**Scope of vignette:**
- authorised products (with marketing authorisation)
- decision process about routine use (and not individual requests for reimbursement)
- submissions for P&R made by manufacturers

**Green = related to/any special considerations for rare disease and ultra-rare disease treatments**

| **The Netherlands** | **Standard reimbursement and HTA process for pharmaceutical products** |
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| Overview of health system and P&R/HTA process | Combined tax and social insurance based health system [1]<br><br>The Dutch Ministry of Public Health, Welfare and Sport is responsible for the final decision on whether to reimburse a treatment from the basic health care insurance package.<br><br>The National Health Care Institute (Zorginstituut) maintains the basic health care package and funding, and advises the Dutch Ministry of Public Health, Welfare and Sport on the basic health care package. It maintains contact with stakeholders, prepares reports and meetings, and collects necessary information. [2, 3]<br><br>The Scientific Advisory Board (WAR) advises the Zorginstituut about scientific evaluation, while the Insured Package Advisory Committee (ACP) advises on social impacts. Both committees are comprised of external experts. [3] |
| Differentiation of rare disease treatments in the P&R system | EMA orphan designation |
| Eligible medicines | All new drugs |
| Process | There are four phases to the advisory process of the Zorginstituut:<br><br>1. Exploring: establishing relevant arguments and the need for information (scoping) - WAR and ACP can already be included in this phase.<br><br>2. Collecting, presenting and assessing relevant information in relation to the criteria and other arguments (assessment) –Zorginstituut assesses scientific reports, issues summarizing conclusion, and sends this to involved parties for comments. WAR advises on the assessment reports.<br><br>3. Naming arguments, determining their role and whether they contribute to positive or negative advice (appraisal) - arguments are formulated based on info from previous two phases. These are publicly debated within the ACP. The Zorginstituut uses a deliberative form of Multi-Criteria Decision Analysis (MCDA) to give a clear structure to the debate and clearly |

| The Netherlands | Standard reimbursement and HTA process for pharmaceutical products |
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| | see which arguments are agreed or disagreed upon. The eventual result is positive or negative advice.<br><br>4. Formulating (positive or negative) advice with the support of the arguments - ACP presents outline of advice to the Zorginstituut, which, based on input from WAR, ACP and all involved parties, approves the advice to send to the Minister. The Zorginstituut informs all relevant parties, and the Minister makes the final decision. [3]<br><br>Like all other pharmaceuticals, OMPs are reimbursed via the basic insurance package. [4]<br><br>There is only the standard process and the same assessment criteria are used.<br>During the appraisal phase rarity can be an argument in formulating positive advice.<br><br>The Zorginsituut only assesses some orphan drugs. Drugs with high budget impact (> 50 million), or high price per patient per year + budget impact higher than 10 million are not automatically reimbursed. These products are first assessed by the Zorginstituut and a price negotiation is carried out by the minister of health.<br><br>If an orphan drug is not assessed by the Zorginstituut, health insurers must determine if the legal criterion of 'proven effective' is met, and then health insurers can reimburse. They do not have the same HTA process, because they must only determine clinical effectiveness. Since last year health insurers, together with patients and the centre of expertise, compose an orphan drug arrangement (start- and stop, indication committee, and data collection) and negotiate the price in the case of expensive ultra-rare drugs. |
| Disease specific expert input (e.g. clinicians or patients in any stage of the process) | Patients organisations, care professionals, care-providers, manufacturers and health insurers provide their expertise and experience in various phases of the process. They can ask questions, respond to draft documents and consultation documents and have discussions with the ACP. [3] |
| Key domains in assessment | - Clinical-effectiveness (it is acknowledged that for RDTs sufficient evidence or evidence of high quality is not always possible)<br>- Cost-effectiveness<br>- Other [3] |
| Evidentiary requirements | Criteria are the same for all interventions, but in some cases lower levels of evidence/more uncertainty are accepted (in case of clinical effectiveness) when there are arguments that a RCT is not necessary nor feasible. This can be the case with orphan or ultra-orphan drugs.<br><br>In the case of orphan drugs the level of evidence is most of the time low to very low. This is not a reason to conclude that it has not proven effective. The Zorginstituut, with the help of the WAR, decides if there is enough confidence that the intervention is more effective than standard care.<br><br>It is always determined in advance what the appropriate evidence profile is with the help of a checklist, and GRADE is used to assess the quality of the evidence. |

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| PROMs | Health-related quality of life questionnaires (e.g. EQ5D or SF36) are used to assess quality of life as one of the outcome measures used in assessment of relative effectiveness (if it is measured), and is also used in assessing cost-effectiveness.<br><br>The questionnaires used should be validated. |
| Appraisal framework | In addition to key domains:<br>- Necessity (severity and burden of disease - important for RDTs)<br>- Feasibility<br>- Health problem and current use of technology<br>- Description of intervention and its characteristics<br>- Safety<br>- Ethical analysis<br>- Organizational aspects<br>- Social aspects (people with greatest need might receive precedence, e.g. rare diseases)<br>- Legal aspects [3]<br><br>After establishing that an intervention is effective, cost-effectiveness is assessed.<br>If cost-effectiveness is favourable, attention is given to whether serious arguments exist for nevertheless issuing negative advice.<br><br>In orphan drugs, cost-effectiveness is almost always unfavourable, so the next question is whether serious arguments exist for nevertheless issuing positive advice. Arguments for reimbursing a treatment that is not cost-effective generally relate to *justice, fairness and equality*.<br><br>Rarity could be an argument to accept an unfavourable cost-effectiveness, however, uncertainty about the size of the effect and the duration is many times also an argument not to pay the highest price. Most of the time the advice is not to reimburse at the price proposed by the manufacturer, but to negotiate.<br><br>Rarity, high burden of disease, children, curative (instead of palliative), great effect on survival or quality of life are the most important appraisal aspects that could benefit RDTs. |
| Reimbursement decision | Yes/no decision: reimburse/do not reimburse<br><br>For the evaluation, aspects are taken into consideration as follows:<br><br>Is the treatment effective? (no - do not reimburse) if yes:<br>- What is the burden of disease (high/med/low)?<br>- Cost effective? (if yes, look for significant arguments not to reimburse, otherwise reimburse),<br><br>If no:<br>- Look for substantial arguments for reimbursing anyway. If they exist, reimburse. |

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| Pricing process | Ministry sets maximum allowable prices for medicines based on external reference pricing with four selected countries (Belgium, France, Germany, UK). [5]<br><br>The Law on Medicinal Prices (Wet geneesmiddelenprijzen (WGP)) applies to all medicines. Based on the price level in the named countries a price is set.<br><br>In extramural care, drugs that are reimbursed are placed on a list (het geneesmiddelenvergoedingen system GVS). For mutually replaceable drugs, one price is set that will be reimbursed. If the price of one of the drugs is higher than the price that is reimbursed, a patient can choose to pay the difference. In the case of drugs with very high prices and no or hardly any competition, the Minister can choose to negotiate a price. These negotiated prices are not public.<br><br>In the case of expensive drugs in hospital care, the Nederlandse Zorgautoriteit fixes the reimbursement price. |
| Managed entry agreements | - Other, not specified<br><br>Note: In the Netherlands relative effectiveness must be proven for reimbursement. However, when there is not enough evidence yet, but the intervention is very promising (plus other criteria), there is some budget for conditional reimbursement. Evidence of (cost)effectiveness must be gathered during this period of conditional reimbursement. If quality of evidence is low to very low and will be reimbursed, an OMP arrangement is required in which appointments are made about start- and stop criteria, use of an indication committee and data gathering, so in the long run it can be concluded if an effect on the critical endpoint is found. |
| Main challenges in appraising medicines for rare diseases (tick all that apply) | **X Lack of good quality clinical data (in combination with a very high price)**<br>☐ Lack of real world data<br>☐ Introducing value for money<br>**X Monitoring treatment efficacy**<br>**X Managing budget impact**<br>☐ Lack of criteria/transparency of OMP P&R processes<br>☐ Making arrangements to work for all stakeholders<br>**X Lack of long-term meaningful outcomes** |
| Impact of special processes | Conditional reimbursement is a fairly new instrument, no experiences yet with orphan drugs |
| Proposed policy change | None |
| Joint initiatives | BeNeLuxA, EUnetHTA |
| | |
| SOURCES | |
| 1 | https://international.commonwealthfund.org/countries/netherlands/ |
| 2 | https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute |

| The Netherlands | Standard reimbursement and HTA process for pharmaceutical products |
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| 3 | https://english.zorginstituutnederland.nl/publications/reports/2018/09/05/package-advice-in-practice---deliberations-for-arriving-at-a-fair-package |
| 4 | Package management for orphan drugs - word doc |
| 5 | https://www.government.nl/topics/medicines/keeping-medicines-affordable |

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This vignette was compiled based on information provided by country experts and desk research. The information provided may be incomplete or contain inaccuracies. If you have any comments or updates, please email us at the following email addresses:

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