Product Assessment Form**

Decision Making Criteria	Guidance on Evidence
Nature of the condition	<ul style="list-style-type: none"> <li>• Description of symptoms and functioning with current treatment</li> <li>• Limitations of current treatment options</li> <li>• Effect on carers' quality of life</li> </ul>
Impact of the new technology	<ul style="list-style-type: none"> <li>• Summary of key efficacy findings from section 3 of NPAF</li> <li>• Summary of any important adverse events associated with treatment from section 4 of NPAF</li> <li>• Summary of key clinical effectiveness points from section 5 of NPAF including clinical significance of health gain associated with treatment</li> <li>• Discussion of spectrum of benefits within the patient group and potential for treatment continuation rules</li> </ul>
Costs to the NHS and Personal Social Services	<ul style="list-style-type: none"> <li>• Summary of year 1 and year 5 gross and net budget impact from section 7 of the NPAF, with and without PAS where relevant</li> <li>• Assessment of any significant budget impacts falling on any non-NHS organisations</li> <li>• Summary of key uncertainties in relation to budget impact</li> </ul>
Value for money	<ul style="list-style-type: none"> <li>• Summary of the base-case cost-effectiveness ratio or cost-consequence analyses, from the economic analysis in section 6.</li> <li>• Summary of key sources of uncertainty in the economic analysis and impact on base-case cost-effectiveness ratio</li> </ul>
Impact beyond direct health benefits and on specialist services	<ul style="list-style-type: none"> <li>• Impact of the technology in allowing patients to contribute to society / improve family functioning/continue in education</li> <li>• Impact on carers quality of life of the new treatment (note development of formal tools such as Carer Experience Scale)</li> <li>• Cost-effectiveness ratios showing the adoption of a wider perspective on costs and benefits</li> <li>• Assessment of impact on NHS staffing, infrastructure and training requirements</li> </ul>

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