**European Network for Health Technology Assessment**

**EUnetHTA JA2**

**WP7 DELIVERABLE**

**Evidence submission**

**templates to support**

**production of core HTA**

**information and rapid**

**assessments:**

**Pharmaceuticals**

**evidence submission**

**template long version**

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Joint Action on HTA 2012-2015

**Evidence submission templates to support production of core HTA information and rapid assessments: Pharmaceuticals evidence submission template long version**

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WP 7 Lead Partner: Haute Autorité de Santé (HAS)

WP Subgroup Coordinator: National Institute for Health and Care Excellence (NICE)

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Notes are available from the EUnetHTA website for agencies to use when adapting the submission template for regional, national or joint processes.

EUnetHTA pharmaceuticals evidence submission template

Long version

[Technology name]

[Indication for use]

[Company/Sponsor]

Abbreviations

*For agency completion*

Date of receipt:

Identifier:

*Contact details for administrative purposes*

Name of contact person:

Address of contact:

Telephone number:

Email address:

ATC: anatomical therapeutic chemical

CI: confidence interval

CONSORT: consolidated standards of reporting trials

DSM: Diagnostic and Statistical Manual of Mental Disorders

EMA: European Medicines Agency

EPAR: European Public Assessment Report

HRQOL: health-related quality of life

HTA: health technology assessment

ICD: International Classification of Diseases

ITT: intention-to-treat

PRISMA: preferred reporting items for systematic reviews and meta-analyses

QOL: quality of life

RCT: randomised controlled trial

RMP: risk management plan

SD: standard deviation

SPC: summary of product characteristics

STROBE: strengthening the reporting of observational studies in epidemiology

US: United States

VnR: Nordic Article Number

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**Using this evidence submission template**

This evidence submission template contains suggestions to companies about what information to include, *highlighted in blue*, which agencies can adapt as necessary. There are also ‘form fields’ that prompt companies for their response, for example *[add details here]*. To insert a response, a company should click once anywhere within the highlighted text and then type in their response. This overwrites the section that was highlighted. To delete a form field, click anywhere within the highlighted text and press DELETE.

Description and technical characteristics of the technology

Summary of the characteristics of the technology

*In no more than 6 bullet points describe key statements about the technology and its regulatory status.*

*For example, include statements that describe the key features of the technology and its authorisation status.*

* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*

Characteristics of the technology

1. In table 1 provide an overview of the technology.

Table 1: Features of the technology

|  |  |
| --- | --- |
| Non-proprietary name |  |
| Proprietary name |  |
| Marketing authorisation holder |  |
| Class |  |
| Active substance(s) |  |
| Pharmaceutical formulation(s) |  |
| ATC code |  |
| Mechanism of action |  |

1. In table 2, summarise the information about administration and dosing of the technology.

Table 2: Administration and dosing of the technology

|  |  |
| --- | --- |
| Method of administration |  |
| Doses  |  |
| Dosing frequency |  |
| Average length of a course of treatment |  |
| Anticipated average interval between courses of treatments |  |
| Anticipated number of repeat courses of treatments |  |
| Dose adjustments |  |

1. In table 3 provide information about the different packs available.

Table 3: Pack information

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Pack size | Strength | Form | Pack code (if available, for example VnR code or barcode) |
| Pack 1 |  |  |  |  |
| *[Insert line for each pack available]* |  |  |  |  |

1. State the context and level of care for the technology, for example primary healthcare, secondary healthcare, tertiary healthcare, outside health institutions or as part of public health or other.

*[add details here]*

1. State who administers the technology, including:
	* the professionals who administer and make decisions about starting or stopping the technology
	* whether patients or their carers administer the technology.

*[add details here]*

1. State the claimed benefits of the technology, including whether the technology should be considered innovative.

*For example, whether the technology has increased safety, health benefits, compliance and improved features of administration compared with existing technologies.*

*[add details here]*

Regulatory status of the technology

*If the technology is not approved and launched in any country include the information that is expected to be approved. If the approval is relevant across countries indicate the countries to which the approval applies.*

1. Complete table 4 with the marketing authorisation status of the technology in the country of application and, if applicable, in other European countries and the US, Canada and Australia.

*[add details here]*

1. State the authorisation procedure.

*For example, centralised, mutual recognition, decentralised procedure.*

*[add details here]*

1. State whether the technology has any special status.

*For example, orphan, generic, biosimilar classification.*

*[add details here]*

1. State any other indications not included in the assessment for which the technology has marketing authorisation in any European country.

*[add details here]*

1. State any contraindications or groups for whom the technology is not recommended.

*[add details here]*

1. State whether there are any ongoing procedures for new indications for the technology or ongoing procedures relating to existing indications in Europe.

*Specify the date approval is expected, if known.*

*Include changes to the marketing authorisation currently in progress.*

*[add details here]*

1. Describe the main issues discussed by the EMA or other regulatory organisation in granting a marketing authorisation for the indication under assessment.

*Refer to issues that are or will be reflected in the regulatory (draft) assessment report (for example, the EPAR).*

*If appropriate, state whether these issues led to special conditions being attached to the marketing authorisation (for example, exceptional circumstances or conditions to the marketing authorisation).*

*[add details here]*

1. Describe any undertakings in the context of the marketing authorisation.

*Include requests for additional clinical studies or follow-up studies.*

*Include special pharmacovigilance monitoring or RMP.*

*[add details here]*

Table 4: Regulatory status of the technology

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Country** | **Organisation issuing approval** | **Verbatim wording of the (expected) indication(s)** | **(Expected) Date of approval** | **Type of approval (full, conditional, exceptional)** | **Launched (yes/no).****If no include proposed date of launch** | **Marketing authorisation number (if available)** |
| Country of application |
|  |  |  |  |  |  |  |
| Other countries |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

Health problem and current clinical practice

Summary of issues relating to the health problem and current clinical practice

*In no more than 6 bullet points describe key statements about the health problem and current clinical practice.*

*For example, include statements about the proposed use or target population, unmet needs of treatment and how the technology may address these.*

* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*

Overview of the disease or health condition

1. Define the disease or health condition in the scope of this assessment.

*If available include a standardised code such as the ICD code or the DSM code (and the version of the code).*

*If relevant describe the main subtypes and/or stages of the disease or health condition.*

*[add details here]*

1. Briefly describe the known causes or risk factors for developing the disease or health condition.

*[add details here]*

1. For the stages and/or subtypes of disease being considered in the assessment, describe the natural course of the disease or health condition without treatment.

*Include any prognostic factors that may affect the course of the disease or health condition.*

*[add details here]*

1. Present an estimate of prevalence and/or incidence for the disease or health condition including recent trends.

*This information may be tabulated or displayed graphically.*

*Include absolute numbers of patients.*

*[add details here]*

1. Describe the symptoms and burden of the disease or health condition for patients.

*Include aspects such as pain, disability, psychosocial issues, or other determinants of morbidity and quality of life from a patient perspective.*

*[add details here]*

1. Describe the consequences of the disease or health condition for society.

*Include aspects such as disease-specific mortality and disability, and life years lost from a population perspective.*

*[add details here]*

1. Describe the aspects of the burden of disease that are targeted by the technology, that is, those that are expected to be reduced by the use of the technology.

*[add details here]*

Target population

*The target population may be the population identified in the marketing authorisation or a target group of patients using the technology for which the company wants reimbursement.*

1. Describe the target population and the proposed position of the target population in the patient pathway of care.

*[add details here]*

1. Provide a justification for the proposed positioning of the technology and the definition of the target population.

*[add details here]*

1. Estimate the size of the target population. Include a description of how the size of the target population was obtained and whether it is likely to increase or reduce over time.

*[add details here]*

Clinical management of the disease or health condition

1. Describe the clinical pathway of care for different stages and/or subtypes of the disease being considered in the assessment.

*Include a list of relevant guidelines. Table 5 provides a suggested presentation when there are multiple relevant guidelines.*

*Include a diagram of the care pathway. When there are significant variations in care, more than one diagram may be required.*

1. State the technologies currently used in the clinical pathway for which the proposed technology is an alternative, or an additional treatment.

*For non-pharmacological alternatives, the description should include the type of management for example, inpatient or outpatient care, community practice, emergency care and the extent to which the procedure is standardised.*

*There is a separate section for describing the comparators in the assessment – see section 2.4.*

*[add details here]*

1. Describe any issues relating to current clinical management, for example, unmet needs, uncertainty about best practice, variations in management and management of specific patient groups.

*[add details here]*

1. Describe the pathway of care that incorporates the new technology if the technology were to be adopted for use.

*If a diagram of the existing care pathway has been included, this may be updated to show how the new technology will change the pathway of care. More than one diagram may be required.*

*[add details here]*

Suggested table 5: Relevant guidelines for diagnosis and management

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of society/organisation issuing guidelines** | **Date of issue or last update** | **Country/ies to which guideline applies** | **Summary of recommendations****(Level of evidence/grade of recommendation for the indication under assessment)** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| Include a link to relevant guidelines if publicly available |

Comparators in the assessment

1. On the basis of the alternatives presented, identify the technologies to be used as comparator(s) for the assessment.

*[add details here]*

1. Provide a justification for the choice of the comparators in the assessment.

*Comparators can differ from the technology in their mechanism of action (whether physical, chemical or mechanical).*

*If the comparators are different from the technologies identified as alternatives to the intervention or the technologies to which the intervention will be added, provide a justification for the differences.*

*[add details here]*

Current use of the technology and comparators

Summary of issues relating to current use of the technology and comparators

*In no more than 6 bullet points describe key statements about the current use of the technology and the use of the comparators.*

*For example, include statements about the availability and reimbursement status of the technology in other countries, the populations in which the technology is currently used (if available), and the regulatory and reimbursement status of comparators.*

* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*

Current use of the technology

*Complete only if the technology is available in one or more European countries.*

1. Describe the experience of using the technology, for example the health conditions and populations, and the purposes for which the technology is currently used. Include whether the current use of the technology differs from that described in the (expected) authorisation.

*[add details here]*

1. Indicate the scale of current use of the technology, for example the number of people currently being treated with the technology, or the number of settings in which the technology is used.

*[add details here]*

1. Indicate how the scale of current use is expected to change in the future if the technology is introduced.

*[add details here]*

Reimbursement and assessment status of the technology

*Complete only if the technology has been launched in a European country.*

1. Complete table 6, indicating the reimbursement status of the technology in Europe.
2. Complete table 7, summarising the existing reimbursement and assessment recommendations in European countries.

*Complete the table only for the indication(s) under consideration in this assessment.*

*Include recommendations arising from reimbursement processes and from conclusions of health technology assessments that did not result in a reimbursement decision.*

*Give the reasons for the rejection of reimbursement or restrictions placed on reimbursement (if available).*

Table 6: Overview of the reimbursement status of the technology in European countries

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country and issuing organisation**  | **Technology-specific or indication-specific reimbursement decision (if indication-specific state for which indication(s) reimbursement considered)\*** | **Status of recommendation (positive/negative/ongoing/not assessed)** | **Date of decision** | **If positive, level of reimbursement\*\***  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| Include a reference to any publicly available guidance documents\*For indication-specific recommendations include a new row for each indication\*\*For example full reimbursement or only partial reimbursement. If partial reimbursement give a percentage of reimbursement |

Table 7: Summary of reimbursement recommendations in European countries for the technology

|  |  |  |
| --- | --- | --- |
| **Country and issuing organisation**  | **Summary of reimbursement and assessment recommendations and restrictions** | **Summary of reasons for rejections and restrictions (if available)** |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
| For countries with indication-specific reimbursement include only the recommendations for the indication under assessmentInclude a reference to any publicly available guidance document |

Current use of the comparators

*This section relates to the comparators in the assessment, these may be pharmacological or non-pharmacological.*

1. Indicate the number of people in the target population estimated to receive treatment with each of the comparators.

*[add details here]*

1. Describe the variations in how much the comparators are used across countries or regions or settings, if any.

*[add details here]*

1. Complete table 8 for each of the comparators in the assessment with their regulatory and reimbursement status.

*[add details here]*

Table 8: Regulatory and reimbursement status of comparators

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Comparator name** | **Regulatory authorisation status (yes/no/ongoing)** | **Status of reimbursement recommendation (positive/negative/ongoing)** | **Date of reimbursement decision** | **If positive, level of reimbursement\*** | **Restrictions on reimbursement** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| \*Indicate if the comparator has complete or partial reimbursement. If partial reimbursement give a percentage of reimbursement |

Investments and tools required

Summary of issues relating to the investments and tools required to introduce the technology

*In no more than 6 bullet points describe key statements about the investments and tools required to use the technology.*

*For example, include statements about the equipment and resources required to use the technology and how this differs from the comparators.*

*For example, include statements about any new equipment, premises and personnel that will be required if the technology is introduced, or equipment, premises and personnel that will no longer be required.*

* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*

Requirements to use the technology

1. State whether using the technology requires another technology.

|  |  |
| --- | --- |
| **Technology is associated with:** | **Response: yes/no****If yes, include name of associated technology** |
| Pharmaceutical |  |
| Medical device |  |
| Procedure |  |

1. If any special conditions are attached to the regulatory authorisation more information should be provided, including reference to the appropriate sections of associated documents (for example the EPAR, user manual, SPC). Include:
	* conditions relating to settings for use (for example, inpatient or outpatient, presence of resuscitation facilities)
	* restrictions on professionals who can use or may prescribe the technology
	* conditions relating to clinical management (for example, patient monitoring, diagnosis, management and concomitant treatments).

*[add details here]*

1. Describe the treatments (for example, for side-effects) that may be required by patients using the technology.

*If all treatments are described in response to question 2, state here that there are no additional requirements.*

*[add details here]*

1. Describe the tests, investigations and monitoring required by patients using the technology.

*If all tests, investigations and monitoring are described in response to question 2, state here that there are no additional requirements.*

*[add details here]*

1. Describe the facilities required to use the technology.

*For example, purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises for storage and reconstitution of chemotherapy pharmaceuticals equipped with fume cupboards.*

*If all facilities are described in response to question 2, state here that there are no additional requirements.*

1. Describe the equipment required to use the technology.

*If all equipment is described in response to question 2, state here that there are no additional requirements.*

*[add details here]*

1. Describe the supplies required to use the technology.

*For example, syringes, needles, pharmaceuticals and contrast agents, fluids, bandages.*

*[add details here]*

Procedures required to use the technology

*Complete this section only if the technology is associated with a procedure.*

1. State whether the procedure was developed alongside the technology or was previously carried out with a different technology or without the technology.

*[add details here]*

1. Describe the procedure. Include:
* the type of approach (for example, direct, percutaneous, vascular, endoscopic)
* whether or not guidance is required (for example, ultrasound, echo-Doppler, X-ray)
* for each of step of the procedure, the duration of the step and the type and role of each person involved (for example, physician performing the procedure, anaesthetists, nurses).

*[add details here]*

1. Describe the technical platform (that is, the equipment in the room in which the procedure is performed) and the environment necessary for performing the procedure.
* In particular, specify whether or not the procedure must be performed in an operating theatre.
* If the procedure does not need to be performed in an operating theatre, state whether a particular pre-existing technical platform is required.

*[add details here]*

1. State the number of times the procedure needs to be repeated for the treatment to be complete.

*For procedures involving multiple organs or lesions indicate whether all organs or lesions may be treated in a single procedure.*

*Indicate if replacement or removal procedures may also be required.*

*[add details here]*

1. Describe whether anaesthesia is required, include details about the methods used (for example, general, local, loco-regional, sedation, analgesia).

*[add details here]*

1. If more than one procedure may be used, compare their similarities or differences (for example, in terms of technicality, duration of the procedure, technical platform).

*[add details here]*

Investments, disinvestments and changes in service organisation

*Complete this section to describe the investments that are needed in order to use the technology (that is, the resources not currently available that will need to be put in place for the technology to be introduced).*

*This section should highlight any differences in requirements for use between the technology and the treatments currently being used.*

1. Describe any additional skills and training that will need to be provided for the professionals who will administer the technology:
	* Describe the type of training and any training materials required (individual and/or group sessions, number and length of sessions, number and qualifications of trainers).
	* If the technology requires a specific skill that is developed over a period of time using the technology, an estimate should be provided of the number of patients a professional needs to treat (as a total number or per year) in order to reach an acceptable minimum standard.
	* Explain the extent to which the training and quality assurance measures may affect the efficacy and safety of the technology.

*[add details here]*

1. Describe any training that will be needed for patients and/or their carers.

*[add details here]*

1. Describe any additional human resources required to implement the technology, for example new employees.

*[add details here]*

1. Describe any changes to current services that are needed to introduce the technology. Include:
* any tests or investigations needed for selecting or monitoring patients that are over and above usual clinical practice
* any equipment, or organisational and technical conditions that will require investment before the technology can be introduced
* any investment in infrastructure
* any programmes and services that will have to be increased due to introduction of the technology (rehabilitation, nursing etc.).

*Consider possible effects on services earlier and later in the care pathway.*

*[add details here]*

1. Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed if the technology is introduced.

*If an existing procedure is replaced: include the replacement rate and the volume of procedures replaced.*

*[add details here]*

Clinical effectiveness and safety

Summary of the clinical effectiveness

*In no more than 6 bullet points describe key statements relating to the clinical effectiveness of the technology.*

*For example, include statements about the benefit of the technology compared to alternative technologies currently used.*

* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*

Summary of safety

*In no more than 6 bullet points describe key statements relating to the safety of the technology.*

*For example, include statements about the relative safety of the technology compared to alternative technologies currently used.*

* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*
* *key statement*

Identification and selection of relevant studies

*This section should describe how relevant studies were identified:*

* *studies of the technology in the indication under assessment*
* *studies of the comparators (if applicable).*
1. Specify the research question or problem statement used to guide the searches.

*For example, the patients, intervention(s), outcomes, comparator(s) and study types used to develop the searches.*

*[add details here]*

1. State the databases and trial registries searched and, when relevant, the platforms used to do this.

*[add details here]*

1. State the date the searches were done and any limits (for example date, language) placed on the searches.

*[add details here]*

1. Include as an appendix the search terms and strategies used to interrogate each database or registry.

*For bibliographic databases: Include the complete search strategies (with the names of the interfaces), the years covered by the search, the date of the last search and the number of hits per line.*

*For study registries: Include the search terms, the input interface (for example, basic search or advanced search), and the number of hits retrieved.*

*If a search filter is used (that is, a predefined combination of search terms to filter references with a specific content), provide a reference to the filter used.*

1. In table 9, state the inclusion and exclusion criteria used to select studies and justify these.

Table 9: Inclusion and exclusion criteria

|  |  |
| --- | --- |
| Inclusion criteria | Population:Intervention(s):Comparator(s):Outcomes:Settings (if applicable):Study design:Language restrictions:Other search limits or restrictions applied: |
| Exclusion criteria | Population:Intervention(s):Comparator(s):Outcomes:Settings (if applicable):Study design:Language restrictions:Other search limits or restrictions applied: |

1. Provide a flow chart showing the number of studies identified and excluded. The [PRISMA statement](http://www.prisma-statement.org/statement.htm) can be used; the PRISMA flow chart is included below, as an example.
2. Describe any additional methods to those described above, that were used to identify ongoing and unpublished studies.

*[add details here]*

PRISMA flow chart

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Relevant studies

*Studies should be ordered by study design (RCT and non-RCT [if applicable]) and status (complete and ongoing).*

*Include all the studies that were used in the evidence synthesis, including (if applicable) studies of comparator technologies.*

*For assessments where there are a lot of studies, more than one table may be needed; for example dividing the evidence by complete and ongoing studies, randomised and non-randomised evidence or evidence for the technology versus evidence for the comparator(s).*

1. In table 10 provide a list of the relevant studies identified.

Table 10: List of all relevant studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study reference/ID** | **Name and registration number** | **Conflicts of interest\*** | **Dates of study (start and [expected] completion date)** | **Study location or regions**  | **Source of identification\*\***  | **Available documentation\*\*\*** | **Status****(ongoing/****complete)** |
| *Randomised controlled trials* |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| *Non-randomised studies* |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| \*Highlight studies sponsored by the company\*\*For example, company-sponsored trial, trial registry, bibliographic database\*\*\*Include references to all linked documents and indicate the expected date of publication for any unpublished clinical studies |

Main characteristics of studies

*Further information on the presentation of study information can be found in the* [*CONSORT statement*](http://www.consort-statement.org/checklists/view/32-consort/66-title) *for randomised controlled trials, and* [*STROBE guidelines*](http://www.strobe-statement.org/index.php?id=available-checklists) *for observational studies.*

*Include all the studies that were used in the evidence synthesis, including (if applicable) studies of comparator technologies.*

*Include ongoing and unpublished studies if these data are available.*

1. In table 11, describe the main characteristics of the studies.
2. In table 12, provide information about the study methodology.

Table 11: Characteristics of the studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study reference/ID** | **Objective** | **Study design** | **Eligibility criteria** | **Intervention and****Comparator****(N enrolled)** | **Primary outcome measure and follow-up time point** | **Secondary outcome measures and follow-up time points** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

Table 12: Description of study methodology

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study reference/ID** | **Method of recruitment** | **Method of randomisation** | **Method of allocation concealment** | **Methods of blinding**  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

1. For the technology under consideration, describe any groups of patients excluded from the studies and the rationale for their exclusion. Indicate if these groups are included (or expected to be included) in the marketing authorisation.

*[add details here]*

1. For each study describe how sample size was determined.

*[add details here]*

1. For each study provide a flow diagram of the numbers of patients moving through the trial.

*Include: patients evaluated for enrolment, those assigned to a treatment category, patients who received treatment as allocated, patients who completed follow-up and patients included in the main analyses.*

*Tables submitted to the regulatory authorities showing patient flow may be used.*

*[add details here]*

1. For each study provide a comparison of patients (including demographic, clinical and social information [if applicable]) in treatment arms at baseline.

*Tables submitted to the regulatory authorities showing patients’ baseline demographic characteristics may be used if available.*

*[add details here]*

Individual study results (clinical outcomes)

*Include all the studies that were used in the evidence synthesis, including (if applicable) studies of comparator technologies.*

*Include ongoing and unpublished studies if these data are available.*

1. Describe the relevant endpoints, including the definition of the endpoint, methods of data collection and methods of analysis (table 13).

*The study results presented should reflect the outcomes relevant to the evidence synthesis including, if available, mortality, morbidity, function, (health-related) quality of life and patient satisfaction.*

*If the endpoint uses a scale, state how it was validated; if this uses responder analyses, state and justify the responder definition.*

1. If any outcomes, studies or study arms are excluded from the summary of clinical outcomes provide a justification for their exclusion (table 14).
2. Provide a summary of the study results for each relevant comparison and outcome (see example tables 15 and 16).

*Data should be presented according to intention-to-treat. Alternative presentations of the data should be justified.*

*In the case of survival analyses, Kaplan-Meier curves that include the number of patients at risk at various time points should be provided.*

*If non-comparative data are included in the submission the summary of outcomes should include measures over time (for example baseline, and post-intervention). Estimates should be presented as unadjusted estimates and as estimates adjusted for potential confounders. The confounders used in the adjustment should be stated and their use justified (see example table 17).*

Table 13: Methods of data collection and analysis of *[state outcome]*

|  |  |  |  |
| --- | --- | --- | --- |
| **Study reference/ID** | **Endpoint definition** | **Method of data collection** | **Method of analysis**  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Table 14: Excluded data from the summary of study results

|  |  |  |
| --- | --- | --- |
| **Study reference/ID** | **Excluded information****(e.g. whole study/study arm/study outcome)** | **Justification for exclusion** |
| Studies of technology under consideration |
|  |  |  |
| Studies of comparator technologies (if applicable) |
|  |  |  |

Example table 15: Results summary for *[state outcome]* (dichotomous)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study reference/ID** | **Outcome intervention****n/N (%)** | **Outcome** **Comparator****n/N (%)** | **Absolute difference\*****(95% confidence interval)****(p value)** | **Relative difference\*****(95% confidence interval)****(p value)** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| \*Specify the type of difference presented in the submissionOrder studies by their comparison, e.g. all studies comparing the intervention with comparator x are listed first, followed by all studies comparing the intervention with comparator y. A study may appear in the table more than once if it has more than two treatment arms. |

Example table 16: Results summary for *[state outcome]* (continuous)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study reference/ID** | **Outcome intervention****N=****Mean/Median (SD)** | **Outcome** **Comparator****N=****Mean/Median (SD)** | **Absolute difference\*****(95% confidence interval)****(p value)** | **Relative difference\*****(95% confidence interval)****(p value)** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| \*Specify the type of difference presented in the submissionOrder studies by their comparison, e.g. all studies comparing the intervention with comparator x are listed first, followed by all studies comparing the intervention with comparator y. A study may appear in the table more than once if it has more than two treatment arms. |

Example table 17: Results summary *[insert study reference]* (non-comparative studies)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **Intervention****Baseline** **N=** | **Follow-up** **(insert time point)****N=** | **Absolute difference\*****(95% confidence interval)** | **Relative difference\*****(95% confidence interval)** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| \*Specify the type of difference presented in the submissionThe table may need to be adapted to include multiple time pointsInclude in the table numbers of outcome events (n/N) or summary measures (mean/median and SD) |

Individual study results (safety outcomes)

*Include all the studies of the technology that were used in the evidence synthesis, including (if applicable) studies of comparator technologies.*

*Include ongoing and unpublished studies when these data are available.*

1. For the technology, tabulate patient exposure to the technology and the comparator for each of the studies providing safety data.

*See example table 18; tables from regulatory documents may also be used. For non-comparative studies complete only the column for the technology.*

Example table 18: Exposure to technology

|  |
| --- |
| **Study *x*** |
| **Duration / frequency of exposure (e.g. months, days, weeks, permanently implanted)** | **Technology under investigation** | **Comparator** | **Total** |
| Duration 1 (n/N=; %) |  |  |  |
| Duration 2 (n/N=; %) |  |  |  |
| Duration 3 (n/N=; %) |  |  |  |
| Mean |  |  |  |
| SD |  |  |  |
| Median |  |  |  |
| Minimum |  |  |  |
| Maximum |  |  |  |
| Patient years |  |  |  |

1. Describe the relevant endpoints, including the definition of the endpoint, methods of data collection and methods of analysis (table 19).

*The study results presented should reflect the safety outcomes relevant to the evidence synthesis.*

*If the endpoint uses a scale, state how it was validated; if this uses responder analyses, state and justify the responder definition.*

1. If any outcomes, studies or study arms are excluded from the summary of safety outcomes provide a justification for their exclusion (table 20).
2. For the technology, tabulate the number of patients who permanently or temporarily discontinued treatment for each study providing safety data.

*See example table 21; tables from regulatory documents providing the same information may also be used.* *For non-comparative studies complete only the row for the intervention.*

1. For the technology, and the comparator, tabulate the total adverse events, frequency of occurrence (as a %), absolute and relative risk and 95% CI reported in each of the clinical studies. Categorise the adverse events by frequency, severity and system organ class.

*Example table 22 provides an overview of adverse events. Table 23 is given as an example of a more detailed presentation of the data. When presenting data specify: the number of patients, the number of events and the absolute and relative risk (with 95% confidence intervals). Order data by system class and frequency of events. For non-comparative studies complete only the column for the intervention.*

*Tables from regulatory documents providing the same information may also be used.*

*Repeat for each study providing safety data.*

Table 19: Methods of data collection and analysis of *[state outcome]*

|  |  |  |  |
| --- | --- | --- | --- |
| **Study reference/ID** | **Endpoint definition** | **Method of data collection** | **Method of analysis**  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Table 20: Excluded data from the summary of study results

|  |  |  |
| --- | --- | --- |
| **Study reference/ID** | **Excluded information****(e.g. whole study/study arm/study outcome)** | **Justification for exclusion** |
| Studies of technology under consideration |
|  |  |  |
| Studies of comparator technologies (if applicable) |
|  |  |  |

Example table 21: Discontinuation and disruption of treatment by study

|  |  |  |  |
| --- | --- | --- | --- |
| **Studies** | **Reason for permanent discontinuation of treatment** | **Reason for temporary discontinuation of treatment**  | **Number without post-discontinuation data** |
|  |  | **Adverse events****N (%)** | **Lack of efficacy****N (%)** | **Other****N (%)** | **Adverse events****N (%)** | **Other****N (%)** | **N (%)** |
| Study | Intervention |  |  |  |  |  |  |
|  | Comparator |  |  |  |  |  |  |
| Study | Intervention |  |  |  |  |  |  |
|  | Comparator |  |  |  |  |  |  |

Example table 22: Overview of adverse events

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Study [insert study reference or identifier]** | **Study [insert study reference or identifier]** | **Study [insert study reference or identifier]** |
|  | **Intervention (n = x)****n (%)** | **Comparator (n = x)****n (%)** | **Relative risk (95% CI)**  | **Risk difference (95% CI)** | **Intervention** **(n = x)****n (%)** | **Comparator (n = x)****n (%)** | **Relative risk (95% CI)**  | **Risk difference (95% CI)** | **Intervention** **(n = x)****n (%)** | **Comparator (n = x)****n (%)** | **Relative risk (95% CI)**  | **Risk difference (95% CI)** |
| Total number of adverse events |  |  |  |  |  |  |  |  |  |  |  |  |
| Total number of serious adverse events |  |  |  |  |  |  |  |  |  |  |  |  |
| Total number of deaths |  |  |  |  |  |  |  |  |  |  |  |  |
| Total number of adverse events leading to temporary or permanent treatment withdrawal |  |  |  |  |  |  |  |  |  |  |  |  |
| Total number of withdrawals from the study because of adverse events |  |  |  |  |  |  |  |  |  |  |  |  |
| Adapted from European Public Assessment Reports published by the European Medicines AgencyFrom tables 3a and 5 of the EUnetHTA safety guideline |

Example table 23: Frequency and severity of adverse events

|  |
| --- |
| **Study [insert study reference or identifier]** |
| **System organ/class/adverse events** | **All grades** | **Serious adverse events** | **Death** |
| **Intervention (n = x)****n (%)** | **Comparator (n = x)****n (%)** | **Relative risk** **(95% CI)**  | **Risk difference (95% CI)** | **Intervention (n = x)****n (%)** | **Comparator (n = x)****n (%)** | **Relative risk (95% CI)**  | **Risk difference (95% CI)** | **Intervention (n = x)****n (%)** | **Comparator (n = x)****n (%)** | **Relative risk (95% CI)**  | **Risk difference (95% CI)** |
| Class 1 (for example, nervous system disorders) |
| Adverse event 1 |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event 2 |  |  |  |  |  |  |  |  |  |  |  |  |
| Class 2 (for example, vascular disorders) |
| Adverse event 3 |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event 4 |  |  |  |  |  |  |  |  |  |  |  |  |
| CI, confidence intervalAdapted from European Public Assessment Reports published by the European Medicines AgencyFrom tables 3a and 5 of the EUnetHTA safety guideline |

Subgroups

1. Describe which subgroup(s) were analysed in the clinical trials of the technology under assessment.

*Indicate which subgroups were pre-specified and if any were identified post-hoc. Provide a justification for consideration of post-hoc subgroups.*

*[add details here]*

1. State which papers are relevant to the subgroup analyses.

*[add details here]*

1. Specify the methods of subgroup analysis used in the clinical trials.

*[add details here]*

1. Give the results of the subgroup analyses from the clinical trials.

*Provide the results of subgroup analyses from the individual studies for the technology of interest. Subgroup analyses completed as part of evidence synthesis should be included in the evidence synthesis sections.*

*Subgroup analyses should include identification of patient groups who may be more likely to be harmed through use of the technology, as well as those groups who may have differing treatment effects.*

*[add details here]*

Risk of bias at study level: randomised controlled trials

*Include all studies used in the evidence synthesis, including (if applicable) studies of comparator technologies.*

*Include ongoing and unpublished studies if these data are available.*

1. For each RCT identified give the adequacy of:
* Random sequence generation (was the method used to generate the allocation or randomisation sequence adequate to produce comparable groups?)
* Allocation concealment (was the method used to mask the sequence of allocation to the intervention adequate?)
* Blinding (were patients, medical personnel and statistical investigators appropriately blinded with respect to intervention assignment?)
* Completeness of the data for each outcome considered (was the amount, nature or handling of incomplete outcome data adequately described?)
* Selective outcome reporting (were all relevant pre-specified outcomes reported independently by the results?)
* Other sources of bias (is the trial free from other aspects that affect the risk of bias, for example, early interruption of the study because of the benefits without an appropriate stopping rule, use of non-validated measurement instruments, incorrect statistical analysis?)

*Information can be included in a table (see table 24). Please explain any high risk of bias in text below the table.*

Table 24: Risk of bias at study level: randomised studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study reference/****ID** | **Adequate generation of a randomisation sequence** | **Adequate allocation concealment** | **Blinding** | **Incomplete outcome reporting** | **Selective outcome reporting unlikely?** | **Overall risk of bias** |
| **Patient** | **Medical personnel (carer, investigator, outcome assessor)** |
|  | Yes/no/unclear | Yes/no/unclear | Yes/no/unclear | Yes/no/unclear | Yes/no/unclear | Yes/no/unclear | Low/high |
|  |  |  |  |  |  |  |  |
| Note: an answer ‘yes’ indicates a low risk of bias, and an answer ‘no’ indicates high risk of biasIf the answer is ‘unclear’ or ‘no’, please give reasons for the classification |

Risk of bias at outcome level: randomised studies

*Include all outcomes included in the evidence synthesis.*

1. For each study outcome included in the evidence synthesis, state whether:
* the outcome assessor was blinded
* intention-to-treat (ITT) was appropriately implemented
* selective outcome reporting is unlikely
* the study is free from other (outcome-specific) aspects that affect the risk of bias.

*The information can be included in a table (see table 25).*

Table 25: Risk of bias outcome level for *outcome x*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study reference/ID** | **Blinding of outcome assessors** | **ITT appropriately implemented**  | **Selective outcome reporting unlikely** | **Is the study free of other outcome-specific aspects that can affect the risk of bias** | **Overall risk of bias** |
|  | Yes/no/unclear | Yes/no/unclear | Yes/no/unclear | Yes/no/unclear | Low/High |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

*Repeat the table for each outcome included in the evidence synthesis.*

Risk of bias: non-randomised studies

*Include all studies that were used in the evidence synthesis, including (if applicable) studies of comparator technologies.*

*Include ongoing and unpublished studies if these data are available.*

*Risk of bias assessment results can be displayed separately for each outcome. Therefore separate assessment of risk of bias at the outcome level is not required for non-randomised studies.*

1. For each non-randomised study identified, state whether there is:
* Bias due to confounding (is confounding of the effect of intervention likely in this study?)
* Bias in the selection of patients into the study (how was the treatment group determined for each patient?)
* Bias in the measurement of interventions (is intervention status well defined and unaffected by knowledge of the outcome or risk of the outcome?)
* Bias due to departures from intended interventions (was intention-to-treat [ITT)] appropriately implemented?)
* Bias due to missing data (are outcome data or intervention status reasonably complete?)
* Bias in the measurement of outcomes (was outcome measurement objective and comparable across intervention groups or was the definition of case status [and control status if applicable] based on objective criteria?)
* Bias in the selection of the reported results (were all relevant outcomes reported?)
* Comparability at baseline (were the characteristics of selected groups comparable at baseline?)
* Overall bias.

*If non-comparative data are included in the submission, other aspects of internal validity should be reported.*

*Information can be included in a table (see table 26).*

Table 26: Risk of bias at study level: non-randomised studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study reference/** **ID****Outcome** | **Bias due confounding**  | **Bias in selection of patients into the study** | **Bias in measurement of interventions**  | **Bias due to departures from intended interventions**  | **Bias due to missing data** | **Bias in measurement of outcomes** | **Bias in selection of the reported result** | **Overall bias**  |
|  | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] | [Low/moderate/serious/critical/NI] |
| NI=No informationInsert reasons for the classification chosen |

Methods of evidence synthesis

*This section is reviewed alongside the sections on identification of relevant studies, main characteristics of the studies, study results and risk of bias. The studies included in these sections and their referencing should be consistent throughout these sections to enable review of the approach used.*

1. State the type of synthesis (for example, narrative, meta-analysis, indirect or mixed treatment comparison).

*If more than one study is available and if studies are sufficiently similar, they should be combined quantitatively in a meta-analysis or network meta-analysis (as appropriate)*. *The approach taken should be justified including the decision not to combine studies quantitatively.*

*[add details here]*

1. State the outcomes included in the synthesis and the time point for the collection of outcome data. Justify the inclusion and exclusion of outcomes and the time point.

*State which outcomes are important for the assessment and why.*

*[add details here]*

1. State whether any syntheses of subgroup data are being presented. Justify the subgroups chosen.

*[add details here]*

1. State the comparators included in the synthesis, indicate with justification whether any comparators have been added to the synthesis (for example, to help create a network of evidence) or excluded from the synthesis (for example, because of an absence of data).

*[add details here]*

1. Where a quantitative approach is used, list the studies informing the synthesis showing the comparisons made by the studies. Justify any exclusions from the synthesis (see tables 27 and 28).

*For network meta-analyses: If any additional studies are included to generate links in the network, mark which studies these are. For network meta-analyses network diagrams may be used as an alternative to table 27.*

Table 27: Studies included in synthesis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study reference/ID** | **Intervention** | **Comparator 1** | **Comparator 2** | **Comparator 3 (add more columns as needed)** |
|
| Example: |  |  |  |  |
| Smith 1990 | *x* | *x* |  |  |
| Smith 1994 | *x* |  | *x* |  |
|  |  |  |  |  |

Table 28: Studies excluded from synthesis

|  |  |
| --- | --- |
| **Study reference/ID** | **Reasons for exclusion** |
|  |  |
|  |  |
|  |  |
|  |  |

1. Describe the methods used to synthesise the evidence.
* Meta-analysis: state methods and models used and justify these. If Bayesian methods are used, justify the priors chosen.
* Indirect or mixed treatment comparisons: state the statistical model, software and whether a fixed or random effects model has been used. Justify the choice of methods. If Bayesian methods are used, justify the priors chosen.

*The computer code and tables of study data entered into the indirect or mixed treatment comparison (including the outcomes data and numbers of patients in each of the trial arms for each outcome synthesised) should be included in an appendix.*

* Narrative review: give details of the methods used.

*[add details here]*

1. Discuss the extent to which the studies may be considered (1) homogeneous as a group and (2) representative of the target population and treatments.

*Indicate the impact, or lack of impact, differences between studies or differences between the studies and the target population or treatments may have on the relative treatment effects. State whether differences are accounted for in the analyses.*

*[add details here]*

1. State how heterogeneity in the relative treatment effects was assessed and give evidence of the degree of heterogeneity in each of the pairwise comparisons.

*If heterogeneity is identified consider possible explanatory factors.*

*Indicate whether any adjustments have been made to account for heterogeneity in the relative treatment effects.*

*[add details here]*

1. If network meta-analysis is used, state how consistency between direct and indirect comparisons was assessed. Highlight any inconsistencies in comparisons.

*[add details here]*

1. State how publication bias was assessed and give evidence to justify whether or not publication bias is presumed to be present.

*[add details here]*

1. Describe the sensitivity analyses done. If the conclusions are sensitive to outliers or influential studies, present the sensitivity analyses as part of the results of evidence synthesis.

*[add details here]*

Results of evidence synthesis

*This section includes a structured presentation of the outcomes of the evidence synthesis for comparative effectiveness and safety for all outcomes examined.*

*Answer ‘unknown’ when there is no evidence on a stated outcome.*

*Tabulate the results of any quantitative synthesis, presenting the relative effects of the technology against each of the relevant comparators.*

*Present Forest plots for meta-analyses.*

*Include the results of any subgroup and/or sensitivity analyses.*

1. State the effects of the technology versus the comparator(s) on mortality.

*[add details here]*

1. State the effects of the technology versus the comparator(s) on the following aspects of morbidity:
* severity and frequency of symptoms and findings
* progression of disease
* body functions.

*[add details here]*

1. State the effects of the technology versus the comparator(s) on the following aspects of quality of life (QOL):
* generic health-related quality of life (HRQOL)
* disease-specific HRQOL
* work productivity
* activities of daily living.

*[add details here]*

1. State the effects of the technology versus the comparator(s) on aspects of patient satisfaction.

*[add details here]*

1. Highlight the difference in the risks and any differences in the severity of adverse events of the technology and the comparator(s).

*[add details here]*

Conclusions

1. Provide a general interpretation of the evidence base considering the benefits associated with the technology relative to those of the comparators.

*The considerations should include, if relevant, differences between the intervention and comparator(s) (if any) for:*

* *mortality*
* *morbidity*
* *disease progression*
* *function*
* *(health-related) quality of life, and*
* *patient satisfaction.*

*[add details here]*

1. Provide a general interpretation of the evidence base considering the harms associated with the technology relative to those of the comparators.

*The considerations should include, if relevant, differences between the intervention and comparator(s) (if any) for:*

* + *nature and severity of harms*
	+ *relationship of the harms to dosage and frequency of application*
	+ *changes over time or in other settings*
	+ *susceptible patient groups*
	+ *harms that can arise from the people who use or maintain the technology.*

*[add details here]*

Strengths and limitations

1. Summarise the internal validity of the evidence base, taking into account the study quality, the validity of the endpoints used as well as the overall level of evidence. Include a statement about the consistency of the results in the evidence base.

*[add details here]*

1. Provide a brief statement of the relevance of the evidence base to the scope of the assessment.

*Consider the relevance of the population, intervention, comparators and outcomes. Discuss the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.*

*[add details here]*

1. Identify any factors that may influence the extent to which the study results may be applied to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of which patients are suitable for the technology.

*Consider the geographical and clinical setting of the studies and how these and other factors could affect the reproducibility of findings when the technology is used in routine clinical practice.*

*[add details here]*

Safety risk management

1. Comment on whether there is a need to optimise or limit the use of the technology, or to monitor the use of the technology, to minimise potential risks to safety.

*Consider risks to patients and professionals.*

*If applicable relate relevant issues to the risk management plan.*

*[add details here]*

For products already available:

1. Describe any changes made to the marketing authorisation as a result of safety issues.

*Respond to this question only if the pharmaceutical is already launched.*

*[add details here]*

1. Describe any other harms that have come to light after granting of the marketing authorisation or that have been identified outside of clinical trials (for example, from pharmacovigilance and spontaneous reporting).

*Respond to this question only if the pharmaceutical is already launched.*

*[add details here]*

**References**

*[add details here]*

**Example presentation of a search strategy**

|  |  |
| --- | --- |
| Database name | EMBASE |
| Search interface | Ovid |
| Search date  | 8 December 2014 |
| Period covered | 1980 to 2014 (week 50) |
| Search filter | Filter for randomized controlled trials Wong 2006 [1] |
| # | Search terms | Results |
| 1 | Meglitinide/ | 848 |
| 2 | Nateglinide/ | 1686 |
| 3 | Repaglinide/ | 2118 |
| 4 | (glinid\* or meglitinid\* or nateglinid\* or repaglinid\*).ab,ti. | 1069 |
| 5 | (starlix or novonorm or novo norm or prandin).ab,ti. | 32 |
| 6 | (105816-04-4 or 135062-02-1).rn. | 2854 |
| 7 | or/1-6 | 3467 |
| 8 | Diabetes mellitus/ | 224164 |
| 9 | Non Insulin dependent Diabetes mellitus/ | 91081 |
| 10 | (diabet\* or niddm or t2dm).ab,ti. | 379777 |
| 11 | or/8-10 | 454517 |
| 12 | (random\* or double-blind\*).tw. | 650136 |
| 13 | placebo\*.mp. | 243550 |
| 14 | or/12-13 | 773621 |
| 15 | and/7,11,14 | 719 |