Role of centralized review processes for making reimbursement decisions on new health technologies in Europe

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Background: The purpose of this study was to compare centralized reimbursement/coverage decision-making processes for health technologies in 23 European countries, according to: mandate, authority, structure, and policy options; mechanisms for identifying, selecting, and evaluating technologies; clinical and economic evidence expectations; committee composition, procedures, and factors considered; available conditional reimbursement options for promising new technologies; and the manufacturers’ roles in the process.

Methods: A comprehensive review of publicly available information from peer-reviewed literature (using a variety of bibliographic databases) and gray literature (eg, working papers, committee reports, presentations, and government documents) was conducted. Policy experts in each of the 23 countries were also contacted. All information collected was reviewed by two independent researchers.

Results: Most European countries have established centralized reimbursement systems for making decisions on health technologies. However, the scope of technologies considered, as well as processes for identifying, selecting, and reviewing them varies. All systems include an assessment of clinical evidence, compiled in accordance with their own guidelines or internationally recognized published ones. In addition, most systems require an economic evaluation. The quality of such information is typically assessed by content and methodological experts. Committees responsible for formulating recommendations or decisions are multidisciplinary. While criteria used by committees appear transparent, how they are operationalized during deliberations remains unclear. Increasingly, reimbursement systems are expressing interest in and/or implementing reimbursement policy options that extend beyond the traditional “yes,” “no,” or “yes with restrictions” options. Such options typically require greater involvement of manufacturers which, to date, has been limited.

Conclusion: Centralized reimbursement systems have become an important policy tool in many European countries. Nevertheless, there remains a lack of transparency around critical elements, such as how multiple factors or criteria are weighed during committee deliberations.

Keywords: reimbursement, centralized review, health technologies, Europe

Introduction
The past decade has seen unprecedented growth in the number of new, often high-cost, health technologies and consumer demand for access to them. It has also seen increased public awareness and scrutiny of decisions about which technologies to include in the basket of publicly insured services.1–3 To improve the legitimacy of such decisions and optimize health outcomes through the effective use of increasingly strained health care resources, many payers, particularly those in Europe, have established centralized systems for determining the reimbursement status of new health technologies.4,5
In this invited review, we compare these systems across selected countries in Northern, Southern, Western, Eastern, and Central Europe, examining:

- Their mandate, authority, organizational structure, and policy options
- Mechanisms for identifying, selecting, and evaluating technologies
- Clinical and economic evidence expectations
- Review committee composition, procedures, and key factors considered during deliberations
- Use of conditional reimbursement options for enabling access to promising new technologies around which considerable uncertainty related to clinical and/or economic value exists
- The role of manufacturers in steps comprising the reimbursement review process.

**Methods**

This review is based upon findings from a comprehensive search for publicly available information on centralized reimbursement systems in selected European countries. Peer-reviewed literature published in English over the past decade (ending in January 2011) was located using a structured search strategy that combined relevant controlled vocabulary terms, ie, MeSH and EMTREE (eg, “technology, medical,” “reimbursement mechanisms,” “decision-making,” “technology assessment,” “health policy”) and free text terms (eg, “pharmaceuticals,” “medical devices,” “coverage,” “funding,” “centralized review,” “health technology assessment,” and “reimbursement,” the full search strategy being available from the authors). Such terms were identified through an analysis of words used to index references familiar to the authors. The strategy was applied to several health-related electronic bibliographic databases, including PubMed, MEDLINE, EMBASE, HealthSTAR, CINAHL, EconLit, PASCAL, SCOPUS, International Pharmaceutical Abstracts, Web of Science, and the UK Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, and Health Technology Assessment).

For comprehensiveness, reference lists of retrieved papers and the most recent issues of health policy-related journals were hand-searched.

A search for gray (unpublished) literature (eg, working papers, conference abstracts, reports, presentations, government documents) was also performed using the Google® search engine and terms from the main search strategy. In addition, the following dedicated gray literature databases were scanned: the New York Academy of Medicine’s Gray Literature database, Knowledge Utilization database, Systematic Reviews for Management and Policy Making, and National Health Service Evidence in Health and Social Care. Separate searches for information on centralized reimbursement processes within health care systems of the top 30 European countries ranked according to gross domestic product per capita by the World Bank were also conducted. This number was considered sufficient to capture the full spectrum of such processes. For each country, the websites of relevant ministries (eg, health, social affairs, economics), translated into English with Google Translate®, were scanned for documents describing legislation and other policies and processes for making reimbursement decisions on new health technologies, including pharmaceuticals, medical devices, diagnostic tests, and procedures.

Documents retrieved from the various searches were reviewed independently by two of the authors. Published papers unrelated to the introduction of individual health technologies (eg, those on macrolevel priority setting) were excluded. Because the purpose of this review was to examine current actual processes, papers proposing specific decision-making tools or discussing one component of decision-making were also excluded. Information on process-related characteristics of the centralized reimbursement systems, including perceived strengths and weaknesses, was extracted using a standardized, pretested data abstraction form. To ensure it reflected the current policy environment, the following individuals were consulted: corresponding authors of published papers, contacts listed on organizations’ websites, and European policy experts with whom the authors were already acquainted.

Extracted information was tabulated to facilitate the identification of patterns or trends across country-specific reimbursement processes, and subsequently analyzed qualitatively using content analysis and constant comparison techniques.

**Results**

Of the 30 European countries initially identified for the review, information on centralized reimbursement processes could only be found for 23. Therefore, the review included the following 23 countries: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Norway, Poland, Portugal, Scotland, Slovakia, Spain, Sweden, Switzerland, the Netherlands, the United Kingdom, and Wales.
Mandate of centralized reimbursement systems

The majority (18/23) of countries have established centralized reimbursement processes to support coverage decision-making for either pharmaceuticals or pharmaceuticals and devices needed for their delivery. In general, eligible pharmaceuticals comprise those requiring a prescription. Two-thirds of such processes review both inpatient and outpatient pharmaceuticals (12/18), while one-third (6/18) considers those administered in outpatient settings only (Table 1). The remaining five countries have invested in centralized reimbursement systems that span medical devices, procedures, and pharmaceuticals (Table 1). Despite differences in the scope of technologies included, such processes share a similar mandate to determine the reimbursement status of new technologies. In most of the countries, this amounts to a decision on whether to add the technology to a “positive list” (ie, list of insured services). However, a small proportion of the countries also maintain a “negative list” (ie, a list of nonreimbursable services), broadening the mandate of their centralized reimbursement systems to include decisions resulting in active exclusion of some technologies from the benefit plan (Table 1). In legislation governing most systems (13/23), decisions are authoritative (ie, must be implemented), rather than advisory (ie, recommendations). Given that the price of a technology can significantly influence assessments of value for money and affordability, many of the countries have also incorporated pricing into the mandates of such systems (discussed in detail later). Finally, all consider at least three funding decision options, ie, provide, do not provide, and provide with restrictions or conditions (ie, restrict use to specific providers or patients meeting certain criteria, Table 1). In addition, approximately one-third have introduced a fourth option, ie, provide while additional evidence is collected. The latter comprises a provisional funding arrangement in which the technology is reimbursed in the interim while information needed to reduce uncertainties in existing evidence is collected to support a definitive decision.

Assessment of health technologies in centralized reimbursement systems

Approaches to the identification of technologies for review by centralized reimbursement systems vary across countries (Table 2). Broadly, there are three strategies: technologies may be submitted by manufacturers seeking coverage for newly licensed pharmaceuticals (13/23); they may be referred by potential payers (eg, government, sickness funds) or users (eg, hospitals, providers, patients), as well as manufacturers (8/23); or they may be identified by payers or users only (2/23). Systems limited to consideration of reimbursement applications from manufacturers alone typically review submissions in order of receipt, unless a technology is eligible for “fast tracking,” which moves it to the front of the queue. In countries with such mechanisms (eg, the Netherlands), eligibility criteria include technologies (mainly pharmaceuticals) used to treat rare or life-threatening conditions for which no alternatives beyond best supportive care exist. Some countries (eg, Scotland and Norway) have more closely linked centralized regulatory and reimbursement processes in order to reduce overall inefficiencies in technology policy. Specifically, pharmaceuticals are automatically sent to the centralized reimbursement system for review upon market approval. In systems that accept referrals from multiple stakeholders, technology selection and/or prioritization criteria have been established. For example, Germany’s Federal Joint Committee, which determines which technologies to review, takes into account clinical relevance, cost implications, and potential “risks” related to the technology and its introduction into the health care system.6 In the UK, the topic selection panel of the National Institute of Health and Clinical Excellence, whose members include health care providers and patient representatives, formulate recommendations following consideration of: the burden of disease for which the technology targets; anticipated clinical impact (ie, whether the technology represents a significant medical advance that could yield substantial health benefits); potential impact on National Health Service costs and resources; alignment of the technology with broader government priority areas; concerns over appropriateness of use in practice; and potential for national guidance to add value.7 Recommendations are forwarded to the Department of Health, which makes the final decision.

Across centralized reimbursement systems, technology identification and selection is followed by some form of health technology assessment (Table 2). This involves collection and synthesis of evidence (clinical and, in most cases, economic), the findings of which are presented in an assessment report, and critical appraisal of the relevance, quality, and generalizability of that evidence. The results of the latter are summarized in an evaluation report. Responsibility for the preparation of these reports varies. In systems where a manufacturer’s submission initiates the reimbursement review process, the assessment report is part of the submission (Table 2). Therefore, its preparation rests with the
Table 1 Centralized reimbursement system and mandate

| Country          | Centralized reimbursement review/decision-making body (role)                     | Technology scope               | Decision problem                                                                 |
|------------------|--------------------------------------------------------------------------------|--------------------------------|----------------------------------------------------------------------------------|
| Austria          | • Association of Austrian Social Security Institutions (decisions)55           | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)55                            |
|                  | • Pharmaceutical Evaluation Board/Austrian Medicines Evaluation Commission (recommendations)51,56-58 | – Outpatient                   | • Do not provide as publicly insured service (nonreimbursable)55                |
| Belgium          | • Minister of Social Affairs (decisions)                                      | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)21                           |
|                  | • Commission on reimbursement of medicines/Drug Reimbursement Committee (recommendations)54-63 | – Outpatient                   |                                                                                 |
| Czech Republic   | • State Institute for Drug Control (decisions)55-47                           | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)65                           |
|                  | • Danish Medicines Agency (decisions)58-70 Reimbursement Committee (recommendations)48-70 | – Outpatient                   | • Provide as publicly insured service (reimbursable)80                           |
| Estonia          | • Ministry of Social Affairs (decisions)72                                     | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)72                           |
|                  | • Pharmaceuticals Committee (recommendations)72                               | – Outpatient                   |                                                                                 |
| Finland          | • Pharmaceuticals Pricing Board (decisions)64,73,74                             | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)75                           |
|                  | • Pharmaceuticals Pricing Board Expert Group (recommendations)75               | – Outpatient                   | • Do not provide as publicly funded service (nonreimbursable)74                |
| France           | • Ministry for Health and Social Security (decisions)20,78                    | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)80                           |
|                  | • French National Authority for Health (recommendations)78                    | – Outpatient                   |                                                                                 |
| Germany          | • Federal Joint Committee (decisions)19                                       | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)55                           |
|                  | • Institute for Quality and Efficiency in Health Care (recommendations)19      | – Outpatient                   | • Do not provide as publicly funded service (nonreimbursable)55                |
|                  | • Institute for Quality and Efficiency in Health Care (recommendations)19      | – Inpatient78                  | Note: Must not exclude technologies for which there is no alternative18,81       |
| Greece           | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)83,84 | • Pharmaceuticals               | • Classify pharmaceutical into therapeutic category85                           |
| Hungary          | • Ministers of Health and Finance (decisions)                                | • Pharmaceuticals               | • Provide as publicly insured service88                                           |
|                  | • National Health Insurance Fund Administration Health Technology Assessment Committee (recommendations)88,89 | – Outpatient                   | • Do not provide as publicly funded service (nonreimbursable)89                |
| Ireland          | • Health Service Executive (decisions)91,92                                   | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)92                           |
| Italy            | • Italian Medicines Agency Technical Scientific Committee (decisions)79       | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)21                           |
|                  | • Italian Medicines Agency Pricing and Reimbursement Committee (recommendations)75 | – Outpatient                   |                                                                                 |
| Norway           | • Norwegian Medicines Agency (decisions)98                                    | • Pharmaceuticals               | • Provide as publicly insured service (reimbursable)98                           |
|                  | • Department of Pharmacoconomics (recommendations)98                          | – Outpatient                   |                                                                                 |
| Decision “scope” | Reimbursement | Linkage to pricing | Available decision options | Provide | Do not provide | Provide with restrictions | Provide while additional evidence is collected |
|------------------|---------------|---------------------|-----------------------------|---------|---------------|--------------------------|-----------------------------------------------|
| Y                | Yes<sup>56,59</sup> | Yes<sup>51,56,59</sup> | Yes<sup>56</sup> | Yes<sup>56</sup> | Yes<sup>54</sup> | Not specified |                               |
| Y                | Yes<sup>51</sup> | Yes<sup>51</sup> | Yes<sup>51</sup> | Yes<sup>51</sup> | Yes<sup>51</sup> | Yes<sup>51</sup> |                               |
| Y                | Yes<sup>67</sup> | Yes<sup>67</sup> | Yes<sup>65</sup> | Yes<sup>65</sup> | Yes<sup>65</sup> | Not specified |                               |
| Y                | Yes<sup>68</sup> | No<sup>68</sup> | Yes<sup>28,69</sup> | Yes<sup>28,69</sup> | Yes<sup>28,69</sup> | Not specified |                               |
| Y                | Yes<sup>72</sup> | Yes<sup>72</sup> | Yes<sup>72</sup> | Yes<sup>72</sup> | Yes<sup>72</sup> | No<sup>72</sup> |                               |
| Y                | Yes<sup>74</sup> | Yes<sup>74</sup> | Yes<sup>77</sup> | Yes<sup>77</sup> | Yes<sup>77</sup> | No<sup>74</sup> |                               |
| Y                | Yes<sup>16,20,22,78</sup> | Yes<sup>16,20,22,78</sup> | Yes<sup>20</sup> | Yes<sup>20</sup> | Yes<sup>20</sup> | Yes<sup>16,20</sup> |                               |
| Y                | Yes<sup>79</sup> | Yes<sup>79,84</sup> | Yes<sup>79</sup> | Yes<sup>79</sup> | Yes<sup>79</sup> | Yes<sup>79</sup> |                               |
| Y                | Yes<sup>85</sup> | Yes<sup>87</sup> | N/A | N/A | N/A | N/A |                               |
| Y                | Yes<sup>88</sup> | Not specified | Yes<sup>90</sup> | Yes<sup>90</sup> | Yes<sup>90</sup> | Not specified |                               |
| Y                | Yes<sup>91</sup> | No<sup>91</sup> | Yes<sup>91</sup> | Yes<sup>91</sup> | Yes<sup>91</sup> | No<sup>91</sup> |                               |
| Y                | Yes<sup>96,97</sup> | Yes<sup>96,97</sup> | Yes<sup>96</sup> | Yes<sup>96</sup> | Yes<sup>96</sup> | Yes<sup>96</sup> |                               |
| Y                | Yes<sup>98</sup> | Yes<sup>98</sup> | Yes<sup>98</sup> | Yes<sup>98</sup> | Yes<sup>98</sup> | Not specified |                               |

(Continued)
Table 1 (Continued)

| Country      | Centralized reimbursement review/decision-making body (role)                                                                 | Technology scope                                                                 | Decision problem                                                                 |
|--------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Poland       | • Ministry of Health (decisions)                                                                                           | • Pharmaceuticals                                                                | • Provide as publicly insured service (reimbursable)                             |
|              |                                                                                                                                 | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
| Portugal     | • Ministry of Health (decisions)                                                                                           | • Pharmaceuticals                                                                | • Provide as publicly insured service (reimbursable)                             |
|              | • INFARMED (recommendations)                                                                                              | – Outpatient                                                                     |                                                                                  |
|              | • Scottish Medicines Consortium (recommendations)                                                                             | – Inpatient                                                                      |                                                                                  |
| Scotland     | • National Health Service Scotland (decisions)                                                                             | • Pharmaceuticals                                                                | • Provide as publicly insured service (reimbursable)                             |
|              | • Scottish Medicines Consortium (recommendations)                                                                             | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
| Slovakia     | • Ministry of Health (decisions)                                                                                           | • Pharmaceuticals                                                                | • Provide as publicly insured service (reimbursable)                             |
|              | • Reimbursement Committee for Medicinal Products (recommendations)                                                          | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
| Spain        | • Ministry of Health Directorate General of Pharmacy and Health Products (decisions)                                        | • Pharmaceuticals                                                                | • Do not provide as publicly funded service (non-reimbursable)                    |
|              |                                                                                                                                 | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
| Sweden       | • Dental and Pharmaceutical Benefits Board (decisions)                                                                       | • Pharmaceuticals                                                                | • Provide as publicly funded service (reimbursable)                              |
|              |                                                                                                                                 | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | • Devices (for administration of pharmaceuticals)                               |                                                                                  |
| Switzerland  | • Swiss Federal Office of Public Health (decisions)                                                                           | • Pharmaceuticals                                                                | • Provide as publicly funded service (reimbursable)                              |
|              | • Federal Drug Commission (recommendations)                                                                               | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
| The Netherlands | • Ministry of Health, Welfare and Sport (decisions)                                                                            | • Pharmaceuticals                                                                | • Provide as publicly funded service (reimbursable)                              |
|              | • Medicinal Products Reimbursement Committee of the Dutch Healthcare Insurance Board (recommendations)                         | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – High cost                                                                       |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
| United Kingdom | • National Institute for Health and Clinical Excellence (decisions)                                                         | • Pharmaceuticals                                                                | • Provide as publicly funded service (reimbursable)                              |
|              | • Technology Appraisals Committee (recommendations)                                                                          | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |
|              | • Technology Appraisals Committee (recommendations)                                                                           | • Devices                                                                        |                                                                                  |
|              |                                                                                                                                 | • Procedures                                                                      |                                                                                  |
| Wales        | • Ministry for Health and Social Services (decisions)                                                                         | • Pharmaceuticals                                                                | • Provide as publicly funded service (reimbursable)                              |
|              | • All Wales Medicines Strategy Group (recommendations)                                                                         | – Outpatient                                                                     |                                                                                  |
|              |                                                                                                                                 | – Inpatient                                                                      |                                                                                  |

manufacturer. Most systems have developed a standard template/structure for the report and submission guidelines to which manufacturers must adhere. These guidelines largely include content/information requirements and internationally accepted methods for synthesizing and analyzing evidence. In two of the countries, responsibility for the assessment depends upon the type of review (“appraisal”). Both France and the UK have created “single technology appraisal” and “multiple technology appraisal” processes. “Single technology appraisals” compare the candidate technology with a limited number of alternatives for a specific, well-defined indication (eg, disease stage). Their scope most closely resembles processes based upon manufacturers’ submissions. “Multiple technology appraisals” consider either several indications for a candidate technology or several technologies (along with the candidate technology) for a condition at one or more points in its course, taking a disease management approach. The assessment report for a single technology appraisal is prepared by the manufacturer. For a multiple technology appraisal, the report is drafted either internally with support...
from external content and methodological experts (France) or by an independent academic group (the UK). Finally, in some countries, technical staff of a dedicated health technology assessment body or the centralized reimbursement system itself undertake the assessment report, regardless of the scope (eg, Germany).

With one exception (the UK), responsibility for preparing the evaluation report that accompanies each assessment also lies with technical staff and, if necessary, external experts. The National Institute of Health and Clinical Excellence commissions independent academic groups to evaluate assessments submitted by manufacturers as part of its single technology appraisal process.

Clinical and economic evidence expectations of centralized reimbursement systems
Centralized reimbursement systems have issued their own guidelines or endorsed internationally recognized published ones specifying clinical and economic evidence.
Table 2 Comparison of processes for identifying, selecting, and assessing technologies

| Country       | Centralized reimbursement review/decision-making body (role)                                                                                                                                                                                                 | Technologies to be considered for review                                                                                                                                                                                                 |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Austria       | • Association of Austrian Social Security Institutions (decisions)15<br>• Pharmaceutical Evaluation Board (recommendations)54                                                                                                                                 | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals48                                                                                                                                                                                                             |
| Belgium       | • Minister of Social Affairs (decisions)<br>• Commission on reimbursement of medicines/Drug Reimbursement Committee (CRM) (recommendations)7                                                                                                                                 | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals17                                                                                                                                                                                                                  |
| Czech Republic| • State Institute for Drug Control (decisions)45                                                                                                                                                                                                             | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals15                                                                                                                                                                                                                 |
| Denmark       | • Danish Medicines Agency (decisions)68,85,121<br>• Reimbursement Committee (recommendations)68,122                                                                                                                                                           | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals89                                                                                                                                                                                                                  |
| Estonia       | • Ministry of Social Affairs (decisions)79<br>• Pharmaceuticals Committee (recommendations)72                                                                                                                                                               | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals78                                                                                                                                                                                                                  |
| Finland       | • Pharmaceuticals Pricing Board (decisions)37,47,74<br>• Pharmaceuticals Pricing Board Expert Group (recommendations)75                                                                                                                                   | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals99                                                                                                                                                                                                                  |
| France        | • Ministry for Health and Social Security (decisions)31,78<br>• French National Authority for Health (recommendations)38                                                                                                                                      | Depends on type of appraisal11,20<br>Single technology appraisal<br>Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals and devices<br>• Health care professional associations seeking reimbursement for procedures<br>Multiple technology appraisals<br>Typically classes of pharmaceuticals or categories of devices<br>Referred by:<br>• Health care professional associations<br>• Ministry of Health<br>• National Union of Health Insurance Funds<br>• Patient and/or carer organizations120 |
| Germany       | • Federal Joint Committee (decisions)19<br>• Institute for Quality and Efficiency in Health Care (recommendations)19                                                                                                                                       | Referred by:<br>• Associations represented by Federal Joint Committee<br>• Ministry of Health<br>• Institute for Quality and Efficiency in Health Care<br>• Federal commissioner of patient affairs<br>• Patient and/or carer organizations168 |
| Greece        | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)35                                                                                                                                                                  | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals89                                                                                                                                                                                                                  |
| Hungary       | • Ministers of Health and Finance (decisions)<br>• National Health Insurance Fund Administration (recommendations)38,89                                                                                                                                  | Referred by:<br>• Manufacturers seeking reimbursement for newly approved pharmaceuticals<br>• National Health Insurance Fund Administration88                                                                                                                                                   |
### Technology selection

| Technology selection | Health technology assessment | Evaluation of evidence provided (evaluation report) |
|----------------------|-----------------------------|---------------------------------------------------|
| Typically considered in order received<sup>68</sup> | Manufacturer through submission requirements<sup>53</sup> | Technical staff within Association of Austrian Social Security Institutions (Department of Pharmaceutical Affairs – pharmacological and medical-therapeutic assessment; Health Economics Team – economic assessment)<sup>53</sup> |
| Typically considered in order received<sup>17</sup> | Manufacturer through submission requirements<sup>9</sup> | Technical staff within CRM supported by external experts<sup>4</sup> |
| Typically considered in order received<sup>65</sup> | Manufacturer through submission requirements<sup>66</sup> | Technical staff within State Institute for Drug Control<sup>65</sup> |
| Typically considered in order received<sup>68</sup> | Manufacturer through submission requirements<sup>66</sup> | Technical staff within Danish Medicines Agency supported by external experts, if necessary<sup>46</sup> |
| Not specified | Manufacturer through submission requirements<sup>12</sup> | Technical staff within Estonian Health Insurance Fund and State Agency of Medicines<sup>72</sup> |
| Typically considered in order received<sup>23</sup> | Manufacturer through submission requirements<sup>122</sup> | Technical staff within Pharmaceuticals Pricing Board supported by external experts<sup>122</sup> |

### Single technology appraisals

- Typically considered in order received<sup>10</sup>

### Multiple technology appraisals

- Selection criteria not specified

### Evaluation of evidence provided (evaluation report)

- Technical staff within Institute for Quality and Efficiency in Health Care supported by external experts<sup>123</sup><sup>124</sup>
- Methods must comply with guidelines of the Ministry of Health and Social Affairs and Health<sup>122</sup>

### Determined by Federal Joint Committee

- Selection criteria:
  1. Clinical relevance
  2. Cost implications
  3. “Risks”
- Not specified
- Not specified

### Evaluation of evidence provided (evaluation report)

- Technical staff within Institute for Quality and Efficiency in Health Care supported by external experts<sup>123</sup><sup>124</sup>
- Methods must comply with guidelines of the Ministry of Health and Social Affairs and Health<sup>122</sup>

### Technical staff within Transparency Committee in the Reimbursement and Medicinal Products

- Not specified
- National Technology Assessment Office of the National Institute for Strategic Health Research<sup>70</sup>
- Technical staff within National Technology Assessment Office of the National Institute for Strategic Health Research<sup>70</sup>

### (Continued)
| Country        | Centralized reimbursement review/decision-making body (role)                                                                 | Technologies to be considered for review                                                                                                      |
|---------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Ireland       | • Health Service Executive (decisions)97,92                                                                                                                                              | Referred by:                                                                                                                                   |
|               |                                                                                                                                                                                         | • Manufacturers seeking reimbursement for newly approved pharmaceuticals91                                                                 |
|               |                                                                                                                                                                                         | Referred by:                                                                                                                                   |
|               |                                                                                                                                                                                         | • Department of Health and Children of the Health Services Executive for new and existing devices and diagnostic tests that might “incur a high cost or have a significant budget impact”91 |
| Italy         | • Italian Medicines Agency Technical Scientific Committee (decisions)94                                                                                                                 | Referred by:                                                                                                                                   |
|               | • Italian Medicines Agency Pricing and Reimbursement Committee (recommendations)95                                                                                                       | • Manufacturers seeking reimbursement for newly approved pharmaceuticals27                                                                     |
| Norway        | • Norwegian Medicines Agency (decisions)98                                                                                                                                               | Referred by:                                                                                                                                   |
|               | • Department of Pharmacoeconomics (recommendations)99                                                                                                                                     | • Manufacturers seeking reimbursement for newly approved pharmaceuticals44                                                                    |
| Polan         | • Ministry of Health (decisions)99                                                                                                                                                       | Referred by:                                                                                                                                   |
| Portugal      | • Ministry of Health (decisions)                                                                                                                                                          | • Manufacturers seeking reimbursement for newly approved pharmaceuticals99                                                                    |
|               | • INFARMED (recommendations)16-45                                                                                                                                                         | Referred by:                                                                                                                                   |
| Scotland      | • National Health Service Scotland (decisions)35                                                                                                                                       | • Manufacturers seeking reimbursement for newly approved pharmaceuticals15                                                                    |
|               | • Scottish Medicines Consortium (recommendations)                                                                                                                                          | • Automatic within 12 weeks of market launch15                                                                                                   |
| Slovakia      | • Ministry of Health (decisions)                                                                                                                                                          | Referred by:                                                                                                                                   |
|               | • Reimbursement Committee for Medicinal Products (recommendations)105,107,129,136                                                                                                      | • Manufacturers seeking reimbursement for newly approved pharmaceuticals15                                                                    |
| Spain         | • Ministry of Health Directorate General of Pharmacy and Health Products                                                                                                                 | Referred by:                                                                                                                                   |
|               | • Inter-Ministerial Pricing Commission (decisions)31,108                                                                                                                                  | • Ministry of Health (newly approved pharmaceuticals)108                                                                                        |
| Sweden        | • Dental and Pharmaceutical Benefits Board (decisions)15,109,110                                                                                                                       | Referred by:                                                                                                                                   |
|               |                                                                                                                                                                                         | • Manufacturers seeking reimbursement for newly approved pharmaceuticals15                                                                    |
|               |                                                                                                                                                                                         | • Dental and Pharmaceutical Benefits Board (for pharmaceuticals approved prior to 2002)132,134                                                   |
| Switzerland   | • Swiss Federal Office of Public Health (decisions)                                                                                                                                       | Referred by:                                                                                                                                   |
|               | • Federal Drug Commission (recommendations)116,115                                                                                                                                       | • Manufacturers seeking reimbursement for newly approved pharmaceuticals116                                                                   |
|               |                                                                                                                                                                                         | • Patients and carers                                                                                                                             |
|               |                                                                                                                                                                                         | • Hospitals and hospital groups                                                                                                                |
|               |                                                                                                                                                                                         | • Health care professional associations                                                                                                         |
|               |                                                                                                                                                                                         | • Federal Office of Public Health114,117                                                                                                |
| The Netherlands| • Ministry of Health, Welfare and Sport (decisions)                                                                                                                                       | Referred by:                                                                                                                                   |
|               | • Medical Products Reimbursement Committee of the Dutch Healthcare Insurance Board (recommendations)116                                                                            | • Manufacturers seeking reimbursement for newly approved pharmaceuticals116                                                                   |
|               |                                                                                                                                                                                         | • University hospital federations, health care professional associations, and Dutch Healthcare Insurance Board for high-cost inpatient pharmaceuticals |
| Technology selection | Health technology assessment | Evaluation of evidence provided (evaluation report) |
|----------------------|------------------------------|---------------------------------------------------|
| • Not specified       | • Manufacturer through submission requirements\(^{53,125}\) | • Technical staff within National Centre for Pharmacoeconomics, supported by external clinical experts\(^{93}\) |
|                      | • Methods must comply with Irish Health Technology Assessment Guidelines\(^{92}\) | |
| • Typically considered in order received\(^{27}\) | • Manufacturer through submission requirements\(^{126}\) | • Members of Technical Scientific Committee\(^{126}\) |
|                      | • Methods must comply with Italian submission guidelines\(^{37}\) | |
| • Not specified       | • Manufacturer through submission requirements\(^{34}\) | • Technical staff within Norwegian Medicines Agency and Department of Pharmacoeconomics\(^{38}\) |
|                      | • Methods should comply with internationally recognized systematic review guidelines\(^{24}\) | • Technical staff within Ministry of Health\(^{79}\) |
| • Not specified       | • Manufacturer through submission requirements\(^{99}\) | • Agency for Health Technology Assessment\(^{127}\) |
| • Not specified       | • Manufacturer through submission requirements\(^{35}\) | • Technical staff within INFARmed supported by external experts\(^{26}\) |
| • Exclusion criteria: | • Manufacturer through submission requirements\(^{28}\) | • Technical staff within Scottish Medicines Consortium supported by external experts\(^{128}\) |
| Already appraised by National Institute of Health and Clinical Excellence through its multiple technologies appraisal process\(^{21}\) | • Methods must comply with Scottish Medicines Consortium systematic review and economic guidelines\(^{14}\) | • Working group for pharmacoeconomics and outcomes research\(^{121}\) |
| • Not specified       | • Manufacturer through submission requirements\(^{131}\) | |
| • Not specified       | • Manufacturer through invitation to submit information to Inter-Ministerial Pricing Commission\(^{21}\) | • Inter-Ministerial Pricing Commission\(^{21}\) |
| • For new pharmaceuticals: typically considered in order received | • For new pharmaceuticals: Manufacturer through submission requirements\(^{126}\) | • For new pharmaceuticals: Technical staff within Dental and Pharmaceutical Benefits Board\(^{124}\) |
| • For older pharmaceuticals: Overall sales volume\(^{34,135}\) | • For older pharmaceuticals: Technical staff within Dental and Pharmaceutical Benefits Board supported by external experts\(^{126}\) | • For older pharmaceuticals: Technical staff within Dental and Pharmaceutical Benefits Board supported by external experts\(^{126}\) |
| • Not specified       | • Manufacturer through submission requirements\(^{131}\) | • Federal Drug Commission\(^{124}\) |
| • Not specified       | • Technical staff within Dutch Healthcare Insurance Board\(^{117}\) | • Technical staff within Dutch Healthcare Insurance Board\(^{117}\) |
|                      | • Methods must comply with internationally recognize systematic review guidelines and Dutch Healthcare Insurance Board economic guidelines\(^{117}\) | |

(Continued)
requirements for assessment reports (Tables 3 and 4). These guidelines state topics to be addressed and the types of information accepted for addressing them. In most cases (16/23), specified clinically-related topics are similar and include: burden of illness and/or characteristics of the target patient population; therapeutic claim of the candidate technology; safety; efficacy; and effectiveness (preferably comparative effectiveness) across relevant patient subgroups (Table 3). Additionally, several require information on current management or the place of the candidate technology within existing treatment pathways (eg, France and the UK), and its proposed frequency and duration of use (eg, Austria). Across systems and where reported, there is a shared preference for information on health outcomes that represent final clinical endpoints related to mortality, morbidity, and quality of life. Less frequently, information on adverse events/complications is also required. This may be explained by the fact that a prerequisite for reimbursement review is typically regulatory approval. Therefore, systems may view reconsideration of adverse events, which relate to the safety of a technology, unnecessary. In systems proposing or stipulating the use of quality-adjusted life-years (7/23), change in health-related quality of life is to be measured in patients and then valued in the public or general population (eg, the UK). Surrogate outcomes are discouraged or not accepted unless well validated (eg, Germany). Lastly, some systems elicit the views of patients and or carers in identifying topic specific outcomes and their relative importance (eg, Germany).

In general, centralized reimbursement systems state a preference for head-to-head randomized controlled trials comparing the candidate technology with standard care, no active treatment/best supportive care, or placebo (if no alternatives exist, Table 3). However, increased interest in evidence of “comparative effectiveness” over “comparative efficacy” among most reimbursement systems has led to requests for inclusion of head-to-head randomized controlled trials conducted in “naturalistic settings” (ie, pragmatic trials, in the UK) and other direct comparative studies (observational and experimental in design), the collective findings of which may offer a more accurate prediction of the behavior of the technology in general clinical practice (eg, France, Germany, and Sweden). Also, there appears to be emerging recognition of the need for flexibility in evidence expectations under certain circumstances. Recently, Germany’s Institute for Quality and Efficiency in Health Care, which conducts
### Technology selection

**Selection criteria:**
- Burden of disease (population affected, mortality, and morbidity)
- Resource impact (National Health Service costs and resources)
- Clinical importance
- Policy importance (alignment with government priority areas)
- Inappropriate variations in practice
- Likelihood of national guidance adding value

**Technology selection panel composition:**
- Health care providers (specialists, general practitioners, and public health professionals)
- Patient representatives

Typically considered in order received

### Health technology assessment

#### Synthesis and analysis of evidence (assessment report)

- Single technology appraisals
  - Manufacturer through submission requirements
  - Methods must comply with National Institute for Health and Clinical Excellence systematic review and economic guidelines

- Multiple technology appraisals
  - Independent academic group

#### Evaluation of evidence provided (evaluation report)

- Single technology appraisals
  - Independent academic group
  - Welsh Medicines Partnership

- Multiple technology appraisals
  - Independent academic group

Most centralized reimbursement systems (20/23) have made mandatory the inclusion of a formal economic evaluation/analysis for either some (ie, those for which alternative(s) exist(s), eg, Germany, or those offering “added therapeutic value,” eg, Austria and Belgium, or all candidate technologies to inform deliberations around “value for money” and/or “efficiency.” In the latter case, the type of evaluation is rarely stipulated, because options available depend, in part, on the magnitude of the incremental benefit of the technology over its comparators. However, a rationale must be presented, and methods adopted must comply with economic guidelines developed or endorsed by the centralized reimbursement system (Table 4). For technologies that appear to offer “added therapeutic value” (ie, are more effective), some systems indicate a preference for certain types of evaluations, such as cost-utility analysis by Ireland’s Health Service Executive. Others state explicitly which types will not be accepted, such as cost-benefit analysis by Belgium’s Drug Reimbursement Committee. In addition to a formal economic evaluation, the Institute for Quality and Efficiency in Health Care in Germany requires an efficiency frontier analysis, which assesses the relative value of different technologies within a given therapeutic area. Regarding the perspective to be taken for...
**Table 3** Comparison of clinical evidence requirements

| Country      | Centralized reimbursement review/decision-making body (role)                                                                 | Clinical evidence requirements                                                                 |
|--------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Austria      | • Association of Austrian Social Security Institutions (decisions)55                                                        | • Target patient population and indications (therapeutic claim)                                 |
|              | • Pharmaceutical Evaluation Board (recommendations)34                                                                   | • Pharmacology                                                                                  |
|              | • Minister of Social Affairs (decisions)                                                                               | • Safety                                                                                        |
|              | • Commission on reimbursement of medicines/Drug Reimbursement Committee (recommendations)59,92                           | • Efficacy                                                                                      |
|              | • Target patient population and indications (therapeutic claim)                                                          | • Effectiveness (across population subgroups)                                                    |
|              | • Frequency and duration of treatment65                                                                                  | • Efficacy                                                                                      |
|              | • Efficacy                                                                                                               | • Effectiveness (across population subgroups)                                                    |
|              | • Target patient population and indications (therapeutic claim)                                                          |                                                                                                |
|              | • Safety                                                                                                                 |                                                                                                |
| Czech Republic | • State Institute for Drug Control (decisions)55                                                                          | Safety                                                                                          |
|              | • Danish Medicines Agency (decisions)20,69,21                                                                            | Efficacy                                                                                       |
|              | • Reimbursement Committee (recommendations)60,21                                                                            | Effectiveness                                                                                   |
| Denmark      | • Ministry of Social Affairs (decisions)71                                                                               |                                                                                                |
|              | • Pharmaceuticals Committee (recommendations)67                                                                           |                                                                                                |
| Estonia      | • Ministry of Social Affairs (decisions)72                                                                                | Target patient population and indications (therapeutic claim)                                    |
|              | • Pharmaceuticals Committee (recommendations)67                                                                           | Safety                                                                                          |
| Finland      | • Pharmaceuticals Pricing Board (decisions)21,74,76                                                                        | Efficacy                                                                                       |
|              | • Pharmaceuticals Pricing Board Expert Group (recommendations)75                                                          | Effectiveness (across population subgroups)                                                    |
|              | • Target patient population and indications (therapeutic claim)                                                          |                                                                                                |
|              | • Severity and burden of illness                                                                                          |                                                                                                |
|              | • Effectiveness (across population subgroups)76                                                                         |                                                                                                |
| France       | • Ministry for Health and Social Security (decisions)20,78                                                                | Target patient population and indications (therapeutic claim)                                    |
|              | • French National Authority for Health (recommendations)20,78                                                             | Current management                                                                              |
|              | • Place of technology in care pathway                                                                                     | Place of technology in care pathway                                                              |
|              | • Safety                                                                                                                 | Safety                                                                                          |
|              | • Efficacy                                                                                                               | Efficacy                                                                                       |
|              | • Effectiveness (across population subgroups)16                                                                         | Effectiveness (across population subgroups)                                                    |
| Germany      | • Federal Joint Committee (decisions)39                                                                                    | Target patient population and indications (therapeutic claim)                                    |
|              | • Institute for Quality and Efficiency in Health Care (recommendations)53,141                                             | Severity and burden of illness                                                                   |
|              | • Target patient population and indications (therapeutic claim)                                                          | Safety                                                                                          |
|              | • Severity and burden of illness                                                                                          | Efficacy                                                                                       |
|              | • Effectiveness (across population subgroups)9                                                                           | Effectiveness (across population subgroups)                                                    |
| Greece       | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)65                                | Safety                                                                                          |
|              | • Efficacy                                                                                                               | Efficacy                                                                                       |
|              | • Effectiveness145                                                                                                       | Effectiveness (across population subgroups)                                                    |
| Preferred clinical outcomes | Type | Source |
|----------------------------|------|--------|
| • Not specified            | Preference for:  
  • Double-blind randomized controlled trials  
  • Systematic reviews and meta-analyses of randomized controlled trials complying with internationally recognized guidelines | Published, peer-reviewed studies  
 Unpublished reports and studies may be accepted in exceptional circumstances  
 Commercial, in-confidence data |
| • Morbidity                | Preference for:  
  • Randomized controlled trials  
  • Observational head-to-head comparative studies  
  • Effectiveness studies (over efficacy studies)  
  • Minimum of one positive superiority trial on primary endpoints against active control or placebo (if no alternative treatments exist) | Published, peer-reviewed studies  
 Unpublished reports and studies  
 Abstracts not accepted |
| • Adverse events/complications | Preference for:  
  • Randomized controlled trials comparing pharmaceutical to standard care | Published, peer-reviewed studies |
| • Quality of life          | Preference for:  
  • Randomized controlled trials comparing pharmaceutical to standard care  
  Evidence from other available direct comparative experimental and observational studies, as well as meta-analyses, should be included | Published, peer-reviewed studies |
| • Overall survival/mortality | Preference for:  
  • Head-to-head, double-blind randomized controlled trials  
  • Other direct comparative studies  
  • Post-market studies  
  • Systematic reviews and meta-analyses of randomized controlled trials complying with internationally recognized guidelines | Published, peer-reviewed studies  
 Current national and international clinical practice guidelines  
 Expert opinion  
 Surveys of practice  
 Commercial, in-confidence data |
| • Morbidity                | Preference for:  
  • Randomized controlled trials comparing pharmaceutical to placebo, standard care, or no active treatment  
  Evidence from other available direct comparative experimental and observational studies, as well as systematic reviews and meta-analyses complying with internationally recognized guidelines, should also be included  
  • If no treatment alternative exists, well-documented case series acceptable | Published, peer-reviewed studies  
 Commercial, in-confidence data not accepted unless it can be published |
| • Overall survival/mortality | Preference for:  
  • All clinical trials | Not specified |
| • Quality of life          | Preference for:  
  • Randomized controlled trials | Not specified |
| • Side effects             | Preference for:  
  • Randomized controlled trials | Published, peer-reviewed studies |
| • Adverse events/complications | Preference for:  
  • Randomized controlled trials | Published, peer-reviewed studies |
| • Duration of illness      | Preference for:  
  • Randomized controlled trials | Published, peer-reviewed studies |
| • Health status            | Preference for:  
  • Randomized controlled trials | Published, peer-reviewed studies |
| • Topic specific outcomes identified in consultation with patient organizations | Preference for:  
  • Not specified | Not specified |
| • Validated surrogate outcomes | Preference for:  
  • Not specified | Not specified |

(Continued)
| Country       | Centralized reimbursement review/decision-making body (role) | Clinical evidence requirements |
|--------------|-------------------------------------------------------------|--------------------------------|
| **Hungary**  | • Ministers of Health and Finance (decisions)               | • Severity and burden of illness |
|              | • National Health Insurance Fund Administration             | • Current management            |
|              | (recommendations)                                           | • Safety                        |
|              | • Efficacy                                                  | • Effectiveness (across population subgroups) |
|              | • Italy Medicines Agency Technical Scientific                | • Safety                        |
|              | Committee (decisions)                                       | • Efficacy                      |
|              | • Italian Medicines Agency Pricing and Reimbursement        | • Effectiveness (across population subgroups) |
|              | Committee (recommendations)                                 |                                 |
| **Ireland**  | • Health Service Executive (decisions)                      | • Target patient population and indications (therapeutic claim) |
|              |                                                             | • Severity and burden of illness |
|              |                                                             | • Current management            |
|              |                                                             | • Safety                        |
|              |                                                             | • Efficacy                      |
|              |                                                             | • Effectiveness (across population subgroups) |
| **Italy**    | • Italian Medicines Agency Technical Scientific Committee   | • Severity and burden of illness |
|              | (decisions)                                                 | • Current management            |
|              | • Italian Medicines Agency Pricing and Reimbursement        | • Safety                        |
|              | Committee (recommendations)                                 | • Efficacy                      |
|              | • Target patient population and indications (therapeutic claim) | • Effectiveness (across population subgroups) |
|              | • Severity and burden of illness                            |                                 |
|              | • Current management                                        |                                 |
|              | • Place of technology in care pathway                       |                                 |
|              | • Safety                                                    |                                 |
|              | • Efficacy                                                  |                                 |
|              | • Effectiveness (across population subgroups)               |                                 |
| **Norway**   | • Norwegian Medicines Agency (decisions)                    | • Target patient population and indications (therapeutic claim) |
|              | • Department of Pharmacoeconomics (recommendations)         | • Severity and burden of illness |
|              |                                                             | • Current management            |
|              |                                                             | • Place of technology in care pathway |
|              |                                                             | • Safety                        |
|              |                                                             | • Efficacy                      |
|              |                                                             | • Effectiveness (across population subgroups) |
| **Poland**   | • Ministry of Health (decisions)                            | • Severity and burden of illness |
|              |                                                             | • Current management            |
|              |                                                             | • Place of technology in care pathway |
|              |                                                             | • Safety                        |
|              |                                                             | • Efficacy                      |
|              |                                                             | • Effectiveness (across population subgroups) |
| **Portugal** | • Ministry of Health (decisions)                            | • Severity and burden of illness |
|              | • INFARMEDE (recommendations)                               | • Current management            |
|              |                                                             | • Place of technology in care pathway |
|              |                                                             | • Safety                        |
|              |                                                             | • Efficacy                      |
|              |                                                             | • Effectiveness (across population subgroups) |
| **Scotland** | • National Health Service Scotland (decisions)              | • Target patient population and indications (therapeutic claim) |
|              | • Scottish Medicines Consortium (recommendations)           | • Severity and burden of illness |
|              |                                                             | • Current management            |
|              |                                                             | • Place of technology in care pathway |
|              |                                                             | • “Comparative” safety          |
|              |                                                             | • Efficacy                      |
|              |                                                             | • Effectiveness (across population subgroups) |
| **Slovakia** | • Ministry of Health (decisions)                            | • Target patient population and indications (therapeutic claim) |
|              | • Reimbursement Committee for Medicinal Products             | • Severity and burden of illness |
|              | (recommendations)                                           | • Current management            |
|              | • Patient acceptance                                        | • Safety                        |
|              | • Efficacy                                                  | • Efficacy                      |
|              | • Effectiveness                                             | • Frequency and duration of treatment |
|              | • Target patient population and indications (therapeutic claim) |                                 |
|              | • Severity and burden of illness                            |                                 |
|              | • Current management                                        |                                 |
|              | • Safety                                                    |                                 |
|              | • Efficacy                                                  |                                 |
|              | • Effectiveness                                             |                                 |
| **Spain**    | • Ministry of Health Directorate General of Pharmacy and     | • Target patient population and indications (therapeutic claim) |
|              | Health Products; Inter-Ministerial                        | • Severity and burden of illness |
|              | Pricing Commission (decisions)                             | • Current management            |
|              |                                                             | • Safety                        |
|              |                                                             | • Efficacy                      |
|              |                                                             | • Effectiveness                  |
| Preferred clinical outcomes | Type | Source |
|-----------------------------|------|--------|
| • Not specified              | Preference for: Randomized controlled trials | Published, peer-reviewed studies |
| • Morbidity                 | Preference for: Randomized controlled trials | Not specified |
| • Overall survival/mortality | Preference for: Randomized controlled trials comparing pharmaceutical to standard care | Not specified |
| • QALYs – measured in patients but valued by public/society | Evidence from other available direct comparative experimental and observational studies, as well as systematic reviews and meta-analyses complying with Irish Health Technology Assessment Guidelines, should also be included | Not specified |
| • All other health benefits accrued by individuals | Preference for: Systematic reviews and meta-analyses complying with internationally recognized guidelines | Not specified |
| • Morbidity                 | Preference for: Head-to-head, double-blind randomized controlled trials | Published, peer-reviewed studies |
| • Overall survival/mortality | Preference for: Other direct comparative studies | Unpublished reports and studies |
| • Quality of life            | Preference for: Systematic reviews and meta-analyses complying with internationally recognized guidelines | Unpublished reports and studies |
| • Morbidity                 | Preference for: Randomized controlled trials | Published, peer-reviewed studies |
| • Overall survival/mortality | Preference for: Effectiveness studies of target population (over efficacy studies) | Not specified |
| • Quality of life            | Preference for: Comparative clinical trials | Not specified |
| • Morbidity                 | Preference for: Other study designs accepted, but rationale must be provided | Published, peer-reviewed studies |
| • Overall survival/mortality | Preference for: Randomized controlled trials required | Unpublished reports and studies |
| • Quality of life            | Preference for: Comparative observational studies accepted | Expert opinion |
| • QALYs (strongly preferred) | Preference for: If no head-to-head studies available, indirect comparison required | Submissions from patient and carer organizations |
| • Morbidity                 | Preference for: Comparative studies | Published, peer-reviewed studies |
| • Overall survival/mortality | Preference for: Randomized controlled trials | Unpublished reports and studies with negative findings |
| • Adverse events/complications | Preference for: Evidence from other available direct comparative experimental and observational studies should also be included | Not specified |
| • Quality of life            | Preference for: | Not specified |

(Continued)
the economic evaluation, the proportion of systems adopting a “payer,” “societal,” or both “payer” and “societal” perspective is similar. Among systems considering a payer’s perspective only, costs to be captured are often restricted to those directly related to care associated with the use of the candidate technology throughout the course of a disease or condition (ie, direct costs to the health care system). One exception is the National Institute of Health and Clinical Excellence, which specifies inclusion of direct and indirect costs to the National Health Service and Personal Social Services. In systems requiring a societal perspective, costs specified comprise direct costs to not only the health care system, but also services beyond health care and indirect (lost productivity) costs. However, they must be reported separately (eg, Finland, Portugal, and the Netherlands). In Sweden, The Dental and Pharmaceutical Benefits Board has taken a wider view on indirect costs, requesting that time lost by patients and carers be considered, along with lost productivity. Thus, its methods broadly resemble those of “holistic” economic analysis, a technique initially developed for economic evaluations of public programs, the costs and benefits of which are often complex. Nevertheless, considerable debate over the valuation of items such as “time lost” within academic and policy communities remains. This may be why other systems employing a societal perspective have assumed a narrower position on eligible indirect costs. With respect to the choice of comparator for the economic evaluation, almost all systems specify use of one of the following: “standard care,” “the most commonly used alternative,” or “alternative most likely to be replaced.” France also requires separate analyses with two additional comparators, ie, the most recently reimbursed alternative and the least expensive alternative. In Belgium, if the candidate technology represents an “addon” treatment, the comparator must constitute current treatment without the candidate technology. Further, the use of “offlabel” treatments as the comparator is not permitted. All systems rely upon sensitivity analyses to assess the stability of estimates generated through the economic evaluation, but few stipulate the type. Among those that do, probabilistic sensitivity analysis is the most commonly prescribed (eg, Belgium, Germany, Scotland, Slovakia, the UK, and Wales).
| Preferred clinical outcomes | Type | Source |
|----------------------------|------|--------|
| Morbidity                  | Preference for: randomized controlled trials comparing pharmaceutical to standard care | • Commercial, in-confidence data |
| Overall survival/mortality | Systematic reviews or meta-analyses complying with internationally recognized guidelines | • Commercial, in-confidence data |
| Quality of life            | Evidence from other available direct comparative experimental and observational studies should also be included | • Commercial, in-confidence data |
| QALYs (preferred)         | Not specified | • Not specified |
| Morbidity                  | Preference for: head-to-head randomized controlled trials | • Published, peer-reviewed studies |
| Overall survival/mortality | Systematic reviews or meta-analyses complying with internationally recognized guidelines | • Published, peer-reviewed studies |
| Quality of life            | Evidence from other available direct comparative experimental and observational studies should also be included | • Published, peer-reviewed studies |
| QALYs – measured in patients but valued by public/society | Not specified | • Published, peer-reviewed studies |
| Morbidity                  | Preference for: all types of clinical studies accepted, but greater importance given to high quality ones | • Published, peer-reviewed studies |
| Overall survival/mortality | Systematic reviews or meta-analyses complying with internationally recognized guidelines | • Published, peer-reviewed studies |
| Quality of life            | Effectiveness studies of target population (over efficacy studies) | • Published, peer-reviewed studies |
| QALYs (preferred)         | Randomized controlled trials conducted in “naturalistic” settings | • Published, peer-reviewed studies |
| Morbidity                  | Systematic reviews or meta-analyses complying with internationally recognized guidelines | • Published, peer-reviewed studies |
| Overall survival/mortality | Evidence from other available direct comparative experimental and observational studies should also be included | • Published, peer-reviewed studies |
| Quality of life            | Evidence from health care professionals, administrators, government, and manufacturers | • Published, peer-reviewed studies |
| QALYs – measured in patients but valued by public/society | Published, peer-reviewed studies | • Published, peer-reviewed studies |

In recent years, affordability has become an increasingly important consideration for centralized reimbursement systems, with almost all of those included in this review (where information could be found) requiring a budget impact analysis (Table 4). However, some waive this analysis in certain circumstances, eg, when no alternative treatment exists (Belgium). Although information describing the specific costs to be included appears scarce, based on that available, they mirror those for the economic evaluation of the same technology. Specifically, if the economic evaluation is limited to direct costs, so must the budget impact analysis, eg, Hungary and Ireland.

Reimbursement decisions: review committee composition, procedures, and key factors

In most of the centralized reimbursement systems, the assessment and evaluation reports are sent to and scrutinized by a review committee (sometimes referred to as an appraisal committee). While the composition of this committee varies across systems, it is usually multidisciplinary, with members representing payers, administrators, health care providers, and academia (eg, health economists, Table 5). Approximately one-third have also appointed patient representatives to their respective committees (eg, Sweden, Switzerland, and the UK), although not always as voting members (Germany), and one-fifth include manufacturers (Belgium, Switzerland, the UK, and Wales). In most systems, the authority of the review committee is advisory (ie, makes recommendations). Aside from lists of factors/criteria considered (Table 6), publicly available procedural information on committee deliberations is often limited to conditions under which presentations/testimonials from external experts (including patients) are sought or accepted and whether an incremental cost-effectiveness ratio threshold is employed. Among the exceptions is France. There, review committees (the Commission d’Evaluation des Medicaments (CEM), followed by the Transparency Commission) adhere to a two-stage process. First, the CEM assigns a “medical benefit” or “SMR” level/
| Country               | Centralized reimbursement review/decision-making body (role)                                                                                                                                                                                                 | Economic analysis Required                                                                 | Economic analysis types accepted                                                                 | Perspective/costs included |
|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------|
| Austria               | • Association of Austrian Social Security Institutions (decisions)<sup>35</sup>                                                                                                                      | Yes for:  • "innovative products providing substantial therapeutic benefit"<sup>21</sup> | • Any type, but rationale for selection must be provided<sup>21</sup>                                                                         | • Payer<sup>21</sup> |
|                       | • Pharmaceutical Evaluation Board (recommendations)<sup>34</sup>                                                                                                                                                                                                | • "where no comparable medical preparation exists"<sup>21</sup>                                                                                       | • Should comply with internationally recognized phar-macoeconomic guidelines<sup>21</sup>       | • Costs not specified |
| Belgium               | • Minister of Social Affairs (decisions)<sup>25</sup>                                                                                                                                                                                                       | Yes for:  • Pharmaceuticals with added therapeutic value relative to existing alternatives (Class I)<sup>11,17</sup> | • Cost effectiveness                                                                                                                                                                                                 | • Payer<sup>21</sup> |
|                       | • Commission on reimbursement of medicines/drug reimbursement committee (recommendations)<sup>34</sup>                                                                                                       | • Not required for orphan pharmaceuticals<sup>32</sup>                                                                                          | • Cost utility                                                                                                   | • Direct costs only<sup>11,17</sup> |
| Czech Republic        | • State Institute for Drug Control (decisions)<sup>24</sup>                                                                                                                                                                                                     | Yes<sup>34</sup>                                                                                                                                  | • Cost effectiveness                                                                                     | • Payer<sup>21</sup> |
| Denmark               | • Danish Medicines Agency (decisions)<sup>34,38,21</sup>                                                                                                                                                                                                | No, but often included to justify high price<sup>54,71,140</sup>                                                                            | • Cost effectiveness                                                                                     | • Direct costs<sup>118</sup> |
|                       | • Reimbursement Committee (recommendations)<sup>34,21</sup>                                                                                                                                                                                                    | No information found Method not found                                                                                                             | • Cost utility                                                                                              | • Societal<sup>21</sup> |
| Estonia               | • Ministry of Social Affairs (decisions)<sup>72</sup>                                                                                                                                                                                                       | Yes<sup>84,129</sup>                                                                                                                                  | • Cost minimization rationale for selection must be provided<sup>39</sup>                              | • Direct costs within and outside of the health care system (should be reported separately)<sup>19</sup> |
|                       | • Pharmaceuticals Committee (recommendations)<sup>72</sup>                                                                                                                                                                                                     | • Reimbursement status in other European Union countries<sup>55</sup>                                                                          | • Rationale must be provided<sup>21</sup>                                                                        | • Direct and indirect costs – presented separately<sup>26</sup> |
| Finland               | • Pharmaceuticals Pricing Board (decisions)<sup>72,74,76</sup>                                                                                                                                                                                               | Yes for:  • Pharmaceuticals considered for reimbursement in one of the special refund categories<sup>74,76</sup> | • Any type, but rationale for selection must be provided<sup>26</sup> | • Payer<sup>179</sup> |
|                       | • Pharmaceuticals Pricing Board Expert Group (recommendations)<sup>75</sup>                                                                                                                                                                                     | • Multiple technology appraisals of pharmaceuticals<sup>10</sup>                                                                                | • Methods must comply with Ministry of Social Affairs and Health guidelines<sup>29</sup>             | • Direct and indirect costs – presented separately<sup>26</sup> |
| France                | • Ministry for Health and Social Security (decisions)<sup>79,78</sup>                                                                                                                                                                                      | Yes for:  • Multiple technology appraisals of pharmaceuticals<sup>10</sup>                                                                                | • Any type, but rationale for selection must be provided<sup>21</sup> | • Varies, but should take the widest possible perspective – rationale for selection must be provided<sup>84</sup> |
|                       | • French National Authority for Health (recommendations)<sup>78</sup>                                                                                                                                                                                               | • Methods must comply with French economic guidelines<sup>35</sup>                                                                                     | • Direct costs; may include indirect costs, but must be presented separately<sup>22</sup>          |                            |
| Comparator | Sensitivity analysis | Systematic review of economic analysis studies | Budget impact analysis Required | Costs included | Other economic information |
|------------|----------------------|-----------------------------------------------|--------------------------------|----------------|----------------------------|
| • Most commonly used alternative<sup>21</sup> | Yes – type not specified<sup>21</sup> | Yes | No information found | N/A | • 3 year market sales forecast  
• Price in other European Union countries  
• Reimbursement status in other European Union countries<sup>15</sup> |
| • Most commonly used alternative OR  
• Alternative most likely to be replaced  
• If add-on: current treatment without add-on<sup>17</sup>  
• Off-label treatments not acceptable<sup>11</sup>  
Rationale must be provided | Probabilistic<sup>17</sup> | Yes<sup>17</sup> | Yes<sup>11</sup> | • Direct costs only<sup>11,17</sup> | • Price  
• Reimbursement status in other European Union countries<sup>11,17</sup> |
| No information found | Method not specified | No information found | Yes<sup>18</sup> | No information found | No information found  
• Reimbursement status in other European Union countries  
• Estimated consumption (number of patients and utilization)<sup>10</sup> |
| • Most commonly used alternative<sup>19</sup>  
Rationale must be provided | Method not specified | Method not specified, but key parameters associated with uncertainty should be explored<sup>18</sup> | No information found | No information found | No information found  
• Reimbursement status in other European Union countries  
• Estimated consumption (number of patients and utilization)<sup>10</sup> |
| • Most commonly used alternative OR  
• Standard care<sup>139</sup>  
Rationale must be provided | Method not specified | No information found | No information found | No information found | No information found  
• Reimbursement status in other European Union countries  
• Estimated consumption (number of patients and utilization)<sup>10</sup> |

(Continued)
**Table 4 (Continued)**

| Country       | Centralized reimbursement review/decision-making body (role)                                                                 | Economic analysis Required                                                                                                                                                                                                 | Economic analysis types accepted                                                                 | Perspective/costs included                                                                 |
|---------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Germany       | • Federal Joint Committee (decisions)¹⁹  
• Institute for Quality and Efficiency in Health Care (recommendations)²⁹,³⁴,¹⁴⁶ | Yes for:  
• Technologies where alternative treatment exists⁸,¹⁸  
• Cost effectiveness  
• Cost utility  
• Cost minimization/cost comparison¹⁸  
Efficiency frontier analysis¹²  
No information found | Any one of:  
• Cost effectiveness  
• Cost utility  
• Cost minimization/cost comparison¹⁸  
No information found | • Payer  
• Patient²³  
• Direct and indirect costs⁸ |
| Greece        | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)³⁵,¹⁴⁰ | Yes for:  
• Pharmaceuticals eligible for reference price system⁸⁵ | Preference for:  
• Cost effectiveness  
• Cost utility¹⁴³  
• Payer  
• Societal (also recommended)  
Report results from each perspective separately¹⁶³ | No information found |
| Hungary       | • Ministers of Health and Finance (decisions)  
• National Health Insurance Fund Administration (recommendations)⁶⁶,⁹⁰,¹⁰² | Yes¹⁴⁴ | Preference for:  
• Cost utility¹⁰  
Any one of the following may be acceptable if rationale is provided:  
• Cost benefit  
• Cost effectiveness  
• Cost minimization/cost comparison¹⁴⁷,¹⁶⁵  
• Methods must comply with Irish Healthcare Technology Assessment Guidelines¹⁴⁶  
• Methods must comply with Italian pharmacoeconomic guidelines¹⁴⁸  
• Payer¹⁴⁷  
• Direct costs only¹⁴⁷ | • Payer¹⁴⁷  
• Direct costs only¹⁴⁷ |
| Ireland       | • Health Service Executive (decisions)⁹¹,⁹² | Yes¹⁴⁶ | Preference for:  
• Cost utility¹⁰  
Any one of the following may be acceptable if rationale is provided:  
• Cost benefit  
• Cost effectiveness  
• Cost minimization/cost comparison¹⁴⁷,¹⁶⁵  
• Methods must comply with Irish Healthcare Technology Assessment Guidelines¹⁴⁶  
• Methods must comply with Italian pharmacoeconomic guidelines¹⁴⁸  
• Societal AND  
• Payer¹⁴⁸  
• Direct and indirect costs¹⁴⁸ | • Payer¹⁴⁷  
• Direct costs only¹⁴⁷ |
| Italy         | • Italian Medicines Agency Technical Scientific Committee (decisions)⁹⁴  
• Italian Medicines Agency Pricing and Reimbursement Committee (recommendations)⁹⁶ | Yes for:  
• Pharmaceuticals with a favorable “risk/benefit profile”⁹⁷,¹⁴⁸ | Preference for:  
• Cost utility  
• Cost effectiveness¹⁴⁸  
• Methods must comply with Italian pharmacoeconomic guidelines¹⁴⁸  
• Payer¹⁴⁸ | • Societal AND  
• Payer¹⁴⁸ |
| Norway        | • Norwegian Medicines Agency (decisions)⁹⁹  
• Department of Pharmaco economics (recommendations)⁹⁹ | Yes for:  
• Pharmaceuticals with added therapeutic value relative to existing alternatives⁴⁴ | Preference for:  
• Cost-value analysis¹⁵⁰  
Any one of the following may be acceptable if rationale is provided:  
• Cost benefit  
• Cost effectiveness  
• Cost utility  
• Cost consequence  
• Cost minimization/cost comparison¹⁴⁸  
• Methods must comply with Norwegian pharmacoeconomic guidelines⁹⁸ | • Societal AND  
• Payer¹⁵⁰ |
| Comparator | Sensitivity analysis | Systematic review of economic analysis studies | Budget impact analysis | Other economic information |
|------------|---------------------|-----------------------------------------------|-----------------------|---------------------------|
| • Most commonly used alternative OR<br>• Most effective alternative OR<br>• Minimum standard care | One-way and multi-way (performed as probabilistic) | Yes | Yes, except when no alternative exists | No information found | No information found |
| No information found | No information found | No information found | Yes | No information found |
| • Standard care | Yes, but type not specified | No information found | Yes | No information found |
| • Standard care | Probabilistic and deterministic | No information found | Yes | No information found |
| • Most commonly used alternative | Methods not specified, but should involve multi-way analysis | No information found | Yes | No information found |
| • Most commonly used alternative OR<br>• Least expensive alternative | Probabilistic preferred | No information found | Yes, aggregate added expense to health service for first 5 years | No information found |

(Continued)
Table 4 (Continued)

| Country | Centralized reimbursement review/decision-making body (role) | Economic analysis Required | Economic analysis types accepted | Perspective/ costs included |
|---------|---------------------------------------------------------------|-------------------------------|---------------------------------|-----------------------------|
| Poland  | • Ministry of Health (decisions)89,146                         | Yes for:                      | • Cost effectiveness           | • Societal AND              |
|         |                                                                | • Pharmaceuticals with added  | • Cost utility84                | • Payer167                  |
|         |                                                                | therapeutic value relative    |                                 |                             |
|         |                                                                | to existing alternatives84    |                                 |                             |
|         | • Economic analysis Budget impact analysis Other economic     |                               |                                 |                             |
|         | types accepted                                                |                               |                                 |                             |
|         | • Comparator Sensitivity analysis                              |                               |                                 |                             |
|         | • Systematic review of economic analysis studies               |                               |                                 |                             |
| Portugal| • Ministry of Health (decisions)84,160                         | Any one of:                   | • Societal191                   |                             |
|         | • INFARMED (recommendations)84,160                            | • Cost benefit                | • Direct costs                  |                             |
|         |                                                                | • Cost effectiveness          | • Indirect costs: only those   |                             |
|         |                                                                | • Cost utility                | related to lost productivity191|                             |
|         | • Cost minimization/ cost comparison; rationale for selection  | • Methods must comply with   | • Payer190                     |                             |
|         |                                                                 | SMC economic guidelines192    |                                 |                             |
|         | • Methods not specified                                        |                              |                                 |                             |
|         | • Cost effectiveness                                          |                              |                                 |                             |
|         | • Cost utility                                                |                              |                                 |                             |
|         | • Cost minimization/ cost comparison; rationale for selection  |                              |                                 |                             |
|         | • Cost benefit not accepted                                    |                              |                                 |                             |
|         | • Methods must comply with national economic guidelines192    |                              |                                 |                             |
|         | • Direct costs                                                |                              |                                 |                             |
|         | • Cost effectiveness                                          |                              |                                 |                             |
|         | • Cost utility                                                |                              |                                 |                             |
| Scotland| • National Health Service Scotland (decisions)30               | Any one of the following may | • Societal191                   |                             |
|         | • Scottish Medicines Consortium (recommendations)              | be acceptable if rationale is| Direct costs192                  |                             |
|         |                                                                | provided:                    | • Payer190                     |                             |
|         | • Cost effectiveness                                          | • Cost benefit                |                                 |                             |
|         | • Cost utility                                                | • Cost effectiveness         |                                 |                             |
|         | • Cost minimization/ cost comparison                          | • Cost utility                |                                 |                             |
|         | • Methods must comply with clinical practice guidelines193    | • Cost benefit not accepted193|                                 |                             |
| Slovakia| • Ministry of Health (decisions)105,106                        | Preference for:              | • Societal AND                  |                             |
|         | • Reimbursement Committee for Medicinal Products (recommendations)105,107 | • Cost effectiveness         | • Payer190                     |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | • Cost utility                | Present separately              |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | (if pharmaceutical has impact on quality of life) |                             |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | • Cost minimization/ cost     |                                 |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | comparison                   |                                 |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | • Cost benefit                |                                 |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | • Cost effectiveness         |                                 |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | • Cost utility                |                                 |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | • Cost minimization/ cost     |                                 |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | comparison                   |                                 |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | • Cost benefit                |                                 |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | • Cost effectiveness         |                                 |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | • Cost utility                |                                 |                             |
|         | • Ministry of Health Directorate General of Pharmacy and      | • Cost minimization/ cost     |                                 |                             |
|         | • Inter-Ministerial Pricing Commission (decisions)21,108,173   | comparison                   |                                 |                             |

(Continued)
| Comparator | Sensitivity analysis | Systematic review of economic analysis studies | Budget impact analysis | Other economic information |
|------------|----------------------|-----------------------------------------------|-----------------------|----------------------------|
| • Alternative most likely to be replaced OR | Methods not specified | No information found | Yes84 | No information found |
| • Most commonly used alternative OR | Methods not specified | No information found | No101 | N/A |
| • Least expensive alternative OR | | | | |
| • Standard care compliant with clinical practice guidelines101 | | | | |
| • Most commonly used alternative | Probabilistic168 | No information found | Yes20 | No information found |
| • Standard care101 | | | | |
| • Alternative most likely to be replaced OR | Probabilistic168,152 | Yes152 | Yes Estimated over first 5 years84 | No information found |
| • Most commonly used alternative | Multi-way10 | No information found | Yes, comparing “corresponding products”10 | No information found |
| • Standard care10 | | | | |
| Rationale must be provided | | | | |

(Continued)
score to the candidate technology (a new pharmaceutical). The score is based on a five-point scale, with “I” representing “major medical benefit” and “V” representing “insufficient to justify reimbursement.” Upon approval of the score by the Minister, the CEM then compares the technology with already reimbursed alternatives in order to formulate an opinion on the “improvement in medical benefit” or “ASMR” level. Six possible levels exist, ranging from I (major innovation) to VI (negative opinion regarding inclusion on the benefit list). Therefore, “innovativeness” is viewed as the size of the incremental clinical benefit achieved by the candidate technology. The opinion of the CEM is forwarded to the Transparency Commission, who makes a formal recommendation on the ASMR classification. This classification is, in turn, used to negotiate price and reimbursement rate. In Germany, the “innovativeness” of a technology is also based on whether it offers “added therapeutic value.” Moreover, it plays an important role in determining the content of subsequent committee deliberations, because “cost-benefit” analyses are only taken into account when a technology has been deemed

| Country      | Centralized reimbursement review/decision-making body (role)                                                                 | Economic analysis Required                                                                 | Economic analysis types accepted                                                                 | Perspective/ costs included                  |
|--------------|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------|
| Sweden       | • Dental and Pharmaceutical Benefits Board (decisions)\(^1\),\(^{109}\)                                                       | Yes, if requested\(^{27}\)                                                                   | Any one of:                                                                                        | • Societal                                    |
|              |                                                                                                                             |                                            | • Cost effectiveness                                                                            | • Direct costs                               |
|              |                                                                                                                             |                                            | • Cost utility                                                                                 | • Indirect costs: lost productivity and lost time for patients and carers\(^{14},^{15}\) |
| Switzerland  | • Swiss Federal Office of Public Health (decisions)\(^{12}\),\(^{14}\)                                                          | No, but should be included if available\(^{15},^{172}\)                                     | No information found                                                                           | No information found                         |
| The Netherlands | • Ministry of Health, Welfare and Sport (decisions)                                                                        | Yes\(^7\)                                                                                 | • Cost effectiveness                                                                            | • Societal                                    |
|              | • Pharmaceutical Reimbursement Committee of the Dutch Healthcare Insurance Board (recommendations)\(^{16}\)                |                                            | • Cost utility                                                                                 | • Direct costs                               |
|              | • National Institute for Health and Clinical Excellence (decisions)                                                        |                                            | • Methods must comply with Dutch Healthcare Insurance Board economic guidelines\(^{14},^{173}\) | • Indirect costs may be included but must be reported separately\(^{154}\)                   |
| United Kingdom | • Technology Appraisals Committee (recommendations)\(^{2}\)                                                                     |                                            | • Cost effectiveness                                                                            | • Payer\(^{13},^{157}\)                     |
| Wales        | • Ministry for Health and Social Services (decisions)\(^{20}\)                                                             | Yes\(^{174}\)                                                                              | Any one of:                                                                                        | • Direct and indirect costs to National Health Service and Personal Social Services |
|              | • All Wales Medicines Strategy Group (recommendations)\(^{28}\)                                                            |                                            | • Cost effectiveness                                                                            | • Societal\(^{23}\)                          |
### Table 4 (Continued)

| Comparator                                                                 | Sensitivity analysis | Systematic review of economic analysis studies | Budget impact analysis Required | Costs included | Other economic information |
|---------------------------------------------------------------------------|----------------------|-----------------------------------------------|---------------------------------|---------------|-----------------------------|
| • Most commonly used alternative<sup>15</sup>                            | Not specified        | No information found                          | No information found            |               |                             |
| No information found                                                      |                      |                                               |                                  |               |                             |
| • Most commonly used alternative OR <sup>13,157</sup>                   | One-way, multi-way, and probabilistic<sup>15</sup> | No information found                          | Yes<sup>15,174</sup>            | No information found |                             |
| • Most relevant reimbursed alternative<sup>13,157</sup>                  | Probabilistic<sup>137</sup> | Yes<sup>13,157</sup>                           | Yes<sup>13,157</sup>            | No information found |                             |
| • Most commonly used alternative OR                                      | Probabilistic<sup>28</sup> | Yes<sup>28</sup>                               | Yes<sup>28,174</sup>            | No information found |                             |

Innovative.<sup>18–24</sup> The review committee of the Italian Medicines Agency, ie, the Technical Scientific Committee, explicitly weighs both the availability of existing treatments and the extent of clinical benefit in its assessment of a new pharmaceutical’s innovativeness. The two attributes are scored separately and then combined to determine whether it represents an “important,” “moderate,” or “modest” innovation.<sup>25</sup> This rating, along with the category of clinical value to which the pharmaceutical has been assigned, is sent to a second review committee, ie, the Pricing and Reimbursement Committee, which negotiates price and reimbursement status with the manufacturer.<sup>26,27</sup>

Regardless of the reimbursement system, one of the main goals of the review committee is to determine the “therapeutic value” of a candidate technology. Broadly, its assessment combines consideration of clinical benefit with that of clinical need, taking into account key factors related to each dimension. For clinical need, they comprise, at a minimum, burden of illness (prevalence of severity) of the target condition and availability of alternatives. For clinical benefit,
| Country   | Centralized reimbursement review/decision-making body (role)                                                                 | Committee composition                                                                                                                                                                                                 | Steps in review/decision-making process                                                                                                                                                                                                                                                                  | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms                                      |
|----------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------|---------------------------------|
| Austria  | • Association of Austrian Social Security Institutions (decisions) 55                                                      | 20 voting members: • 3 academics  
• 10 from sickness funds  
• 2 from physicians associations  
• 2 from economic chamber  
• 2 from federal chamber of labour  
• 1 from Austrian chamber of pharmacists | 1. Manufacturer submits application for reimbursement to Association of Austrian Social Security Institutions  
2. Internal staff (Department of Pharmaceutical Affairs) prepare evaluation of application (pharmacological and therapeutic) based on evidence presented in application, and assigns pharmaceutical to 1 of 6 categories of therapeutic value – pharmaceuticals classified into categories 5 or 6 can request price above average European Union price  
3. Health economics team evaluates cost effectiveness of pharmaceutical relative to comparable alternatives  
4. Pharmaceutical Evaluation Board deliberates over both evaluation reports and prepares report  
5. Pharmaceutical Evaluation Board sends report to manufacturer for comment  
6. Pharmaceutical Evaluation Board prepares reimbursement recommendation, taking into account responses received from manufacturer  
7. Deputy director of Association of Austrian Social Security Institutions reviews recommendations and makes final decision 55,56,58 | No 51                                               | 180 days (includes pricing and reimbursement decision) 56,58 | • Decision may be appealed to Independent Pharmaceuticals Commission 56,58 |
| Belgium  | • Minister of Social Affairs (decisions)  
• Drug Reimbursement Committee (recommendations) 36,50                                                                       | 31 members (23 voting including chair): • 7 academics  
• 8 from sickness funds  
• 4 physicians  
• 3 from pharmacist associations  
Nonvoting:  
• 2 from pharmaceutical industry  
• 1 from generic pharmaceutical industry  
• 4 from Ministries of Public Health, Social Affairs, and Economic Affairs, and Federal Public Service Budget | 1. Manufacturer submits application for reimbursement to Secretariat of Drug Reimbursement Committee Includes incremental cost-effectiveness ratio (ICER) if Class I claim (added therapeutic value compared to existing alternatives) and simultaneously submits pricing dossier to Federal Public Service economy  
2. Brief overview report of product characteristics prepared  
3. Staff within Bureau of Drug Reimbursement Committee, supported by experts, prepare evaluation of pharmaceutical’s safety, efficacy, effectiveness, applicability, and convenience based on evidence submitted by manufacturer; pricing commission simultaneously examines pricing dossier, determines maximum price, and notifies manufacturer  
4. Drug Reimbursement Committee discusses and approves evaluation report  
5. Drug Reimbursement Committee sends report to manufacturer | No 62                                               | 150 days (includes pricing and reimbursement) 51 | • Decision may be appealed on procedural grounds only  
• Heard by administrative court |
Reimbursement of European health technologies

Czech Republic

- State Institute for Drug Control (decisions) 
- No information found

No

- 1 from National Institute for Health and Disability Insurance

6. Staff prepare draft recommendations, taking into account evaluation report, price from manufacturer, and responses received from manufacturer

7. Drug Reimbursement Committee discusses and approves (by 2/3 majority vote) draft recommendations

8. Drug Reimbursement Committee sends draft recommendations to manufacturer, who must reply within 10 days; manufacturer may request a hearing

9. Drug Reimbursement Committee prepares final recommendations, taking into account responses received from manufacturer

10. Minister receives recommendations, seeks advice from Minister of Budget and financial administration, and makes final decision

Denmark

- Danish Medicines Agency (decisions)
- Reimbursement Committee (recommendations)

Maximun of 7 members: Must include:
- 2 general practitioners
- 1 representative of the regions

No

1. Manufacturer submits application for reimbursement to State Institute for Drug Control

2. Internal staff (Department for Price and Reimbursement Regulation) consult with medical experts, health economists, and patient groups, and prepare evaluation report; assess safety, efficacy, and clinical use first, and then financial aspects

3. State Institute for Drug Control makes decision on price and level of reimbursement, based on evaluation report

4. Health economics expert(s) evaluate(s) economic analysis, if submitted

5. Reimbursement Committee reviews evaluation report, price survey, and review of economic analysis and makes reimbursement recommendation to Danish Medicines Agency

6. If negative, Danish Medicines Agency sends draft recommendations to manufacturer

7. Danish Medicines Agency Board makes final decision

(Continued)
Table 5 (Continued)

| Country    | Centralized reimbursement review/decision-making body (role) | Committee composition | Steps in review/decision-making process | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms |
|------------|-------------------------------------------------------------|------------------------|----------------------------------------|-------------------------------------|------------------------------|-------------------|
| Estonia    | • Ministry of Social Affairs (decisions)72                  | No information found   | No information found                    |                                     | No information found         | No information found |
|            | • Pharmaceuticals Committee (recommendations)72             |                        |                                        |                                     |                              |                   |
|            | 7 members of Pharmaceuticals Pricing Board:                 |                        |                                        |                                     |                              |                   |
|            |   • 2 from Ministry of Social Affairs and Health           |                        |                                        |                                     |                              |                   |
|            |   • 2 from Social Insurance Institution (Kela)             |                        |                                        |                                     |                              |                   |
|            |   • 1 from Ministry of Finance                             |                        |                                        |                                     |                              |                   |
|            |   • 1 from National Agency for Medicines                   |                        |                                        |                                     |                              |                   |
|            |   • 1 from National Research and Development Centre for Welfare and Health | |                                        |                                     |                              |                   |
|            | 7 members of Expert Group:                                 |                        |                                        |                                     |                              |                   |
|            |   • Includes individuals with medical, pharmacological, health economics, and social insurance expertise75,181 | |                                        |                                     |                              |                   |
| Finland    | • Pharmaceuticals Pricing Board (decisions)73,76            | 7 members of Pharmaceuticals Pricing Board: | 1. Manufacturer submits application for reimbursement to Pharmaceuticals Pricing Board secretariat | No 181                             | 180 days (includes pricing and reimbursement decision)181 | Decision may be appealed to Supreme Court181 |
|            | • Pharmaceuticals Pricing Board Expert Group (recommendations)75 |                        | 2. Internal staff, with support from Expert Group, prepare evaluation report based on evidence submitted by manufacturer |                        |                              |                   |
|            | 7 members of Expert Group:                                 |                        | 3. Expert Group reviews report and formulates opinions |                        |                              |                   |
|            |   • Includes individuals with medical, pharmacological, health economics, and social insurance expertise75,181 | | 4. Pharmaceuticals Pricing Board Secretariat presents summary of report and opinions, along with written statement regarding the potential impact of the pharmaceutical on its budget provided by Kela, to Pharmaceuticals Pricing Board |                        |                              |                   |
|            | 7 members of Expert Group:                                 |                        | 5. Pharmaceuticals Pricing Board formulates recommendations |                        |                              |                   |
|            |   • Includes individuals with medical, pharmacological, health economics, and social insurance expertise75,181 | | 6. If negative, Pharmaceuticals Pricing Board sends recommendations to manufacturer, who may choose to lower price or provide additional evidence |                        |                              |                   |
|            | 7. Pharmaceuticals Pricing Board makes final decision74,122,181,182 | | 8. If positive, Pharmaceuticals Pricing Board recommends pharmaceutical for reimbursement |                        |                              |                   |
| France     | • Ministry for Health and Social Security (decisions)20,70   | Transparency Committee within French National Authority for Health: | Single technology appraisals | No 20                              | • 90 days for inpatient pharmaceuticals (includes pricing and reimbursement) | • May appeal recommendation to French National Authority for Health, requesting a hearing or providing written comments |
|            | • French National Authority for Health (recommendations)20  | 20 voting members (includes chair): | 1. Manufacturer submits application for reimbursement to French National Authority for Health secretariat |                      |                              |                   |
|            | 4 from “public institutions”                                |                        | 2. Internal staff prepare evaluation report based on evidence submitted by manufacturer (focuses on clinical effectiveness, target population, conditions of use, and already reimbursed technologies) |                        |                              |                   |
Reimbursement of European health technologies

3 from main health insurance fund
1 from pharmaceutical industry
12 with medical and pharmacological expertise

7 Specialist subcommittees of clinical experts

3. External clinical and methodological experts review evaluation report
4. Commission d'Evaluation des Medicaments reviews evaluation report and expert opinions to appraise the “medical benefit” of the pharmaceutical (on a 5 point scale; I – major to V – insufficient to justify reimbursement)
5. Minister makes final decision on the medical benefit level/score
6. Commission d'Evaluation des Medicaments then performs comparative assessment of pharmaceutical with already reimbursed alternatives to appraise the “improvement in medical benefit” (on a 6 point scale; 1 – major innovation to VI – negative opinion regarding inclusion on benefit list)
7. Transparency Commission considers advice received from Commission d'Evaluation des Medicaments and assigns an “improvement in medical benefit” classification to the pharmaceutical
8. Once positive reimbursement recommendation is received, the Comite Economique des produits de Sante = negotiates price with manufacturer and the Union Nationale des Caisses d'Assurance Maladie fixes the reimbursement rate
9. Minister for Health and Social Security makes final decision on reimbursement level and price

Multiple technology appraisals
1. French National Authority for Health approves technology topic for multiple technology appraisals
2. French National Authority for Health conducts consultations with relevant stakeholders and the Interdisciplinary Economic Evaluation and Public Health Committee to define scope and protocol for multiple technology appraisals
3. Internal staff and/or independent academic group prepares assessment report (includes clinical review and economic analysis)
4. Interdisciplinary Economic Evaluation and Public Health Committee and external experts review assessment report
5. Stakeholders receive assessment report for comment
6. Stakeholders also consulted through working group meetings
7. Appropriate health technology assessment specialist subcommittee appraises report and comments and formulates recommendations
8. French National Authority for Health Board reviews and approves recommendations

180 days for outpatient pharmaceuticals (includes pricing and reimbursement)

Once decision has been made, may appeal to administrative court

(Continued)
Table 5 (Continued)

| Country     | Centralized reimbursement review/decision-making body (role) | Committee composition | Steps in review/decision-making process | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms |
|-------------|-------------------------------------------------------------|-----------------------|----------------------------------------|-------------------------------------|------------------------------|-------------------|
| Germany     | • Federal Joint Committee (decisions)¹⁹                         | 13 members including representatives from:                  | 1. Federal Joint Committee makes decision to assess technology and notifies Institute for Quality and Efficiency in Health Care   | No¹⁸                          | No information found        | • May not appeal recommendations   |
|             | • Institute for Quality and Efficiency in Health Care         | • Associations of physicians, dentists, and physiotherapists | 2. Institute for Quality and Efficiency in Health Care appoints internal staff to manage and/or conduct assessment                  |                                  |                              | • Decision may be appealed to administrative court¹⁹ |
|             | (recommendations)¹⁹                                          | • Hospital associations                                     | 3. Institute for Quality and Efficiency in Health Care carries out consultations with external clinical experts and patient/carer organizations to define assessment scope and protocol |                                  |                              |                                 |
|             |                                                               | • Sickness funds                                             | 4. Institute for Quality and Efficiency in Health Care posts draft scope and protocol on website for public comment                 |                                  |                              |                                 |
|             |                                                               | • Patient organizations (nonvoting)¹⁸,¹⁹                     | 5. Internal staff, supported by external experts, prepare assessment, first considering clinical benefit or innovativeness (ie, is the first active ingredient or offers therapeutic improvement); if deemed noninnovative, technology is assigned to 1 of 3 groups (1: identical active ingredient; 2: therapeutically comparable and one active ingredient; 3: therapeutically comparable and two active ingredients); technologies with similar efficacy/effectiveness must demonstrate comparable efficiency through findings from efficiency frontier analysis¹¹⁹; if deemed innovative (ie, offers added therapeutic value over already reimbursed alternatives), “cost-benefit” analysis is performed to set maximum reimbursable amount; if technology treats life-threatening condition for which there are no alternatives, cost must not be considered¹⁸,¹⁹ |                                  |                              |                                 |
|             |                                                               |                                                               | 6. Institute for Quality and Efficiency in Health Care steering committee reviews draft report and recommendations for quality assurance |                                  |                              |                                 |
|             |                                                               |                                                               | 7. Institute for Quality and Efficiency in Health Care posts draft report and recommendations on website for public comment |                                  |                              |                                 |
|             |                                                               |                                                               | 8. Staff prepare final report, incorporating comments received and recommendations, and submit it to the Institute for Quality and Efficiency in Health Care steering committee for final quality assurance review and then to the Board for final approval |                                  |                              |                                 |
|             |                                                               |                                                               | 9. Board sends recommendations to Federal Joint Committee, who makes final decision¹¹²,¹¹⁴,¹²⁴,¹⁴⁴ |                                  |                              |                                 |
| Country | Key Committees/Decisions | Reimbursement Process | 90 Days (includes pricing and reimbursement decision) | Decision Appeal Committee |
|---------|--------------------------|----------------------|---------------------------------------------------|---------------------------|
| Greece  | Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)\(^{85,86}\) | 1. Manufacturer submits application for reimbursement to Transparency Committee in the Reimbursement and Medicinal Products<br>2. Transparency Committee in the Reimbursement and Medicinal Products recommends classification of pharmaceutical into pre-existing therapeutic category based on “therapeutic and pharmacoeconomic effectiveness”<br>3. Transparency Committee in the Reimbursement and Medicinal Products sends classification recommendation to Ministry of Health and Social Security for approval<br>4. Price set taking into account products already included in assigned category or average of the 3 lowest European prices\(^{186}\) | 90 days | No information found |
| Hungary | Ministers of Health and Finance<br>• National Health Insurance Fund Administration Technology Appraisal Committee (recommendations)\(^{88,89}\) | 1. Manufacturer submits application for reimbursement to Transparency Secretariat of National Health Insurance Fund Administration (pharmaceutical division)<br>2. Transparency Secretariat registers and checks application for completeness and then determines whether application should undergo simplified procedure or normal procedure; normal procedure applies to new agents, indications, routes of administration, and combinations<br>3. National Health Insurance Fund Administration Department of Pharmaceuticals prepares a preliminary evaluation<br>4. If application is assigned to normal procedure, Transparency Secretariat transfers it to Technology Assessment Office of the National Institute for Strategic Health Research<br>5. Assessment Office prepares assessment report comprising a systematic review of clinical evidence and economic analysis<br>6. Technology Appraisal Committee deliberates over report, preliminary evaluation of pharmaceutical department, and advice from professional colleges, and formulates a recommendation<br>7. Director of pharmaceutical division approves recommendation and forwards it to the Ministers of Health and Finance\(^{102,108}\) | No information found | Decision may be appealed to Appeals Committee Includes representatives from: • Ministry of Health • Ministry of Finance • Ministry of Economy • National Institute of Pharmacy • Prime Minister's office\(^{80}\) |
| Ireland | Products Committee of Corporate Pharmaceuticals Unit of Health Service Executive (decisions)\(^{91,92}\) | 1. Products Committee of Health Service Executive selects technology for assessment OR manufacturer submits application for reimbursement to Health Service Executive<br>2a. If Products Committee selects technology, Health Service Executive notifies manufacturer of referral to National Centre for Pharmacoeconomics | 90 days | Decision may be appealed to designated expert committee\(^{91}\) |

(Continued)
| Country | Centralized reimbursement review/decision-making body (role) | Committee composition | Steps in review/decision-making process | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms |
|---------|-------------------------------------------------------------|-----------------------|----------------------------------------|-------------------------------------|-----------------------------|---------------------|
| Italy   | • Italian Medicines Agency Technical Scientific Committee (decisions)¹⁹ | Technical Scientific Committee: Includes 17 members: • Health care providers • Pharmacists | 1. Manufacturer submits application for reimbursement to Italian Medicines Agency 2. Technical Scientific Committee reviews submission and formulates advice on clinical value, assigning it to one of three reimbursement classes: A – fully reimbursable – essential | No¹²⁶ | 180 days (includes pricing and reimbursement decision)¹⁸⁸ | No information found |

²b. If manufacturer submits application, staff prepare preliminary evaluation report based on evidence from manufacturer
³a. Staff within National Centre for Pharmacoeconomics appointed to comprise review group
³b. Products Committee reviews evaluation report and decides whether to refer technology to National Centre for Pharmacoeconomics for formal pharmacoeconomic evaluation or recommend reimbursement
⁴a. Review group meets with manufacturer to determine scope and requirements for evaluation
⁴b. If referred, National Centre for Pharmacoeconomics conducts pharmacoeconomic evaluation
⁵a. Manufacturer prepares pharmacoeconomic submission, which includes cost-effectiveness and budget impact analyses
⁵b. National Centre for Pharmacoeconomics sends pharmacoeconomic evaluation to manufacturer for comment
⁶a. Review group prepares evaluation report based on manufacturer’s submission
⁶b. National Centre for Pharmacoeconomics prepares final pharmacoeconomic evaluation, incorporating manufacturer’s comments
⁷a. National Centre for Pharmacoeconomics sends report to manufacturer for comment
⁷b. National Centre for Pharmacoeconomics sends evaluation to Products Committee, who makes reimbursement decision
⁸a. Review group prepares final evaluation report, incorporating manufacturer’s comments
⁹a. National Centre for Pharmacoeconomics sends report to Products Committee, who makes reimbursement decision

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1.  Manufacturer submits application for reimbursement to Italian Medicines Agency
2.  Technical Scientific Committee reviews submission and formulates advice on clinical value, assigning it to one of three reimbursement classes: A – fully reimbursable – essential
3.  Staff within National Centre for Pharmacoeconomics appointed to comprise review group
4.  Review group meets with manufacturer to determine scope and requirements for evaluation
5.  Manufacturer prepares pharmacoeconomic submission, which includes cost-effectiveness and budget impact analyses
6.  Review group prepares evaluation report based on manufacturer’s submission
7.  National Centre for Pharmacoeconomics prepares final pharmacoeconomic evaluation, incorporating manufacturer’s comments
8.  Review group prepares final evaluation report, incorporating manufacturer’s comments
9.  National Centre for Pharmacoeconomics sends report to Products Committee, who makes reimbursement decision

¹²⁶

180 days (includes pricing and reimbursement decision)¹⁸⁸

No information found
Reimbursement of European health technologies

Italian Medicines Agency Pricing and Reimbursement Committee (recommendations)\textsuperscript{26}

- Pharmacologists
- Pricing and Reimbursement Committee: Includes 12 members:
  - Academics
  - Health care providers
  - Administrators responsible for managing pharmaceutical services\textsuperscript{26}

- Pharmacists
- Health care providers
- Researchers

Products and those intended for chronic diseases;
H – Fully reimbursable in hospitals; and C – non-reimbursable. Pharmaceuticals in classes A and H are further assigned to one of three classes: I – treatments for serious diseases; II – treatments to reduce or eliminate risk of serious diseases; and III – treatments for non-serious diseases

1. Technical Scientific Committee then assesses the degree of innovation offered by the technology, considering 2 factors: 1) availability of existing treatments and 2) extent of therapeutic benefit; scores on each factor are combined to determine if pharmaceutical represents “important,” “moderate,” or “modest therapeutic innovation”

2. Submission and Technical Scientific Committee evaluation are sent to Pricing and Reimbursement Committee

3. Pricing and Reimbursement Committee reviews advice and contacts manufacturer to negotiate reimbursement status and price

4. Pricing and Reimbursement Committee submits report containing negotiation outcomes to Technical Scientific Committee, who makes final decision

5. Norway

- Norwegian Medicines Agency (recommendations/decisions)\textsuperscript{34,98}
- Ministry of Health and Care Services (recommendations/decisions)
- Department of Pharmacoeconomics (recommendations)\textsuperscript{98}

- No information found

Process depends on anticipated budget impact of pharmaceutical: If < 5 million Krone/year:

1. Manufacturer submits application for reimbursement to Norwegian Medicines Agency
2. Norwegian Medicines Agency Department of Pharmacoeconomics staff prepare evaluation report based on evidence submitted by manufacturer
3. Norwegian Medicines Agency reviews evaluation report and makes reimbursement decision

If > 5 million Krone/year:

1. Manufacturer submits application for reimbursement to Norwegian Medicines Agency
2. Norwegian Medicines Agency Department of Pharmacoeconomics staff prepare evaluation report based on evidence submitted by manufacturer
3. Norwegian Medicines Agency reviews evaluation report and consults with national Advisory Committee for Drug Reimbursement
4. Norwegian Medicines Agency sends evaluation report to Ministry of Health and Care Services
5. Ministry consults with National Council for Health Care Priorities to determine whether pharmaceutical would be viewed as “money well spent”

No\textsuperscript{34} 180 days (includes pricing and reimbursement decision)\textsuperscript{34} No information found

(Continued)
| Country | Centralized reimbursement review/decision-making body (role) | Committee composition | Steps in review/decision-making process | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms |
|---------|-------------------------------------------------|------------------------|--------------------------------------|-----------------------------------|-------------------------------|-------------------|
| Poland  | Ministry of Health (decisions)  
Agency for Health Technology Assessment Consultative Council and Drug Management Team (recommendations) | Consultative Council: 12 voting members including representatives from:  
- Ministry of Health (7)  
- Polish Chamber of Physicians (1)  
- Chief Pharmaceutical Council (1)  
- Supreme Council of Nurses and Midwives  
- National Health Fund 127  
Drug Management Team: Includes representatives of:  
- Minister of Finance  
- Minister of Economy and Labour  
- Minister of Social Policy  
- National Health Fund | 6. Ministry formulates recommendation; if positive, it is sent to Parliament for approval34,98,189  
1. Manufacturer submits application for reimbursement to Ministry of Health  
2. Ministry of Health sends application to the Agency for Health Technology Assessment  
3. Agency for Health Technology Assessment staff prepare evaluation report based on evidence from the submission and information received from invited experts  
4. Agency for Health Technology Assessment Consultative Council meets to review report, hear from experts, and formulate recommendations  
5. Director of Agency for Health Technology Assessment issues reimbursement recommendation to Minister of Health  
6. Drug Management Team within Ministry of Health negotiates maximum reimbursement price  
7. Ministry of Health makes final decision on reimbursement and price100,127,190 | No information found | 180 days (includes pricing and reimbursement decision) 100 | None127 |
| Portugal | Ministry of Health (decisions)  
INFARMED (recommendations) 44 | No information found | 1. Manufacturer submits application for reimbursement to INFARMED following approval of maximum price by Directorate General of Economic Activities  
2. External experts prepare evaluation report based on evidence submitted by manufacturer (includes pharmacotherapeutic and pharmacoeconomic information demonstrating added therapeutic value and proposed reimbursement price) and assigns “grade” of innovation and added therapeutic value (compared to already reimbursed alternatives)  
3. Economists analyze pharmacotherapeutic information from manufacturer to determine “economic advantage”; if pharmaceutical offers added therapeutic value or treats a condition for which there are no alternative therapies, economic advantage should be demonstrated through formal economic analyses conducted by the manufacturer | No information found | 90 days (includes pricing and reimbursement decision) 96 | Decision may be appealed to administrative court96 |
4. Using findings from both reports, INFARMED formulates reimbursement recommendation
5. If negative, INFARMED contacts manufacturer, who may present additional information
6. INFARMED submits recommendations to Minister, who makes final decision

Scotland
- National Health Service Scotland (decisions)
- Scottish Medicines Consortium (recommendations)
1. Manufacturer submits application for reimbursement to Scottish Medicines Consortium
2. Internal staff ("assessment team"), supported by clinical and economic experts, prepare evaluation report based on evidence submitted by manufacturer
3. New Drugs Committee reviews report and prepares draft recommendations for the Scottish Medicines Consortium
4. New Drugs Committee also sends draft recommendations to manufacturer for comment
5. Manufacturer sends comments to Scottish Medicines Consortium, which also considers submissions received from patient interest groups
6. Scottish Medicines Consortium formulates final recommendations and forwards them to the National Health Service Boards, Area Drug and Therapeutics Committees, manufacturer, and competitor(s)

1. No fixed threshold, but range of £20,000–£30,000/QALY used as a guide

Slovakia
- Ministry of Health (decisions)
- Reimbursement Committee for Medicinal Products (recommendations)
1. Manufacturer submits application for reimbursement, including proposed maximum retail price, to Ministry of Health
2. Staff evaluate pharmaceutical using evidence from manufacturer to determine where its ICER lies in the accepted ICER threshold range
3. One of 22 specialist working groups then evaluates the pharmaceutical according to its anatomic and therapeutic classification

1. No fixed threshold, but range of €20,000–€26,500/QALY used as a guide

- Decisions may be appealed on process-related and scientific grounds
- For process-related appeals: Manufacturer contacts Scottish Medicines Consortium secretariat, Chair, or New Drugs Committee to resolve issues through discussion
- For scientific disputes: May resubmit or convene independent panel appointed by Scottish Medicines Consortium

(Continued)
| Country       | Centralized reimbursement review/decision-making body (role) | Committee composition                                                                 | Steps in review/decision-making process                                                                                                                                                                                                                                                                                                                                                               | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms                      |
|--------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------|-------------------------------------|
| Spain        | • Ministry of Health Directorate General of Pharmacy and Health Products; Inter-Ministerial Pricing Commission (decisions)21,108 | Inter-Ministerial Pricing Commission: Includes representatives from:  
  • Ministry of Health  
  • Ministry of Economy  
  • Ministry of Industry132 | 1. Ministry of Health initiates reimbursement decision-making process upon receipt of notice of market approval for new pharmaceutical  
  2. Ministry of Health invites manufacturer to provide all relevant information to Inter-Ministerial Pricing Commission  
  3. Internal staff of Ministry of Health prepare evaluation report  
  4. Inter-Ministerial Pricing Commission reviews report and makes reimbursement and pricing decision108,132 | No132  
  180 days (includes pricing and reimbursement decision)132 | No information found |  

  • Decision may be appealed on procedural grounds only132,192  
  • Board may reconsider decision before appeal is heard by administrative court192 |
| Sweden       | • Dental and Pharmaceutical Benefits Board Expert Board (decisions)15,109 | Expert Board: Includes 11 members and a chair:  
  • Pharmacologist (1)  
  • Health economists (4)  
  • Patient representatives (2)  
  • Health care providers (3)15,109 | 1. Manufacturer submits application for reimbursement  
  2. Internal staff (executive officer, health economist, and legal expert) review submission to determine if application contains sufficient evidence  
  3. Dental and Pharmaceutical Benefits Board sends copy of application to Pharmaceutical Benefits Group for County Councils for review  
  4. Internal staff prepare evaluation report and draft recommendations in the form of a “memorandum”  
  5. Dental and Pharmaceutical Benefits Board sends copy of memorandum to manufacturer for review  
  6. Manufacturer may request a meeting with the Board, during which it can present case, dispute arguments which form the basis of recommendations, and refute factual errors  
  7. Meeting of Expert Board held – memorandum, manufacturer’s comments, and any feedback received from the Pharmaceutical Benefits Group are reviewed; external experts may be invited to participate in deliberations;  
  8. Expert Board makes final reimbursement decision15,109 | No fixed threshold, but €45,000/QALY used as a guide192 | 180 days (includes pricing and reimbursement decision)192 |  

  • Decision may be appealed on procedural grounds only15,33,192  
  • Board may reconsider decision before appeal is heard by administrative court192 |
| Switzerland  | • Swiss Federal Office of Public Health (decisions)  
  • Federal Drug Commission (recommendations)113,114 | Federal Drug Commission: Includes 25 voting members representing:  
  • Academics (4)  
  • Physicians (3)  
  • Pharmacists (3) | 1. Manufacturer submits application for reimbursement  
  2. Federal Drug Commission reviews application and makes a classification recommendation: pharmaceutical may be classified into one of five categories of relative effectiveness:  
  1 – Therapeutic breakthrough; 2 – Therapeutic progress; 3 – Saving compared to other drugs; 4 – No therapeutic progress and no savings; and 5 – Not appropriate for the social health insurance | No information found | No information found |  

  • Decision may be appealed to Federal Office of Public Health114 |
The Netherlands

- Ministry of Health, Welfare and Sport (decisions)
- Dutch Healthcare Insurance Board Committee (CHF) (recommendations)\(^{36}\)

Committee of the Dutch Healthcare Insurance Board includes:
- A maximum of 24 members with expertise in various medical disciplines, health sciences, and economics
- 2-3 nonvoting members from the Ministry\(^{21,117}\)
- Includes:
  - 3 Dutch Healthcare Insurance Board board of directors
  - 6 members with health and social security insurance expertise\(^{21}\)

For outpatient pharmaceuticals:
1. Manufacturer submits application for reimbursement to Minister of Health
2. Internal staff prepare evaluation, which includes 4 draft reports (summary, pharmacotherapeutic, pharmacoeconomic, and budget impact assessments based on evidence from manufacturer, as well as independently conducted literature review); if deemed necessary, staff may consult with manufacturer, external experts, and stakeholders
3. CHF reviews report and consults with manufacturer and other stakeholders
4. Staff revise report, incorporating results of CHF deliberations and comments from manufacturer and other stakeholders
5. Dutch Healthcare Insurance Board sends revised report to manufacturer and stakeholders for comment
6. CHF meets to discuss revised report and comments received and prepare final advice
7. Dutch Healthcare Insurance Board board of directors receives final report, which is also sent to manufacturer and stakeholders appointed by Dutch Healthcare Insurance Board for comment
8. Dutch Healthcare Insurance Board board of directors meet to discuss final report and comments received and formulate recommendations; may consult with the Appraisal Committee
9. Alternatively, Steps 7 and 8 may be skipped, with the Board chair drafting a recommendation
10. Dutch Healthcare Insurance Board sends final recommendations to the Minister of Healthcare, Welfare, and Sport

No fixed threshold, but €20,000/ QALY used as a guide\(^{31}\)

- 90 days for outpatient pharmaceuticals
- 60 days for inpatient pharmaceuticals\(^{31}\)

- Decision may be appealed on procedural grounds only
- Appeal is heard by administrative court\(^{21}\)

(Continued)
| Country       | Centralized reimbursement review/decision-making body (role) | Committee composition | Steps in review/decision-making process                                                                                                                                                                                                 | Use of cost-effectiveness threshold | Timelines for review/decision | Appeals mechanisms |
|--------------|-------------------------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-----------------------------|----------------------|
| United Kingdom | • National Institute for Health and Clinical Excellence (decisions)  
• Technology Appraisals Committee (recommendations) |
|              | Includes:  
• Academics (e.g., health economists)  
• Health care providers in National Health Service  
• Representatives from patient and carer organizations  
• Manufacturers |
|              | 1. Minister makes final reimbursement decision, which includes classifying the pharmaceutical into one of three categories:  
Annex IA – Therapeutic equivalent value;  
Annex IB – Therapeutic added value; and  
Annex 2 – Conditional reimbursement  
For high-cost inpatient pharmaceuticals:  
1. Dutch Federation of University Hospitals, Dutch Hospitals Association, Medical Specialists Association, and Dutch Health Insurance Organization may submit reimbursement application (in the form of additional funding) for high cost inpatient pharmaceuticals  
2. Dutch Healthcare Insurance Board prepares evaluation report, which includes evidence on therapeutic value, projected budget impact, and plan for collecting pharmacoeconomic information in daily practice, and formulates recommendations (process similar to that described above)  
3. Dutch Healthcare Insurance Board sends final report and recommendations to the Dutch Healthcare Authority  
4. Dutch Healthcare Authority formulates recommendation on whether pharmaceutical should be provisionally added to the Expensive Drug List  
5. Minister of Health, Welfare, and Sport makes final decision | No fixed threshold, but range of £20,000–£30,000/QALY used as a guide |
|              | Single technology appraisal  
1. Topics selection panel selects technology for review  
2. National Institute for Health and Clinical Excellence invites stakeholders (i.e., consultees and commentators (cannot make a submission or appeal recommendation)) to participate  
3. Nonmanufacturer consultees invited to nominate clinical and/or patient experts to take part in Technology Appraisals Committee meetings  
4. Manufacturer completes evidence submission (assessment)  
5. Independent academic group commissioned to review submission, along with information received from consultees and nominated experts, and prepare evaluation report  
6. Technology Appraisals Committee meets to review evaluation report and hear from nominated clinical and patient experts | Single technology appraisal approximately 39 weeks | • Final recommendations may be appealed on procedural grounds only  
• Appeals may only be initiated by consultees identified at the beginning of the assessment and who are not representing National Health Service trusts or local boards |
7. Technology Appraisals Committee formulates draft recommendations, which are presented in appraisal consultation document.
8. Appraisal consultation document made available to stakeholders for comment.
9. Technology Appraisals Committee meets to consider comments and formulate final recommendations (final appraisal determination).
10. Technology Appraisals Committee submits final recommendations to Guidance Executive.

Multiple technology appraisal
Same as single technology appraisal process except:
1) Formal scoping process to develop review protocol is required; 2) Independent academic group conducts assessment (rather than the manufacturer); 3) Independent academic group attends Technology Appraisals Committee meetings.

Wales
- Ministry for Health and Social Services (decisions)
- All Wales Medicines Strategy Group New Medicines Group (recommendations)

Includes:
- Physicians
- Pharmacists
- Pharmacologists
- Health economist
- Nurse
- Patient representative
- Representative from pharmaceutical industry association

1. Manufacturer submits application for reimbursement (“Form A”) to All Wales Medicines Strategy Group.
2. All Wales Medicines Strategy Group determines whether application requires full appraisal; if yes, manufacturer must submit “Form B”.
3. All Wales Medicines Strategy Group identifies and invites clinical experts and patient organizations to submit written statements.
4. Internal staff prepare evaluation report, which includes Form A, Form B, and additional relevant information.
5. Report sent to manufacturer for comment.
6. All Wales Medicines Strategy Group New Medicines Group meets to review evaluation report and comments received and formulate draft recommendations.
7. Staff prepare final report and draft recommendations (ie, preliminary appraisal), which is sent to manufacturer and posted on website.
8. New Medicines Group meets to deliberate over final report, recommendations, and manufacturer’s response.
9. New Medicines Group formulates final recommendation, which is included in final appraisal.
10. Minister makes reimbursement decision, based on final appraisal from New Medicines Group.

No fixed threshold, £20,000/QALY used as a guide.

No information found

• Decisions may be appealed on process-related and scientific grounds.
• For process-related appeals: Appeals submitted to Welsh Medicines Partnership, who discusses case with All Wales Medicines Strategy Group Chair and senior staff.
• For scientific disputes: Independent review process initiated.

Appeal is heard by Appeals Panel appointed by National Institute for Health and Clinical Excellence board.

Decisions may be appealed on process-related and scientific grounds.
• For process-related appeals: Appeals submitted to Welsh Medicines Partnership, who discusses case with All Wales Medicines Strategy Group Chair and senior staff.
• For scientific disputes: Independent review process initiated.

Appeal is heard by Appeals Panel appointed by National Institute for Health and Clinical Excellence board.

Decisions may be appealed on process-related and scientific grounds.
• For process-related appeals: Appeals submitted to Welsh Medicines Partnership, who discusses case with All Wales Medicines Strategy Group Chair and senior staff.
• For scientific disputes: Independent review process initiated.
Table 6 Comparison of key factors considered during committee deliberations

| Country          | Centralized reimbursement review/decision-making body (role)                                                                 | Clinical need                                                                 | Clinical benefit/value*                                                                 |
|------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Austria          | • Association of Austrian Social Security Institutions (decisions)35 • Pharmaceutical Evaluation Board (recommendations)36  | Disease burden (severity and number of patients) Yes35, Yes38                     | Place of technology in care pathway/strategy Not specified                                |
|                  | Belgium                                                                                                                   | Availability of alternatives Yes31                                                                 | Safety (risk–benefit ratio; harm–benefit ratio) Yes9                                  |
|                  | • Ministry of Health and Social Affairs (decisions) • Drug Reimbursement Committee (recommendations)4,60                    |                                                                                   |                                                                                        |
| Czech Republic   | • State Institute for Drug Control (decisions)40,176                                                                          | Not specified                                                                 | Yes9                                                                                   |
|                  | Denmark                                                                                                                  | Not specified                                                                 |                                                                                        |
|                  | • Danish Medicines Agency (decisions)68,69,121 • Reimbursement Committee (recommendations)38,51                           | Not specified                                                                 |                                                                                        |
|                  | Estonia                                                                                                                  | Yes64                                                                             |                                                                                        |
|                  | • Ministry of Social Affairs (decisions)72 • Pharmaceuticals Committee (recommendations)72                               | Yes64                                                                             |                                                                                        |
| Finland          | • Pharmaceuticals Pricing Board (decisions)14,76,177 • Pharmaceuticals Pricing Board Expert Group (recommendations)75      | Yes81                                                                             |                                                                                        |
| France           | • Ministry for Health and Social Security (decisions)20,78 • French National Authority for Health (recommendations)28      | Yes35                                                                             |                                                                                        |
| Germany          | • Federal Joint Committee (decisions)74 • Institute for Quality and Efficiency in Health Care (recommendations)19,24       | Yes79                                                                             |                                                                                        |
|                  | Greece                                                                                                                   | Yes76                                                                             |                                                                                        |
|                  | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)83                                  | Yes76                                                                             |                                                                                        |
| Hungary          | • Ministers of Health and Finance • National Health Insurance Fund Administration (recommendations)56                  | Yes84                                                                             |                                                                                        |
| Ireland          | • Health Service Executive (decisions)97,92,147                                                                              | Yes125,145                                                                      |                                                                                        |
| Efficacy/effectiveness | Side effects | Acceptability (tolerance, convenience) | Cost-benefit ratio (cost-effectiveness; efficiency; “value for money”) | Impact on health resources/affordability (budget impact) | Innovativeness | Other |
|------------------------|--------------|----------------------------------------|-------------------------------------------------|-------------------------------------------------|----------------|-------|
| Yes15                  | Not specified| Not specified                          | Yes (“pharmaco-economic evidence”)58            | Yes55                                             | Yes52           | • Price in other European Union countries58 |
| Yes (across patient subgroups)7 | Yes7 | Yes11,17                               | Yes11,17                                       | Yes11,17                                         | Yes35           | • Feasibility of implementation11,17 |
| Yes44                  | Not specified| Yes66                                  | Yes84                                          | Not specified                                    |                | • Market price11,17 |
| Yes (across patient subgroups)21,68 | Yes21,68 | Not specified                          | Yes21,68                                       | Not specified                                    |                | • Social needs11,17,21 |
| Yes24                  | Not specified| Not specified                          | Yes84                                          | Not specified                                    |                | • Clinical practice guidelines188 |
| Yes (across patient subgroups)181 | Not specified | Not specified                          | Yes181                                         | Not specified                                    |                | • Public interest25 |
| Yes15                  | Yes89       | Yes80                                  | Not specified                                  | Yes80                                           | Yes35           | • Reasonableness of price relative to therapeutic value21,68 |
| Yes13                  | Not specified| Not specified                          | Yes119                                         | Yes113                                          | Yes19           | • “Cost efficiency”140 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Research and development15 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Level of uncertainty in supporting evidence181 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Price in other European Union countries181 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Market forecast and share25 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Daily cost of treatment per day75 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Public health impact18,35 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Costs relative to current treatment199 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Daily cost of treatment186 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Reimbursement status in other European Union countries186 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Equity28 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Level of uncertainty in supporting evidence125 |
| Yes18                  | Not specified| Not specified                          | Yes (“pharmaco-economic effectiveness”)186     | Not specified                                    |                | • Wider societal costs and benefits165 |

(Continued)
| Country      | Centralized reimbursement review/decision-making body (role)                                                                 | Clinical need | Place of technology in care pathway/strategy | Clinical benefit/value* |
|--------------|----------------------------------------------------------------------------------------------------------------------------|---------------|---------------------------------------------|--------------------------|
| Italy        | • Italian Medicines Agency Technical Scientific Committee (decisions)⁶⁴  
• Italian Medicines Agency Pricing and Reimbursement Committee (recommendations)⁷⁶                                        | Yes³⁷         | Not specified                               | Yes⁹⁶                    |
| Norway       | • Norwegian Medicines Agency (decisions)⁹⁸  
• Department of Pharmacoeconomics (recommendations)⁷⁸                                                                           | Yes³⁴         | Not specified                               | Yes¹⁴⁹                   |
| Poland       | • Ministry of Health (decisions)⁹⁹                                                                                              | Yes³⁴         | Not specified                               | Yes³⁴                    |
| Portugal     | • Ministry of Health (decisions)                                                                                           | Yes³⁶         | Not specified                               | Yes³⁶                    |
| Scotland     | • National Health Service Scotland (decisions)⁷⁰  
• Scottish Medicines Consortium (recommendations)                                                                         | Yes¹⁰⁴        | Not specified                               | Yes¹⁰⁴                   |
| Slovakia     | • Ministry of Health (decisions)                                                                                           | Yes¹⁰⁶        | Not specified                               | Yes¹⁰⁶                   |
| Spain        | • Ministry of Health Directorate General of Pharmacy and Health Products; Inter-Ministerial Pricing Commission (decisions)²¹,¹⁰⁸ | Yes¹³²        | Not specified                               | Yes¹⁰                    |
| Sweden       | • Dental and Pharmaceutical Benefits Board Expert Board (decisions)¹⁵,⁰⁹,¹¹⁰                                                | Yes²¹         | Not specified                               | Yes²¹                    |
| Switzerland  | • Swiss Federal Office of Public Health (decisions)                                                                                   | Not specified | Not specified                               | Not specified            |
| Efficacy/effectiveness | Side effects | Acceptability (tolerance, convenience) | Cost-benefit ratio (cost-effectiveness; efficiency; “value for money”)* | Impact on health resources/affordability (budget impact) | Innovativeness | Other |
|------------------------|--------------|----------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------|-------|
| Yes (across patient subgroups) | Not specified | Not specified | Yes \(^{27}\) | Yes \(^{27}\) | Yes \(^{27}\) | Yes \(^{20}\) |
| Yes (across patient subgroups) | Not specified | Not specified | Yes \(^{24}\) | Yes \(^{24}\) | Not specified |
| Yes \(^{34}\) | Not specified | Not specified | Yes \(^{24}\) | Yes \(^{24}\) | Not specified |
| Yes \(^{44}\) | Not specified | Not specified | Yes \(^{24}\) | Yes \(^{24}\) | Not specified |
| Yes \(^{44}\) | Not specified | Not specified | Yes \(^{104}\) | Yes \(^{104}\) | Yes \(^{30}\) |
| Yes \(^{106}\) | Yes \(^{106}\) | Yes \(^{106}\) | Yes \(^{34},^{105}\) | Yes \(^{84},^{106}\) | Not specified |
| Yes (across patient subgroups) \(^{32}\) | Not specified | Not specified | Not specified | Yes \(^{122}\) | Yes \(^{108}\) |
| Yes (across patient subgroups) | Not specified | Not specified | Yes \(^{21}\) | No \(^{21}\) | Not specified |
| Yes \(^{58}\) | Not specified | Not specified | Yes (“value for money”) \(^{109}\) | Not specified | Yes \(^{108}\) |
| Yes \(^{108}\) | Not specified | Not specified | Yes (“value for money”) \(^{109}\) | Not specified | Yes \(^{108}\) |

(Continued)
Table 6 (Continued)

| Country          | Centralized reimbursement review/decision-making body (role)                                                                                                                                                                                                 | Clinical need                                                                 | Clinical benefit/value*                                                                 |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| The Netherlands  | • Ministry of Health, Welfare and Sport (decisions)                                                                                                                                                    | Disease burden (severity and number of patients)                                | Safety (risk–benefit ratio; harm–benefit ratio)                                           |
|                  | • Dutch Healthcare Insurance Board Committee of the Dutch Healthcare Insurance Board (recommendations)                                                                                               | Availability of alternatives                                                   | Not specified                                                                           |
|                  |                                                                                                                                                                                                                                                       | Place of technology in care pathway/strategy                                  | Yes45                                                                                     |
|                  |                                                                                                                                                                                                                                                       |                                                                              |                                                                                  |
| United Kingdom   | • National Institute for Health and Clinical Excellence (decisions)                                                                                                                        |                                                                              | Yes202                                                                                  |
|                  | • Technology Appraisals Committee (recommendations)                                                                                                                                         |                                                                              |                                                                                  |
|                  |                                                                 書                                                                                                                                                                                      |                                                                              |                                                                                  |
| Wales            | • Ministry for Health and Social Services (decisions)                                                                                                                                              |                                                                              |                                                                                  |
|                  | • All Wales Medicines Strategy Group (recommendations)                                                                                                                                       |                                                                              |                                                                                  |
|                  |                                                                 書                                                                                                                                                                                      |                                                                              |                                                                                  |

Notes: *in a well-defined population; †price proportionate to effect; §cost efficiency takes into account costs of treatment per patient, as well as costs of compensatory allowance due to lost income and costs of restoring patients’ capacity to work; ‡efficiency of resource use within a single therapeutic area relative to existing interventions; ¥not a formal criterion.

they include at least safety (risk–benefit ratio) and efficacy/effectiveness, on the basis of which an overall estimate of the ratio of the benefits to harms of a candidate technology is estimated (Table 6). While a further goal shared by most review committees is to formulate an opinion on whether the candidate technology represents “value for money” or an efficient use of resources, their approach to accomplishing this differs. Approximately one-third are guided by, but not compelled to adhere to, a predefined incremental cost-effectiveness threshold or threshold range. Typically, if the incremental cost-effectiveness for a candidate technology lies below the threshold, it is deemed cost-effective or good value for money. If it lies above the threshold, additional factors are taken into account when judging acceptability (eg, uncertainties in estimates of outcomes, the severity of condition, and wider societal benefits). Across systems whose committees do not refer to an incremental cost-effectiveness threshold, approaches to operationalizing “value or money” appear vague, with information largely limited to statements such as “reasonableness of cost relative to therapeutic value” (Table 6). Similarly, although all but one of the systems (Sweden) list “affordability” or “impact of the candidate technology on health system resources” among factors/criteria considered by their respective review committees, no information describing processes for deciding whether or not a technology is affordable could be found.

Equity or ethical implications comprise decision-making factors/criteria (explicitly or implicitly) in one-third of
Table 6 (Continued)

| Efficacy/effectiveness | Side effects | Acceptability (tolerance, convenience) | Cost-benefit ratio (cost-effectiveness; efficiency; “value for money”)* | Impact on health resources/affordability (budget impact) |
|------------------------|--------------|----------------------------------------|-------------------------------------------------|----------------------------------------|
| Yes35,317               | Yes35        | Yes35                                  | Yes35,317                                       | Yes421,201                             |
|                        |              |                                        |                                                 |                                        |
| Yes (across patient subgroups)322 | Not specified | Not specified | Yes202                                        | Not specified                          | Yes35,197                          |
|                        |              |                                        |                                                 |                                        |
| Yes (across patient subgroups)328 | Not specified | Not specified | Yes28                                        | Yes174                                | Yes28                              |

Notes: *in a well-defined population; †price proportionate to effect; ‡cost efficiency takes into account costs of treatment per patient, as well as costs of compensatory allowance due to lost income and costs of restoring patients’ capacity to work; §efficiency of resource use within a single therapeutic area relative to existing interventions; ¶not a formal criterion.

 systems. For example, Sweden’s Dental and Pharmaceutical Benefits Board stipulates two principles that decisions must reflect, ie, the “need and solidarity principle” (patients in the greatest need or “worse off” must be given priority) and the “human value principle” (sociodemographic characteristics of patient populations cannot influence decisions).31,33 Along with “solidarity,” the Norwegian Medicines Agency explicitly takes into account “equity,” as do review committees in Hungary and Poland.34–36 However, the way in which this is accomplished during deliberations is not clear. Committees using an incremental cost-effectiveness threshold to guide decisions implicitly incorporate equity by virtue of the assumptions underpinning the incremental cost-effectiveness calculation (ie, each quality-adjusted life-year [QALY] carries the same weight, regardless of the characteristics of the patients receiving it (eg, age, gender, social status, income). Consideration of additional, often competing ethical principles by these committees is operationalized through “exception” conditions under which the normal “efficiency” expectations do not need to be met (eg, “last chance” therapies, orphan technologies, life-extending, end-of-life treatments).37 Under such conditions, not all QALYs are deemed equal. Rather, a form of “solidarity” premium is applied, where, for example, QALYs gained in the later stages of disease are given greater weight. While there is little disagreement over the importance of instituting “exception” conditions as a means of ensuring that reimbursement decisions embody the broader values of the population,
### Table 7 Comparison of conditional reimbursement policy options for managing decision uncertainties

| Country      | Centralized reimbursement review/decision-making body (role)                                                                 | Policy options for addressing decision-making uncertainties                                                                 |
|--------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Austria      | • Association of Austrian Social Security Institutions (decisions)<sup>15</sup>                                                | • Yes – for “highly innovative” pharmaceuticals without evidence of effectiveness and “efficiency”                           |
|              | • Pharmaceutical Evaluation Board (recommendations)<sup>36</sup>                                                            | • Association of Austrian Social Security Institutions may remove pharmaceutical from benefit list in the wake of new clinical or economic evidence |
|              | • Manufacturer may suggest delisting pharmaceutical<sup>27</sup>                                                            | • Manufacturer may suggest delisting pharmaceutical<sup>27</sup>                                                            |
| Belgium      | • Minister of Social Affairs (decisions)                                                                                     | • Yes – automatic reassessment of pharmaceuticals offering added therapeutic value 1.5 to 3 years after inclusion on benefit list |
|              | • Drug Reimbursement Committee (recommendations)<sup>9</sup>                                                                 | • Minister of Social Affairs or manufacturer may suggest delisting a pharmaceutical<sup>11,49</sup>                            |
| Czech Republic | • State Institute for Drug Control (decisions)<sup>25</sup>                                                                     | No information found                                                                                                           |
| Denmark      | • Danish Medicines Agency (decisions)<sup>48,71,21</sup>                                                                      | Manufacturer may request a surcharge of up to 30% over the basic reimbursement level if evidence suggests pharmaceutical demonstrates “superior” therapeutic benefits<sup>14</sup> |
|              | • Reimbursement Committee (recommendations)<sup>48,72</sup>                                                                     | No information found                                                                                                           |
| Estonia      | • Ministry of Social Affairs (decisions)<sup>12</sup>                                                                           | No information found                                                                                                           |
|              | • Pharmaceuticals Committee (recommendations)<sup>72</sup>                                                                     | No information found                                                                                                           |
| Finland      | • Pharmaceuticals Pricing Board (decisions)<sup>13,74,75</sup>                                                                  | No information found                                                                                                           |
|              | • Pharmaceuticals Pricing Board Expert Group (recommendations)<sup>15</sup>                                                     | No information found                                                                                                           |
| France       | • Ministry for Health and Social Security (decisions)<sup>20,78</sup>                                                           | No information found                                                                                                           |
|              | • French National Authority for Health (recommendations)<sup>38</sup>                                                          | For pharmaceuticals                                                                                                             |
|              | • Yes – for all pharmaceuticals                                                                                               | No information found                                                                                                           |
|              | • Automatic reassessment every 3 to 5 years after inclusion on benefit list<sup>16,203</sup>                                 | For medical devices                                                                                                           |
|              | • French National Authority for Health (recommendations)<sup>38</sup>                                                          | • Yes – for devices                                                                                                             |
|              | • Automatic reassessment within 5 years of inclusion on benefit list<sup>20,162</sup>                                      | • Automatic reassessment within 5 years of inclusion on benefit list<sup>20,162</sup>                                      |

Continued (“real-world” effectiveness is necessary)
### Reimbursement as part of a formal study

| Risk-sharing schemes/ payment by results | Other |
|------------------------------------------|-------|
| No information found | No information found | No information found |

| No information found | Financially or clinically based: |
|----------------------|----------------------------------|
|                      | • For pharmaceuticals offering added therapeutic value for which the Drug Reimbursement Committee formulated a negative reimbursement recommendation |
|                      | Financially based: |
|                      | • Price-volume agreements – “Provision Fund” established – Advances paid by manufacturers are used to cover 75% of overrun |

| No information found | Clinically based: |
|----------------------|-------------------|
|                      | • Example: “No cure no pay” scheme for valsartan for high blood pressure |
|                      | • Individual level schemes |
|                      | – Patient may apply for reimbursement on an individual basis, which requires evidence of treatment effect for continued reimbursement |
|                      | – Typically for patients who have exhausted all other options |
|                      | – Period of reimbursement varies |

| No information found | Financially based: |
|----------------------|-------------------|
|                      | • For all new pharmaceuticals – price-volume agreements mandatory for 1 year following reimbursement decision |

| No information found | No information found |
|----------------------|----------------------|

### Other

| Creation of Special Solidarity Fund |
|-------------------------------------|
| • Grants, on an individual basis, reimbursement of pharmaceuticals for rare diseases or rare indications unavailable in Belgium |
| • Only granted if patient meets certain criteria and has exhausted all other treatment options |
| • Must be prescribed by relevant specialist |
| • Reimbursement decisions made by College of Medical Doctors Directors |

### May provide provisional coverage for a set period during which “real-world” effectiveness and/or economic implications must be assessed through a study:

| To be carried out: |
|--------------------|
| 1) By skilled teams in a limited number of selected centers |
| 2) Under well-defined conditions of use |
| 3) Using a protocol approved by French |

### For pharmaceuticals

| Financially based: |
|--------------------|
| • Price-volume agreements |
| – Manufacturer must “pay back” the cost of sales exceeding those forecasted for the first 4 years |
| – Pharmaceuticals exempt from such schemes for various periods depending on their “improvement in medical benefit” |

### For pharmaceuticals for serious or rare diseases

| May be granted temporary access in a hospital setting for 1 year |
| May establish “innovation point of contact” and an internal multidisciplinary network |

(Continued)
| Country  | Centralized reimbursement review/decision-making body (role) | Policy options for addressing decision-making uncertainties | Value-based pricing/reimbursement |
|---------|-------------------------------------------------------------|-------------------------------------------------------------|----------------------------------|
| Germany | • Federal Joint Committee (decisions)¹⁹  
          • Institute for Quality and Efficiency in Health Care (recommendations)¹⁹ | No information found | No information found |
| Greece  | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)²⁰  
          • Institute for Quality and Safety in Health Care | No information found | No information found |
| Hungary | • Ministers of Health and Finance  
          • National Health Insurance Fund Administration (recommendations)³⁰,³¹ | No information found | No information found |
| Ireland | • Products Committee of Corporate Pharmaceuticals Unit of Health Service Executive (decisions)³¹,³² | No information found | No information found |
| Italy   | • Italian Medicines Agency Technical Scientific Committee (decisions)³³  
          • Italian Medicines Agency Pricing and Reimbursement Committee (recommendations)³⁴ | No automatic/routine reassessment, with the exception of pharmaceuticals reimbursed under condition that additional studies would be conducted²⁵ | No information found |

(Continued)
Reimbursement as part of a formal study | Risk-sharing schemes/ payment by results | Other
--- | --- | ---
National Authority for Health Transparancy Committee • Applies to pharmaceuticals that: 1) Target a large population; 2) May be prescribed outside their labeled indications; or 3) May have a significant impact on health care organizations• Also applies to medical devices – French National Authority for Health specifies study protocol(20) For medical devices and procedures • May provide provisional coverage for a set period during which “real-world” effectiveness and/or economic implications must be assessed through a study204
No information found For pharmaceuticals financially based: • Price-volume agreements – “target agreements”: if prescription volume target is exceeded by 25%, manufacturers must “pay back” sickness funds (eg, insulin analogs, olanzapine, risperidone, clopidogrel, zolendronate, mycophenolic acid, everolimus, and cyclosporine)41 No information found
No information found Financially based: • Price-volume agreements – 12% of reimbursed sales must be paid to the Ministry by the manufacturer – If Ministry spending on pharmaceutical exceeds agreed-to budget, the manufacturer must refund the Ministry an additional amount based on a predefined formula41 No information found
No information found Clinically based: • Pharmaceutical initially reimbursed by National Health Service at 50% or 100% for a fixed number of treatment cycles, after which it is only reimbursed for patients achieving predefined clinical response; manufacturer may be required to refund the cost of pharmaceutical in non-responding patients (eg, sunitinib, sorafenib, dasatinib, and nilotinib) • Registries used to track outcomes included in scheme67 • Manufacturer initially provides pharmaceutical at no cost for a fixed period, after which National Health Service pays for pharmaceutical in patients achieving predefined clinical response (eg, donepezil)41 No information found
For pharmaceuticals classified as “potentially innovative” • May require manufacturer to conduct additional studies within 3 years • Pharmaceuticals for patients enrolled in the studies must be covered by the manufacturer25 • Have established ongoing registries to monitor prescribing and assess “therapeutic value” in practice (real-world settings) in order to inform future management and reimbursed pricing decisions (eg, cetuximab, lenalidomide, ibritumomab, tiuxetan, palifermin, tempofin, and trastuzumab)41
Clinically based: • Pharmaceutical initially reimbursed by National Health Service at 50% or 100% for a fixed number of treatment cycles, after which it is only reimbursed for patients achieving predefined clinical response; manufacturer may be required to refund the cost of pharmaceutical in non-responding patients (eg, sunitinib, sorafenib, dasatinib, and nilotinib) • Registries used to track outcomes included in scheme67 • Manufacturer initially provides pharmaceutical at no cost for a fixed period, after which National Health Service pays for pharmaceutical in patients achieving predefined clinical response (eg, donepezil)41
No information found
• Individual reimbursement – Patients may be granted individual reimbursement of pharmaceuticals not on the benefit list if: 1) No alternative exists 2) Requested pharmaceutical is available in other European Union states 3) Clinical trials are underway 4) Pharmaceutical is already reimbursed for a different indication96,205 • Establishment of “innovative medicines fund” – Commits 20% of available resources to reimbursement of “innovative” pharmaceuticals, ranked from most to least innovative using the following criteria: 1) Treats serious conditions that are life-threatening or cause hospitalization or permanent disability

(Continued)
Table 7 (Continued)

| Country  | Centralized reimbursement review/decision-making body (role) | Policy options for addressing decision-making uncertainties | Value-based pricing/reimbursement |
|----------|-------------------------------------------------------------|-------------------------------------------------------------|----------------------------------|
| Norway   | • Norwegian Medicines Agency (recommendations/decisions)34,98  | • Pharmaceuticals may be reassessed as part of ongoing therapeutic class reviews34 | No information found |
|          | • Ministry of Health and Care Services (recommendations/decisions) |
|          | • Department of Pharmacoeconomics (recommendations)98       |                                                                             |                                  |
|          | No information found                                        |                                                                             |                                  |
| Poland   | • Ministry of Health (decisions)99                         | No information found                                                      | No information found |
|          | • Drug Management Team (recommendations)99                  |                                                                             |                                  |
| Portugal | • Ministry of Health (decisions)                           | No information found                                                      | No information found |
|          | • INFARMED (recommendations)44,101                         |                                                                             |                                  |
| Scotland | • National Health Service Scotland (decisions)39           | • Yes – for all pharmaceuticals                                          | No information found |
|          | • Scottish Medicines Consortium (recommendations)          | • Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected to be available38 |                                  |
|          | No information found                                        | • Reimbursement price may be adjusted to reflect actual costs and benefits once such information becomes available (e.g., continuous intraduodenal infusion of levodopa/carbidopa for advanced Parkinson’s disease)209 |                                  |
|          | No information found                                        | • "Innovation premium" – Granted to innovative pharmaceuticals (i.e., therapeutic breakthrough products) |                                  |
| Slovakia | • Ministry of Health (decisions)                           | No information found                                                      | No information found |
|          | • Reimbursement Committee for Medicinal Products (recommendations)105,106 |                                                                             |                                  |
| Spain    | • Ministry of Health Directorate General of Pharmacy and Health Products; Inter-Ministerial Pricing Commission (decisions)31,108 | No information found                                                      | No information found |
| Sweden   | • Dental and Pharmaceutical Benefits Board Expert Board (decisions)15,206–209 | • Yes – for all pharmaceuticals                                          | No information found |
|          | • Swedish Pharmacoeconomics (recommendations)112,114        | • Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected to be available31,125 |                                  |
|          | • Pharmaceuticals may also be reassessed as part of ongoing therapeutic class reviews31,125 | • Reimbursement price may be adjusted to reflect actual costs and benefits once such information becomes available (e.g., continuous intraduodenal infusion of levodopa/carbidopa for advanced Parkinson’s disease)209 |                                  |
|          | • Swiss Federal Office of Public Health (decisions)         | No information found                                                      |                                  |
|          | • Federal Drug Commission (recommendations)112,114          |                                                                             |                                  |
| Country          | Centralized reimbursement review/decision-making body (role) | Risk-sharing schemes/ payment by results | Other |
|------------------|---------------------------------------------------------------|------------------------------------------|-------|
| Norway           | • Norwegian Medicines Agency (recommendations/decisions)34,98 | • Reimbursement as part of a formal study |       |
|                  | • Ministry of health and Care Services (recommendations/decisions) | • Risk-sharing schemes/ payment by results |       |
|                  | • Department of Pharmacoeconomics (recommendations)98         | • Other                                    |       |
|                  | • Pharmaceutical may be reassessed as part of ongoing therapeutic class reviews34 | • Individual reimbursement               |       |
|                  |                                                               | • 2) Used for risk factors for serious conditions |       |
|                  |                                                               | • 3) Used for nonserious conditions25,188 |       |
|                  |                                                               | • If fund is overspent, manufacturers participate in refunding the system proportional to market share95 |       |
|                  |                                                               | • Financially based:                      |       |
|                  |                                                               | • Expenditure cap                         |       |
|                  |                                                               | • Cost per patient per year cannot exceed a certain amount (eg, bevacizumab)41 |       |
| Poland           | • Ministry of health (decisions)99                            | • No information found                    |       |
|                  | • Drug Management Team (recommendations)99                    | • No information found                    |       |
|                  |                                                               | • No information found                    |       |
| Portugal         | • Ministry of health (decisions)                              | • Financially based:                      |       |
|                  | • inFARMED (recommendations)44,101                            | • Price-volume agreements                |       |
|                  |                                                               | • Growth rate in pharmaceutical expenditures fixed per year; if exceeded, manufacturers must refund the system up to 69.6% of the coverage up to a predetermined amount, eg, €35 million (2006)44 |       |
| Scotland         | • National health Service Scotland (decisions)30              | • No information found                    |       |
|                  | • Scottish Medicines Consortium (recommendations)             | • No information found                    |       |
|                  | • Yes – for all pharmaceuticals                               | • Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected128 |       |
| Slovakia         | • Ministry of health (decisions)                              | • No information found                    |       |
|                  | • Reimbursement Committee for Medicinal Products (recommendations)105,106 | • No information found                    |       |
|                  |                                                               | • No information found                    |       |
| Spain            | • Ministry of health Directorate general of Pharmacy and health Products; Inter-Ministerial Pricing Commission (decisions)21,108 | • No information found                    |       |
| Sweden           | • Dental and Pharmaceutical Benefits Board Expert Board (decisions)15,206–209 | • Yes – for all pharmaceuticals           |       |
|                  | • Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected51,135 | • Pharmaceuticals may also be reassessed as part of ongoing therapeutic class reviews51,135 |       |
|                  | • Reimbursement price may be adjusted to reflect actual costs and benefits once such information becomes available (eg, continuous intraduodenal infusion of levodopa/carbidopa for advanced Parkinson’s disease)209 | • May require submission of evidence from studies collecting “real-world” data on clinical, economic, and quality of life outcomes205,209 |       |
|                  | • May require submission of evidence from studies collecting “real-world” data on clinical, economic, and quality of life outcomes205,209 | • No information found                    |       |
| Switzerland      | • Swiss Federal Office of Public Health (decisions)           | • No information found                    |       |
|                  | • Federal Drug Commission (recommendations)113,114            | • No information found                    |       |
|                  |                                                               | • “Innovation premium”– granted to innovative pharmaceuticals (ie, therapeutic breakthrough products) |       |

(Continued)
### Table 7 (Continued)

| Country       | Centralized reimbursement review/decision-making body (role) | Policy options for addressing decision-making uncertainties | Value-based pricing/reimbursement |
|---------------|-------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------|
| The Netherlands | • Ministry of Health, Welfare and Sport (decisions) <br>• Dutch Healthcare Insurance Board Committee of the Dutch Healthcare Insurance Board (recommendations)³¹ | • Yes – for all pharmaceuticals <br>• Automatic reassessment – time period not specified¹¹,¹²,¹³¹ | – Surcharge of ≤20% of external reference price is added for a maximum of 15 years¹¹,¹²,¹³¹<br>No information found |
| United Kingdom | • National Institute for Health and Clinical Excellence (decisions) <br>• Technology Appraisals Committee (recommendations)⁷ | • Yes – for all technologies <br>• Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected to be available¹³,²⁹,³⁷ | • Proposed “flexible pricing” scheme:<br>– Manufacturers can adjust the price of a pharmaceutical in response to emerging additional evidence on actual benefit or approval of a new indication which alters the value that the pharmaceutical offers to patients<br>– National Institute for Health and Clinical Excellence assesses whether new price and evidence represents “value for money” and may veto a new price on an existing indication⁴⁵,⁴⁶ |
### Table 7 (Continued)

| Country | Centralized reimbursement review/decision-making body (role) | Policy options for addressing decision-making uncertainties |
|---------|---------------------------------------------------------------|----------------------------------------------------------|
| The Netherlands | • Ministry of health, Welfare and Sport (decisions) • Dutch healthcare insurance Board Committee of the Dutch healthcare insurance Board (recommendations) | - Yes – for all pharmaceuticals  
- Automatic reassessment – time period not specified  
- Surcharge of 20% of external reference price is added for a maximum of 15 years113,114,205 |
| United Kingdom | • National Institute for Health and Clinical Excellence (decisions) • Technology Appraisals Committee (recommendations) | - Yes – for all technologies  
- Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected to be available13,29,157  
- Proposed “flexible pricing” scheme:  
  - Manufacturers can adjust the price of a pharmaceutical in response to emerging additional evidence on actual benefit or approval of a new indication which alters the value that the pharmaceutical offers to patients  
  - National Institute for Health and Clinical Excellence assesses whether new price and evidence represents “value for money” and may veto a new price on an existing indication45,48  
- “Innovation pass”  
  - Selected “innovative” technologies are made available for 3 years, during which studies to collect data needed to inform standard National Institute for Health and Clinical Excellence processes are conducted46 |

For pharmaceuticals “Patient access schemes”42  

Financially based:  
- Manufacturer proposes discounts or rebates to reduce the cost of a pharmaceutical to the National Health Service, thus improving its cost-effectiveness  
  - Manufacturer must obtain approval for such a scheme from the Department of Health prior to National Institute for Health and Clinical Excellence review29,212–214  
- Expenditure cap  
  - Cost per patient per year cannot exceed a certain amount (eg, ustekinumab and erlotinib)45  
  - Clinically based:  
    - Manufacturer covers the cost of initial fixed number of cycle(s) of treatment, after which National Health Service pays for patients achieving predefined clinical response (eg, sunitinib)45  
    - National Health Service covers the cost of initial fixed number of cycles of treatment, after which manufacturer refunds the cost of treatment in patients failing to achieve predefined clinical response (eg, bortezomib)40  
    - National Health Service covers the cost of the pharmaceutical for a fixed period, after which the price is reduced or refunds are issued to achieve predefined iCER (eg, interferon β, glatiramer acetate, and azathioprine)45  

- End-of-life medicines guidance  
  - Pharmaceuticals used to extend life by at least 3 months for patients with less than 24 months to live may be reimbursed, even if iCER exceeds threshold range17–18  
  - Pharmaceuticals for rare conditions guidance  
    - May be reimbursed when iCER exceeds threshold range if:  
      - Target conditions in which incidence <7000 patients/year in the UK  
      - There is sufficient evidence demonstrating that pharmaceutical offers substantial average increase in life expectancy over alternatives205  

No information found  

No information found  

(Continued)
considerable debate around definitions/qualifiers (eg, what constitutes “last chance”? or by what period of time must a technology lengthen survival in order to be regarded as “life-extending”?) remains. Finally, the following factors are simply listed as criteria/factors by a small proportion of committees: alignment with government priorities; feasibility; and/or risk of off-label use of the technology (Table 6).

In general, systems aim to complete single technology reviews within 180 days of submission/identification of candidate technology, the time period prescribed by the European Union Transparency Directive. Based on tracking data, the actual time required appears to depend primarily on whether the assessment report accompanies a reimbursement application (eg, Belgium) or is undertaken (internally or externally) by the system once a technology is identified for review (eg, the UK, Table 5). In the latter case, review times can be 90 days or less (eg, Denmark and France).20,38

The majority of systems have established mechanisms for appealing recommendations or decisions. Briefly, there are two main types of disputes, ie, those related to process and those amounting to disagreements over the interpretation of the evidence. In approximately one-third of systems, acceptable grounds for appeals are those of the first type only (“failed to act in accordance with processes”)39. For the most part, appeals are heard by an expert panel appointed by the respective health care organization or “payer” (eg, Ministry of Health, Table 5). Alternatively, they must be filed in an administrative court (eg, Germany and Sweden).

Conditional reimbursement enabling access to new technologies

Increasingly, reimbursement systems are expressing interest in and/or implementing reimbursement policy options that extend beyond the traditional “yes,” “no,” or “yes with restrictions” options. Such policy options take the form of provisional reimbursement arrangements, in which funding for a technology is provided in the interim while evidence needed to make a definitive decision is collected.40 Collectively referred to as “Access with Evidence Development” (AED) schemes, they have emerged in response to calls for mechanisms that balance access to new technologies with the need to ensure their safe, effective, and efficient introduction and use in the health care system. In recent years, these calls have heightened, as tension between payers and manufacturers, patients, and providers has intensified. Many new high-cost technologies are supported by limited, albeit promising, evidence. Therefore, reimbursement decisions are made under conditions of considerable uncertainty, with significant risks and consequences of “getting it wrong” (wasted scarce resources and poor health outcomes). AED schemes attempt to reduce such risks through “managed entry” of new technologies into everyday clinical practice. There are three main types, ie, coverage linked to an outcomes guarantee, coverage as part of a study, and automatic reassessment (Table 7). Often referred to as “risk-sharing” schemes, “patient access schemes,” and “payment by results,” the first type consists of contractual arrangements between payers and manufacturers, where payment is tied to the achievement of an outcome, be it financial or health-related.41,42 Such schemes have been employed in approximately one-third of the systems in this review (Table 7). They include financially-based price–volume agreements, where manufacturers must “pay back” the cost of sales exceeding those forecasted (eg, Belgium, France, Germany, Hungary, Portugal),41,43,44 and expenditure caps, in which manufacturers cover the cost of “treatment” in patients for whom costs over a fixed time period exceed a prespecified amount (eg, Italy, the UK).41,45 Health-related risk sharing arrangements, also called “no cure no pay” schemes, have been implemented by a smaller proportion of systems (Belgium, Denmark, Italy, the UK).41,45–47 Under such schemes, continued reimbursement of a technology (usually a pharmaceutical for a rare disorder or cancer) requires evidence of a predefined treatment effect. The second type, “coverage as part of a study,” involves provision of interim funding by payers in order to conduct studies designed to collect specific information needed to fill key evidence gaps.

| Table 7 (Continued) |
|---------------------|
| **Country** | **Centralized reimbursement review/decision-making body (role)** | **Policy options for addressing decision-making uncertainties** | **Value-based pricing/reimbursement** |
| Wales | • Ministry for Health and Social Services (decisions) • All Wales Medicines Strategy Group New Medicines Group (recommendations)\(^{20}\) | • Yes – for all pharmaceuticals • Automatic reassessment, but review period varies with the pharmaceutical; depends upon when additional evidence is expected to be available\(^{174}\) | No information found |

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Typically, such evidence gaps relate to the effectiveness and/or cost implications of the technology in “real world” settings. Funding may be partial (costs of the technology and/or health care associated with its use) or full (all health care and research costs). This type of scheme constitutes a policy option in approximately one quarter of the reimbursement systems, the majority of which have mandates that span pharmaceutical and nonpharmaceutical technologies (eg, France, Germany, the UK, Table 7). Eligible technologies vary across systems, but often include those defined as “innovative” (eg, granted an “innovation pass” in the UK) and those anticipated to significantly impact health care organization budgets (eg, the Netherlands). The third type of AED scheme, “automatic reassessment,” comprises a programmed review of a reimbursement decision following a fixed period on the “benefit list” or when additional evidence is available. It has become a part of the policy framework in half of the reimbursement systems included in this review, with most requiring reassessments of all technologies within their decision-making scope (Table 7). Despite the appeal of AED schemes, evidence of their effectiveness is both limited and mixed. Recent reviews have highlighted the challenges involved in both their design and implementation. Such challenges primarily stem from the need to reach consensus among stakeholders on the terms of the scheme. Often, considerable time and resources have been required to resolve disagreements over elements such as the value proposition, outcomes to be measured and for what period, how the scheme should be funded, and to whom its oversight should be handed. Further, negotiations have, in some cases, resulted in complex arrangements that failed to generate the evidence needed to support a policy decision and/or created a significant administrative burden on payers and providers involved in its implementation. In an effort to address these issues, guidelines for conducting AED schemes, derived from international experiences to date, were recently published. Moreover, some systems have proposed alternative approaches to dealing with decision uncertainties. For example, earlier this year, National Institute of Health and Clinical Excellence announced a new form of value-based reimbursement termed “flexible pricing.” Under this approach, manufacturers adjust the price of a technology (pharmaceutical) in response to additional evidence of actual benefit to patients as it emerges. The National Institute of Health and Clinical Excellence subsequently assess this evidence, along with the proposed price, and determines whether the technology represents “value for money.” If a negative opinion is reached, the National Institute of Health and Clinical Excellence may veto the proposed price. Given the potential benefits of such an approach (eg, reduced administrative burden and system resource requirements) it has already sparked interest among the National Institute of Health and Clinical Excellence’s counterparts across Europe.

Role of manufacturers in steps comprising the reimbursement review process

Few reimbursement systems have established roles for manufacturers beyond referral of a technology for review and the opportunity to comment on draft reports and/or preliminary recommendations (Table 8). Where “multiple technology appraisal” processes exist and assessment reports are commissioned or undertaken by the reimbursement system, manufacturers may participate in defining the scope or protocol of the assessment (France, Germany, the UK) or submit information to the group preparing such reports (Germany, Ireland, Spain, the UK). Among systems that prepare the evaluation report only, about half invite manufacturers to contribute information (Scotland, Italy, Sweden, the UK, Wales). Involvement of manufacturers otherwise appears limited to single examples, eg, able to participate in consultations during the assessment (France) or attend review committee meetings (Wales).

Conclusion

Centralized reimbursement systems have become an important policy tool in many European countries. Their introduction has, inarguably, brought greater consistency to

| Reimbursement as part of a formal study | Risk-sharing schemes/ payment by results | Other |
|----------------------------------------|------------------------------------------|-------|
| No information found                   | No information found                     | No information found |
Table 8  Comparison of the role of manufacturers in centralized reimbursement processes

| Country     | Centralized reimbursement review/decision-making body (role)                                                                 | Refer technology topics for reimbursement consideration | Participate in defining scope and/or protocol of assessment | Comment on draft protocol | Participate in consultations during assessment | Submit information to group preparing assessment report |
|-------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|--------------------------|-----------------------------------------------|--------------------------------------------------------|
| Austria     | • Association of Austrian Social Security Institutions (decisions)35 • Pharmaceutical Evaluation Board (recommendations)16 | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| Belgium     | • Minister of Social Affairs (decisions) • Drug Reimbursement Committee (recommendations)39,60                              | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| Czech Republic | • State Institute for Drug Control (decisions)35,176                                                                        | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| Denmark     | • Danish Medicines Agency (decisions)46,80,121 • Reimbursement Committee (recommendations)46,121                             | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| Estonia     | • Ministry of Social Affairs (decisions)27 • Pharmaceuticals Committee (recommendations)72                                 | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| Finland     | • Pharmaceuticals Pricing Board (decisions)75,76,16 • Pharmaceuticals Pricing Board Expert Group (recommendations)75         | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| France      | • Ministry for Health and Social Security (decisions)20,78 • French National Authority for Health (recommendations)78         | Yes                                                      | Yes (multiple technology appraisals)                      | No                       | Yes (multiple technology appraisals)          | No (multiple technology appraisals)                    |
| Germany     | • Federal Joint Committee (decisions)19 • Institute for Quality and Efficiency in Health Care (recommendations)19            | No                                                       | Yes                                                      | Yes                      | No                                            | Yes                                                    |
| Greece      | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions)19                                   | Yes                                                      | N/A                                                      | N/A                      | N/A                                           | N/A                                                    |
| Country          | Centralized reimbursement review/decision-making body (role) | Refer technology topics for reimbursement consideration | Participate in defining scope and/or protocol of assessment | Comment on draft protocol | Participate in consultations during assessment | Submit information to group preparing assessment report | Present views during committee meetings | Nominate clinical and/or patient experts to make oral presentation to committee | Attend committee meeting | Comment on report and/or draft recommendations | Appeal recommendations or decisions |
|------------------|-------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|---------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------|
| Austria          | • Association of Austrian Social Security institutions (decisions) | 55                                                     | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | No                                             | Yes                                           | No                                         |
| Belgium          | • Minister of Social Affairs (decisions)                      | 9,60                                                   | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | Yes, if recommendation is negative            | Yes                                           | Yes                                        |
| Czech Republic   | • State institute for Drug Control (decisions)               | 65,176                                                 | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | No                                             | Yes                                           | No                                         |
| Denmark          | • Danish Medicines Agency (decisions)                         | 68,69,121                                              | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | Yes                                           | Yes                                           | No (recommendations only)                     |
| Estonia          | • Ministry of Social Affairs (decisions)                      | 72                                                     | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | No                                             | Yes                                           | No                                         |
| Finland          | • Pharmaceuticals Pricing Board (decisions)                   | 73,74,76                                               | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | Yes, if recommendation is negative            | Yes                                           | No                                         |
| France           | • Ministry for health and Social Security (decisions)         | 20,78                                                  | Yes (multiple technology appraisals)                     | n/A (single technology appraisals) | No (multiple technology appraisals) | n/A (single technology appraisals) | No (multiple technology appraisals) | n/A (single technology appraisals) | Yes                                           | Yes (decisions only)                         | No                                         |
| Germany          | • Federal Joint Committee (decisions)                        | 19                                                     | No                                                       | Yes                        | Yes                                           | No                                               | No                                                  | No                                         | Yes                                           | Yes                                           | No                                         |
| Greece           | • Transparency Committee in the Reimbursement and Medicinal Products (makes decisions) | 85                                                     | n/A                                                      | n/A                       | n/A                                           | No                                               | No                                                  | No                                         | No                                             | Yes                                           | No                                         |

(Continued)
| Country | Centralized reimbursement review/decision-making body (role) | Refer technology topics for reimbursement consideration | Participate in defining scope and/or protocol of assessment | Comment on draft protocol | Participate in consultations during assessment | Submit information to group preparing assessment report |
|---------|-------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|--------------------------|-----------------------------------------------|--------------------------------------------------|
| Hungary | • Ministers of Health and Finance  
• National Health Insurance Fund Administration (recommendations) |
|         | Yes N/A N/A N/A N/A No information found                                |                                                        |                                                          |                                                        |                                                      |
| Ireland | • Health Service Executive (decisions) |
|         | Yes N/A N/A N/A Yes                                                    |                                                        |                                                          |                                                        |                                                      |
| Italy   | • Italian Medicines Agency Technical Scientific Committee (decisions)  
• Italian Medicines Agency Pricing and Reimbursement Committee (recommendations) |
|         | Yes N/A N/A N/A No                                                   |                                                        |                                                          |                                                        |                                                      |
| Norway  | • Norwegian Medicines Agency (decisions)  
• Department of Pharmacoeconomics (recommendations) |
|         | Yes N/A N/A N/A No information found                                   |                                                        |                                                          |                                                        |                                                      |
| Poland  | • Ministry of Health (decisions)  
• INFARMED (recommendations) |
|         | Yes N/A N/A N/A No information found                                   |                                                        |                                                          |                                                        |                                                      |
| Portugal| • Ministry of Health (decisions)  
• INFARMED (recommendations) |
|         | Yes N/A N/A N/A No information found                                   |                                                        |                                                          |                                                        |                                                      |
| Scotland| • National Health Service Scotland (decisions)  
• Scottish Medicines Consortium (recommendations) |
|         | Yes N/A N/A N/A No                                                   |                                                        |                                                          |                                                        |                                                      |
| Slovakia| • Ministry of Health (decisions)  
• Reimbursement Committee for Medicinal Products (recommendations) |
|         | Yes N/A N/A N/A No information found                                   |                                                        |                                                          |                                                        |                                                      |
| Spain   | • Ministry of Health Directorate General of Pharmacy and Health Products; Inter-Ministerial Pricing Commission (decisions) |
|         | No No No Yes Yes                                                     |                                                        |                                                          |                                                        |                                                      |
| Sweden  | • Dental and Pharmaceutical Benefits Board Expert Board (decisions) |
|         | Yes N/A N/A N/A N/A                                                   |                                                        |                                                          |                                                        |                                                      |
| Country     | Centralized reimbursement review/decision-making body (role) | Refer technology topics for reimbursement consideration | Participate in defining scope and/or protocol of assessment | Comment on draft protocol | Participate in consultations during assessment | Submit information to group preparing assessment report | Nominate clinical and/or patient experts to make oral presentation to committee | Attend committee meeting | Comment on report and/or draft recommendations | Appeal recommendations or decisions |
|-------------|-------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------|--------------------------|-----------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------|-----------------------------|----------------------------------------------------------|-------------------------------|
| Hungary     | • Ministers of health and Finance • national health insurance Fund Administration (recommendations) | Yes | n/A | n/A | n/A | n/A | n/A | n/A | n/A | Yes |
| Ireland    | • health Service Executive (decisions) | Yes | n/A | n/A | n/A | n/A | Yes | No | No | No | Yes | No |
| Italy       | • Italian Medicines Agency Technical Scientific Committee (decisions) • Italian Medicines Agency Pricing and Reimbursement Committee (recommendations) | Yes | n/A | n/A | n/A | No | Yes | No | No | No | Yes | No |
| Norway      | • Norwegian Medicines Agency (decisions) • Department of Pharmacoeconomics (recommendations) | Yes | n/A | n/A | n/A | No | Yes | No | No | No | Yes | No |
| Poland      | • Ministry of health (decisions) | Yes | n/A | n/A | n/A | No | Yes | No | No | No | No | No |
| Portugal    | • Ministry of health (decisions) • inFARMED (recommendations) | Yes | n/A | n/A | n/A | No | Yes | No | No | No | Yes | No |
| Scotland    | • national health Service Scotland (decisions) • Scottish Medicines Consortium (recommendations) | Yes | n/A | n/A | n/A | No | Yes | No | No | Yes | Yes | No |
| Slovakia    | • Ministry of health (decisions) • Reimbursement Committee for Medicinal Products (recommendations) | Yes | n/A | n/A | n/A | No | Yes | No | No | No | Yes | No |
| Spain       | • Ministry of health Directorate general of Pharmacy and health Products; inter-Ministerial Pricing Commission (decisions) | No | No | No | Yes | Yes | No | No | No | No | No | No |
| Sweden      | • Dental and Pharmaceutical Benefits Board Expert Board (decisions) | Yes | n/A | n/A | n/A | n/A | Yes | Yes | No | Yes | Yes | No |

(Continued)
processes and an improved sense of legitimacy to decisions. Nevertheless, there remains a lack of transparency around critical elements, such as how multiple factors or criteria are weighed during committee deliberations. Further, empirical studies evaluating the extent to which centralized reimbursement systems with advisory as opposed to decision-making authority are able to reduce inequities in access to new technologies within jurisdictions appear sparse.

Given the rapid pace with which new technologies that appear promising are now entering the market and the need to work alongside broader government industrial policies for encouraging innovation in an economic climate that demands prudent use of strained health care resources, the adoption of AED schemes by reimbursement systems seems inevitable. However, until more information on the outcomes of initiatives such as flexible pricing in the UK becomes available, their implementation should be approached with caution.

Disclosure
The authors report no conflicts of interest in this work.

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### Table 8: Country Centralized Approaches to Reimbursement

| Country          | Role | Review/Decisions | Reimbursement Topics for Consideration |参与到会议 | 发表意见 | 参与政策制定 | 参与评估报告 | 上诉建议或决定 | 信息来源 |
|------------------|------|------------------|----------------------------------------|------------|----------|------------|------------|----------------|-----------|
| Wales            | King | No               | No                                     | No         | No       | Yes         | Yes         | Yes            | Yes       |
| Kingdom          | United | No               | No                                     | Yes        | No       | No         | Yes         | Yes            | Yes       |
| Netherlands      | Dutch | No               | No                                     | Yes        | Yes      | No         | Yes         | Yes            | Yes       |
| Switzerland     | Swiss | No               | No                                     | Yes        | Yes      | No         | Yes         | Yes            | Yes       |
|                  |      |                  |                                        | N/A (single technology appraisals) | No       | Yes       | Yes         | Yes            | Yes       |

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