Health Technology Assessment

Mandatory joint EU assessments are coming at last

The European Commission unveiled at the end of January 2018 a much-anticipated legislative proposal on health technology assessment (HTA), which aims to improve business predictability and create equal access for patients by addressing key problems within the current system.[1]

This will essentially formalise a voluntary project on joint HTA called EUnetHTA that has been in existence for over a decade. The proposed legislation takes the form of a regulation (*Regulation on Health Technology Assessment*) that would be directly applicable in the EU member states. Once adopted, it would enter into force after three years.

This article explains how HTA is currently conducted in the EU, and what the new regulation is expected to achieve.

The current system for assessing the relative effectiveness of a new medicinal product in the EU – the first step towards getting reimbursement – takes place after a product has received a marketing authorisation. But unlike the marketing authorisation, which is the result of a single, centralised procedure carried out at European level, the HTA is conducted at national level by more than 50 separate agencies, each of which may have different data requirements. At the very least, companies may be performing the same task several times, just to secure the HTA of a single product.

Mindful that this duplication of effort is costly, the Commission helped launch EUnetHTA in 2005. EUnetHTA stands for the European Network for Health Technology Assessment and is a project under which around 80 organisations work together to establish a common HTA methodology. The project has been successful, but not enough to address ongoing HTA fragmentation, which is why the Commission is now proposing to formalise the concept in a regulation.

The proposed regulation would only require member states to coordinate on the clinical elements of HTA, based on EUnetHTA's so-called Core Model. Cost effectiveness analysis would remain a national responsibility, according to the Commission.

The joint clinical assessments would be limited to medicinal products undergoing the centralised marketing authorisation procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication, and certain classes of medical devices and *in vitro* diagnostics (e.g. those that address an unmet medical need).

The EUnetHTA Core Model

EUnetHTA's HTA Core Model is a methodological framework for the production and sharing of HTA information.[2] It can be used for carrying out Rapid Relative Effectiveness Assessments (REAs) or full assessments. 'Relative effectiveness' is the extent to which a drug, medical device, *in vitro* diagnostic or other medical intervention does more good than harm, compared to one or more alternatives.

Rapid REAs focus on four clinical domains: health problem and current use of technology; description and technical characteristics; safety; and clinical effectiveness. Full assessments look at the four clinical domains plus five further domains of a non-clinical nature: costs and economic evaluation; ethical analysis; organisational aspects; patient and social aspects; and legal aspects.

The type of assessment envisaged under the proposed regulation would build on the methodologies used in Rapid REAs, which EUnetHTA has piloted extensively under programmes called Joint Actions. The final report would be similar to those developed under the current Joint Action. These scientific reports analyse and describe the relative effects of the technology observed for patient-relevant health outcomes (e.g. relative effects on survival, disease symptoms or side effects), weighed against one or more comparators, for certain subgroups of population and health outcomes/ endpoints.

One such assessment was carried out on Novartis' midostaurin used with standard chemotherapy for *FLT3* mutation-positive acute myeloid leukaemia (AML) patients who are fit for intensive chemotherapy.[3] This is an orally administered multi-target receptor tyrosine kinase inhibitor, which was designated as an orphan medicinal product in 2004 and received EU marketing authorisation in September 2017.

The manufacturer provided a systematic literature review of the evidence, which was critically assessed by the Finnish Medicines Agency and the Norwegian Medicines Agency. Three studies formed the basis for the assessment (RATIFY, IIT (AMLSG 16-10/CPKC412DE02T) and UK NCRI AML17 trials), two of which were included in the marketing authorisation holder's submission file, as presented in the clinical study report.

At the time, there were several treatments recommended for AML, but none was specific for *FLT3* mutation-positive AML. The most relevant comparators were: standard induction and consolidation chemotherapy (cytarabine in combination with daunorubicin 60 mg/m2/day during the induction phase); and induction and consolidation chemotherapy with daunorubicin 90 mg/m2 /day during the induction phase.

Stem cell transplant (SCT), azacitidine and gemtuzumab ozogamicin (GO) were identified as potential comparators during the early scoping for this assessment, but they were later excluded. SCT is considered for all eligible patients irrespective of the use of midostaurin, so it could not be used. Azacitidine is used in patients who are not suitable for intensive chemotherapy and thus this did not represent the patient group that was defined in the scope of the assessment. Finally, although GO had been prescribed in France under a compassionate-use programme since 2014, it was not considered a relevant comparator because of its limited use in selected patients in only one member state.

The safety profile of treatment with midostaurin in combination with standard induction and consolidation

chemotherapy was deemed comparable to standard induction and consolidation chemotherapy. However, exfoliative dermatitis and device-related infections occurred more frequently in patients receiving midostaurin. Furthermore, QTc prolongation was observed in midostaurin patients. Deaths during the study treatment and 30-day follow-up periods occurred more frequently in patients over 60 compared with those who were younger.

The assessment report concluded that midostaurin in combination with standard induction and consolidation chemotherapy was more effective than standard induction and consolidation chemotherapy alone. However, based on the evidence assessed there was greater uncertainty regarding use of the drug in continuation therapy.

The assessors advised that further research was required on the effects of midostaurin in the older population because patients over 60 years had not been studied in a randomised clinical trial. They also recommended that health-related quality of life and disease-specific quality of life should be studied because this evidence was lacking.

The proposed HTA regulation

The above snapshot of the midostaurin report gives a sense of what might be expected under the HTA regulation. Member states would have to use these reports as part of their overall HTA process at national level and would not be permitted to repeat clinical assessments, unless they could justify grounds for doing so. The aim for medicinal products would be to have the final report available around the time of the marketing authorisation decision.

A newly established Coordination Group on HTA led by the EU member states would manage the joint clinical assessments, from appointing HTA bodies as assessor and co-assessor to approving the joint reports which would later be published by the Commission. In addition, the Coordination Group would be responsible for member state collaboration on joint scientific consultations (described below), the identification of emerging health technologies (horizon scanning) and voluntary cooperation on areas outside the scope of joint clinical assessments such as non-clinical assessments.

Under the regulation, health technology developers could request a joint scientific consultation (early dialogue) with the Coordination Group in the development phase. This would allow them to seek the advice of HTA bodies on the data and evidence likely to be required as part of a potential future joint clinical assessment, such as design of clinical trials, relevant comparators and patient-relevant outcomes. "The joint scientific consultation could be HTA only or in parallel with the regulatory scientific advice provided by the European Medicines Agency," confirmed the Commission.

MedNous asked Finn Boerlum Kristensen, the former director of the EUnetHTA Secretariat, about how the data requirements for HTAs might differ from those for regulatory reviews. "They will try to get closer to real world situations where the technology/pharmaceutical is used in clinical practice by estimating the effectiveness of the intervention. In the early stages this will build a lot on the same evidence as the regulatory work on efficacy/safety, but will be combined with application of indirect comparisons and network meta-analysis and information on, for example, epidemiologic data and current clinical and healthcare practice from various data sources," he said.

Now an independent consultant, Mr Kristensen advised companies to "listen very carefully to what their market access people are saying in terms of what the HTAs and payers are asking for – and more than that, they should bring the people in development and the market access people together very early in the process – and invite the regulatory people as well, but not *only* the regulatory people."

Overall, the European Federation of Pharmaceutical Industries and Associations (Efpia) views the proposals as a positive step. However, "a high-level framework of the joint clinical assessment framework should be included in the primary legislation which clarifies that procedural rules and clinical assessment methodology should be in line with agreed best practice and as such will evolve over time," Efpia director market access/HTA Tina Taube commented to *MedNous*.

As for horizon scanning, Efpia believes it is a reasonable tool in the short term, but "a clear definition of what it includes and what information is needed is crucial as it should focus on publicly available high-level product information," said Mrs Taube. Moreover, she said that prioritisation of products based on horizon scanning to be selected for the joint work cannot be supported if it leads to delayed access for 'non-priority products.'

What happens next?

It is hoped that the Council of Ministers and the European Parliament can reach an agreement on the regulation before the parliamentary elections in May 2019. Once the regulation enters into force (shortly after its final adoption), there will be a three-year transition period before it becomes applicable.

During this period the Commission plans to adopt tertiary legislation, which will set out the details of the methodology to be used in the joint clinical assessments, a spokesperson said.

Joint clinical assessments will be phased in gradually during the transition period. Following this, all medicinal products covered by the regulation and granted marketing authorisation in a given year will be assessed, while a selection of eligible medical devices will undergo assessment.

References:

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2. EUnetHTA, HTA Core Model® Version 3.0, 25 January 2016, https://www.eunethta.eu.

3. EUnetHTA, Rapid assessment of pharmaceutical technologies using the HTA Core Model® for Rapid REA, Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukaemia, Project ID: PTJA01, 6 November 2017, https://www.eunethta.eu.

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